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The Lancet Breast Cancer Commission Report

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The Lancet Breast Cancer Commission Report

Executive summary

The Lancet Breast Cancer Commission, a diverse multidisciplinary international group, are unanimous in our determination to improve the lives of all people everywhere who live with or who are at risk of breast cancer. We came together in July 2021 and are committed to raising the standard of breast cancer care to close the equity gap in that care which exists between and within countries. Over a 2-year period, we brainstormed ideas, scoped the literature, obtained funding for dedicated pilot research which has provided new data, and produced this Commission report with a single purpose: to reduce the impact that breast cancer has on society.

Lancet Breast Cancer Commission new findings

Our Lancet Breast Cancer Commission report highlights that, despite tremendous advances in breast cancer research and treatment in recent decades leading to a 40% reduction in breast cancer mortality in some high-income countries (HICs), there remain gross inequities with many groups being systematically left behind, ignored, and even forgotten. Our findings suggest this is mistaken as people with breast cancer are indispensable to our socioeconomical fabric and culture.

We show that the number of people living with metastatic breast cancer (MBC) is currently unknown as cancer registries do not record relapse. Many patients with MBC feel abandoned, isolated, alone, and may not receive appropriate care, both in high and low-middle income countries: this should and can be tackled. With adequate evidence-based resources and a shift in the current negative societal attitudes toward the disease, it may be possible to cure some patients with MBC, treat most, alleviate the suffering of all, and forget or abandon no-one.

We have identified that the hidden costs of breast cancer and associated suffering are considerable, varied, and with far-reaching impact. Costs and suffering can be financial, physical, psychological, emotional, and social; these impact on children, families, local communities, and wider society. These can occur at all stages of breast cancer and are evident even within health services that are free at the point of delivery. Exposing and reducing both costs and suffering provides incentive for policymakers to invest in prevention, early detection, cost-effective therapy, and optimal management of breast cancer.

We demonstrate that improving patient communication and decision making in breast cancer improves quality of life and body image, but also adherence to therapy which can impact on survival. Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, there could be an opportunity to regain power and emerge stronger than before, with people exercising empowerment in other areas of their lives.

Lancet Breast Cancer Commission reinforces and builds on existing evidence

We acknowledge that early detection of breast cancer is of fundamental importance and should be available to all individuals wherever they live. We encourage broadening breast cancer early detection efforts in low- and middle-income countries (LMICs) from a narrow focus on mammographic screening, which may be unaffordable or unachievable in limited resource settings, to include breast cancer 'early diagnosis' as recommended by the World Health Organisation (WHO).

Every country that successfully reduced national breast cancer mortality rates between 1990 and 2020 now has at least 60% of invasive breast cancers at stages I or II. Recent evidence shows that awareness and education focusing on finding and treating symptomatic (palpable) breast cancers when they are first discoverable promotes stage-shifting toward or even surpassing this 60% threshold, a finding that

is especially relevant for women younger than screening age, as well as older women living in regions where limited healthcare access prevents more progressive early detection efforts to be employed.

Lancet Breast Cancer Commission roadmap for change

We have developed an inclusive evidence-based roadmap to address these urgent breast cancer challenges. The roadmap is divided into 6 themes:

Prevent - breast cancer is the most common cancer worldwide and, by 2040, the annual incidence of new breast cancers is predicted to be over 3 million cases per year, with the incidence rising most rapidly in low- and middle-income countries. The mindset that this upward trajectory is inevitable and therefore acceptable should be changed - action now can prevent many of these future breast cancers.

We emphasise that breast cancer risk factor education is vital but should be combined with policy change to support sustained behaviour change and decrease health inequalities. Policy makers should reject commercial marketing for products that increase breast cancer risk. Co-ordinated approaches to systematically identify individuals at increased risk of breast cancer and to offer them evidence-based prevention interventions, are proposed as an aspirational goal to be developed through ongoing research.

Personalise - science and clinical research can facilitate equitable and prompt access to the right breast cancer treatment at the right time for each individual whilst respecting personal needs and preferences. Better targeting of existing treatments through development of validated biomarkers is needed to identify those people who benefit the most and to reduce treatment burden for those likely to have more toxicity than gain. We identify the need to develop and facilitate novel, efficient, patient-centred, translational clinical trials and enable a research culture and infrastructure to ensure these can be undertaken across the globe.

Digital health technology can facilitate personalised breast cancer care through integration of multi-modal complex datasets; promote flexible, coordinated care particularly for vulnerable patients; democratise access to research; and decentralise trial participation. We suggest that, if used optimally, digital health technology can alleviate inequities in breast cancer rather than drive them.

Include - our Commission report places MBC as a central theme and urges for inclusion of this important group. We justify why optimal MBC management is valuable to individuals, families, and society. We show results of the Commission's international health care professionals survey, which suggests that there is a growing belief that patients with some subtypes of MBC can be treated as chronic illnesses for many years, and some patients may even be cured.

In addition to collecting data on cancer incidence and stage at presentation, we call for high-quality data on cancer relapse worldwide to include not just those with MBC, but other metastatic cancers. We recommend that stigma around MBC can be addressed through education and awareness of all stakeholders and society.

We must **Collaborate** to close the equity gap through global early diagnosis, treatment frameworks, and innovative technology. Women with low incomes and those from minoritised populations in all countries often have their breast cancer diagnosed at late-stage with a high-risk of dying from their cancer. The early diagnosis inequity gap will widen without intervention. Equitable access to early diagnosis and treatment is a fundamental need for all individuals to improve breast cancer survival and quality-of-life.

In collaboration with the WHO Global Breast Cancer Initiative, we call for action to deliver ‘stage-shifting’, as a sustained decline in breast-cancer mortality rates is achieved by diagnosing at least 60% of invasive cancers at stage I-II. We show that tools to achieve this 60% threshold can be achieved through population-based mammographic screening programmes when they are feasible to establish and operate sustainably, but early detection approaches should be adapted to local context and resources. We suggest that technology innovations could catalyse the speed and efficacy of early breast cancer diagnosis and treatment implementation globally, and these should be combined with an integrated health systems policy, education, and advocacy.

Identify - the hidden costs and serious health-related suffering of breast cancer goes unmeasured in global health metrics, so its alleviation is not prioritised by policymakers. Our Commission calls for new and validated tools to capture the myriad of costs and suffering experienced by patients, caregivers, and families experiencing breast cancer.

We also indicate the urgency of developing metrics to measure the full benefits that patients and society places on alleviating suffering related to breast cancer. These novel tools could influence policy makers to set new priorities for breast and other cancers to guarantee that supportive and palliative care is available to all and at every stage of the breast cancer pathway, alongside financial protection to prevent catastrophic and impoverishing health expenditure from direct and indirect health care costs and lost family income.

Communicate - being female is the greatest risk factor for breast cancer and women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings. As such, our final theme focuses on communication and empowerment related to breast cancer. We suggest that prioritising patient autonomy regarding medical treatment is paramount to close the gender equity gap and will have broader impacts for the physical, social, and financial wellbeing of women globally.

We propose a framework to improve communication and aid decision making for those with breast cancer. Placing patients at the centre of clinical communication and empowering them to exercise their voices, become fully informed, and choose their level of involvement in decisions about their care, is an achievable and worthwhile goal worldwide. Health communication training should be person-centred and include: eliciting patients’ core values and preferences for information; explaining goals of care, risk-benefit communication; skills to help estimate and explain prognosis and share serious news; skills to empathically but honestly respond to questions; and consideration of local cultural traits and individual differences.

Measurable indicators of change and future work

Our inclusive road map for change is evidence-based and includes new compelling data. It is designed for everyone with any connection to breast cancer but is particularly aimed at policymakers. We have suggested detailed measurable indicators of progress in this road map, with targets and suggested responsible groups. These indicators are designed to be actionable, auditable, and to facilitate lobbying for change.

Our work with the Lancet Breast Cancer Commission will not end with this publication, as it has catalysed lasting partnerships between co-authors, as well as with other Commissions and key international organisations and patient groups. As a result, we have on-going collaborative research and will continue to strive to raise the bar and close the equity gap for breast cancer.

Panel 1 - Summary of the Lancet Breast Cancer Commission key messages

The Lancet Breast Cancer Commission report shows glaring inequities, with many groups with breast cancer being systematically left behind and forgotten. This is a global blunder. People with breast cancer are indispensable to our socioeconomical fabric and culture.

New findings:

- The number of people living with metastatic breast cancer (MBC) is unknown and many do not receive appropriate care. With adequate resources and a shift in attitudes, it may be possible to cure some patients with MBC, treat most, alleviate the suffering of all, and abandon no-one.
- Hidden breast cancer costs and suffering can be financial, physical, psychological, emotional, and social; these impact children, families, communities, and wider society. Exposing and reducing costs and suffering provides incentive for policymakers to invest in prevention, early detection, cost-effective therapy, and optimal management of breast cancer.
- Improving patient communication in breast cancer improves quality of life and body image, but also adherence to therapy which can impact survival. Breast cancer robs many patients of power, but through good communication and facilitating patient autonomy, there could be an opportunity to regain power, emerge stronger than before, and exercise empowerment in other areas of their lives.

Roadmap for change

An inclusive roadmap addresses these urgent breast cancer challenges through 6 themes:

- Society should **prevent** as many as possible of the 3 million new breast cancers per year that are predicted to occur by 2040 through a united global policy change to minimise modifiable risk factors, as well as coordinated, systematic personalised risk prevention programmes.
- Health systems and clinicians should **personalise** the right treatment at the right time for each individual whilst respecting personal needs and preferences.
- We call for high-quality cancer registry data on cancer relapse to be collected worldwide, to **include** not just those with MBC, but other metastatic cancers.
- **Collaboration** is key to close the equity gap through global early diagnosis, treatment frameworks and innovative technology.
- We should **identify** what value society places on relief of the hidden costs and suffering related to breast cancer, and to measure the benefits of addressing these costs.
- Placing patients at the centre of clinical **communication** and empowering them to exercise their voices about their breast cancer care is an achievable and worthwhile worldwide goal.

Introduction

Scientific advances that have dramatically improved what is possible for breast cancer prevention and treatment contrast starkly with the reality of failure to deliver good care to most patients with breast cancer around the world. The Lancet Breast Cancer Commission calls for raised awareness and change to ensure the translation of evidence into policy and practice for breast cancer care and prevention.

In 2020, over 2.3 million women were diagnosed with breast cancer, and breast cancer caused 685,000 deaths globally.¹ In addition, around 1% of the total incidence of breast cancer occurs in men. Breast cancer is now the world's most prevalent cancer; at the end of 2020, 7.8 million women were alive having been diagnosed in the previous 5 years, with an unknown number of people living with metastatic breast cancer.¹

Breast cancer affects people in every country, but large geographical variations exist around the world. For example, annual incidence rates range from <40 per 100,000 females in some Asian and African countries, to over 80 per 100,000 in Australia/New Zealand, Northern America, and parts of Europe.

Economic transitioning countries carry a disproportionate share of breast cancer deaths. The breast cancer burden is predicted to increase to more than 3 million new cases per year (an increase of 40%) and more than 1 million deaths per year (an increase of 50%) by 2040. In low human development index (HDI) countries, the numbers of new cases and deaths are anticipated to double by 2040¹, and in medium HDI countries the incidence and mortality are predicted to increase by 70% and 60% respectively.

In 2020, 4.4 million women died from cancer worldwide, leaving behind 1.04 million maternal orphans, and 25% of these orphans lost their mother to breast cancer.² Importantly, there is a strong inverse correlation between the HDI and the number of new maternal orphans per 100 female cancer deaths.³ It is estimated that for every 100 women who die of breast or cervical cancer in African countries, between 14 and 30 children will die as a result.² Thus, the chronic social disruption and financial harm of breast cancer will continue to disproportionately impact low and middle-income countries (LMICs) for generations to come. In addition, deep gender, ethnic, and socioeconomic divides exist both within and between countries.⁴ Breast cancer represents one of the most significant examples of the gender, racial, and ethnic inequities in oncology.⁵

Despite these stark statistics, biomedical advances have produced dramatic improvements in breast cancer outcomes over the last 30 years, and this has contributed to falling mortality rates, but mostly in higher income countries. A crucial pivotal point for breast cancer has been reached globally, whereby either current inequities both between and within countries widen irreparably, or society unites to ensure equitable access to evidence-based breast cancer prevention and care as a fundamental right for all.

The Lancet Breast Cancer Commission – structure and aim

It is against this background that the Lancet Breast Cancer Commission convened in July 2021. Its aim is to provide a new perspective on an old and seemingly insurmountable global problem and identify key areas for change to influence global policy and ultimately improve lives of those affected by breast cancer.⁶ The Commission is multidisciplinary and diverse in terms of geographical distribution (high-, middle- and low-income countries are represented), gender, ethnicity, professional role, career-level and includes patient advocate commissioners with lived experience of early and metastatic breast cancer (*see supplementary material 2 for all those involved*). The first commission meeting identified 5 workstreams, each with 2 co-chairs, to co-ordinate scoping and evidence synthesis with assistance from early career researchers around 12 key questions identified by the group.⁶ Main meetings were held quarterly over 2 years. The vast majority were virtual, with one 2-day meeting in Cambridge in summer 2022. Workstream meetings were held in between, and work that was carried out consisted of literature reviews, an international healthcare professionals' survey, and new research projects, some of which were funded specifically to produce new data to inform the Commission report. The Breast Cancer Commission is collaborating with other key groups including the Lancet Commission on Cancer And Health Systems,⁷ and Lancet Commission on Global Access to Palliative Care and Pain Relief,⁸ the WHO Global Breast Cancer Initiative, and the ABC Global Alliance.

Each section starts with a summary and ends with suggested measurable indicators for change. Any forward-looking document runs the risk of being seen as platitudinous rather than radical: gilding the surface of what happens rather than getting to the roots of the problem. The commissioners felt it important therefore that their work led to real change for the sake of breast cancer patients, past, present, and future, worldwide. We decided to include a set of indicators that would reflect specific changes that we felt are needed to empower real change. These indicators were drafted by the leads of the six final themes, focussed not only on what the indicator could be, but also who or what should be responsible for ensuring their delivery, and were based on the appraisal of evidence accumulated during the two years, and then shared with the whole commissioning group for comments and

revisions. Whilst they are therefore in essence ‘expert opinion’, they are based on hundreds of years’ collective understanding of breast cancer as a global and system problem, and aimed at being broad, practical, and adaptable to specific contexts. The specific numerical targets were drafted in the same way and chosen as being likely to engineer real change for patients, whilst acknowledging that there are always challenges in changing systems.

Individuals with or at risk of breast cancer are referred to variously as ‘individuals’, ‘patients’ and sometimes ‘women’ throughout the report, but the Commission acknowledges that definitions are much broader, for example including men and transgender people who may experience considerable stigma and inequity (*see supplementary material 3 developed through the Commission - Towards Breast Cancer Care Equity: Considerations for Sexual and Gender Minority Persons*). A glossary of terms used within the report is also available in supplementary material 1.

The Commission report is *not* a textbook chapter or review of the biomedical management of breast cancer but, in response to the very real inadequacies and inequities in global breast cancer care, it is a call to action on specific important global challenges, each coupled with the opportunities for positive change. We propose this compelling evidence-based narrative to start the journey of positive change for all those affected by breast cancer, now and in the future.

Theme 1: Breast Cancer Prevention

Panel 2 - Summary for breast cancer prevention

- **Action now could prevent** as many as possible of the 3 million new breast cancers per year that are predicted to occur by 2040.
- Breast cancer risk factor education is vital but should be combined alongside policy change to support sustained behaviour change and decrease health inequalities.
- Governments and policy makers should have the will, courage, and integrity to reject lobbying from vested interest groups that profit from exposing populations to breast cancer risk factors.
- Approaches to systematically identify individuals at increased risk of breast cancer and to offer them evidence-based prevention interventions should be implemented and refined through on-going research.

Worldwide, women have on average a 1 in 12 risk of breast cancer by age 75, and the incidence is rising.^{9,10} With the current trajectory, by 2040, an estimated 3 million individuals will be diagnosed each and every year.⁹ This upward trajectory is neither acceptable nor inevitable: action now can prevent many of these future cancers. Prevention potentially offers the most cost-effective strategy for breast cancer control and would reduce the impact of breast cancer on individuals and all aspects of society.^{11,12}

There are two complementary approaches to primary prevention:

- i) Population prevention - minimising risk factor exposure for all women, regardless of their personal breast cancer risk. Understanding to what extent each risk factor contributes to the number of individuals with breast cancer in a population, can inform the focus of education programs in partnership with policy change to drive population prevention.
- ii) Personalised prevention through targeted delivery of intensified prevention interventions. First, identifying the 20-30%^{13,14} of women at substantially higher than average risk of breast cancer using existing tools; refining these tools and their implementation through on-going research and development. Based on an individual's risk, offering proven interventions to substantially reduce breast cancer risk, such as inexpensive medications or, for those at very high risk, preventive surgery.

Breast Cancer Risk Factors

The most important risk factor for breast cancer is being a woman, and risk generally increases with increasing age. At least 5% of breast cancer is attributable to rare inherited pathogenic variants in major breast cancer predisposition genes, of which half are due to *BRCA1* and *BRCA2*.^{15,16} Women with pathogenic variants in these genes are at substantially increased risk for breast cancer and can be identified by genetic testing. There are other more common genetic variants that individually increase breast cancer risk very little, but clustering of several variants in one individual can lead to larger increases in breast cancer risk.¹⁷ The polygenic risk score summarises a person's risk of breast cancer attributable to their individual profile of these common variants.¹⁷ Other established breast cancer risk factors include: family history of breast cancer, a history of radiation exposure (involving breast), non-invasive breast conditions such as atypical hyperplasia and lobular carcinoma in situ, being taller, reproductive history, and modifiable risk factors such as alcohol consumption, being overweight, physical inactivity, limited or no breast feeding in parous women, exogenous female hormone use, and breast density (modifiable with the use of medications).¹⁸⁻⁴⁰

See Panel 3 - Major Potentially Modifiable Breast Cancer Risk Factors.

Panel 3 - Major Potentially Modifiable Breast Cancer Risk Factors

Post-menopausal overweight and obesity:

- Associated with post-menopausal breast cancer, especially in oestrogen receptor (ER) and progesterone receptor (PR) positive tumours.^{24,27,30-32}
- Worldwide, 110,000 breast cancers were attributable to obesity in 2012²⁷, mostly in North America, Western and Eastern Europe and Latin America.²⁷
- The percentage of breast cancers attributable to obesity is around 8-13% in some HIC^{24,38}, and is up to 28% in post-menopausal African American women.⁴⁰

Alcohol:

- Alcohol is a well-established carcinogen.^{41,42}
- There is no 'safe' consumption threshold: 13% of all cancer attributable to alcohol in Europe in 2017 was due to 'light-moderate' consumption (20g/2 standard drinks per day), of which half were breast cancers.⁴³
- Compared with non-drinkers, relative risk of breast cancer is 9%, 13%-23% and 60% higher in women who consume up to 15g (2 units), 12.5-50g (1.5-6 units) or 50g+ (6+ units) of alcohol per day, respectively.^{44,45}
- 98,300 breast cancers (i.e. 4% of all breast cancers globally and 8%-16% in some HICs) were attributable to alcohol in 2020.^{24,26,28}
- Cessation or a sustained reduction in consumption reduces cancer incidence.⁴⁶

Breastfeeding:

- The percentage of breast cancer cases attributable to not breast-feeding in the UK is 4.7%²⁴, but is not well defined in LIC and LMIC.⁴⁷
- The relative risk of breast cancer decreases by 4.3% for every 12 months of breastfeeding.⁴⁸
- Reduces the risk of triple negative breast cancer, an aggressive subtype that is more common in younger women and those with African ancestry.⁴⁹⁻⁵¹

Physical Inactivity:

- Is associated with an increased risk of breast cancer, independent of body size.³³
- Between 2%-10% of breast cancers are attributable to physical inactivity in HICs.³⁸
- Breast cancer disability-adjusted life years (DALYs) attributable to low physical activity are highest in HICs, but LICs have the fastest increase in low physical activity-associated DALYs.²⁹

Exogenous Hormone Use (HRT):

- Combined oestrogen-progestogen HRT increases breast cancer risk, which increases with longer duration of use. For current users of combined HRT for 1-4 years, relative risk is 1.60.^{11,52} This excess risk is not seen for oestrogen only HRT⁵² but unopposed oestrogen should not be used by women with a uterus because of the increased risk of uterine cancer.¹¹
- The relative risk of breast cancer in current users of combined oral contraceptives is 1.24.⁵³ This risk declines after cessation with no excess risk 10 years later.⁵³ Risk is similar with other forms of hormonal contraception.^{35,36}
- The percentage of breast cancer attributable to HRT and hormonal contraceptives in the UK is 2.1% and 0.8% respectively.²⁴

Population breast cancer prevention

Up to one quarter of breast cancers in HICs could be prevented by modifying risk factors (Figure 2).^{18,23-}

²⁷ The proportion of breast cancer attributable to each risk factor varies by world region and socio-demographic index (SDI).^{54,55} Deriving global population attributable risk estimates is difficult due to

limited epidemiological studies in LIC and LMIC⁴⁷, however it is estimated that 21% of breast cancer deaths worldwide could be attributed to alcohol, post-menopausal overweight and obesity, and physical inactivity.³⁸

Population-wide approaches to breast cancer prevention have mainly focused on education to motivate individual responsibility in reducing exposure to risk factors. There is low community awareness about modifiable risk factors for breast cancer in most countries.⁵⁶⁻⁶² Educational interventions can increase knowledge about risk factors⁶³, however knowledge alone is not generally sufficient for sustained behaviour change.

There is evidence that some breast cancer prevention strategies work for some people. For example, women who followed the American Cancer Society guidelines on weight control, physical activity, alcohol intake and diet⁶⁴ had 22-31% lower risk of breast cancer compared to women who were less adherent.^{65,66} Reliance on individual responsibility, while empowering for some, may be perceived as a 'blame culture' for others. Changing health behaviour to reduce the risk of breast cancer may be more challenging for women struggling with other health and social problems. For example, a small proportion of women are unable to breastfeed and must have access to formula milk. Another example is the positive dose-response relationship between obesity-related cancer mortality in the US and 'food deserts' (fewer healthy food resources) and 'food swamps' (higher access to fast food). The same study demonstrated higher rates of poverty and non-hispanic Black residents in regions with high obesity-related cancer mortality, demonstrating the complex intersection between cancer, ethnicity, and poverty.⁶⁷

In contrast, policy and legislative change have the potential to reach an entire population and, in some cases (such as taxation), can have the greatest impact in disadvantaged groups, reducing deprivation-based inequalities in harms attributable to risk factors.⁶⁸⁻⁷² Increased tobacco tax has consistently resulted in immediate and sustained reduction in the prevalence of smoking in both HIC and LICs⁷¹⁻⁷³, when coupled with other policies which increase the financial and social cost of smoking. In addition, the introduction of plain paper packaging of tobacco products in Australia was associated with a 25% reduction in cigarette smokers over the subsequent 3 years.⁷⁴

A key aspiration of this Commission is to help policymakers recognise that the current predicted upward trajectory of breast cancer incidence can be modulated by policies that reduce risk factor exposure at the population level. Development and delivery of such policies will require governments to demonstrate strong political will and integrity in resisting lobbying by industries that might be adversely affected by the policy changes. Implementation of education strategies will be needed to support and enhance policy changes. The top targets are alcohol consumption, obesity, physical inactivity, and inadequate breastfeeding (*see Figure 2: Approximate proportion of breast cancers in high income countries due to more readily modifiable breast cancer risk factors*).

Public health policy

There are existing World Health Organisation (WHO) endorsed recommendations to reduce harmful alcohol use⁷⁵, inadequate breast-feeding⁷⁶, overweight and obesity⁷⁷, and physical inactivity.⁷⁸ The WHO provides policymakers a list of recommended cost-effective interventions to address these risk factors.⁷⁹ Examples of recurring policy recommendations include a focus on taxation, marketing regulation, and restrictions on the availability of alcohol and certain foods.^{75,77,79} Implementation of these policies is variable.^{80,81} Tracking how effectively these policies have been implemented is hampered by inadequate data collection on the prevalence of breast cancer risk factors in some regions, such as adequate breast feeding.⁸² For improved policy implementation, there needs to be adequate data collection to understand the effectiveness of proposed interventions in different local contexts.⁸³

Common barriers to public health policy implementation include lack of prioritisation, perceived insufficient evidence base, the power and influence of industry over governments, variation in complex political and policy systems, and lack of resources.^{84,85} Obesity, alcohol consumption, and inadequate breast feeding are all heavily influenced by the food (including baby milk formula) and alcohol industries. Policies and legislation that limit the influence of these industries and reduce exposure of the population to risk factors is essential, as well as policies which promote protective behaviours, such as breast feeding or expressing at work.

Many of the alcohol and food industry strategies to increase consumption resemble those of the tobacco industry, so successful tobacco policies can be used to inform harm reduction policy agendas (*Panel 4 - Public health policy case study: comparing and contrasting approaches to tobacco and alcohol*). Like tobacco policies, prioritisation of sustainable, high-impact, and cost-effective alcohol and food policies supported by legislation addressing affordability and availability is needed. Restrictions on advertising and sponsorship, and penalties for false advertising should be enforced. Warning labels and public education campaigns should be independent of industry influence. Regarding physical inactivity, governments should prioritise urban planning that promote physical activity, such as providing adequate walking paths and open spaces.

Role of education in facilitating successful policy implementation

Education at a community level is important so that policies have ‘social validity’ and are acceptable.⁸⁶ Policies that are not well understood are often unpopular and are difficult to implement, as seen during the COVID-19 pandemic where differences in public communication could potentially explain some of the observed differences in adherence to government recommended interventions across different countries.⁸⁷ Therefore, multisector and multi-stakeholder action and partnership are needed^{85,86} from politicians, celebrities (such as sporting heroes), civil organisations, and healthcare providers to encourage successful policy change at a population level.

Existing recommendations call for breast cancer awareness campaigns to target everyone.⁸⁸ The U.S. Education and Awareness Requires Learning Young (EARLY) Act aims to develop age-appropriate education initiatives for young women and their healthcare professionals to increase knowledge regarding breast cancer.⁸⁹ Introducing teaching on breast cancer in the high school health education curriculum may increase awareness and knowledge about breast cancer risk factors^{90,91}, through intergenerational transmission of knowledge.⁹¹ Other educational methods are required, particularly where there is limited access to high school education. This could include cooperation with local authorities, faith leaders and traditional healers, as well as using social media, and engaging celebrities as ambassadors to convey the importance of breast cancer awareness.

Panel 4 - Public health policy case study: comparing and contrasting approaches to tobacco and alcohol		
	Tobacco	Alcohol
WHO recommendations	6 “MPOWER” tobacco control strategies: ⁷¹ M: Monitor tobacco use and prevention policies. P: Protect people from tobacco smoke. O: Offer help to quit smoking. W: Warn about the dangers of tobacco.	WHO recommended policies: ^{75,92-94} • Make alcohol less affordable. • Ban or restrict alcohol marketing. • Raise public awareness on risks of alcohol and cancer – 5 facts information sheet – includes message that cancers due to alcohol are preventable. • Enforce drink driving laws.

	E: Enforce bans on tobacco advertising, promotion and sponsorship. R: Raise taxes on tobacco.	• Provide interventions for hazardous drinking.
Barriers to reduction in risk factor exposure	Tobacco use is reducing in countries implementing most MPOWER measures, but: • Over 80% of the world's 1.3 billion tobacco users live in LIC and LMIC.⁷¹ • 41 of 49 countries yet to adopt a single MPOWER measure are LIC and LMIC.⁷¹ Lack of policy adoption facilitates market expansion through aggressive marketing, low prices, 3rd party advocacy to influence policy makers, branding tobacco industry activities as corporate social responsibility initiatives.⁶⁹	WHO recommended policies: ^{75,92-94} Barriers to alcohol control as health priority: • Influence of alcohol industry in policy making. • Lack of political will and investment. • Limited capacity to develop and implement control interventions. • Lack of robust studies and data collection. Alcohol regulation barriers: • Industry self-regulation. • Lack of international regulation. • Differences in cultural norms and context between countries. • Informally/illegally produced products challenge regulation. • Digital marketing more challenging to regulate. • Inappropriate branding alcohol industry activities as corporate social responsibility initiatives.⁹²⁻⁹⁴
Public health policy implementation	<u>Packaging</u> Health warnings on cigarettes have led to lower initiation and increased cessation rates of smoking.⁹⁵ Plain paper packaging of cigarettes in HIC reduces appeal of tobacco products, decreases uptake, and increases cessation of cigarette smoking.^{96,97} Available evidence suggests same behavioural effect possible in LMIC.⁹⁸	<u>Packaging</u> Health warnings on alcoholic beverages are generally subject to voluntary action by the industry and have not been associated with a consistent change in alcohol consumption.⁹⁹⁻¹⁰⁴ Learning from tobacco control, policymakers should consider regulation of alcohol packaging that is independent of industry influence.
	<u>Taxation and price regulation:</u> • Taxation has consistently been demonstrated to reduce cigarette consumption.^{71,73,102,103}	<u>Taxation and price regulation:</u> • A 10% increase in alcohol price is associated with an average decrease of 5% in consumption.¹⁰⁵ • 10% increase in minimum alcohol price in Canada was associated with 8% reduction in consumption within 2 years¹⁰⁶, and reduced alcohol-related:

		• deaths by 32% • hospital admissions by 9% • traffic violations by 19% • crime by 9% • Introduction of minimum unit pricing for alcohol in Scotland in 2018 was associated with reduced deaths and hospitalisations, especially in the lowest socioeconomic groups.⁶⁸
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Systematic risk assessment and personalised prevention

Current practice in HIC involves selective risk assessment and genetic testing of women who typically have already developed breast cancer with certain additional criteria such as young age or family history or Ashkenazi heritage or triple negative breast cancer subtype. Germline mutations resulting in the highest breast cancer risk (e.g. *BRCA* mutations) are present in a small percentage of women. However, a much larger group of women are at moderately increased risk of breast cancer and these women typically receive no personalised risk assessment, nor are they offered tailored prevention strategies, unless they seek out information or testing. Effective medical and surgical interventions can reduce risk in women who are at substantially greater than population risk for developing breast cancer. Medications (tamoxifen, including a low dose option^{107,108}, raloxifene or aromatase inhibitors) taken daily for 3 to 5 years reduce the relative risk of breast cancer by 30%-60%¹⁰⁸⁻¹¹⁶ and should be considered for women at increased risk. Tamoxifen is an affordable option in LMIC and LIC countries. These medications approximately halve the risk of hormone receptor positive breast cancer in randomised trials that tested the intervention across diverse populations.^{108-113,117} Further research is needed to ascertain which patients are likely to benefit most from preventative breast cancer medicines and what is the lowest efficacious dose to give the least side effects.¹¹⁸ For hormone receptor negative breast cancer prevention, trials of the RANK ligand inhibitor, denosumab, are underway.^{119,120} Bilateral mastectomy reduces the relative risk of breast cancer by over 90%, and should be accessible for those at very high risk, such as those with high penetrance pathogenic variants in breast cancer predisposition genes.¹²¹ However, it is important that these women are supported to feel empowered to make their own informed decision considering both potential benefits and risks (see section 6: Communication and Empowerment).

If a woman is unaware that her breast cancer risk is substantially elevated above that of the general population, then she misses the opportunity to access proven prevention strategies. Therefore, the first step in personalised breast cancer prevention is high-quality risk assessment. Proactive, systematic breast cancer risk assessment for all women (rather than just for those who request it or who are diagnosed with cancer), followed by personalised advice about effective, evidence-based preventive interventions for those at increased risk, should become an integral part of high-quality care. This is an aspirational goal that health systems and policymakers should start moving towards by using the existing assessment tools available locally. These may range from basic to more sophisticated methods depending on local infrastructure and resource, that can be developed and refined over time. Engagement of health services researchers and implementation scientists will be required to elucidate the most appropriate implementation pathways for each health care setting, taking into account health system structure and resources and sociocultural setting.

How systematic risk assessment could be achieved

Risk assessment would need to commence at a young age (e.g. 25 - 30 years) to facilitate identification of, and preventive interventions for, those who are at high risk for early-onset breast cancer (e.g.

carriers of *BRCA1* pathogenic variants). Comprehensive risk assessment of all genetic and non-genetic risk factors may not be necessary when assessing risk in very young women; systematic population-based assessment of high penetrance genetic factors alone may be an appropriate first risk assessment step. This might consist of offering testing to all young women for major breast cancer predisposition genes. Studies are already examining the feasibility and acceptability of this type of genetic risk assessment in young people.¹²² Women with a pathogenic *BRCA1* or *BRCA2* variant and a history of breast cancer in a first degree relative are at higher risk than those without an affected first degree relative¹²³. Therefore, in resource-poor settings where population genetic testing is not feasible, initial assessment of family cancer history to triage those for genetic testing might be another approach. However, not all women have an informative family structure (e.g. due to adoption, genocide, young maternal death from non-cancer causes, lack of cancer work up and/or diagnosis for family members, etc) so reliance on family history could lead to inequities.

At subsequent timepoints in an individual's life trajectory, more comprehensive risk assessment considering other genetic and non-genetic risk factors will be needed, particularly to identify women at moderate risk of breast cancer. This is a much larger group than women at very high risk. A potential subsequent timepoint for more comprehensive risk assessment could be at age 40 or when an individual considers that her childbearing is complete and risk-reducing medication such as tamoxifen could be considered. Earlier opportunities for risk assessment could be at the time of maternity care and or cervical screening. Targeted prevention interventions, such as risk-reducing medications, in women at moderate risk could potentially substantially reduce population breast cancer incidence. Risk assessment would need to occur at regular intervals, perhaps every 10 years to account for i) changing risk factors in an individual that alter the risk assessment and ii) advances in medical knowledge that might inform risk assessment. Systematic risk assessment using risk assessment algorithms that have been validated in the relevant population could be embedded in broader routine health care, specifically in i) primary care and ii) cancer screening and early detection programs. Countries that already have population-wide mammographic screening programmes could consider incorporating routine risk assessment, linked to prevention interventions and advice, within these programmes.¹²⁴⁻¹²⁶ This would be opportune as mammographic density is an important risk factor for breast cancer.¹²⁷

There are several tools, based on mathematical algorithms, available to estimate a woman's breast cancer risk according to her risk factor profile. No one algorithm or tool is best in all circumstances.¹²⁸ Algorithms such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model (BOADICEA)¹²⁹ and the Breast Cancer Intervention Study model (IBIS)¹³⁰ which integrate both genetic and non-genetic risk factors tend to perform best in most settings.¹³¹

The optimal validated algorithm for systematic breast cancer risk assessment will vary between settings, depending on the ethnic and age characteristics of the population being assessed and the availability of risk factor information in each setting. It should be easy to use and affordable. Validated risk assessment tools can be adapted and calibrated to evaluate performance in the local context. For example, the BCRAT tool has been validated for use in white women, Black/African American women, Hispanic women and for Asian and Pacific Islander women in the United States.¹³²⁻¹³⁴ Risk assessment tools have been adapted for Korean, Nigerian, Chinese and Mexican populations, as well as for Black and mammographically screened populations in the United States.^{55,124,135-139} Recent attempts at using genetic ancestral composition to expand polygenic risk assessment to women of diverse ancestries are a step towards improving equity in breast cancer risk assessment.¹⁴⁰ In women undergoing age-based population mammographic screening, risk estimation tools that incorporate mammographic density are likely to be valuable, although only likely to be feasible if automated measures of mammographic density are available.¹⁴¹ There is increasing research regarding use of artificial intelligence-based risk models which incorporate mammographic data to address this issue.¹⁴²⁻¹⁴⁵ Risk

assessment tools that also provide tailored risk management advice based on local guidelines, the woman's absolute risk level, and other factors that affect risk management decisions are also desirable.^{146,147}

Research needed to support systematic risk assessment and personalised risk management

To successfully implement proactive and systematic breast cancer risk assessment to drive delivery of targeted preventive interventions, stakeholders and funders will need to understand the potential benefits and invest in on-going research. Implementation of evidence-based access to genetic testing for breast cancer risk will be important. In addition, there should be evidence that systematic breast cancer risk assessment is clinically effective in preventing or downstaging breast cancer, results in behaviour change and risk-appropriate uptake of preventives. Currently there is very little prescribing of preventive medications; workforce education is a major barrier. Clinician capability and knowledge has been identified as a major barrier to the discussion of, and prescribing of, risk-reducing medications.^{148,149} This will need to be addressed, and resources prioritised for successful widespread implementation of preventive medications that can bridge the current large evidence-implementation gap. Research will also need to demonstrate that systematic risk assessment does not significantly increase anxiety and show it can be implemented in a variety of healthcare systems.

A measure of progress is the proportion of women who undergo personalised risk assessment, access to genetic testing for major breast cancer predisposition genes, and the uptake of risk appropriate prevention interventions. In countries with high quality collection of administrative data this could be assessed through data linkage. Monitoring the change in the prevalence of key modifiable risk factors such as alcohol, obesity, and breast feeding, using existing tools such as the Global Cancer Observatory, the Global Health Observatory, and the Global Breastfeeding Collective Scorecards may be another marker of progress, emphasising the need for countries to adequately collect these data.¹⁵⁰⁻¹⁵² Moreover, reductions in the sale of alcohol and baby milk formula would also indicate progress.

Future work and potential wider impact

As an immediate action, equitable access to effective resources and interventions is vital for successful breast cancer prevention globally. Research into novel prevention strategies should be prioritised. This would include medications which target molecular pro-survival signals^{117,153}, medications that mimic the breast cancer protection mechanisms from pregnancy and lactation^{154,155}, and vaccines that boost the immune system.¹⁵⁶

Many breast cancer risk factors such as alcohol, post-menopausal obesity or overweight, physical inactivity, and limited or no breastfeeding also predispose to other non-communicable diseases. For example, breast feeding is well recognised to be beneficial to both maternal and child health.^{49,66} Modification of the prevalence of these risk factors may have wider reaching benefits for other health conditions. Successful implementation of personalised prevention approaches in breast cancer could also pave the way for similar approaches to other cancers such as colorectal cancer.

Figure 1: Approaches to breast cancer prevention

Prevention of breast cancer requires a dual approach.

- 1) **population prevention** to minimise risk factor exposure for all women, regardless of their personal breast cancer risk. This can be achieved by policies that reduce exposure to harmful risk factors, such as alcohol and obesity, and that increase exposure to protective factors such as physical activity and breastfeeding. Education of the population can facilitate the ability of governments to legislate what may otherwise be unpopular policies. Education can also lead to risk factor optimisation by individuals, but sustained behaviour change is difficult to achieve with education alone.
- 2) **personalised prevention** based on a woman's risk of breast cancer. This requires identification of those at increased risk, preferably through proactive, systematic risk assessment of all individuals, not just those that ask for it. This should be followed by risk-stratified prevention interventions based on the individual's risk. Over 20% of women in most populations are likely to be at increased risk and should consider use of risk reducing medications (such as tamoxifen, raloxifene, anastrozole or exemestane) and those at highest risk (such as those with germline pathogenic variants that greatly increase risk), can consider risk reducing surgery (bilateral mastectomy).

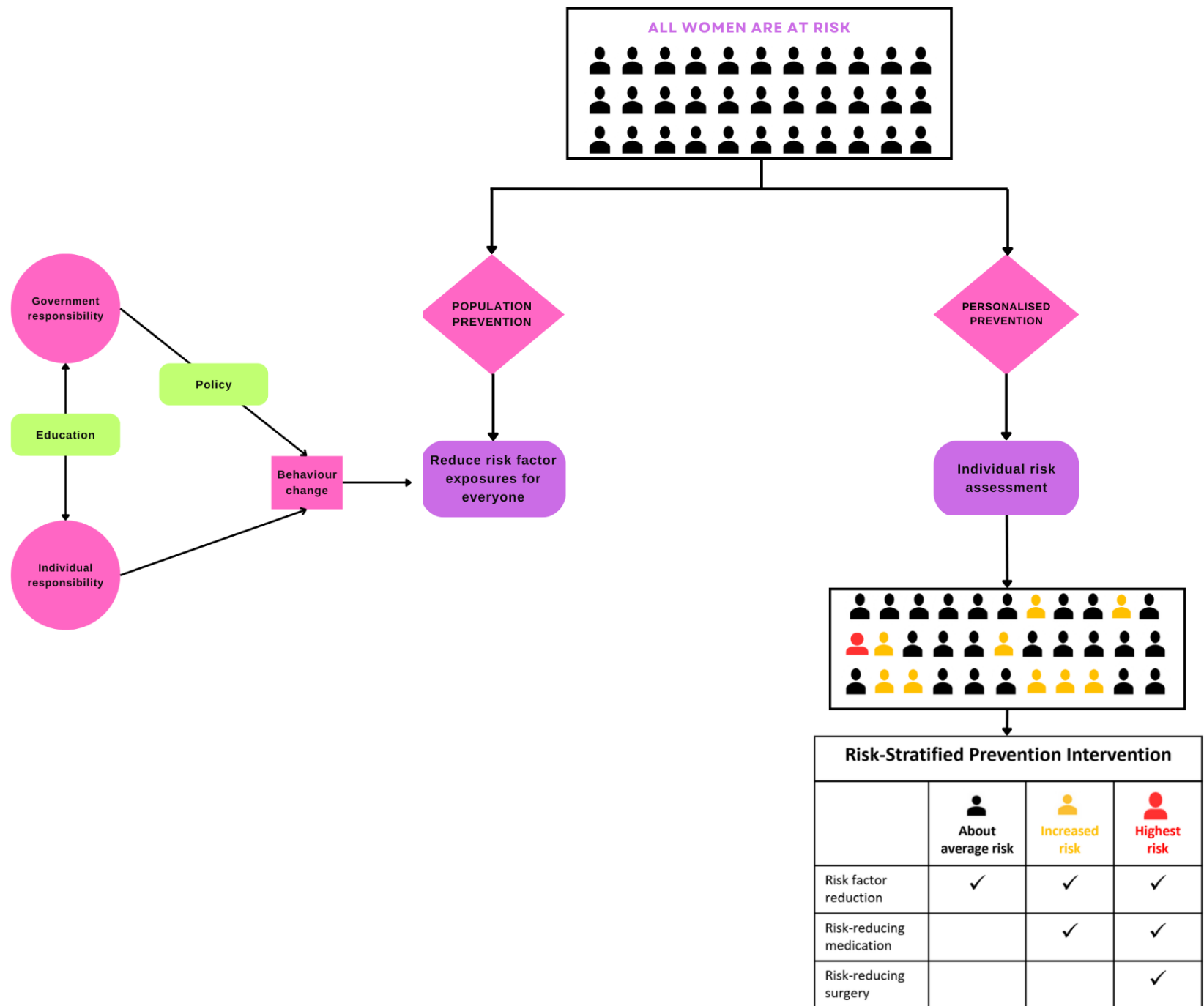
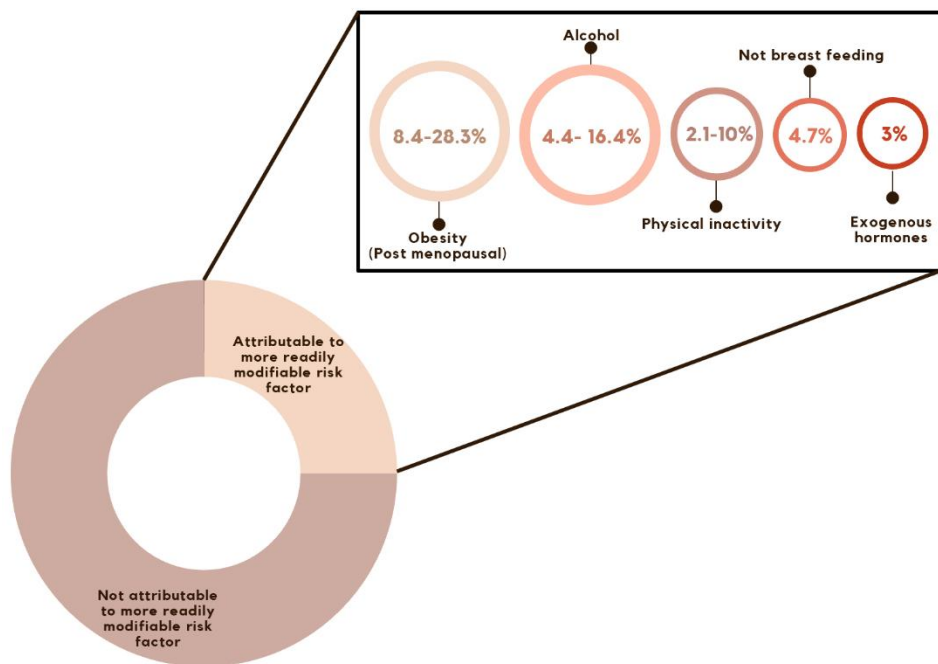


Figure 2: Approximate population attributable risks in high income countries of more readily modifiable breast cancer risk factors



	Panel 5 - Lancet Breast Cancer Commission proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Theme 1: Breast cancer prevention						
Alcohol and commercial milk formula.	Effectively control alcohol and commercial milk formula advertising and sponsorship.	Alcohol use and using commercial milk formula rather than breastfeeding are important modifiable causes of breast cancer globally.	Legislation.	Ministries of Health in Collaboration with Commerce.	95% of countries legislating fully the UNICEF Code for advertising and promotion of commercial milk formula products & adhering to the WHO 'Best buys' with respect to alcohol advertising.	Close current loopholes in advertising.
Parental leave and supportive work environment for breastfeeding and expressing.	Ensure adequate publicly funded parental leave and provision of paid breaks and nursing facilities on return to work.	Working women should be supported to breastfeed if they choose. Supporting breastfeeding reduces breast cancer risk and provides other important health benefits to mothers and children.	Legislation.	Ministries of Health.	Statutory access to at least 18 weeks, and preferably 26 weeks of parental leave at 100% pay. Mandatory provision of paid breaks and nursing-expressing facilities on return to work.	
Non-alcoholic sugar sweetened beverages (SSBs).	Limit consumption of SSBs.	SSBs contribute to weight gain and obesity that increase non communicable disease (NCD).	Measure change in the total volume of sugar sold from soft drinks.	Ministries of Health.	Tax SSBs to raise the retail price at least 20%.	Tax according to sugar content may encourage reformulation

						and shift to lower sugar content drinks.
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Theme 2: Personalising breast cancer treatment

Panel 6 - Summary for personalising breast cancer treatment

Breast cancer research and digital health can facilitate equitable and prompt access to the right breast cancer treatment at the right time for each individual whilst respecting personal needs and preferences.

- Better targeting of existing treatments through development of validated accessible biomarkers is needed to identify those people that benefit the most and to reduce treatment burden for those likely to have more toxicity than gain.
- Development and facilitation of novel, efficient, patient-centred, translational clinical trials to enable a research culture and infrastructure across the globe are required.
- Digital health can facilitate innovation through integration of multi-modal complex datasets; promote flexible, coordinated care particularly for vulnerable patients; democratise access to research and decentralise trial participation.
- If used optimally, digital health technology can alleviate inequalities in breast cancer rather than drive them.

There have been extraordinary advances in breast cancer discovery biology and translational and clinical research in the last decade. However, without action now, the cost of treatment and research will become unaffordable to all but the privileged few and will increase the equity gap. The Commission has an aspirational goal for all people with breast cancer to access personalised treatment as a universal right, as well as fostering greater patient diversity in clinical trials. For this aspiration to become reality, there must be a substantial shift in how breast cancer treatment and research is undertaken globally. For example, future clinical trials should be risk-adapted and fit for purpose, else breast cancer clinical trials will not be feasible or affordable aside from those motivated and conducted by pharmaceutical companies, and this needs to be recognised by funding agencies and regulators. The Commission proposes that the framework underpinning this aspirational goal can be applied to other cancers and wider range of health conditions.

Panel 7 - Personalised breast cancer treatment requires the following approaches:

1. **Precision** – determining and exploiting the molecular characteristics of each breast cancer and tumour microenvironment by identifying validated accessible biomarkers and adapting treatment to response and/or resistance is necessary for early interventions.
2. **Optimisation** – determining the best cancer-related outcome, with the least toxicity and minimal treatment burden for everyone. Optimisation considers patient co-morbidity, needs and personal preferences, and seeks to reduce breast cancer death in high-risk cancers and allow the safe reduction of treatment burden in good prognosis disease where many people may currently be overtreated.
3. **Innovation** – ensuring equity of access with the best use of resources for treatment and clinical trials. Innovation is accelerated through interaction with disciplines outside medicine.
4. **Understanding** – of the role of prognostic biomarkers which determine the risk of disease recurrence (e.g. nodal involvement, stage) and of predictive biomarkers which inform an individual person's likely sensitivity to treatment (e.g. *ER* and *HER2*).

To date, in spite of considerable world-wide efforts true predictive biomarkers such as ER and HER2, are rare with benefit for treatment largely determined by absolute risk dictated by the many individual and composite factors affecting prognosis. Modelling tumour biology at an individual level will enable mechanisms of cancer progression and drug resistance to be deciphered and permit identification of specific therapeutic targets. Proof of concept has been carried out with genomics, including the identification of *BRCA*, *HER2*, and *PIK3CA* alterations, but this approach is limited.¹⁵⁷ A more detailed

understanding of spatial biology including spatial measurements of gene and protein expression, and single cell analysis are now possible. This will enhance prediction of response to treatments and early indications of metastatic dissemination potential, allowing more precise and potentially earlier treatment of micro-metastatic disease. However, improved model systems are required to predict which patients will benefit from specific treatments, including newer targeted agents such as antibody-drug conjugates, as well as to identify those unlikely to benefit (or indeed suffer harm) from treatment. Living diagnostic tools including ex-vivo models such as organoids, spheroids, and patient-derived xenografts, mean that it is now possible to define which proteins are involved in the progression of cancer and to refine treatment accordingly.¹⁵⁸ This is currently being assessed by drug exposure ex-vivo, but ongoing efforts are testing whether gene editing of living models could model cancer biology in each patient.¹⁵⁹ Once refined, there will be a need to consider the optimum way of integrating the information gained from these models into healthcare systems to support the care of individual patients.

Given the rare nature of many molecular aberrations in cancers, it is possible that many may not appear targetable, or that they are so rare in breast cancer that a clinical trial to test the efficacy of an intervention is not possible. There is a need to rethink drug development and clinical trial design in the era of molecular medicine, whilst acknowledging the global inequalities in access to research. The use of 'pan-cancer' trials may help with understanding of the similarities and differences of molecular markers within and across tumour types. These trials need to integrate both genomics (germline and somatic) and, where relevant, other 'omics'. Biological differences in diverse ethnic populations and the tumour microenvironment for different sub-types and at different stages of breast cancer need to be considered in clinical trial design to enable bespoke treatments.

Combining precision oncology with optimisation and value-based care

The role of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which has undertaken meta-analyses of worldwide evidence from randomised clinical trials for 40 years, has enabled precise estimation of breast cancer treatment effects long beyond the time of a trial's primary endpoint analysis. These seminal analyses have enabled dissection of treatment effects within subgroups and across follow-up period and, with the exception of *ER* and *HER2*, have shown remarkably consistent relative benefits of treatment across different clinical and prognostic patient groups. This leads to an understanding that it will be the absolute potential gain informed by prognosis, which impacts optimised treatment decisions and the concept of precision approaches to treatment choice. Precision approaches have great potential value in the early disease setting, where many patients at present are over-treated, resulting in a significant burden of therapy which is also costly. Optimisation of treatment aims to maintain excellent outcomes whilst reducing financial, physical, and psychological costs. Treatment de-intensification may be achieved by using prognostic biomarkers at the start of the therapeutic pathway to identify patients likely to have very good outcomes due to an intrinsically non-aggressive cancer. More recently, biomarkers have been used to assess dynamic responses to initial therapy and inform whether subsequent treatment components can be safely reduced. One model of this approach is the 'pre-operative window' study, where short duration treatments may be used to identify responsive tumours and improve prediction of outcomes.¹⁶⁰ Another model of use is a full course of neoadjuvant systemic therapy with the pathological response to that treatment assessed at surgery. Patients without a pathological complete response have been shown to benefit from escalation of further therapies (e.g. anti-body drug conjugates or a different chemotherapy agent), whilst those with an excellent response may require less adjuvant therapy to maintain the same excellent oncological outcomes. This approach is being tested in HER2-positive breast cancer in ongoing clinical trials such as HER2-RADICAL (UK) and OPTIMICE (USA).^{161,162}

Despite the rapid advances described previously, most patients with breast cancer continue to be treated with a standardised approach, with primary surgery followed by adjuvant systemic therapies

and radiotherapy. This approach does not consider breast cancer as a highly heterogeneous disease, with a very broad spectrum of risk, ranging from early, low-risk screen-detected disease with favourable biology through to highly aggressive, life-threatening tumours. Furthermore, such a conventional approach does not use all the potentially available information, such as more refined measures of risk or evidence of response to a particular therapy and can lead to suboptimal treatment choices at all points on this risk continuum. This underscores the need for diagnostic precision and optimisation of treatment. However, EBCTCG analyses (*see supplementary material 4: proportional benefits of systemic therapy in reducing distant recurrence rates*) demonstrate that widespread global use of a 5-year course of the endocrine therapy tamoxifen or several months of anthracycline chemotherapy alone reduces breast cancer recurrence and ultimate survival substantially at a modest treatment cost and substantial personal and societal gain.

In many patients with early-stage disease and favourable biology, it is likely that loco-regional therapy alone is curative. There has been a belief that more breast cancer therapy results in improved outcomes, however evidence suggests that in many instances less may be enough. An example is the similar oncological outcomes of breast conserving surgery plus radiotherapy to those of more extensive mastectomy surgery^{163,164}, with the former approach providing improved aesthetic outcomes, better quality of life and increased cost-effectiveness.¹⁶⁵⁻¹⁶⁷ The use of breast conserving approaches, however, is dependent on timely and equitable access to adjuvant radiotherapy. This is not currently available to all across the world and those without access are also denied the potential proven overall survival advantages associated with radiotherapy.¹⁶⁸ Hypofractionation, i.e. giving larger radiotherapy doses in fewer treatments, is another form of optimisation as it decreases the treatment burden for patients, whilst maintaining efficacy with similar or reduced side effects, and is also more cost-effective (*see Supplementary material 5: Case study – Hypofractionated breast radiation therapy*). Allowing all patients informed choice and equitable access to optimal loco-regional treatment is dependent on improved and integrated infrastructure. Optimisation of systemic treatments in early breast cancer include immunotherapy in triple negative breast cancer and reduced duration adjuvant trastuzumab in HER2-positive disease.¹⁶⁹ *See Supplementary material 6: Case Study – Immunotherapy in early TNBC.*

Implementation of stage-shifting strategies (see Theme 4) is likely to increase the proportion of patients where loco-regional therapy will be curative, but this will take some years. Subsequent use of improved precision approaches will allow the identification of patients where treatment may be further de-escalated/optimised. Examples include the omission of radiotherapy in very low-risk disease¹⁷⁰, or de-escalation of surgery by either omission of surgical axillary staging or minimally invasive treatment of the primary tumour.¹⁷¹⁻¹⁷³ Thus, optimisation of treatment is dependent on access to a full range of both diagnostic and therapeutic modalities.

Despite efforts to increase early diagnosis, there will remain a group of individuals with high-risk tumours where treatment optimisation will require escalation of therapy. In this context, neoadjuvant systemic therapy is increasingly used as a standard of care. As previously discussed, this approach provides an opportunity to test reducing therapies in those with a complete pathological response. However, it also enables treatment escalation or alternative treatment strategies in those patients with significant residual disease. Furthermore, this approach may provide an opportunity to tailor loco-regional treatment of the breast and axilla based on response.¹⁷⁴

To ensure optimised treatment, a multidisciplinary approach from diagnosis is essential. Information regarding tumour molecular characteristics is needed to determine an individual's level of risk and therefore their optimal treatment sequence. This information will allow the patient to see the right specialist at the right point in their treatment pathway. All patients with breast cancer need access to multidisciplinary teams and tumour boards at the point of diagnosis to facilitate optimal treatment

planning, and often this is required later to determine subsequent therapies based on initial response or management of recurrence.

It is essential that this multidisciplinary approach of optimal care is applied to all individuals with breast cancer without discrimination of subpopulations. An example is the management of older patients with breast cancer. More than 35% of women diagnosed with invasive breast cancer in the UK are 65 years or older.¹⁷⁵ This proportion is increasing globally because of population demographics and the management of older patients presents a number of challenges.¹⁷⁶ Older patients have the highest breast cancer mortality, when adjusted for tumour characteristics and stage, than any age group, experience greater variation in care and are not eligible for systematic breast screening because of their exclusion from the formative trials.^{175,177} Unfortunately, the mistaken notion that older patients have indolent disease is still all too prevalent. Simple and reliable assessments of co-morbidity and fitness are now routinely available and would allow more consistent care and facilitate ongoing national audit which should remain a priority for this large and growing patient group.

Value-based approaches¹⁷⁸ have a goal of delivering the best possible outcomes for less cost.^{179,180} Value in breast cancer care can be defined as the summation of quality, outcome, cost, and patient preference. Porter and Teisberg introduced the value-based healthcare (VBHC) concept as a strategy to rein in health care expenditure while maintaining or even improving outcome.^{181,182} The VBHC framework consists of understanding the health needs of the patient, designing solutions to improve outcome, integrating learning teams, measuring outcome, and expanding partnerships. However, in many countries the business model of healthcare continues to be followed, contributing to both between- and within-country inequities. Currently, those with breast cancer in rich countries are often overtreated, but in low- and middle-income countries, patients with breast cancer may get little or no care, and indeed in the poorest countries may not even receive a diagnosis. Adopting value-based healthcare for breast cancer has the potential to optimise care in rich countries, to give much needed guidance to low- and middle-income countries to improve outcomes without bankruptcy and help those countries with minimal provision currently to kick-start breast cancer care from ground zero. Sharing technologies and making the outcomes of research freely available will help to establish and maintain value-based breast cancer care and the acceleration of technological change will facilitate this.

Technology enabled breast cancer management

Technology can facilitate the integration of multi-modal data inputs from complex and large datasets to set-up personalised treatment and follow-up. Figure 3 depicts a vision for technology-enabled breast cancer treatment and research. In this vision, data is collected digitally from multiple sources: patient generated data, the environment including the social determinants of health inequities, biological tumour omics and classical clinical, pathological, and treatment data and integrated in a multimodal data model¹⁸³⁻¹⁹² with real-time interpretation and large-scale interoperability. This should allow data exchange within all stakeholders of the oncology healthcare system (patients, providers and researchers at hospital, primary care, and supportive care network) to inform personalised risk-stratified pathways of care that could reduce treatment toxicity, improve survival and quality of life and potentially reduce healthcare costs and burden and inform innovative health policies.^{193,194} Several specific digital health applications can facilitate the implementation of this future vision and already impact clinical care and research in several aspects. We provide examples below (*see Panel 8 - Digital health – terms and applications*).

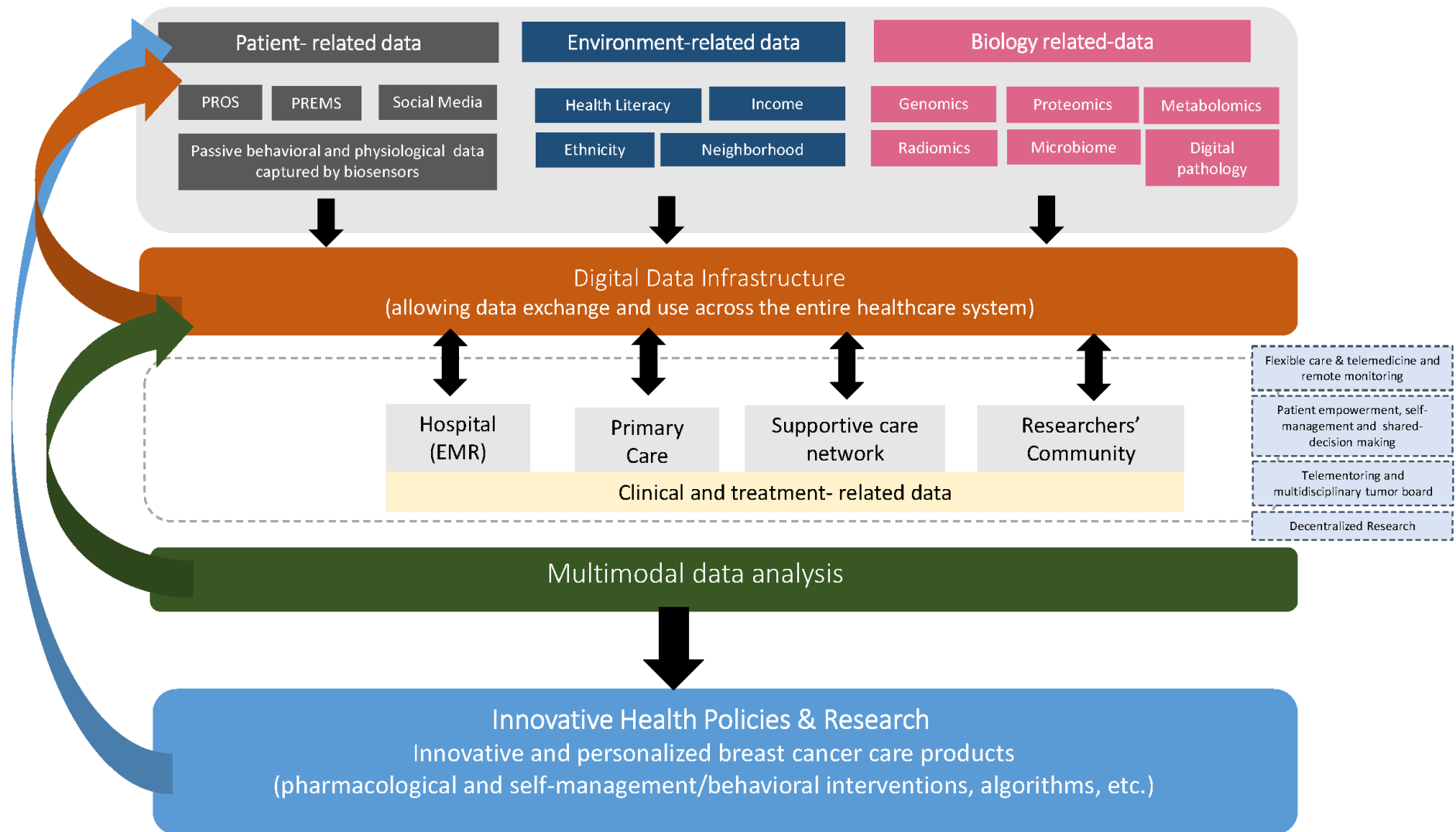
Panel 8 - Digital health - general terms and applications:

- Telemedicine - medical care by healthcare professionals delivered through telecommunication.
- Remote monitoring – real time monitoring of patient’s symptoms or vital signs using technology devices.
- Electronic medical records - digital patient charts allowing data storage, access, and sharing within information governance frameworks.
- mHealth - technology for health through mobile devices.
- Biosensors - capturing physiological and/or behavioural data for patient and medical purposes.
- Digital therapeutics – evidence-based software interventions to prevent, manage, or treat a medical disorder.
- Advanced analytic techniques - evaluating datasets with AI to predict medical events (response, relapse, toxicity).

Improving organisation, quality of care and efficiency of healthcare systems through digital health

Telemedicine and teleradiology. Telemedicine was rapidly implemented in breast cancer care¹⁹⁵⁻¹⁹⁹ during the pandemic. This enabled prioritisation of in-patient care for critical patients, paving the way for decentralised care.^{197,200,201} The level of patient satisfaction was high^{195,196,202} and positive experience²⁰³ was reported among patients across the breast cancer continuum^{195,204}, and within high²⁰⁵ and low^{206,207} resources settings and remote rural areas.¹⁹⁶ Telemedicine has been used in some MDTs for years²⁰⁸, and telephone-led consultations for follow-up breast cancer care have also been used in some settings for decades. A randomised study²⁰⁹ showed that telemedicine was well perceived with no detrimental effect on anxiety or the ability to detect relapses. Telemedicine is seen as a valuable tool to enhance breast cancer care by oncologists²¹⁰ and teleradiology can provide timely diagnostic assessment and efficient breast cancer screening in areas with scarce local radiology support.^{211,212}

Figure 3: Vision for technology-enabled breast cancer treatment and research



- **Remote monitoring.** A breast cancer cluster randomised trial among 20 Canadian centres with 2158 patients receiving chemotherapy demonstrated that nurse-led telephone-based management was associated with lower rates of grade 3 toxicity, although no statistically significant impact was found in hospitalisation rates or patient reported outcomes.²¹³ Several randomised clinical trials have confirmed the benefit of using patient reported outcomes (PROs) as early warning monitoring to avoid or reduce severe treatment related toxicities and increasing quality of life for oncological patients with early and metastatic disease receiving systemic therapy, including patients with breast cancer.²¹⁴⁻²¹⁹ Although remote monitoring is already recommended in oncology²²⁰ and deployed in some healthcare systems²²¹, global real-world implementation is still slow. Efforts regarding awareness, training, integration with electronic medical records, policy, re-imbursement are needed to ensure re-organisation of care to allow real time response to patients ePROs in routine practice.
- **Rehabilitation and self-symptom management.** Delivering comprehensive breast cancer survivorship care, including management of long-term physical and psychosocial consequences of cancer and its treatment, is complex, costly and insufficiently implemented (see Themes 3, 5 and 6).²²² Digital health offers an opportunity to facilitate comprehensive survivorship care and self-management support. Randomised clinical studies have demonstrated that digital support increases quality of life and self-management for patients with breast cancer during the post-treatment follow-up phase.^{223,224} Examples include use of digital cognitive behavioural therapy for fatigue²²⁵, insomnia²²⁶, fear of recurrence²²⁷, and emotional distress.²²⁸ Cognitive rehabilitation after chemotherapy through digital health solutions has also proved promising.²²⁹ Health promotion such as physical activity and weight management programmes can be successfully delivered with digital health solutions.²³⁰⁻²³³ Advances in data interoperability and standardisation are needed to ensure full integration of self-management support and PROs with electronic medical records.²³⁴ Several studies in breast cancer care suggest that the efficacy of digital health tools is related to persistent engagement, and more efforts are needed to understand who will benefit most from digital health solutions and what is required to maximise adoption and engagement.^{235,236}
- **Facilitating the communication within healthcare systems.** Use of electronic health records improves patient safety, operational efficiency, and quality of care.²³⁷ For example, electronic health record integrating tumour board applications save preparation time and reduce errors.²³⁷⁻²³⁹ Electronic health records may also increase patient engagement through automated mammography scheduling, screening reminders, determining eligibility for genetic testing and counselling, identifying patients who would benefit from weight management, and determining clinical trial eligibility.²⁴⁰ Technology can create virtual mapping and linking of the patient's residency with community mobile healthcare professionals and comprehensive cancer centres enabling more flexible care (e.g. anti-HER2 subcutaneous therapies).²⁴¹
- **Telementoring.** Telementoring can enhance training to increase numbers of healthcare practitioners, especially in underserved areas (such as the Project ECHO- Extension for Community Healthcare Outcomes).²⁴² It can support virtual multidisciplinary team meetings (MDM)^{193,243} and enable resources sharing between comprehensive cancer centres and local community hospitals.²⁴⁴ Multi-disciplinary telemedicine resources may also be developed between HICs and LMICs.^{245,246} The COVID-19 pandemic has increased implementation of effective virtual MDM in oncology centres²⁴⁷ and this framework should be further expanded globally to increase patient access to multidisciplinary cancer care.

Digital health as a care equaliser

Effort and careful planning is needed to expand access to technology, but also to ensure that the digital divide does not exacerbate breast cancer care disparities.²⁴⁸

- Technology can be transformative in care and research if health infrastructure is tailored according to the patient's ability to cope and adopt digital devices.²³⁴ In oncology, randomised clinical trials have demonstrated that using low complexity digital health devices to perform weekly symptom monitoring was feasible among patients with lower educational levels, and low eHealth literacy. This led to reduced emergency visits and improvements in quality of life.^{216,217} In the cluster randomised clinical trial PRO-TECT²¹⁷, weekly symptom monitoring with electronic patient reported outcomes was implemented in 52 community-based oncology practices in the United States. The trial included around 20% of patients who had never used email before and 30% with financial difficulties. The option of assessing the symptoms through an automated telephone rather than internet was chosen by 36% of the patients and was associated with older age and lower education. The Accountability for Cancer Care through Undoing Racism and Equity (ACCURE) Pragmatic Quality Improvement Trial led to the elimination of black-white treatment gaps in patients with early stage breast and lung cancer.²⁴⁹ The digital health intervention was composed of i) an automated warning system from patients' electronic health records automatically sending alerts when an appointment is missed; ii) a proactive navigator monitoring the warning system and addressing care barriers; iii) dissemination of race and ethnic feedback to clinical teams on treatment completion rates coupled with a health equity training.
- Machine learning algorithms may be used to decrease breast cancer care disparities, especially in low-income settings. Promising results have been reported for analysing breast cancer mammograms to automate or improve the sensitivity of breast cancer screening²⁵⁰⁻²⁵² and in digital pathology slides to provide timely breast cancer diagnosis. Further work uses AI-algorithms applied in digital pathology for evaluating tumour infiltrating lymphocytes and its correlation with outcomes²⁵³, and a molecular profile and risk of relapse to inform decision making and guide treatments.¹⁸⁵ It is important to ensure that datasets used to train AI-algorithms are representative of the real world breast cancer patient population otherwise there is a risk that such models will not be applicable in clinical practice or may widen inequalities gaps for groups of patients that are usually excluded from research and also face difficulties in accessing care.

Digital health as a tool to enhance research

Digital technology can improve participant access, engagement, trial-related measurements, and interventions. It can enable concealed randomised interventions allocation, and has the potential to transform clinical trials whilst lowering their cost.²⁵⁴ Efficient and generalisable research calls for a representation of all patient groups.²⁵⁵ Nevertheless, groups often facing disparities and difficulties in healthcare are particularly under-represented in oncology research.²⁵⁶⁻²⁵⁸ Barriers include low understanding of research, unconscious bias from researchers, out of pocket costs, and accessibility issues. For further information, see *Supplementary material 7: Opportunities and challenges for digital health in breast cancer care*. Strategies to reduce inequities in access to cancer research include:

- Digital education programmes to improve cultural competence, promote self-assessment and reduce unconscious bias.²⁵⁹⁻²⁶¹
- Automated clinical trial eligibility screening²⁶²⁻²⁶⁴ and matching algorithms.
- Decentralised tools for patient consent, inclusion, study conduct, electronic patient-reported outcomes (ePROs), and digital capturing of study endpoints.²⁵⁴
- Activating community engagement and foster co-design and participatory research.²⁶⁵ Incorporation of ePROs co-developed with patients can capture patient experience and outcomes optimally.²⁵⁴
- Set-up of global clinical trials and equal research collaborations between high and LMICs through innovative digital networks with fully digital clinical trials.²⁶⁶
- Digital navigation support.²⁶⁷

Panel 9 - Take home messages for digital health and breast cancer

- Digital health has been used in breast cancer care to a limited extent over many years, but its use expanded and accelerated during the COVID-19 pandemic.
- Digital health has potential to improve efficiency of healthcare systems, reduce breast cancer care delivery barriers and costs, promote patient empowerment and self-management.
- The use of electronic patient reported outcomes (ePROs) in routine clinical care improves symptom management and quality of life and offers patients an opportunity to participate in their care.
- Digital technology may enable multimodal data integration to inform personalised treatment and follow up plans.
- Digitally enabled clinical trials simplify and accelerate research workflows and can increase community engagement and reach.
- Digital health can promote care equity, especially if technology innovations are co-designed with patients and navigation is provided.
- Digital literacy and social determinants of health, contextual patient factors, confidentiality and information governance, and the healthcare organisation all need to be considered when implementing digital health.
- Policy level actions are required to increase broadband access and to promote large scale digital navigation for populations frequently excluded from healthcare innovations.

Panel 10 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Theme 2: Personalising breast cancer						
Breast cancer diagnosis.	Ensure high-quality breast cancer receptor testing at diagnosis.	Ensuring all patients with breast cancer have access to accurate tumour subtyping to enable appropriate treatment sequencing and selection of endocrine/targeted/chemo-therapies.	Facility records, National audit, national and international certification procedures for breast units.	Facility, Ministry of Health.	>80% (aiming for 95%) of patients have access to accurate tumour subtyping.	Need to ensure global collection of these data.
Multidisciplinary meeting (MDM) review at diagnosis.	Ensure MDM review, linking with expert team members virtually where appropriate.	All patients with a new diagnosis of breast cancer should have their case discussed by a multidisciplinary team to allow optimal treatment planning.	Facility records, national and international certification procedures for breast units.	Facility, Ministry of Health.	>80% (aiming for 95%) patients with new diagnosis to be discussed at MDM.	
Range of treatment for breast cancer.	Appropriate access to appropriate range of surgical, radiotherapy and systemic treatments.	All patients with breast cancer should have access to a full range of treatment modalities to allow equitable treatment choices globally and ensure optimal outcomes.	Facility records, national and international certification procedures for breast units.	Ministry of Health.	100% of patients with breast cancer to have access to full range of treatment modalities.	Integrated Cancer Health System with Regional Infrastructure based on burden of disease in each country.
Breast cancer clinical trials.	Increase global leadership and participation with clinical breast cancer research.	Ensure that patients participating in clinical trials are representative of the global breast cancer patient population and that	Clinical trial registries, PubMed Global patient ID.	Policy makers research funders, higher education institutes.	At least 10% (aiming for >25%) of participants of international breast cancer	Ensure clinical trials are representative and generalisable globally; to

		research leadership includes HICs and LMICs.			trials are from LMICs. At least 10% (aiming for >25%) of all breast cancer trials are led/co-led by LMIC researchers.	build research capacity, infrastructure and expertise globally.
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Theme 3: Optimal inclusive management of metastatic breast cancer

Panel 11 - Summary for metastatic breast cancer

Many patients with metastatic breast cancer (MBC) feel abandoned, isolated, and alone and some do not receive appropriate care – this can and should be tackled.

- The number of people living with MBC is unknown - high-quality cancer registry data needs to be collected worldwide.
- Optimal management of MBC is valuable to individuals and society – stigma and inequity for those with MBC must be addressed.
- There is a growing belief that some subtypes of metastatic breast cancer can be treated as chronic diseases for many years.
- With adequate resources and a shift in attitudes, it may be possible to cure some of these patients, treat most, alleviate the suffering of all and forget or abandon no-one.

Where are we now and where do we want to get to?

In many regions of the world, people with metastatic breast cancer (MBC) are unseen. We do not know globally how many people have MBC²⁶⁸ and this knowledge gap prevents adequate allocation of resources and intensifies stigma and inequity associated with the disease. These patients often have restricted access to treatments despite proven overall survival (OS) benefits, as well as experiencing limitations to supportive care.²⁶⁹⁻²⁷² As a result, individuals with MBC can feel abandoned and stigmatised not only by policymakers and society, but also by healthcare providers and sometimes even the advocacy community. There is an urgent need to address this.

A diagnosis of MBC should not stop a person's contribution to society, either as part of the work force or in unpaid caring roles, and more broadly by contributing to cultural life. Breast cancer predominantly affects women and, globally, women compared with men spend up to 10 times more of their time on unpaid care work.²⁷³ It has been estimated that in 2015 MBC was associated with \$6.6 billion in lost productivity in the US alone, mostly due to days missed at work and home due to illness and premature mortality.²⁷⁴ Inadequate or absent treatment not only has a devastating impact on the patient, their families, and local communities, but also creates an economic disadvantage worldwide (see Panel 12 - *Economic modelling for patients with MBC in Portugal*). Even with the best possible treatments²⁷⁵, 20-30% of those with early breast cancer relapse, so optimal treatment of patients with MBC is valuable to both the individual and society.

A shift in attitudes of policy makers and the public needs to occur to create a world where all patients with MBC are recognised and receive individualised treatment, with an honest but positive approach (see Theme 6). This is important so that patients with MBC feel empowered and are supported to continue to contribute to local communities and wider society.

Panel 12 - Economic modelling study for patients with metastatic breast cancer in Portugal²⁷⁶

The ABC Global Alliance and Centre for Evidence Based Medicine (CEMBE) jointly developed a project aiming to show that allowing women living with MBC to continue to work would be beneficial not only to the patient and her family, but also to the state and to society in general.

Breast cancer is the most common malignancy among women in Portugal, with an incidence rate of 156 per 100,000 women. Given that most diagnoses occur in women aged between 20 and 64 years, studying the impact of breast cancer on the women's labour market is of major economic and social relevance.

This study quantified the productivity costs (i.e. losses) of nonemployment due to MBC in Portugal and evaluated potential labour market policies designed to promote employment in this group. The analysis was based on (i) an original cumulative incidence model that allows estimation of the prevalence of working-aged women with MBC in 2019, and on (ii) an observational study that characterised the employment status and working conditions of patients with MBC in Portugal. To determine productivity costs, the human capital approach was adopted.

A total of 2,151 working age women were estimated to have MBC in 2019, with productivity costs amounting to €28,676,754 over the period 2019-2021. In addition, unemployment subsidies and disability pensions were estimated to be €3,468,866, with a total cost of over €32m. The 3-year period was chosen in view of the median overall survival (OS) of MBC being 3 years.

The researchers modelled the impact of a subsidised, part-time employment scheme designed to encourage women with MBC to continue working. The estimated increased cost of this policy for the government was €11,951,048 over the three-year period 2019-2021. However, a reduction of €14,338,377 in productivity costs (losses), led to a cost-saving of nearly €2.5m over the same 3-year period.

The authors call for changes in labour market laws to enable all patients with metastatic cancers, the right to choose part-time and/or flexible working, without first acquiring employer permission.

Four key themes are identified as crucial areas to be addressed: data collection, individualised management with global equity in access to therapies, multidisciplinary management driven by guidelines, and targeting stigma.

1) Data

It currently is impossible to know the prevalence of MBC since most cancer registries record information on initial diagnosis and death but not on recurrences.^{268,275} This is made more difficult by an increasingly mobile global population, which makes longitudinal tracking challenging. Data protection regulations and laws, although clearly important, render sharing of patient information and cross-checking between databases virtually impossible. In addition, not all cancer registries collect stage at diagnosis.

In HICs, only about 5-10% of patients with breast cancer are metastatic at initial diagnosis, whereas in LMICs, those with de novo Stage III/IV may reach 50-60%.²⁷⁷⁻²⁷⁹ Distinguishing between Stage III (locally advanced) and IV (metastatic) disease in LMICs is problematic given that the definitive diagnosis of Stage IV requires costly imaging and, in some cases metastatic biopsy, to determine distant disease. These investigations often require out-of-pocket payment by patients. As a result, de novo metastatic disease often goes undetected. This is supported by the unusually rapid decline and very poor 3-year overall survival seen in the African Breast Cancer-Disparities in Outcomes (ABC-DO) study.²⁸⁰

In HICs, some national or regional registries have been developed that are specifically dedicated to MBC (*see Supplementary material 8: Table of existing MBC databases*), a development mostly by patient advocates. However, in LMICs data for MBC are largely absent and any reports are primarily single centre analyses.²⁸¹ Data collection in LMICs needs to be made possible by encouraging the establishment of cancer registries funded by government or non-government agencies. For HICs, the solution is complex and will require waivers regarding sharing of information between databases and the development of 'big data' analytical processes (see Theme 2 – digital health). IARC (the International Agency for Research on Cancer) and the ABC Global Alliance are defining the essential

data to be collected and strategies to overcome data collection difficulties for MBC. Getting data collection right will mean MBC can be a beacon of change for global health systems.

2) MBC management should be individualised with equitable access to evidence-based therapies

Cancer directed therapies and overall survival

Outcomes of MBC have improved considerably in the last decade, and patients should not be denied access to life-extending therapies. The median overall survival of MBC has remained at around 2 to 3 years for decades²⁸² but has recently reached 5 years for two of its three main subtypes (HER2 positive and ER positive/HER2 negative), representing approximately 85% of MBC patients.²⁸³⁻²⁸⁵ Some patients may now live up to 10 years or longer with metastatic disease, with some subgroups beginning to be considered as having a 'chronic disease'. MBC is a spectrum of disease, both at a molecular level (see Theme 2) and in terms of disease burden. This includes potentially curable oligometastatic disease, long-term remissions or stabilisations, and more rapidly progressive disease (often the triple negative subtype). Therefore, management of MBC must be individualised, but not just based on biology, but also on patient characteristics, preferences, and toxicities of treatment.

The use of validated tools such as the ESMO Magnitude of Clinical Benefit Scale (MCBS)²⁸⁶ or the ASCO Framework of Value²⁸⁷ allow for cost-effective prioritisation of existing therapies based on their clinical value. Furthermore, the development and use of biomarkers that could allow the identification of patients who derive most benefit, as well as those who do not benefit from these therapies, is crucial to optimise resources and should be a research priority (see Theme 2).

Active management of MBC impacts mortality

The advances in MBC treatments in the past decade have been shown to reduce mortality in the general population by the model-based analysis (CISNET: Cancer and Intervention Surveillance Modeling Network)²⁸⁸ and have contributed between 20-24% of the mortality reduction seen overall (see *Supplementary material 9: Table of therapies known to extend OS or progression-free survival (PFS) in MBC*).

Continuum of care

Supportive and palliative care are crucial parts of the management of MBC and should be incorporated from diagnosis (including supportive care for early breast cancer), through the whole breast cancer journey (see Themes 5 and 6). Early integration of supportive/palliative care has been shown to improve quality of life and reduce depression.²⁸⁹ and there needs to be better education for clinicians, patients and the wider public (see Themes 5 and 6). Definitions have been extensively discussed and proposed by the Lancet Commission on Global Access to Palliative Care and Pain Relief⁸ (see glossary). The importance of early supportive/palliative care involvement has been highlighted in ASCO guidelines, and NCCN Clinical Practice guidelines and in the ABC Guidelines.²⁹⁰⁻²⁹² These fundamental aspects of MBC care are often neglected and there needs to be a transition from traditional siloed care into integrated, patient-centered, holistic management.

In a survey of 240 US oncologists, only 17% said that they refer patients to palliative care upon diagnosis of metastatic disease, despite two-thirds of respondents agreeing that earlier introduction of palliative care leads to better outcomes.²⁹³ In addition, 14% of oncologists reported that they only refer patients to palliative care once all standard of care treatment options are exhausted.²⁹³ Resistance from patients and their families is also a problem, often due to stigma and the perception that palliative care only means end-of-life care. Nearly 40% of the survey respondents reported that this is the main barrier to patients receiving appropriate and timely palliative care.²⁹³ There is a lack of palliative care resources, especially in LMICs but also in HICs, and oncologists and primary care physicians need to focus on symptom control as well as cancer treatments (also see Sections 5 and 6).

Quality of life measurement

The balance between efficacy and toxicity, between survival and quality of life (QoL) or relief of serious health-related suffering (SHS, see Theme 5) is delicate and very personal in the metastatic setting. An additional hurdle is the fact that QoL measurement tools have all been developed for the early cancer setting, and do not accurately capture the most important aspects of the metastatic setting. To overcome this, the EORTC Quality of Life Group has partnered with the ABC Global Alliance and is currently developing a new QoL tool specifically dedicated to MBC, which after validation will be incorporated into clinical trials and clinical practice. In addition, the EU-funded multinational Innovative Medicines Initiative Health Outcomes Observatory (H2O) consortium has recently published core outcome sets for assessing health-related quality of life in patients with metastatic breast cancer, which is in line with the EORTC-ABC Global Alliance work.²⁹⁴ These initiatives will make the evaluation of QoL in MBC more accurate in the future.

Communication

Communicating well with patients throughout their disease journey and giving realistic hope is also extremely important (see Theme 6). Maggie Jencks, a patient with MBC who was fundamental in setting up 'Maggie's centres' in the UK, wrote *'however bad the prognosis, it will still help the patient to know that the median may not be the message'*.²⁹⁵ Suggestions on how to improve patient-HCP communication are given in section 6 - Communication and empowerment.

Equitable access to treatment for MBC

It is crucial to address the global inequities between and within countries, in access to all therapies for MBC (including but not limited to medicines), as well as to supportive care and clinical trials. An example of inequity in access is with trastuzumab use in HER2-positive MBC. Despite the development of highly successful anti-HER2 therapies and trastuzumab being included in the WHO's list of essential medicines, it is often not funded in the metastatic setting. In Brazil, an analysis carried out in 2016 projected that an additional 600 patients with MBC would be alive at 2 years if trastuzumab was available to them, and this figure increased to 768 patients with the addition of pertuzumab.²⁷⁰ Inequitable access is not an issue restricted to LICs; there are often discrepancies in funding within Middle and HICs. An observational study of HER2-positive patients in China carried out in 2017 reported that 27% of those with metastatic disease did not receive trastuzumab at all regardless of local resources.²⁷¹ Observational studies in HER2-positive metastatic patients between 2000 and 2015 have demonstrated that 27-54% in Europe, 12% in the US and 27.1-49.2% in China did not receive trastuzumab or other anti-HER2 therapy as first- and/or subsequent-line treatment.²⁷² A fundamental barrier to accessing trastuzumab is cost, and the availability of effective and safe biosimilars should allow greater use of anti-HER2 therapies.²⁷² Unfortunately, to date price reductions have not been enough to make trastuzumab more available in LMICs.

Panel 13 - Inequity within HICs - New Zealand as a case study

In 2018, the first study of the incidence, treatment, and survival of MBC in New Zealand was carried out.²⁶⁹ Prior to this, the New Zealand Ministry of Health only tracked outcomes for patients with curable breast cancer or de novo metastatic breast cancer and patients with relapsed disease were not counted.²⁶⁹

The study revealed that the median survival after a diagnosis of MBC was 16 months, which was considerably worse than comparable countries (2-3 years).²⁶⁹ There was substantial inequity in outcomes within New Zealand, with five-year survival of MBC significantly worse in the Maori population (5%) than the non-Maori (15%).²⁶⁹ Despite evidence to show that quality of life and survival improved with more lines of treatment given, only 15% of patients with MBC received more than 3 lines of therapy, and 10-30% received no treatments at all.²⁶⁹ There was a lack of awareness or adherence to international guidelines for the treatment of MBC, no national MBC guidelines, and

the possibility for treating oligometastases with curative intent was underexplored.²⁶⁹ There was also restricted access to many therapies proven to be effective in MBC.²⁶⁹ Importantly, for the HER2-positive subtype, only one line of HER2 directed therapy could be used, since trastuzumab use beyond progression was not allowed and there was no access to any of the newer anti-HER2 therapies. This led to a 15-month median survival in patients with this MBC subtype, which in other HICs reaches 5 years. In this subtype, the most important therapeutic approach is to continue to block the HER2 pathway, since leaving it unblocked leads to a much faster death.

Since then, 3 new treatments, including one additional anti-HER2 therapy, have been funded in New Zealand after extensive petitioning, but still many others, including the use of trastuzumab beyond progression, are not publicly funded.²⁹⁶ Furthermore, national guidelines for the management of MBC have been developed.²⁹⁷ Five areas of focus for change to improve these outcomes were identified: drugs, symptom management, medical care, support, and investing in the future.²⁶⁹ The progress made in New Zealand is an outstanding example of recognising the deficit of MBC data locally, analysing and reporting outcomes, and using this information to drive change in order to improve and extend lives for people with MBC.

Panel 14 – Inequity in access to clinical trials

Clinical trials can be beneficial to participating and future patients, but also increase the quality of care within health services.²⁹⁸ Inequity in access to research studies is a problem for patients with all stages of breast cancer including MBC. Randomised clinical trials in oncology are conducted predominantly in HICs and there is often publication and funding bias against trials carried out in LMICs.²⁹⁹ Patient access to oncological clinical trials remains inadequate, particularly to racial and ethnic minority populations, and it is well documented that many ethnic groups are underrepresented.^{300,301} Other patient populations that tend to be underrepresented include older people, patients with several co-morbidities, those of low socio-economic status, and those living in rural areas.³⁰⁰ This reduces the generalisability of trial findings and creates disparity in access to high-quality care.³⁰⁰ This disparity stems from interlinked practices and policies and from barriers at individual (patient and healthcare professional), interpersonal, and system levels.³⁰⁰ In order to overcome this, multilevel interventions are needed to increase world-wide access to trials and stimulate diverse enrollment, including the use of education, training and high-quality communication.³⁰⁰ (See Theme 2 for enabling equitable access to clinical trials through digital health and technology)

3) Multidisciplinary management and the use of evidence-based guidelines

Multidisciplinary care

In early breast cancer, multidisciplinary specialised care and management according to high quality guidelines has contributed greatly to the decrease in mortality, together with screening, early diagnosis and new therapies. The same oncology principles should be applied to MBC management and care. Multidisciplinary management improves health outcomes and quality of life in patients with MBC, for example by offering specialised loco-regional therapies and access to clinical trials, as well as early involvement of palliative care teams and psychosocial support.³⁰²

The European Society of Breast Cancer Specialists (EUSOMA) established multidisciplinary care as one of its mandatory high-quality indicators.³⁰³ Through a collaboration between EUSOMA and the ABC Global Alliance, new quality indicators specifically dedicated to MBC have been established and will soon be incorporated in the certification process.³⁰⁴ The EUSOMA requirements for a specialist breast centre state that at least 50% of metastatic cases must be discussed at a multidisciplinary meeting (MDM) as a minimum, but with the aim of discussing every patient with MBC and ideally at each point

of progression.³⁰² These indicators also recommend that the core team members for a metastatic MDM include a medical oncologist, radiation oncologist, radiologist, breast care nurse, nuclear medicine physician, palliative care specialist, and data manager.³⁰² The ABC international consensus guidelines also emphasise that multidisciplinary input is crucial for the management of MBC and should include at least medical, radiation and surgical oncologists, imaging experts, pathologists, gynaecologists, psycho-oncologists, social workers, specialised oncology nurses, and palliative care specialists.²⁹² There are no specific recommendations for what a metastatic MDM should consist of in the ESMO, ASCO or NCCN breast cancer guidelines. Telemedicine could accelerate widespread implementation of multidisciplinary meetings for MBC (See Theme 2 – Digital Health).

Guidelines

There is often variation in adherence to guidelines by healthcare professionals, both in LMICs and HICs, despite evidence that adherence to clinical guidelines is associated with improved outcomes in breast cancer. For example, a systematic review in the European Union, and a cohort study in Canada both showed that adherence to guidelines is associated with improved disease-free survival and overall survival.^{305,306} The same applies to resource-limited settings; a study in Malaysia found similar improved outcomes in breast cancer survival when treatment was in line with locally adapted management guidelines.³⁰⁷ However, most breast cancer management guidelines available are not context appropriate.³⁰⁸ Therefore, observation of resource-adapted guidelines and support for patients to avoid treatment abandonment, be that for financial or toxicity reasons, should be a priority in MBC management and will translate to improved outcomes (see Theme 4 – WHO 3 pillars). There is evidence that treating according to high quality guidelines is cost-effective and would contribute to avoiding unnecessary costs and optimisation of resources in cancer care.³⁰⁹ Even when guidelines are implemented, treatment abandonment is a huge problem in LMICs and in marginalised and hard-to-reach populations in HICs, sometimes due to toxicities, but frequently secondary to financial reasons and lack of social support.^{310,311} This is another strong argument for improved treatment access and support for patients (see Theme 4 – WHO 3 pillars). Despite the ready availability of many high-quality guidelines in the management of breast cancer, analyses using information within national datasets routinely demonstrate marked care variation. Pursuing small incremental improvements from new drugs in clinical trials is of limited value if they are not used. The translation of evidence into practice is often difficult particularly in LMICs but is a priority.

4) Stigma

Patients with MBC experience stigma from society, policymakers, healthcare professionals, and some patient advocacy groups. This is isolating and can have a huge impact on the physical, social, and emotional functioning of a patient with MBC, leading to worse outcomes.³¹² (see Theme 5) Misconceptions among the general population and healthcare providers, regarding the nature and expected outcomes of MBC, substantially contribute to this. Stigma is responsible for prejudice against these patients within the health system, as well as socially and professionally, which generates isolation, loneliness, and feelings of guilt. Stigma is a major driver of poor health outcomes globally as it can lead to reduced help-seeking, social withdrawal, and can be a barrier to therapy adherence.³¹² As a result, patients are dying earlier due to inadequate care. Education and awareness of all stakeholders and public is paramount: these issues must be highlighted repeatedly, until things are changed.

Characterisation of MBC as a ‘rapidly fatal disease’ contributes to stigma and abandonment. Furthermore, characterisation of EBC as ‘curable if everything is done well’ creates misconceptions about those who develop metastatic disease, even though approximately 30% of patients with early disease will develop MBC despite optimal therapy.³¹³ Slogans such as ‘early detection saves lives’, although extremely important for creating awareness, can promote myths that patients with MBC did not, for example, get a screening mammogram or self-examine. There is a difficult balance between

generating breast cancer awareness and avoiding attributing blame to the individual with MBC. Stigma is accentuated within societies that do not typically acknowledge or discuss mortality, and this can be a very negative experience for patients with MBC.

Quantifying MBC stigma

The Decade Report, an analysis of the MBC status and evolution between 2005 and 2015, included a general population survey analysing awareness of MBC, which consisted of 14,315 participants from 14 countries.²⁷⁷ The results emphasised that public understanding of MBC was limited. Across all countries, 14-61% of respondents agreed with the statement 'there is no point in treating advanced or metastatic breast cancer'.²⁷⁷ 18-49% of participants indicated that 'people with advanced or metastatic breast cancer should not talk about it with anyone other than their physician'.²⁷⁷ Two extreme misconceptions exist among the general population regarding MBC: some believe it is equal to early breast cancer and therefore curable, while others believe it is a terminal illness for which there is no hope. These findings illustrate the striking myths that can fuel stigma and isolation in MBC. Furthermore, the misconception that MBC is a rapid terminal illness leads to prejudicial policy decisions in many LMICs and some HICs, where limited resources are usually dedicated to early detected cancers, cutting short the survival, and increasing the suffering of MBC patients.

Cross-cutting features of health-related stigma and identifying interventions

Stigma has been studied in many medical conditions outside of cancer, for example, HIV and mental health, but often a siloed, disease-specific measurement and intervention approach is suggested.³¹⁴ The concept of 'health-related stigma' could facilitate generic stigma assessment tools and interventions rather than disease-specific, which would be a highly beneficial and cost-effective approach from a health systems perspective.^{314,315}

There are multiple theoretical models describing the cross-cutting elements of health-related stigma.^{314,316-319} It has been shown that a patient-centred but multi-component approach, directed at many socio-ecological levels, is required if stigma is to be effectively addressed.³²⁰ The ABC Global Alliance has created a tool-kit to address unmet needs for hard-to-reach populations and this includes examples of community-based initiatives that target stigma.²⁷⁵ For example, Project PINK BLUE was set up in Nigeria in 2016 to address stigma and misunderstanding around breast cancer.³²¹ The aim of this initiative is to support, empower, and educate people with breast cancer by providing educational materials, financial and telephone support, monthly support groups, and patient navigators.³²¹ Another example is the Male Breast Cancer Global Alliance that was created to address stigma and raise awareness for male breast cancer, with initiatives including breast self-examination cards, support calls and an annual conference.³²²

Panel 15 - Lancet Breast Cancer Commission Healthcare Practitioner survey

We carried out a bespoke web-based survey for healthcare professionals (HCP) globally, to study views and perceptions regarding MBC within the healthcare community (*see supplementary material 10 for full survey results*). Our survey obtained a total of 382 responses. 46% of participants were from Europe with limited representation from North America, Africa, and the Middle East. Most of the respondents (70%) were oncologists with more than 10 years of professional activity, and three-quarters of them had > 50% of their clinical practice devoted to breast cancer.

When asked how many lines of treatment patients receive on average, HR-positive and HER2-positive patients were reported to receive more treatment lines (5 or more and 4 or more, respectively). Patients with triple negative breast cancer received the least treatment with an average of three lines of therapy. These results probably reflect the biology of the disease and the available treatment alternatives within these subtypes.

80% of respondents considered MBC an incurable disease, and when asked whether MBC would become curable within the next decade, most were undecided or disagreed. However, 55% agreed that it may become curable for certain subtypes and, importantly, 75% agreed that MBC will become a chronic disease.

More than 70% of health care professionals reported that they inform patients with MBC that their disease is incurable. They considered they had received adequate communication training and felt confident in communicating difficult issues with patients, such as poor prognosis and death. This does not reflect what patients report. For example, a survey of 185 MBC patients in Mexico revealed that only 52% of patients were aware that their disease was incurable, 31% were not sure, and 17% thought it was curable.³²³ This shows the lack of understanding that some patients have regarding their disease, despite most healthcare professionals feeling confident in their communication skills. This communication gap needs urgent attention if we aim to improve the overall management and the outcomes of MBC (*see section 6 – communication and empowerment*). When asked to rank objectives for MBC patients, 72% of our survey respondents stated quality of life as the most important. Progression free survival and overall survival were also highly ranked, whereas improving communication was felt as being of lower priority. Only 18% were very familiar with the ABC Global Alliance 10 Actions for change, which is an important global initiative to address urgent and actionable gaps in management of patients with MBC.²⁷⁵

This survey of HCPs reflects the negative views associated with MBC that contribute to the stigma patients experience. At the same time, a significant proportion of physicians consider recent treatment advances will have a positive impact on the disease. This may be a good starting point to begin to change the overall negative perception of the disease and consider that not all MBC patients are destined to have poor outcomes.

Potential wider impact outside of MBC

By using breast cancer as a model cancer, we hope that our suggestions for reducing discrepancies and stigma, and improving MBC care, can be applied as a framework for positive change to other cancers. Updating cancer registries is integral to more accurate outcome data collection and better allocation of resources, and this is also important across all tumour types. We strongly urge a shift in mindset and aims when treating people with MBC, as this will be valuable not only to the individual and their family, but also to society.

	Panel 16 - Lancet Breast Cancer Commission proposed measurable indicators of change				
Theme	Definition	Rationale	Data sources	Responsible entity	Target
Theme 3: Optimal inclusive management of metastatic breast cancer					
Data collection on metastatic breast cancer (MBC).	Improvements in cancer registry data collection: stage at diagnosis including de novo metastatic disease and breast cancer relapse data.	Knowing the actual number of people living with MBC would allow a better allocation of resources.	Cancer registries.	Ministry of Health.	Minimum of 70% of cancer registries, aiming at 100%.
Multidisciplinary meeting (MDM) review for MBC.	MBC cases discussed at a multidisciplinary meeting (MDM).	Improve outcomes: survival and quality of life.	Facility records, national and international certification procedures for breast units.	Ministry of Health.	Minimum of 50%, aiming at 95% MBC cases discussed at MDM.
MBC outcomes.	Improvements in median overall survival (OS) of MBC.	Improve outcome.	Cancer registries, Facility records, national and international certification procedures for breast units.	Facility, Ministry of Health.	Record the number of people with MBC and double the median OS in a decade.
End of life care.	Number of patients with breast cancer dying in pain: morphine use as an indicator of suffering.	Improved QoL and reduced suffering.	Pharmacy registries.	Ministry of Health.	Aiming for less than 5% of patients at end of life without access to morphine.
Essential breast cancer	Updates and uptake in WHO	Improve outcomes for MBC.	WHO EML updates, National regulators data.	Ministry of Health.	All MBC patients have access to life saving cancer medicines.

medicines for MBC are affordable globally.	essential medicines to promote equal access.				
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Theme 4: Tackling breast cancer gaps and inequities through global collaboration

Panel 17 - Summary for tackling breast cancer gaps and inequities through global collaboration
Poorer women and minoritised populations often have late-stage breast cancer and are at high-risk of dying from cancer - this equity gap will widen without global collaborative intervention.

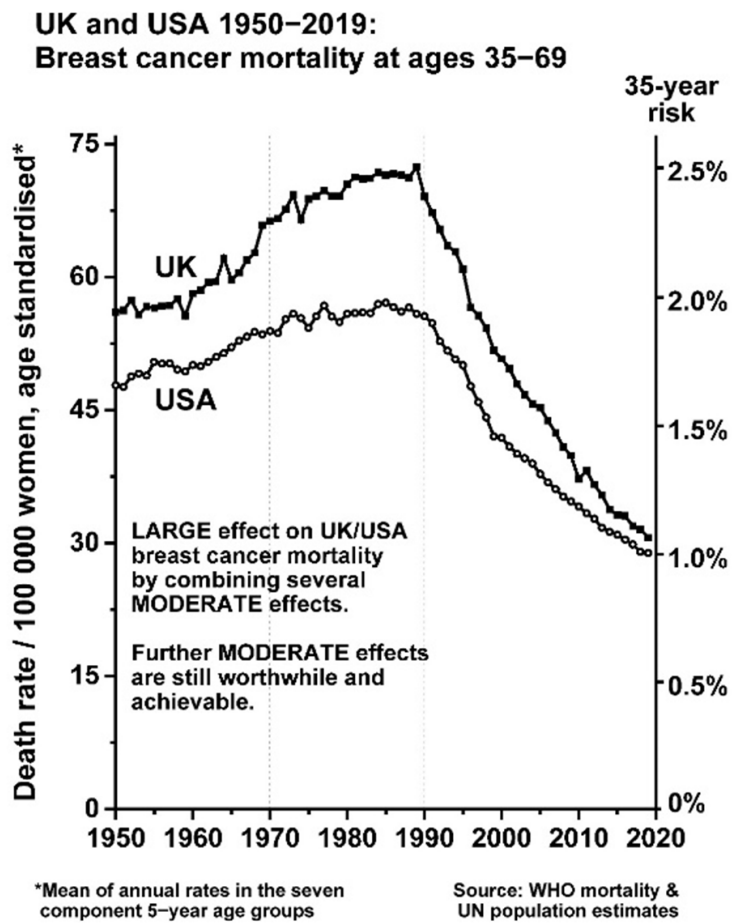
- Equitable access to early diagnosis and treatment is a fundamental need for all individuals to improve breast cancer survival and quality-of-life.
- In collaboration with the WHO Global Breast Cancer Initiative, we call for action to deliver 'stage-shifting' – as a sustained decline in breast-cancer mortality rates is achieved by diagnosing at least 60% of invasive cancers at stage I-II.
- Tools to achieve this 60% threshold can be adapted to local context and resources.
- Technology innovations can catalyse the speed and efficacy of early diagnosis and treatment implementation globally.
- Integrated health systems policy, education, and advocacy are needed – pioneering approaches in breast cancer and can be used as a model for other cancers.

In the early 1990s, many high-income countries witnessed a sea change in diagnosis and coordinated multidisciplinary evidence-based treatment as exemplified by the initiation of the Early Breast Cancer Trialist Collaborative Group. These changes have demonstrated declines in breast cancer mortality rates of around 2% per year or greater (see Figure 4), translating to an overall 40% reduction in breast cancer age-standardised mortality rates (ASMR) over 3 decades.^{324,325} The 40% improvement in age-adjusted breast cancer mortality has not yet been achieved in most low- and middle-income countries.³²⁶ In LMICs, advanced stage at diagnosis and limited diagnostic and treatment capacities contribute to lower breast-cancer survival rates.^{279,327} 5-year breast cancer survival rates exceed 90% in high-income countries, compared to 66% in India and 40% in South Africa.³²⁸ To address this inequity, translation of what has worked well in high-income countries to less well-resourced settings is required, but tailored to local context.

According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to assert that mammographic screening reduces breast-cancer mortality in women 50–74 years of age and limited evidence supporting the same benefit in women ages 45 – 49.³²⁹ While the evidence for the net benefits of mammographic screening is well established for women 50 years of age and above, the obstacles to translation of these findings to implementable strategies in LMICs are significant.³³⁰

In order to reduce breast cancer mortality, early detection including both early clinical diagnosis and screening programmes (*see supplementary material 11*); and effective multimodality treatment are needed.³³¹ (*see Panel 18 - World Health Organization (WHO) Global Breast Cancer Initiative (GBCI) Pillars and Early breast cancer detection*). The infrastructure and processes used for breast cancer management are similar for other adult solid tumours such as colorectal, prostate, and lung cancers. If breast cancer can be managed effectively in a limited resource setting, then improved management of other malignancies is more likely to follow.

Figure 4: An example of the fall in breast cancer mortality in two high-income countries in the last three decades. Graph produced by the Early Breast Cancer Trialists Collaborative Group and shown with their permission.



Panel 18 - World Health Organization (WHO) Global Breast Cancer Initiative (GBCI) Pillars

A population-based analysis demonstrated two health-system characteristics were significantly associated with lower age-standardised mortality rates (ASMR): higher levels of universal health coverage (UHC) levels (funding) and increased numbers of public cancer centres per 10,000 cancer patients (access).³²⁶

In 2021, the GBCI was set up, with the aim of reducing breast cancer mortality by 2.5% per year and potentially preventing 2.5 million premature deaths over 20 years.³³² To achieve this target, GBCI (Figure 1) suggests three sequential care intervals or ‘pillars’ for effective management³³³:

Pillar 1: Health promotion for early detection (pre-diagnostic interval)

Individuals enter the pre-diagnostic interval either by presenting with a breast symptom, such as a lump or breast change; or presenting without symptoms to a screening programme if available. Analysis carried out by GBCI shows that not all countries that achieve a sustained breast cancer mortality reduction have population-based mammographic screening programs.³²⁶ These findings encourage a focus on early detection programs that vary based on the needs assessment of individual countries. Stage shifting is required to increase the fraction of patients initially diagnosed with early-stage disease. Early detection begins with breast-health awareness and the establishment of early diagnosis programs, which identify people with symptoms and signs of possible malignancy and link them to diagnostic services. Breast cancer screening is not appropriate until the required infrastructure and quality-control measures are fully functional. All healthcare systems require the capacity to diagnose symptomatic breast findings in a timely manner, regardless of whether they have mammographic-screening programs.

Pillar 1 key process indicator (KPI): at least 60% of invasive cancers diagnosed at stages I or II.

Pillar 2: Timely breast diagnostics (diagnostic interval)

Breast diagnosis requires clinical evaluation, breast imaging, and tissue sampling from suspicious lesions (triple assessment). The optimal imaging and sampling methodologies will vary, depending on the availability of equipment and trained staff.³³⁴ Treatment delays beyond 90 days lead to lower rates of breast cancer survival.³³⁵ In 2012, Brazil established the ‘60 days law’ - all cancer patients should start treatment within 60 days of diagnosis.³³⁶

Pillar 2 KPI: diagnostic process to take place within 60 days.

Pillar 3: Comprehensive breast cancer management (treatment interval)

Effective treatment requires a multidisciplinary approach from radiology, pathology, surgical oncology, medical oncology, radiation oncology, and supportive oncology. However, these treatment strategies are usually only effective when the entire treatment course is given. Treatment abandonment, in which the patient begins treatment but fails to complete it for reasons other than a clinical decision to stop, is a common problem in LMICs. In the African Breast Cancer Disparities in Outcomes (ABC-DO) study of 5 sub-Saharan African countries, less than 50% of patients started and completed their treatment course.³¹⁰

Pillar 3 KPI: >80% of individuals to complete multimodality treatment without abandonment.

Most HICs have lower rates of later-stage diagnosis and better outcomes, however there can be differences in breast cancer mortality within most HICs, with evidence from the USA (*See Panel 19 - Breast cancer stage disparities in Miami*), Scotland³³⁷, The Netherlands³³⁸, and Australia.³³⁹ All countries across the globe should set out on this journey but they will not all start from the same place. For further reading see stage shifting strategies with and without *functioning screening programmes and future directions are outlined in supplementary materials 12-14.*

Panel 19 – Case history – breast cancer stage disparities in Miami³⁴⁰

Background:

Unmet Social Needs are direct mediators of health outcomes. We aimed to evaluate if 1) city-funded screening mammography is associated with utilisation of screening mammography, 2) Unmet Social Needs are associated with utilisation of screening mammography, and 3) Unmet Social Needs are associated with later-stage disease at diagnosis.

Methods:

Prospective cohort study of stage I-IV breast cancer patients recruited from 2020-2023 at both an underserved safety-net hospital (SNH) and a National Cancer Institute-designated Academic Cancer Center (ACC) who completed the Health Leads Social Needs Screening Toolkit. Univariable and multivariable logistic regression was utilised to evaluate the following primary outcomes: 1) routine screening mammography and 2) AJCC 8th edition clinical stage at presentation.

Findings:

Of the 322 women who completed the Health Leads Social Needs Screening Toolkit, 76% with access to city-funded screening mammography completed a screening mammogram. Patients who presented to the SNH were more likely to present with late-stage disease compared to early-stage disease (31% vs 18%, $p=.04$). On multivariable logistic regression, independent predictors of not completing a screening mammography were having an increasing number of Unmet Social Needs (OR 0.74 95% CI 0.55-0.99, $p=0.047$) and increasing age at diagnosis (OR 0.92 95% CI 0.89-0.96, $p<0.001$). Moreover, increasing Unmet Social Needs (OR 1.38 95% CI 1.01-1.89, $p=.04$) was an independent predictor of late-stage at diagnosis, above and beyond screening mammography.

Interpretation:

Our prospective cohort study found that access to screening mammography did not translate to utilisation of screening mammography, increasing Unmet Social Needs significantly predicted lower rates of screening mammography, and having increasing Unmet Social Needs significantly predicted late-stage diagnosis. This effect transcended recruitment site (SNH vs. ACC), indicating that patients in any hospital setting may benefit from Unmet Social Needs screening to overcome access to care barriers associated with late-stage disease at diagnosis.

Panel 20 - Case study: economic evaluation of breast cancer control in Kenya

In 2020, the Kenyan Ministry of Health partnered with the World Bank to create an investment case for combatting non-communicable diseases. Working in collaboration with WHO the GBCI developed a health-system model to predict breast cancer outcomes and related implementation costs. The resulting Kenya model for early detection proposes a 15-year implementation plan, using a phased implementation approach. During the first five years, health-system strengthening focuses on the establishment of diagnostic services to work-up clinically detectable breast changes, thereby establishing early diagnosis services. In years 6 to 15, Kenya plans to establish screening programs based on a combination of clinical breast examination-led screening and mammogram-led screening, utilising the infrastructure and programming established during the first five years. The following predictions and cost estimates were projected based on the Kenya-specific baseline data and examines outcomes as measured by stage shifting projected to 15-years (Figure 5A), breast cancer survival rates projected to 40-years (Figure 5B), and project associated costs for each development strategy (Figure 6).³⁴¹

Figure 5A: The Kenya Model for early detection and predicted stage shifting over a 15-year period (2022–2037), Kenya

Source: Reproduced with permission of the publisher from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya*³⁴¹

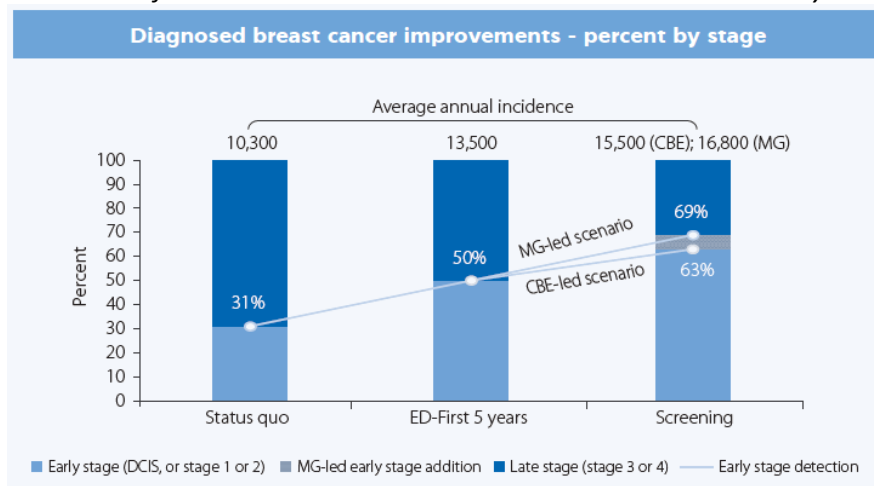


Figure 5B: Predicted breast cancer mortality reductions over 40 years (2022–2062), Kenya

Source: Reproduced with permission of the publisher from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya*³⁴¹

CBE is clinical breast examination; MG is mammogram

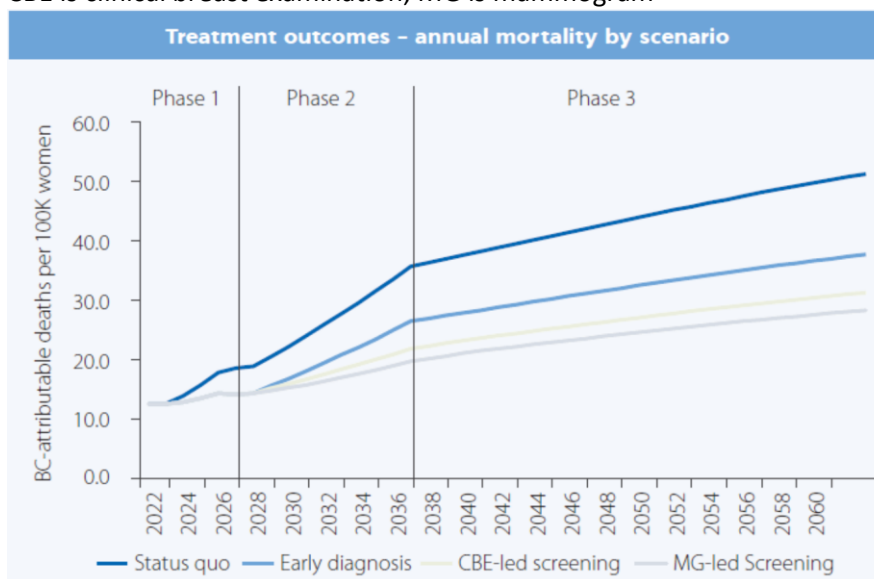


Figure 6: Predicted breast cancer programme and service-delivery costs over a 15-year period (2022–2037), Kenya

Source: Based on data from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya* with the permission of the publisher³⁴¹. CBE is Clinical Breast Examination; MG is Mammogram.

15-year programme and service delivery costs (KES (discounted) and approximate US\$)			
Cost type	Early diagnosis only	CBE-led total 15-years	MG-led total 15-years
Health-system strengthening	KES 8.54 billion (US\$ 69.99 million)	KES 14.56 billion (US\$°118.78 million)	KES 15.94 billion (US\$°127.52 million)
Direct treatment	KES 11.46 billion (US\$°93.73 million USD)	KES 16.74 billion (US\$°136.95 million)	KES 38.41 billion (US\$°311.39 million USD)
Screening	00	KES 1.67 billion (US\$°13.66 million)	KES 19.97 billion (US\$°163.57 million)
Diagnosis	KES 1.46 billion (US\$°11.98 million)	KES 3.46 billion (US\$°28.33 million)	KES 5.34 billion (US\$°43.72)
Treatment	KES 7.42 billion (US\$°60.80 million)	KES 8.77 billion (US\$°71.82 million)	KES 9.77 billion (US\$°80.02 million)
Palliative	KES 2.56 billion (US\$°21.03 million)	KES 2.83 billion (US\$°23.23 million)	KES 2.96 billion (US\$°24.22 million)
Total	KES 19.99 billion (US\$°163.71 million)	KES 31.30 billion (US\$°256.31 million)	KES 53.63 billion (US\$°439.12 million)

Adapting technologies for early breast cancer diagnosis and treatment to local settings

Diagnostic services coupled with treatment provision are the foundation for high quality and effective healthcare delivery³⁴². Through adapting technology to local settings there is a potential to ‘leapfrog’ ahead of existing methods and move closer to equity across all contexts if a framework of ‘smart leapfrogging’ is adopted. Adapting to local context using local knowledge and innovation is also required. A striking example of this is the use of Coca-Cola lorries to deliver essential medicines in rural Zambia, given that Coca-Cola drinks were readily available in remote villages, but anti-diarrhoea kits were not.³⁴³

Leapfrogging technologies fall into two categories: 1) novel technology that augments or bypasses an existing technology or addresses a previously unmet need, and 2) innovation achieved through the reorganisation or reframing of current practices or resources. An example of the first category is automated systems that measure RNA levels to determine breast cancer biomarker status, which may have the potential to bypass immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) where it is currently absent, unreliable, or only available in tertiary care facilities.³⁴⁴⁻³⁴⁶ An example of the second category is the shift to virtual multidisciplinary tumour boards using existing teleconferencing software during the coronavirus disease 2019 (COVID-19) pandemic, which increased access to expert multidisciplinary care to non-tertiary care settings and enabled remote patient consultations (*see Theme 2 – digital health*).

The key principles of smart leapfrogging include defining the specific local context by carrying out a situational analysis to identify gaps that act as critical barriers to equitable access to care, identifying an innovation or technology that may fill the gap and add value to the local context. A limitation in the development and validation of novel technologies is that specific tools can be tested in isolation, without considering how they fit into the healthcare system.

Technologies or innovations shown to be highly effective in high-resource settings may not have the same performance characteristics in a resource-constrained setting, while others might have greater impact.³⁴⁷⁻³⁴⁹ For example, the systematic measurement of breast residual cancer burden (RCB) and stage after neoadjuvant chemotherapy provides prognostic information that helps treatment decisions for subsequent adjuvant therapies. There is negligible cost for measuring residual cancer burden as it is an adaptation of usual pathology practice.³⁵⁰⁻³⁵² However, a prerequisite for a neoadjuvant systemic therapy approach requires a functioning healthcare system to coordinate analysis of results and deliver multimodal therapies in a timely fashion and safer manner.

Novel technologies have been proposed as potential methods for screening, monitoring treatment response, predicting disease progression or relapse, or guiding therapy, which will have wider implications beyond breast cancer diagnosis. A surgical example is the use of magnetic markers that can serve as a non-radioactive and wireless alternative for localisation of sentinel lymph nodes and non-palpable breast lesions, respectively.³⁵³ With standard metal clips, image-guided wire localisation is required. By contrast, with magnetic markers, the surgeon can find the correct region without special assistance from the radiologist. Whole slide imaging and digital pathology can also be used to increase access to expert assessments of response to neoadjuvant therapy in regions where pathology services are limited, allowing for a more personalised and cost-effective therapeutic approach. Moreover, several blood-based technologies (i.e. liquid biopsies) that leverage a broad scope of technologies have emerged, ranging from detection of tumour biomarkers using low-cost methods such as enzyme-linked immunosorbent assays (ELISA), to high complexity methods such as sequencing and methylation profiling of circulating tumour DNA (ctDNA) and cell-free DNA (cfDNA).^{354,355} For example, the United States Food and Drug Administration and European Medicines Agency have approved the use of alpelisib in patients with PIK3CA-mutated metastatic breast cancer,

detected either in ctDNA or tissue.^{355,356} These blood-based methods are still under investigation, and it is unclear what clinical role they will play in the future.

Panel 21 - Smart leapfrogging

Key principles

- Conduct needs assessment/situational analysis to identify gaps and specify local context.
- Identify root causes of the gaps.
- Find or adapt technologies to address gap & able to integrate within health system.
- Assess the value added.
- Determine whether partnerships would be beneficial.

Characteristics of an innovative and leap frogging technology^{357,358}

1. Integration into broader health system:
 - Addresses a specified evidence-to-practice clinical gap.
 - Health system can provide sufficient human resources, education and training, reliable supplies and procurement, maintenance.
 - Clinically relevant turnaround time to guide therapeutic decision-making.
2. Assay characteristics:
 - Robust performance characteristics (sensitivity, specificity, predictive values, precision, and accuracy).
 - Easy to perform and maintain.
 - Easy to interpret and communicate.
 - Cost-effective.
 - Clinically relevant turnaround time to guide clinical decision-making.
3. Quality management and outcome metrics:
 - Well documented structure, processes, roles, responsibilities, and procedures required to achieve effective quality implementation and maintenance (*see Quality System Essentials Table*).³⁵⁹
 - Well defined implementation outcomes that are also linked to service and client outcomes. (*see Proctor's Conceptual Framework for Implementation Outcomes*)³⁶⁰

Patient navigation and equitable access to medications

Access to high-quality breast cancer care may be hampered by delays in diagnosis and treatment.^{361,362} Prioritisation of patients scheduled for diagnostic evaluation according to suspicion of malignancy based on image findings and/or symptoms can reduce health system interval delays. This strategy has been employed by navigation programs in Mexico³⁶³ and Colombia³⁶⁴ that have been successful at reducing the time to diagnosis of breast cancer. In Mexico, the 'Alerta Rosa' program introduced a triage system to stratify and prioritise patients for imaging studies and appointments with breast specialists to accelerate access to diagnostic procedures and treatment. In Colombia, the 'Breast Cancer Early Detection Pilot Program' focused on evaluating care barriers and coordinating timely referrals for early breast cancer detection and prompt access to treatment. A comparable approach was developed in the United Kingdom, which established national referral guidelines requiring that every patient with suspicion of breast cancer should receive a specialist consultation within two weeks of referral by their general practitioner. Adherence to these guidelines resulted in a significant improvement in adequate patient prioritisation and reduction in health system waiting times.³⁶⁵

Equitable access to medications is essential across the breast cancer continuum

This is discussed in *Panel 22 - Equitable access to medicines* and explored further in a *case study on immunotherapy in supplementary material 6*. See also *Theme 3 – metastatic breast cancer*.

Panel 22 - Equitable access to medicines

Access to medicines is a complex and multidimensional problem, with cost being a major barrier to optimal treatment. Access is a worldwide problem, but underserved populations are routinely consistently worse affected. Potential strategies to address drug access include establishing universal health coverage for essential cancer medicines (for both early and metastatic cancers), fair drug pricing, and optimising regulatory demands and improving global supply.³⁶⁶ Treating patients according to context-adapted high-quality guidelines is another important strategy to optimise care and avoids unnecessary waste of resources.⁰

Access to medications released to the market over the last 5 years represents one of the more telling discrepancies clearly related to the different cancer outcomes seen in different regions of the world.³⁶⁷ While the US, Western Europe, and Japan consume approximately 90% of all new medications, the rest of the world population accounts for only the remaining 10%.³⁶⁷ Too frequently, we are seeing a complete dissonance between the price of new cancer medicines and the benefit seen in registration clinical trials. Recent analyses indicate no association between medicine prices and the magnitude of benefit on end points such as progression-free survival, overall survival or objective response rate, suggesting that cancer medicines are priced based on what the market can stand, not the clinical benefits they provide.³⁶⁸ Addressing this inappropriate process in a transparent way is fundamental for the future of breast and other cancer care, as it leads to differential medicine access within HICs, as well as the rest of the world.

The recurrent argument that prices should cover not only the few medications that make it to the market but all the other failed experiments as well, has been questioned by an analysis indicating that cancer medicines have generated returns far in excess of officially reported research and development costs.³⁶⁹ This challenging scenario has led to increasing interest in alternative pricing strategies including different versions of value-based pricing, a discussion that should be encouraged. Affordability of a particular country or region should also be considered. Outcome-based payment is being explored in certain scenarios.³⁷⁰ Different prices according to the different benefits a medicine may have on different indications has been proposed. Also, Food and Drug Administration accelerated approvals could be priced at lower levels to be adjusted after confirmatory evidence is generated.³⁶⁸ Regulators should be more active in withdrawing approval when benefits are not confirmed within clinical trials or when 'real world data' fails to demonstrate benefits.

Furthermore, payers should not be influenced by pharmaceutical industries and should use an objective assessment tool – such as the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale²⁸⁶ or the American Society of Clinical Oncology (ASCO) Framework of Value³⁷¹ – to prioritise cancer medicines that should be approved in each country. Medicines that provide the highest benefit should be approved faster than the ones that provide only marginal benefit. This is crucial in countries with limited resources but, in view of the uncontrolled rise in costs, it is important in HICs as well. Improving access to cancer medicines to all populations is a universal and urgent unmet need.

See *Panel 13 - Inequity within HICs - New Zealand* as a case study, as a breast cancer specific example of improving equity of access to HER2-directed therapies.

Patient advocacy to improve equity in breast cancer detection and care

Health advocacy has been defined in the medical profession as activities related to ensuring access to care, to navigating health systems, mobilising resources and to addressing health inequities, influencing health policy and creating system change.³⁷² Cancer advocacy relates to the application of

these strategies to the cancer care continuum and has been largely led by civil society organisations in many countries.³⁷³ Historically, advocacy has been powerful in bringing about global change in disease and healthcare, but it is not clearly understood by many and lacks a robust evidence base. Even so, it plays a fundamental role within every society and drives the evolution of breast cancer care globally. For example, advocacy efforts could be aligned to the GCBI pillars to facilitate achieving the three major KPIs.

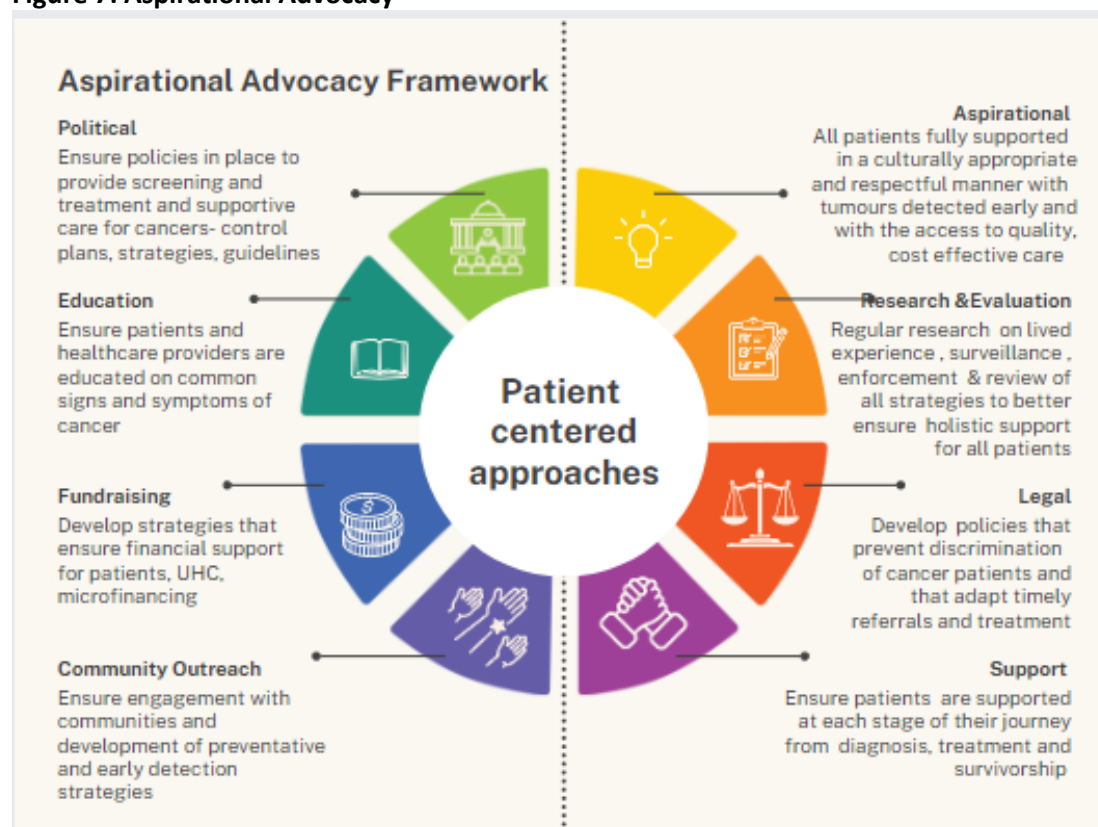
Self-advocacy or patient activation is an important overarching theme in the literature.³⁷⁴ Patients should be empowered to feel control over their body, health, and decision making, for example, regarding breast cancer treatment options (*see Theme 6: Communication and empowerment*). With the understanding of the disease process, self-advocacy may help to push for supporting timely diagnosis and could enhance treatment adherence and completion of care (pillars II and III).

A 'structured' advocacy approach can address awareness and early detection concerns, and treatment and survivorship needs. This organised approach to advocacy can touch on legal, educational, research and policy aspects of care. A proposal by the African coalition of cancer advocates (ACAC) suggests 6 key areas of prioritisation for comprehensive cancer advocacy: political, education, research, fundraising, support, and community outreach.^{375,376} These key tenets must however be contextualised to different settings. *See supplementary material 15* for more information on structured advocacy.

Innovative approaches and strategies need to be considered to enable advocacy to bridge global gaps in care. Advocacy must be contextual but should also leverage existing networks. Developing a cadre of advocates that will engage all stakeholders including policymakers about concerns along the care continuum whether financial, legal or supportive, and provide funding for care is important. Advocates should prompt researchers to ask the relevant questions for their communities, to empower and improve the lived experience of cancer patients and their care givers. This may mark the first steps towards achieving equitable care in many settings. The additive effects of the outputs of these advocacy efforts must be assessed along with the GCBI pillars and targets.

In rethinking approaches to cancer advocacy, we propose an 'aspirational' advocacy framework (*See Figure 7*) which builds on experiences from breast cancer advocacy to form a broader relationship around equity and health. It is important to widen the focus to go beyond the individual need and to target broader platforms in civil society, for example, women's rights. Here, aspirational advocacy could contribute more broadly to women's empowerment, health systems strengthening, anti-poverty efforts, and address violence against women with measurable outcomes. Education of women in LMICs is paramount to develop preventative aspects of breast cancer care as early as possible. This highlights the importance of younger females remaining in formal education settings to enable this transfer of information.

Figure 7: Aspirational Advocacy



Panel 23 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Theme 4: Tackling breast cancer gaps and inequities through global collaboration						
Stage-shifting.	Ensuring prompt diagnosis of breast cancer.	Decrease breast cancer mortality rates and prolong life.	Cancer registries.	Ministries of Health.	60% of all invasive cancers are at stage 1-2 at diagnosis.	WHO Global Breast Cancer Initiative (GBCI) Pillar 1 Key Performance indicator (KPI).
Timely and appropriate treatment.	Evaluation, imaging, tissue sampling and pathology.	Improve breast cancer outcomes.	Facility records, National audit.	Ministries of Health.	Evaluation, imaging, tissue sampling and pathology within 60 days.	WHO GBCI Pillar 2 KPI.
Treatment abandonment as defined by WHO Global Breast Cancer Initiative.	Optimising multimodality treatment without abandonment.	Improve breast cancer outcomes.	Facility records, National audit, national and international certification procedures for breast units.	Ministries of Health.	80% of patients undergo multimodality treatment without abandonment.	WHO GBCI Pillar 3 KPI.
Access to medicines.	Reduce inequalities in access to medicines between and within countries.	Improve breast cancer outcomes.	Time for Harmonization of Global Clinical Trials to decrease time from Food and Drug Administration and European Medicines Agency (FDA/EMA) approval to availability to the patient globally.	Ministries of Health National regulatory bodies.	Time from FDA/EMA approval to availability to the patient less than 6 months for high priority agents, less than 1 year for intermediate priority agents.	Use an objective assessment tool to prioritise cancer medicines for approval in each country.

Theme 5: Identifying the hidden costs of breast cancer

Panel 24 - Summary for hidden costs of breast cancer

Costs of breast cancer and associated suffering are immense - society and policymakers currently see only the tip of an iceberg. These should be exposed and quantified in order to be reduced.

- Costs include financial, emotional, social, and economic costs; these impact on children, families, local communities, and wider society.
- Even within health services that are free at the point of delivery, those affected by breast cancer face additional costs that may particularly impact on the poorest in society.
- Serious health-related suffering goes unmeasured in global health metrics, so its alleviation is not prioritised by policy makers.
- Exposing and reducing costs provides a major incentive for policymakers to invest in prevention, early detection, cost-effective therapy, and optimal management of breast cancer.
- Initial estimates of hidden costs of suffering from breast cancer provided can catalyse new priority-setting tools for breast and other cancers and this research is pivotal and in process as part of the Lancet Commission on Cancer and Health Systems.

The burden of suffering:

Both health systems in general and cancer systems must acknowledge serious health-related suffering (SHS) and, therefore, the value of alleviating this suffering by better investing in appropriate supportive and palliative care.⁸ Yet, the alleviation of SHS which is paramount to patients and their families goes unmeasured in global health metrics and is therefore undervalued.

The Lancet Commission on Palliative Care and Pain Relief⁸ showed that because they are absent in priority setting, many key interventions for alleviating suffering are not considered in either covered health care packages or in universal health coverage. The Commission estimated that over 61 million people per year experience SHS and one-quarter of this is due to cancer. While much of this could be relieved with better access to palliative care and pain relief,⁸ between 80 and 90% of this global need is unmet due to a lack of available workforce, necessary training, health system investment, and equitable access to palliative care medicines.^{8,377} SHS can affect patients throughout the breast cancer trajectory and hence the measure is relevant not only for imminently dying patients (year of death measured by mortality), but also at earlier stages (before year of death). Hence, to accurately count the number of people and their days with SHS (SHS days per year), both mortality and prevalence data are required. A decedent is a person who dies in a given year and can only experience SHS in that year. Non-decedents are people who do not die in that year but may also have SHS. By 2060, it is projected that 16.3 million people each year will die from cancer and will experience SHS. Importantly, breast cancer is predicted to account for the highest proportion of cancer decedent SHS in all countries, but particularly in low and lower-middle income countries.³⁷¹

All people with breast cancer experience suffering at some point in their cancer journey, regardless of stage of illness. This affects their quality of life, relationships, self-perceptions, and independence.³⁷⁸⁻³⁸² Patients may face physical, psychological, spiritual, and existential distress over a long period.³⁸³⁻³⁹⁴ This begins with the realities of diagnosis and continues with fears associated with prognostic uncertainty and the possibility of death. Treatments have collateral physical and psychological impact, and this is added to by the long-term challenges of survivorship (*see CASCARA Panel 26*) with fear of recurrence and possible debilitating symptoms. Families and caregivers of people with breast cancer may also experience extended periods of social suffering and financial hardship.³⁹⁵⁻³⁹⁸ This includes not only out-of-pocket costs for healthcare, but also loss of income of the person with breast cancer and their caregivers, and with the added possibility and vulnerability of orphaned children.

Serious health related suffering (SHS) specific to breast cancer

As part of follow up work for the Lancet Commission on Global Access to Palliative Care and Pain Relief⁸, the measurement of SHS is being updated with a disease-specific approach. In collaboration with the Lancet Commission on Cancer and Health Systems⁷, a pilot study was undertaken on breast cancer with expert providers and patient advocate groups. The group of 14 experts were invited to participate in a three-part process; an online survey, a focus group, and a structured one-to-one interview. Their collective experience was from Jamaica, Haiti, Rwanda, Mexico, Brazil, India, Lebanon, Portugal, United States of America, United Kingdom, Malaysia, and South Africa and they represented breast surgery, medical oncology, radiation oncology, physiotherapy, palliative medicine, and the patient and patient advocacy experience.

The findings showed that SHS is not restricted to metastatic breast cancer but is highly relevant for early-stage disease and for survivorship, though these groups had lower SHS burden compared those with metastatic disease. Non-decedents include patients with early cancer, but also patients with metastatic disease, whose life-expectancy even in LMICs can be several years, and they may continue to suffer from high SHS burden throughout that time. Non-decedents also include patients in survivorship who most probably will not die of breast cancer. Adjuvant systemic therapies (e.g. hormonal therapies and more recently CDK4/6 inhibitors) are used for years into survivorship and can cause toxicity. Patients may also suffer ongoing sequelae from curative surgery, chemotherapy, or radiotherapy. These patients may have a high prevalence of SHS symptoms such as pain or fatigue, and reproductive health challenges. Indeed, the expectation that they are 'symptom-free' within a few years post-treatment veils their need for supportive care.

The expert group agreed that half a year of SHS - about 175 days - is experienced by patients in the last 12 months of life. The typical patient was estimated to need access to about 60mg of opioid morphine equivalent per day in their last year of life to sufficiently manage pain and breathlessness. The expected lifespan for people living with metastatic or locally advanced breast cancer (non-decedents) was estimated to be about 4 years, with an average of close to 70 SHS days per year. The group considered that for both those who died of their breast cancer and those living with the disease, approximately two-thirds of SHS days each year are likely preventable through improved access to care. It is important to note that these estimates refer to a typical patient and mask inequities across and within countries.

The term 'survivor' was challenged by experts and more strongly by patients (*see CASCARA panel below*). In alignment with a person-first language, the term survivorship was preferred which would include disease-free patients following curative therapy, those still undergoing adjuvant therapies, and those with metastatic disease. Survivorship is also a depersonalised term that refers to a health state rather than a nominal patient. This is aligned with an ongoing change of concept for some types of breast cancer, which is perceived now less as a life-limiting disease, and more as a chronic illness.³⁹⁹ (*see Themes 3 and 6*).

There was also some reluctance to use the term palliative care in people with early breast cancer. Whereas experts working in resource-poor settings tended to accept a much broader range of palliative care, experts from high income countries found it difficult to accept the term when treating people with early breast cancer. A broader terminology using 'supportive and palliative care' was found to be acceptable to all experts.

Breast cancer can cause significant social stigma (*see also Theme 3*) and suffering, for example from a feeling of disfigurement and issues with body image, reduced sexual quality of life with diminished feelings of sexual attraction and femininity.⁴⁰⁰⁻⁴⁰⁴ Social stigma, secondary or associative stigma experienced by family members, and self-stigma or internalised shame can result from discriminatory

sociocultural beliefs and practices that reinforce gender roles. These include value-setting based on women's reproductive capacity or potential marital status and the impact of illness on these.³⁷ Due to the prevalence of pre-menopausal breast cancer in LMICs^{70,405-407}, these types of suffering are of particular concern. Women in resource-limited settings are also less likely to have access to reconstructive surgery and assistance with protecting fertility.⁴⁰⁸⁻⁴¹⁰ Men with breast cancer, though a minority, suffer from social stigma related to the diagnosis of what is perceived as a 'women's disease'.⁴¹¹ *See also Theme 2 - Male Breast Cancer Global Alliance.*

The expert panel recommended adding sexual, reproductive, and gynaecological health items to the SHS assessment. Patients are often reluctant to raise these problems in their medical consultations, requiring that healthcare professionals actively address them sensitively (*see Theme 6*). Although these results are based on a small sample of professionals, our exploratory analysis provides a preliminary quantification of suffering, that is primarily based on the provider perspective, to initiate the discussion on the need to assess and treat SHS in patients with breast cancer.

The effort to strengthen measurement of the disease-specific burden of SHS is complementary to ongoing research on the value of suffering alleviation to patients, caregivers, and health systems. This is a component of the linked work with the Lancet Commission on Cancer And Health Systems and in follow-up to the Lancet Commission on Palliative Care and Pain Relief (*see Panel 25*).

Panel 25 - Dimensions of suffering and the value of alleviating suffering among patients with breast cancer: case report from Mexico

The research agenda set out in The Lancet Commission on Global Access to Palliative Care and Pain Relief report⁸ called for in-depth work on the dimensions of suffering as an input into developing more inclusive, effective and patient-responsive indicators for priority setting. As part of the exploratory phase of a multi-country study to identify the dimensions of suffering and the need for palliative care⁴¹², qualitative research was undertaken at the Mexican National Social Security Institute (IMSS) consisting of in-depth interviews with 14 women with breast cancer, receiving care at the IMSS pain clinic in Mexico City and approaching end of life.

The thematic analysis identified two main themes:

- SHS as a multifaceted phenomenon,
- Relief of SHS requiring a joint effort from the patient, family, and health services.

The first theme encompassed intrapersonal SHS (physical and emotional SHS increasing over time due to disease progression), interpersonal SHS (family suffering, psychological, and economic suffering due to job loss and health services scarcities, social suffering, and cultural influence on the SHS perception) as well as differences in SHS according to age and socioeconomic level. The second theme was about SHS relief and included intrapersonal and interpersonal strategies to alleviate SHS, and health services response. The women expressed the importance of SHS relief for everyone and acknowledged the need for a joint effort from the person living with the disease, their family, and health services, including more palliative care services, pain clinics, and innovations to alleviate SHS. The findings are consistent with research on SHS associated with various cancer types and diabetes, including some patients with breast cancer.⁴¹³ Furthermore, these findings are part of ongoing research to understand the meaning of SHS and the value of alleviating SHS in monetary and non-monetary terms across sociocultural, socioeconomic, and health system contexts.

Hidden financial costs from breast cancer

A diagnosis of breast cancer can threaten financial well-being even in countries and for populations that have financial protection through public or private health and disability insurance.⁴¹⁴⁻⁴¹⁸ More systematic monitoring of family income loss, cost-related non-adherence, treatment withdrawal and quality of life would allow identification of these hidden costs and calculation of the true cost of breast cancer to societies.

With the Lancet Commission on Cancer And Health Systems⁷, the Lancet Breast Cancer Commission, initiated a collaboration with partners in several countries to generate country-level, context relevant cost and cost burden data to better inform priority setting for cancer control. Exploratory pilot research in the UK, a country with Universal Health Coverage for cancer care (the National Health Service), was carried out through the *CASCARA (Costs And Supportive CARE in bReast cAnceR) study* (see Panel 26 - CASCARA participant quotes)

The CASCARA (Costs And Supportive CARE in bReast cAnceR) Study

CASCARA is a UK pilot study scoping the economic burden, financial toxicity, and supportive care needs amongst individuals with breast cancer in a high-income country with a National Health Service that is free at the point of use. Online anonymous population-based surveys were designed by researchers from the Lancet Breast Cancer Commission and The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU) in collaboration with volunteers with lived experience of primary and metastatic breast cancer. A patient survey and a carers survey were designed, and these were open from 24/01/2023 to 03/03/2023. Individuals with lived experience of primary or metastatic breast treated in the UK were eligible to complete the CASCARA survey and were asked to provide information relating to their most recent episode disease. This included patients and carers, which may include family and friends. Survey participants were recruited via two main routes. The first was from the Breast Cancer Now Patient Forum. The second was through other charity groups including Macmillan, Cancer Research UK, and Maggie's (Cancer Support Centres). Completion and submission of the survey were taken as consent for participation.

The CASCARA patient survey had 606 responses. 470 and 136 participants reported experience of primary and metastatic breast cancer respectively. 24% of participants had their diagnosis within the last year and 25% of participants had their diagnosis more than 5 years ago. 35% of the participants were aged 41-50 at diagnosis and 33% were aged 51-60. 96% of participants described their ethnicity as White. 69% of participants had a postgraduate degree, degree, or professional qualification. CASCARA carer survey had 30 responses. 70% of participants reported themselves as partner of a patient, 50% were aged 51-60, and 40% were female. 97% described their ethnicity as White, 63% had a postgraduate degree, degree, or professional qualification.

For participants reporting with early breast cancer, 77% of them were in employment at diagnosis and 61% were still in employment at the time of survey completion. With income presented in bracketed ranges (e.g. <£12.5k, £12.5k-£25k, etc), 25% of participants reported a decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=27.5-40) hours compared with 30 (IQR=18-37) hours at the time of survey completion. For those with metastatic breast cancer, 79% were in employment at diagnosis and 40% were still in employment at the time of survey completion. 38% reported decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=28.5-40) hours compared with 24 (IQR=12-37) hours at the time of survey completion. 47% of carers reported change in their employment because of their caring role for the person with breast cancer. 23% of carers reported decrease in income. 27% of carers took compassionate/carer's leave.

20% of participants with early breast cancer and 25% of those with metastatic breast cancer reported difficulty in covering costs of travel for treatment. 27% with early breast cancer and 35% with metastatic breast cancer reported having financial problems. A small proportion of participants also reported loss and change of home, not able to keep up with mortgage or rent, attending foodbanks.

48% of participants reported people dependent upon them, with 41% of participants having dependent children. For those with early breast cancer, 33% could not fulfil their caring responsibilities at diagnosis and 8% at the time of survey completion. For participants with metastatic breast cancer, 41% could not fulfil their caring responsibilities at diagnosis and 26% at the current time. 29% with early breast cancer and 32% with metastatic breast cancer had their family and friends fulfilling their caring responsibilities at diagnosis, whilst 6% with early breast cancer and 21% with metastatic disease needed support from family and friends at the time of survey completion. 33% of carers reported having other people dependent upon them, with 27% of carers having dependent children. 20% could not fulfil their other caring responsibilities at the time the patient was diagnosed, 10% of carers had some or all caring responsibilities left undone and 10% had received support from family and friends.

Nearly all participants reported physical or well-being issues related to breast cancer. For participants with early breast cancer, common issues (>60%) included fatigue (83%), menopausal symptoms (75%), anxiety (71%), pain (67%), loss of confidence (65%), impact on sexual health (62%), memory problems (61%), and concerns regarding body image (60%). For those with metastatic breast cancer, common issues (>60%) included fatigue (88%), menopausal symptoms (78%), memory problems (70%), pain (70%), impact on sexual health (68%), anxiety (66%), loss of confidence (66%), reduced mobility (63%), concerns regarding body image (60%).

51% of participants reporting experience of primary breast cancer and 67% of those metastatic breast cancer disliked the term 'cancer survivor'. 33% of participants reporting experience of primary breast cancer and 47% of those metastatic breast cancer disliked the term 'palliative care'. 79% of participants never heard of the term 'supportive care'. 59% of participants reporting experience of primary breast cancer and 55% of those metastatic breast cancer agreed that 'supportive care' includes all supportive care needs.

CASCARA provides exploratory evidence which is hypothesis-generating for future research. Given the web-based questionnaire dissemination model and limited time frame, the study was limited in its ability to recruit a representative sample of those in the UK affected by breast cancer. Respondents appear to report higher educational attainment levels and higher financial security than would be expected if this sample was truly representative of UK population affected breast cancer, yet continued suffering and unmet was reported.

Subsequent research will form part of the Lancet Commission on Cancer And Health Systems report with a focus on countries and settings where national health insurance is lacking.

Panel 26 - The CASCARA (Costs And Supportive CAre in bReast cAnceR) Study – participant quotes

CASCARA is a UK pilot study scoping the economic burden, financial toxicity, and supportive care needs amongst individuals with breast cancer in a high-income country with a National Health Service that is free at the point of use. Participants had the opportunity to write free text related to the different survey domains and some quotes are illustrated here.

Employment

"Extreme fatigue impacts how much work I can do. Brain fog has led to me making numerous little mistakes."

"I lost my job when I started chemotherapy as I could not cope very well."

"Treatment causes too many side effects to hold down work. Daughter became the main priority as a single parent."

"I am struggling with fatigue and menopause symptoms so needed to reduce my working hours."

Financial situation

'Losing your home and business shatters all future plans.'

"I really struggled to pay for all the things I needed such as new bras, clothing (front fastening shirts and pyjamas) wig, heating when in the house more, etc . I had to scrap any idea of future holidays and also had to get a second job where I could earn a bit more."

"Can't mend a leaking roof. Stopped all nice things such as treats, days out as can't even afford cinema. Cannot afford gym membership need to pay back family who loaned us money to live during treatment."

"I've had to cut back on making memories as I can't afford it with rising cost of travel for treatment."

Caring

'My husband had to take unpaid leave for multiple months.'

"My partner has had to reduce his working hours to cover childcare and that has also impacted on his income."

"My mother now needs care and we are paying for home help to support where I am unable to physical do things."

"My son is often left on his iPad or watching TV while I sleep in the afternoon."

Supportive Care Needs

'Once you have completed active treatment you are considered "well".'

"After radiotherapy finished I was left on my own."

"It took me a long time to ask for help with sexual dysfunction."

"Because I'm in my 30s I've had a lot of pushback from people telling me I don't need the help as much as older patients. I've also had problems as I've lived longer than expected with stage 4. Most help dried up after 6 months."

Attitudes to Terminology

"Cancer survivor":

'I'm not a survivor as I still need monitoring. I see myself as have lived through cancer and it's changed my life forever. I'm now a different person with a different perspective and I will live with its consequences forever. It's the gift that keeps on giving!'

'I hate the whole "battle" analogies of cancer. It's a disease not a battle. Also "cancer survivor" is derogatory to stage 4 patients, as the implication is that they have somehow failed.'

"Palliative care"

'I associate this term with end of life, although I now know this not to be correct.'

'I find it hard to shake off the "end-of-life" meaning. I think a new name should be found, but the services should be available to all breast cancer patients who need them.'

Strategies to tackle SHS and hidden costs from breast cancer

Using the reported figure of 685,000⁴¹⁹ patients worldwide dying each year from breast cancer, and applying the expert group average of suffering days in the last year of life gives an estimated SHS decedent total of over 120 million days each year. In addition, the 7.8 million non-decedent patients with breast cancer⁴¹⁹ accumulate over 520 million additional SHS days. Behind these numbers are patients suffering from pain, dyspnea, fatigue, and other distressing symptoms, who might benefit from supportive or palliative care, but in many regions of the world, and especially for those living in poverty, there is no access to this care. Unfortunately, the poorest in society have the worst palliative and psychosocial services. Meeting this need requires large-scale, global capacity building in palliative care and psychosocial services as a component of comprehensive breast cancer management, and training efforts should begin immediately. Yet, the cancer divide – differences in access to effective screening, diagnosis, and treatment options within resource-constrained health systems fuelled by poverty and inequity – compounds rather than complements the need for palliative care.⁴²⁰ A first step is to recognise and quantify the costs and suffering associated with breast cancer and develop validated tools to incorporate these into global health metrics (see Panel 27 – proposed measurable indicators of change).

Panel 27 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Theme 5: Identifying the hidden costs of breast cancer						
Physical, psychological, social, spiritual, and financial - related serious health related suffering (SHS) in breast cancer care.	Screen patients at intervals throughout the breast cancer trajectory for SHS.	Making the hidden costs of serious health related suffering (SHS) visible in individual health care plans.	Facility records Third party and government records Patient self-reports and develop specific patient-reported outcome measures.	Health care facilities, Ministries of Health.	Screening for serious health-related suffering at diagnosis and key milestones throughout the breast cancer patient pathway as a research tool with an aim for widespread implementation after validation.	Aim to implement suffering-intensity-adjusted life years, a new metric under development for health system performance assessment and quality assurance.
Breast cancer health care costs.	Identify the proportion of each phase of the breast cancer trajectory covered by insurance and proportion of the population with access to this insurance.	Making the hidden costs of financial toxicity visible and identifying which groups are affected and when.	Expansion of national cancer registries.	Ministries of Health.	Upward trajectory year on year for Universal Health Coverage of breast cancer across the continuum of care, aiming at 100%, to eliminate financial catastrophe and impoverishment for all families	Research needed on: out-of-pocket spending on all aspects of breast cancer measured over the breast cancer trajectory.

					experiencing breast cancer. Minimum of poorest 20%, but aiming at 100%, of patients and families receiving public financing and provision of an essential package of supportive and palliative care across the breast cancer pathway.	
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Theme 6: Communication and empowerment in breast cancer

Panel 28 - Summary for communication and empowerment

Being female is the greatest risk factor for breast cancer - women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings.

We propose that a framework to improve communication and decision making for those with breast cancer can be used for women to take control over other aspects of their lives.

- Placing patients at the centre of clinical communication, and empowering them to exercise their voices, become fully informed, and choose their own level of involvement in decisions about their care, is an achievable and worthwhile goal worldwide.
- Improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival.
- Healthcare professional education should include person-centred and culturally sensitive communication skills training, especially when patient literacy or numeracy is limited, or other barriers to participation in decision-making exist.
- Health communication training should include: eliciting patients' core values and preferences for information, explaining goals of care, risk-benefit communication, skills to help estimate and explain prognosis and share serious news, and empathically but honestly respond to questions.
- Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return power and emerge stronger than before.

Introduction and methodology

The Lancet Commission group acknowledged that patient empowerment should be defined as: *being fully informed and supported to confidently participate in decisions about your own health and wellbeing, to the extent which you wish*. We define patient-centred communication as acknowledging the unique background and need for information of each individual patient, considering their situation holistically and working with the patient to define and achieve shared goals in their care.

Some commonly held beliefs ('myths') about the limits to patient empowerment were initially discussed by the Commission group, and a literature search on patient empowerment and communication was conducted to challenge these preconceptions, focused on low- and middle-income countries to ensure cross-cultural considerations (*see supplementary material 16 for search terms*). This literature review informed further group discussion and developed into this Commission report section (*see Panel 29 - Commonly held beliefs*).

Panel 29 - Commonly held beliefs about patient empowerment and communication in breast cancer and actual results of literature search.	
Common beliefs: 'MYTHS'	Literature search results: 'FACT'
MYTH: Publications on communication and shared decision-making are largely from high-income countries and the ideals presented in the literature may only be feasible in high income countries. Outcome from literature review: FALSE	FACT: Patient decision making and communication research in low- and middle-income countries does exist, although there is more from high income countries. - Many different interventions for supporting patient choice have been published in low and middle-income countries, with the overarching theme of adapting communication methods to the socio-economic and cultural circumstances being key to improving patient-clinician dialogue and empowerment.⁴²¹⁻⁴³⁰
MYTH: The extra healthcare professional time invested in inviting patients to share decision making does not meaningfully benefit patients. Outcome from literature review: FALSE	FACT: Evidence supports that improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival.⁴³¹⁻⁴³³
MYTH: Little can be done to improve patient involvement in decision making in low- and middle-income countries. Outcome from literature review: FALSE	FACT: Individual and system level barriers exist to both patient choice of treatment in breast cancer, and patient involvement in decision making.^{323,422,423,434-440} Multiple interventions to overcome barriers to patient choice and involvement in decision making have been successfully trialled in low- and high-income countries.^{425,427-430,441-444}
MYTH: Most alternative treatment is detrimental to patient outcomes. Outcome from literature review: FALSE	FACT: There is evidence that some traditional, complementary, and integrative therapies can be beneficial for symptom management in patients with breast cancer and can be used safely alongside (but not instead of) conventional therapy.⁴⁴⁵

Where are we now?

There is wide global variation in levels of empowerment demonstrated by patients with breast cancer. At one end of the spectrum, involving women in treatment decisions is recognised as crucial, not only to protect individuals' autonomy and dignity, but also because it strengthens the foundation for gender equity beyond the specific context of breast cancer. For example, patient and public involvement and engagement (PPIE) is mandatory for clinical research funding applications in some countries. At the other end of the spectrum, women in many parts of the world have extremely limited bodily, social, and financial autonomy; free choice is unavailable to them not just in breast cancer treatment decisions, but also in their reproductive rights, their family finances, access to education, and myriad other social and political domains.⁴² These stark differences in patient empowerment can occur between countries, but also within a single country, as highlighted by the controversial US Supreme Court ruling which led to the overturning of rights to reproductive autonomy in some states.

Communication, patient empowerment, and patient choice are all inextricably linked. Potential barriers to patient involvement in decision making and choice of treatment are manifold and can occur both at an individual level and system level (see Panel 30 – What are some of the barriers to patient choice of treatment and patient involvement in decision making?).

Panel 30 - What are some of the barriers to patient choice of treatment and patient involvement in decision making?

Individual level

- Lack of literacy and numeracy skills.
- Lack of health education.
- Lack of understanding of prognosis and likelihood of cure.
- Social or geographic isolation.
- Family or faith community objections to treatment or patient involvement.
- Unwillingness to engage with conventional medicine due to preference for traditional healers and remedies.
- Inability or difficulty discussing prognosis, advance care planning, and preferences for end-of-life care.
- Language and communication barriers (e.g. lack of health professional or interpreter speaking same language or dialect, hearing or vision impaired patients).
- Undiagnosed or untreated mental health issues or emotional distress (e.g. anxiety, depression).
- Fear of disclosure of illness due to cultural norms, fear of becoming a burden to others, stigma.
- Poor health professional communication skills (e.g. eliciting patient values, goals, preferences, shared decision-making, discussing prognosis, empathic communication).
- Healthcare professional beliefs that patients are unable to process the information needed to be involved in decision making.
- Healthcare professional inability or unwillingness to culturally adapt services.

System level

- Geographical inaccessibility of treatments.
- Healthcare resource constraints, including infrastructure and healthcare professional time and specialty knowledge limitations.
- High out-of-pocket costs for patients.
- Economic, political, or climate-related crises.
- Unequal patient-provider power dynamics.
- Insufficient psychosocial services at all levels of care.
- Pervasive biomedical models that prevent tailored services and care plans.

Many different types of interventions to support patient autonomy and choice in breast cancer treatment have been published. Examples include translating and validating symptom scales into local languages (e.g. a self-efficacy scale translated into Urdu in Pakistan⁴⁴¹); hyper-local culturally adapted interventions (e.g. performance of a traditional folk play, aimed at raising breast cancer awareness in Bangladesh); and targeted research into population preferences (e.g. discrete choice experiments in Belarus to determine preferences about type of national breast cancer screening programme^{425,442}). Interventions can involve training a small number of trusted community members⁴³⁰ to support patients, or using media and technology to target large numbers to improve breast cancer awareness⁴²⁸, or clinical follow up - for example, using mobile phones to avoid travelling to clinic

appointments in Nigeria.⁴²⁹ The use of decision aids to improve breast cancer decision-making has a long history⁴⁴³, although cultural adaptation of such tools to the local circumstances and languages is critical and research thus far into how to do this more widely is lacking. Recently, interactive, tailored decision tools have been developed to promote the quality of patient decisions⁴⁴⁴, and enhancements to harness insights from psychology about emotional support are being evaluated (SHARES trial NCT04549571⁴⁴⁶). Improving the quality of online information is also important, given that many women with breast cancer now access the internet to obtain information.⁴⁴⁷

Where do we want to get to?

We assert that centring clinical communication on patients and empowering them and their chosen advocates to be as involved as they wish in decisions about their care, is an achievable and worthwhile goal worldwide.

Patient-centred communication is an important goal: in breast cancer, effective communication from healthcare professionals has been shown to improve long-term adherence to therapy^{433,448}, whilst poor communication has long-lasting negative effects on multiple quality of life domains including function, symptoms, body image, lifestyle and other worries scores.⁴⁴⁹ Feeling involved in decisions can provide a lasting positive impact on quality of life⁴³¹, but patient preferences about treatment options and desired degree of involvement in clinical decision making will vary considerably.^{450,451} A central factor in patient satisfaction with the decision making process is the concordance between patients' preferences about involvement in decisions, and their actual experience of involvement.⁴⁵² Empowering patients requires understanding preferences for degree of decision involvement, along with adequate accessible information to allow patients to apply their own values and preferences, to arrive at a decision that is right for them.⁴⁵³ The opportunity for patients to feel listened to and have their questions answered (regardless of perceived relevance of those questions by the clinician) is also key to patient-centred communication.

We acknowledge that informal support persons (e.g. family, friends, or faith representatives) can often play an involved role in decision making, and that such involvement can be both positive or negative for an individual patient's experience. In general, research suggests that a variety of informal decision support persons are utilised across patients from different backgrounds and can provide a positive impact on the treatment deliberation process. The broad concept of relational autonomy has emerged from feminist philosophy and garnered growing attention in clinical ethics discussions. Nevertheless, whilst every individual will be inherently influenced by their unique cultural context and relationships, we advocate that the choice of whom to involve in decision-making or be a 'decision supporter' should remain with the individual patient.

Recognising both between country and within country inequalities, and that available choices for patients about their breast cancer care may be extensive in some settings or extremely limited in others, it is nonetheless always possible to offer some degree of choice to a patient. It is always possible to elicit what matters to a particular patient (what their values are), and to provide them with information in an understandable way that describes their options (even if limited), and to empower the patient to engage in the treatment planning process. Offering someone the opportunity to bring their relative or friend into the consultation is an example of a small choice which costs no additional time or money but improves dignity and autonomy.

Patient-centred communication skills applied by treating healthcare professionals demonstrate a core effect of communication on later quality of life.⁴²³ Helping patients to understand their condition, what their options are and why these options are or are not available, assessing patient preferences and active listening, are all skills which may be applied across national borders and the socioeconomic spectrum. Importantly, such skills can also be learnt and taught; and we propose that education of

healthcare providers should include specific examples of risk-benefit communication and evidence-based medical decision making in a context-specific way to facilitate patient empowerment.

How do we start the journey?

A recent global survey of 382 healthcare professionals conducted by the Lancet Breast Commission group showed that more than 70% of healthcare professionals felt confident they had received adequate communication skills training. This is encouraging, although may not match patient expectations and experience, and it is noteworthy that a substantial minority of professionals did not express confidence in these core skills.^{454,455}

The issue of healthcare professionals' available time for each patient is a difficult one globally. We strongly advocate senior healthcare professionals, researchers, and patient advocates in breast cancer care engaging with policymakers to improve investment in breast cancer care. High-income countries have significantly better overall survival for breast cancer than low- and middle-income countries, and recent modelling suggests scaling up comprehensive breast cancer care to be available globally would not only significantly improve overall survival, but also lead to significant longer term economic returns.⁴⁵⁶ Such large-scale investment is a long-term strategy, as training the appropriate staff, including pathologists, radiologists, oncologists and surgeons, radiographers, chemotherapy, and specialist breast cancer nurses takes many years. Additionally, whilst the ideal for patients and staff would be to have as much consultation time as needed, the reality now in both high- and low-income settings necessitates optimisation of existing resources alongside long-term lobbying for increased investment.

We encourage healthcare professionals to take a patient-centred approach to communication – to focus on assessing what patients need and empowering them to participate, even in just a few minutes, using established communication techniques.^{457,458} We suggest a framework to help develop a patient-centred consultation, acknowledging that this should serve as an iterative and non-linear guide, and be adapted to each consultation. It may not be necessary to include each step or communication skill in every consultation. There are many different ways to achieve the same goal, and any consultation should be culturally adapted to the unique needs of the person with breast cancer, their family (as appropriate), and the local clinical and/or community setting (*Panel 31*, adapted from work of Bylund et al⁴⁵⁹⁻⁴⁶³). The examples given were developed by native speakers of English for use in settings where English is the native language, and alternative wording may be necessary in different settings.

Panel 31 - Framework to help develop a patient-centred consultation		
Strategies	Description of Relevant Skills	Example Talking Points
Build rapport and check understanding	introduce yourself and listen to the patient's story of their healthcare problem (published evidence suggests most patients will speak for under 2 minutes if left to spontaneously tell their story).⁴⁶⁴	'I've had a look through your notes but I'd like to hear from <i>you</i> what your understanding is about what has happened so far and what you are expecting next.'
Set and negotiate agenda for consultation	- State the purpose of the consultation. If there is a decision to be made, that should be made clear. - Specifically ask about the patient's priorities for the consultation and their preferences for information and decision involvement. - Negotiate a consultation that includes goals of both clinician and the patient.	'I am hoping to talk about your options for treatment today. Is there anything else on your mind that you would like to make sure we discuss?' (Negotiate agenda based on patient's response). 'Why don't I begin by discussing treatment options for your breast cancer and then we can address those specific questions you have about possible side effects and your ability to work while you are receiving care. Does that sound like a good plan?' 'Some people like to have lots of information about their illness and some people just want the basics. How much information would you like me to give you today?'
Share information	- Identify and clearly describe all relevant options, as well as associated risks and benefits, including active surveillance, a supportive or palliative (comfort-focussed) approach when appropriate, and/or acknowledging what is achievable in that particular healthcare setting. - Share best, worst, and most likely case scenarios related to treatment outcomes.	'At this stage of illness, we have multiple options to treat your breast cancer. There is a type of chemotherapy that has shown excellent outcomes in women with your type of illness. There are some side effects to the treatment, and we will talk more in detail about these as we go through the consent process. Fatigue, nausea, and low blood counts causing an increased risk of infection are the most common side effects. We can try to minimise some of the side effects with additional medications.' 'I know you are really struggling with your pain right now and it is keeping you from doing many of the things that are important for you. While we continue with radiation, I would like to focus also on symptom control, make sure we are most effectively treating your pain, and provide you with the support you need.'

Convey respect for patient +/- family involvement	• Validate their concerns as important and relevant to this decision, and explicitly encourage patients to ask questions. • State that you fully support the patient's right to make the final decision. • Ask the patient about use of non-prescribed therapies, traditional, complementary, and alternative medicines, and lifestyle changes since their diagnosis of breast cancer as well as medical and drug history. • Ask anyone accompanying the patient if there is anything else important they wish to add or have observed as a caregiver.	• 'What are your thoughts about what we have discussed so far?' • 'What questions do you have?' • (To family member or caregiver) 'I know that you are an important part of the patient's (name) life. Is there anything you think is important that we are missing or that you would like to talk about?'
Empathise	• Acknowledge the patient's emotion and experience. • Validate their experience. • Normalise their emotional response.	• 'It sounds like this has been a hard time. But it also sounds like you have a lot of support from your loved ones.' • 'It would be completely reasonable to take some time off from work to focus on your recovery.' • 'Lots of people talk about feeling overwhelmed during a time like this.'
Review and recommend	• Clarify if the patient has enough information and offer more time for them to decide, if appropriate. • Consider how much the patient wished to be involved in decision making and offer a treatment recommendation if there is one clear best option from a medical perspective, or if the patient has requested the healthcare professional opinion. • When applicable, review multiple options – including no treatment - and state the rationale for your recommendation. Include key risks and benefits and normalise decisions that differ from recommendation. • In the absence of a treatment recommendation from the healthcare professional, validate and support patient decision-making autonomy. In the absence of curative treatment, emphasise	• 'Today we talked about the treatment options available at this time. Do you have a preference about how you would like to proceed?'

	continued supportive or palliative care, where available emphasising ongoing supportive aspects of care for patients and their families.	
Summarise and agree next steps	- Summarise the consultation verbally and ideally provide a short, written summary which includes all options, states any recommendations, and describes the key trade-offs. - Agree on next steps and appropriate follow up or further discussion. - In settings with limited literacy, aim for diagrams or other follow up mechanisms such as another appointment or discussion with a community health navigator.	'I will refer you to our chemotherapy unit and they will be in contact with a date for your first treatment. Please have some blood tests done on your way out so we know it's ok to go ahead with the treatment. If you think of any concerns or questions later, please call us.'

Communication in specific situations

Terminology when discussing breast cancer with patients

We encourage healthcare professionals to choose terminology carefully in their own cultural context.^{465,466} Many patients dislike the term 'survivor' due to fears that the cancer may still later recur, feelings of wanting to return to normal life rather than being defined as a cancer survivor, or connotations of the term 'survivor' with war or other violent events. Similarly, tumour characteristics such as oestrogen receptor or progression status should not be applied to the whole patient—person-centred language is essential. The term 'survivorship,' when used to describe a part of the journey or problems specific to past breast cancer treatment, seems more acceptable to many patients. Whilst it is important to discuss risk of recurrence and long-term modifiable risk factors with patients with breast cancer, some patients may wish to forget their diagnosis and past treatment and not be defined by their previous breast cancer.

Panel 32 - Communication examples	
Examples of inappropriate healthcare professional language around breast cancer:	Examples of more appropriate ways to communicate the same message:
'The patient has progressed'	'The patient has a cancer that has grown and got worse'
'The patient is ER positive'	'The patient has a primary tumour that is ER positive'
'Breast cancer survivor'	'Person who has had breast cancer'
'This patient suffers from breast cancer'	'This patient has breast cancer'
'We will be withdrawing care'	"We will be with you every step of the way and continue to focus on your comfort"
'There is nothing left for us to do'	'Whilst I worry that additional anti-cancer treatments would do more harm than good at this time, we can focus on managing your symptoms and helping you to feel better'

Communication in metastatic breast cancer

A diagnosis of metastatic breast cancer has a lifelong impact on patients receiving it, and as such there are specific areas to consider in patient-centred communication in this setting.

1) The concept of metastatic cancer and goals of treatment

Patients and their family members should be told that metastatic breast cancer is usually incurable, but it is treatable and can often be controlled with treatment for many years. It is important to explain that treatment aims to slow cancer progression, reduce symptoms, improve quality of life, and prolong survival. Many patients receiving chemotherapy for metastatic cancers may not understand that chemotherapy is unlikely to be curative.⁴⁶⁷ Health care professionals need to help patients make the treatment decisions that are best for them. This requires the patient to understand the goals, logistics and side effects of treatment and the clinician to understand the patient's individual preferences, values, and goals for her life (for example wanting to: attend a loved one's wedding; travel; meet a grandchild; avoid any change in appearance). Understanding how a patient prioritises longevity, comfort, and independence is important. The aims of communicating about treatment goals in the metastatic breast cancer setting could not be stated better than by the founder of Maggie's centres (a UK charity providing cancer support centres near hospitals): 'Above all what matters is not to lose the joy of living in the fear of dying.'

2) Prognosis

Prognostic information is vitally important for people living with metastatic breast cancer, for decision making around treatment, finances, work, and for helping patients maximise time with loved ones and prepare for death. Misunderstanding about prognosis is common in people with both early stage and advanced cancer⁴⁶⁸⁻⁴⁷⁰ and is associated with more aggressive and futile treatments at the end of life.^{468,471,472} Patients who want prognostic information may not always ask for this information⁴⁷³ so it is recommended that doctors ask explicitly if, when, and how patients want to talk about prognosis.⁴⁷⁴ It is best not to confront patients with information they do not want. Up to 20% of patients in studies report not wanting to discuss prognosis^{473,475} and decision making does not always require that the patient understand detailed prognostic information.^{468,474}

Estimating and explaining expected survival time is difficult and doctors require guidance and communication skills training that is tailored to the cultural issues and local resources. Studies of oncologists show many report a reluctance to provide estimates of expected survival time.^{476,477} Factors contributing to this include: not knowing how to estimate survival time; fear of getting the estimate wrong; fear of upsetting the patient; fear of negatively affecting the patient-doctor relationship; requests from family to withhold prognostic information; and lack of time during consultations.⁴⁷⁷⁻⁴⁷⁹ Although prognostic information is upsetting, many patients still find it helpful to know the truth and there is no evidence that increased information about prognosis with sensitive communication is harmful to patients, or that it increases anxiety or distress.^{478,480-484} For patients wanting quantitative information on life expectancy, providing ranges for worst-case, typical, and best-case scenarios is more helpful and conveys more hope than providing a single point estimate of median survival.^{485,486} Most patients with advanced cancer surveyed after requesting and receiving their own expected survival time formatted as 3 scenarios reported that the information made sense, helped them make plans and improved their understanding.⁴⁸⁵ The majority also responded that the information about their prognosis was the same as, or better than, they expected before discussing it with their oncologist. Providing ranges for scenarios helps convey the inherent uncertainty of survival estimates and is more accurate than providing a single point estimate.^{485,487,488} Resources are available to help healthcare professionals estimate scenarios for survival time to facilitate conversations about prognosis with their patients.^{489,490}

3) End of life care and advanced care planning

Discussing prognosis often facilitates conversations about priorities, wishes, advance care planning, palliative care services, and hospice and end-of-life care. While these conversations can be difficult, they can also be crucial opportunities to identify new goals of care for the patient and their caregivers beyond disease-directed treatment; these conversations should be part of routine oncological care.⁴⁹¹ Patients with cancer are more likely to receive end-of-life care that is consistent with their preferences when they have had the opportunity to discuss their wishes for end-of-life care with a healthcare practitioner.^{471,491}

Communicating about traditional, complementary, alternative, and integrative medicine (TCIM)

Traditional, complementary, alternative, and integrative medicine are terms often used interchangeably by practitioners of conventional medicine (allopathic medicine), though their meanings may be very different:

- WHO defines traditional medicine as ‘the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness’.⁴⁹²
- Complementary medicine refers to non-mainstream practices used together with conventional medicine.
- Alternative medicine refers to non-mainstream practices used instead of conventional medicine.
- The Society for Integrative Oncology defines integrative oncology as a field based around a patient-centred, evidence-informed approach to cancer care, that uses lifestyle modifications, mind and body therapies, and natural products from different traditions in tandem with conventional cancer treatments.⁴⁹³

A 2012 systematic review of TCIM use in the USA, Canada, Europe, and Australia and New Zealand indicated a prevalence of 40% of people with cancer using some form of TCIM⁴⁹⁴. Women with breast cancer are frequent users of TCIM in both HIC and LMICs – up to 80% use TCIM in some Caribbean populations.⁴⁹⁵ Although many cancer patients use TCIM, their oncology providers have limited knowledge or understanding of this area of medicine.⁴⁹⁶

Exploring and understanding patient TCIM use is a useful part of building rapport and sharing information in a patient-centred consultation, for example:

- ‘Are you currently receiving, or have you previously received care from other healers in the community or other clinicians in the health system before this appointment?’
- ‘Can you tell me more about these treatments or medicines?’

Acknowledging that discussion of TCIM should be nuanced due to potential harmful interactions of some TCIM with chemotherapy and radiotherapy, we encourage clinicians and patients to access evidence-informed information about TCIM, for example:

- ASCO and Society for Integrative Oncology joint Recommendations, see also *Panel 33*.
- Memorial Sloan Kettering Cancer Center guide to herbs, botanicals and other products

Further information and discussion about TCIM can be found in supplementary material 17.

Panel 33 - Society for Integrative Oncology Recommendations - Adapted from ⁴⁹⁷	
Goal	Recommendation
Anxiety/stress reduction	Music therapy Meditation Stress management Yoga
Improvement of depression/mood disorders	Meditation Relaxation Yoga Massage Music therapy
Quality of life improvement	Meditation Yoga
Reduction of chemotherapy-induced nausea and vomiting	Acupressure Acupuncture
Pain management	Hypnosis Acupuncture Music therapy

How do we measure progress in communication and empowerment?

Patient empowerment does not have a universal definition and is more difficult to measure than numeric outcomes like survival. Patient satisfaction with breast cancer care may be a useful surrogate, and should be measured by treating healthcare professionals, ideally both quantitatively and qualitatively. Specifically measuring the degree of involvement of patients in their decision making could also act as a surrogate for patient empowerment. Adherence to proposed therapy is another useful surrogate to include in empowerment-focussed research. Community-based participatory research methods will be integral to understanding and creating interventions that meet patients in the context of their cultural needs and preferences, and assist with dismantling care inequities.⁴⁹⁸⁻⁵⁰¹ Progress can be measured by global research into societal discussion of breast cancer, asking the question: can we freely talk about symptoms, diagnosis, and treatment of breast cancer in all global spheres?

Clinician-facilitated discussions of patients' core values in the setting of newly diagnosed cancer have shown promise in enhancing individual autonomy and leveraging interpersonal supports.^{502,503} Unfortunately, these discussions are often withheld until the end of life. Integrating these conversations regarding 'who the patient is' and 'what is most important to them as a person' can help ensure person-centred decision-making and care planning across the breast cancer continuum, from diagnosis to end-of-life.

A measurable indicator of change is the inclusion of mandatory training in communication for all healthcare professionals and should be measured by both policymakers (as a measure of quality of professional education) and researchers. Training in understanding one's own cultural beliefs and values, recognising and understanding differences in culture, values and beliefs in others, and recognising one's own inherent biases (sometimes called cultural competence or cultural humility⁵⁰⁴), is important to enable healthcare professionals to communicate effectively with all their patients.

The role of patient advocates is to promote issues that are important to them; engaging with policymakers to ensure empowerment and communication are considered as interventions that improve long-term outcomes more affordably than some expensive drugs. The role of policymakers is to mandate and facilitate patient and public involvement in research design and practice in all spheres.

What is the potential wider impact?

Our vision is that empowering patients with breast cancer to be engaged in decisions about their care in all healthcare settings is a step towards wider female empowerment, addressing the lack of bodily, social, and financial autonomy for women in some societies worldwide. As a condition that predominantly affects women, breast cancer constitutes not only a challenge to women's health but an opportunity to identify ways in which provider-level interventions and systems-level changes can facilitate women's power and voice in society more generally. When women are treated with respect and recognised for their key, often underappreciated, role in societies where the division of labour remains gendered, they may begin to identify opportunities in other settings to exercise greater autonomy. Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return power and emerge stronger than before. This is especially important when women have faced marginalisation based on intersecting identity characteristics such as race or socioeconomic status, in addition to marginalisation based on gender.

Panel 34 - Lancet Breast Cancer Commission proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target
Theme 6: Communication and empowerment in breast cancer					
Communication skills training.	Proportion of those who are in regulated healthcare roles receive culturally sensitive person-centred communication skills training.	Healthcare professional communication is key to empowering patients and developing person-centred care.	Facility records, University regulators.	Universities, healthcare facilities.	100% of healthcare professionals in 100% of countries should receive communication skills training.
Patient and public involvement in ethical design of breast cancer research.	Proportion of breast cancer clinical trials which have partnered with Patient and public involvement and engagement (PPIE).	PPIE in research promotes patient empowerment and improves the likelihood of the study being important to patients.	Clinical trials databases, research funding body records.	Ministry of Health, research funding bodies including charities, patient advocacy	100% of breast cancer clinical research in 100% of countries should partner with PPIE from research concept to reporting and translation into practice.

Future Directions

Breast Cancer Prevention

Our vision for prevention is to be able to identify those at substantially increased risk of breast cancer in the whole population and offer them precision prevention strategies to reduce that risk, thus reducing breast cancer incidence. To achieve this, risk assessment will need to be equitable, proactive, and systematic, rather than largely opportunistic as is currently the case. A coordinated approach to the prescription of risk-reducing medications and the care of women who take them is required. Currently this is not considered to be in the domain of either primary care or specialists, and lack of clinician knowledge and confidence is a major barrier to uptake.¹⁴⁸ Catalysed by this Commission, an implementation pilot has commenced in Australia aimed at solving the existing workforce capability gap in a way that is potentially scalable. It will examine if a nurse practitioner led telehealth service can increase uptake and continuation of risk-reducing medications by providing both assessment and prescription before discharging clients back to their primary healthcare provider for ongoing prescriptions. A hotline and, if required, rapid re-entry into the service will be available to support doctors and women in managing side-effects during the full treatment course. At the same time as these precision prevention approaches, better population prevention is needed. Governments can help by prioritising reduction of exposure of their populations to breast cancer risk factors by adjusting health policies. Implementation of simple preventives (e.g. low dose tamoxifen in women <50years) will require increased workforce and training of primary and secondary health care providers. There is a lot of work to be done in education and training of health care practitioners so that risks, benefits, and uncertainties are clearer for individuals to inform their personal lifestyle choices. Specifically, governments must recognise that the rising rates of breast cancer are a major and expensive public health problem and need to legislate for changes, based on those that have been effective in other areas of public health, to reduce exposure to risk factors.

Personalising breast cancer treatment

The breast cancer communities in HIC are making breakthroughs in terms of personalising breast cancer treatments. Perhaps this is most applicable in the early disease setting where there is an increasing recognition that many women at present are over-treated, resulting in a significant burden of treatment which is costly and unnecessary. Emerging technologies will allow the integration of existing clinical data with new molecular data on germline genomics, tumour genomics, pharmacogenomics, and circulating tumour DNA. The aim is to provide a personalised approach for each patient rather than the more common population approach. Optimisation of treatment can preserve the excellent outcomes that have been achieved whilst reducing rising costs; financial, physical, and psychological. Alongside this, AI and allied technologies can democratise this information making it available to be used by everyone. Recognising that each nations' health care system is subtly or, at times radically, different from its neighbours, the leaders for breast cancer would be responsible for interpreting this new information within their own country and for their own citizens. There is no reason once the technological systems have been developed that they could not be applied to every patient with breast cancer. At this point in the technological revolution, the wider medical community needs to 'hold hands with patients' to facilitate best use of all the information that will soon become available.

Once developed, it would be a second order challenge to get advanced communications technology to speak directly to healthcare personnel and patients throughout the world. Applying new technology of assessment would allow personalised information from patients and their tumours to go into algorithms advising best management. Almost certainly in breast cancer this will reduce treatments in most patients, thus saving money to invest in more targeted treatments for those who need them. This approach will allow LMICs to reap the benefits of advancing technology and communications very quickly.

Optimal inclusive management of metastatic breast cancer

In order to fully understand and address the impact of MBC globally, the first crucial step is to collect high-quality metastatic cancer registry data, including relapses. This will ensure patients with MBC are *seen* and should also better guide allocation of resources. There is an urgent need to improve equitable access to evidence-based therapies for MBC, as well as to clinical trials, and we urge that patients are managed with an individualised approach, which includes not only tailoring therapies appropriately to tumour biology, but also evaluating quality of life regularly and incorporating supportive and palliative care from diagnosis and always accounting for patients' preferences. People with MBC should be managed with a multidisciplinary approach and according to high quality context-adapted clinical guidelines, both of which have been shown to improve health outcomes and quality of life. Sadly, MBC remains a stigmatised and poorly understood disease for the general population, policy makers, and even for health care professionals. A change in mentality, moving from a fatalistic to a more optimistic approach to this disease, is needed to truly change the outcomes of patients. We propose measurable indicators of positive change with actionable targets for MBC and we hope that this framework can be applied to other metastatic cancers to induce valuable changes globally.

Tackling breast cancer gaps and inequities through global collaboration

Addressing global inequities cannot be achieved by expecting all countries to play linear catch-up with HICs but must be about an increasing emphasis on the regionalisation of cancer care provision. This requires adoption of approaches to earlier diagnosis and better treatments that are effective in the context where they need to happen. Developing models that encourage the advancement of regional centres of excellence, regional pooled procurement and manufacturing of relevant medications and health related products will ensure greater access at lower costs to all patients. Grassroots advocacy and patient education and empowerment across all regions are needed to ensure that health is acknowledged as a global basic right. Whilst continuing to highlight concerns around health gaps and inequities on a broader global platform, there also needs to be leverage that works to hold regional policy makers and other local stakeholders to account. Investment in developing locality based and contextualised training of a workforce competent across the care continuum is essential. Maintaining links to and support from broader global networks, alongside developing the skill sets necessary to address local and region-specific challenges, will encourage the expansion and retention of the necessary workforce in LMICs. Although innovations and technologies hold promise in mitigating some of these disparities, especially when backed by evidence driven outcomes, they are not a panacea for dysfunctional health systems: deliberate investment in health systems and workforce should remain the bedrock on which innovations rest in all countries of the world. For sustainable global solutions to occur, a multi-faceted approach and persistent commitment is needed; one that harnesses all sectors of society including finance, education, and industry, to address health disparities in breast cancer and other health sectors.

Identifying and responding to the hidden costs of breast cancer

Hidden costs of breast cancer need to be exposed and quantified to be reduced. The hidden costs of breast cancer are myriad and have yet to be fully explored, quantified, and incorporated into the framework of serious health related suffering (SHS) or developed into an inclusive suffering metric that combines physical and psychological, as well as social and spiritual components as experienced by patients, caregivers, and their families. Further, many of the financial costs of breast cancer are overlooked or go unmeasured, including the lost family income of both patients and caregivers. The hidden costs of breast cancer are embedded in and intensified by gender inequity and layer onto poverty and marginalisation. Financial protection and quality service delivery must span the entire breast cancer trajectory, but the design, monitoring and evaluation of these interventions requires a full costing model to identify the necessary financial and non-financial resources required to alleviate more of the breast cancer suffering spectrum. Screening for hidden costs and suffering must be designed to influence priority-setting and resource allocation, around a more informed but also

achievable target of suffering reduction. Strategies must be grounded in and tailored to the specific stages of the breast cancer trajectory. Better understanding and responding to the value that patients, and their caregivers and families place on the alleviation of the suffering associated with the hidden costs of breast cancer - in addition to the reduction of morbidity and mortality – is core to more efficacious and responsive patient-centered care.

Communication and Empowerment in breast cancer

We envisage that reliable and sustainable skills in person-centered communication will be consistently integrated throughout all patient-provider interactions. This will become fundamental to the training of healthcare professionals in breast cancer care, with emphasis on discussing prognosis and encouraging patient participation in decision making. Communication that prioritises empathy, respect, and inclusion, demonstrates recognition of the dignity of the patient and ensures the provision of truly person-centered care. When patient engagement in research design, conduct and evaluation becomes mandatory globally, this will ensure clinical research delivers meaningful answers to research questions of interest and benefit to patients. Policymakers can invest to provide global minimum numbers of treating healthcare staff per capita, which will improve both global survival rates for breast cancer and patient satisfaction with their level of involvement in treatment decision making. By normalising and honouring patient involvement in breast cancer care and decision making, a powerful message will exist of women publicly exercising their voices and rights as citizens, providing opportunities for wider empowerment of women globally.

Conclusion

The Lancet Breast Cancer Commission has produced an evidenced-based inclusive roadmap to address urgent global breast cancer challenges. But the utility of road maps is when they are used, not admired on a shelf. Therefore, we call society to action to scrutinise current approaches to breast cancer, challenge the status quo, and expose practices that create inequity in every country of the world or waste scarce resources. We implore all stakeholders in breast cancer care to disseminate, implement and adapt our roadmap to facilitate changes to practice and outcomes.

We have shown throughout this commission report that data is a powerful promoter for change. Therefore, it is imperative that our breast cancer targets (See *Panel 35*) are measured, used to hold policy makers and communities to account, and to lobby for better, equitable approaches to breast cancer. We anticipate a united, collaborative, and evidence-based approach, empowering patients, families, communities, health care providers and policy makers, to evolve and improve this roadmap. We believe that this will prevent the inevitability of the anticipated 3 million new cases of breast cancer a year, mean that breast cancer is no longer the leading cause of cancer death and provide better visibility and treatment for everyone affected by breast cancer regardless of who they are or where they live.

Panel 35 - Summary of the Lancet Breast Cancer Commission suggested targets for change

Breast Cancer Prevention

- 95% of countries legislating fully the UNICEF Code for advertising and promotion of commercial milk formula products & adhering to the WHO 'Best buys' with respect to alcohol advertising.
- Statutory access to at least 18 weeks, and preferably 26 weeks of parental leave at 100% pay.
- Mandatory provision of paid breaks and nursing-expressing facilities on return to work
- Tax sugar sweetened beverages to raise the retail price at least 20%.

Personalising breast cancer treatment

- >80% (aiming for 95%) of patients have access to accurate tumour subtyping
- >80% (aiming for 95%) patients with new diagnosis to be discussed at multidisciplinary meetings.

- 100% of patients with breast cancer to have access to full range of treatment modalities.
- At least 10% (aiming for >25%) of participants of international breast cancer trials are from LMICs.
- At least 10% (aiming for >25%) of all breast cancer trials are led/co-led by LMIC researchers.

Optimal inclusive management of metastatic breast cancer

- Minimum of 70% (aiming at 100%) of cancer registries recording cancer stage and relapse.
- Minimum of 50%, aiming at 95% MBC cases discussed at multidisciplinary meetings.
- Record the number of people with MBC and aim for doubling the median overall survival in a decade.
- Aiming for <5% of patients at end of life without access to morphine.
- 100% MBC patients have access to life saving cancer medicines.

Tackling breast cancer gaps and inequities through global collaboration

- 60% of all invasive cancers are at stage 1-2 at diagnosis.
- Evaluation, imaging, tissue sampling and pathology within 60 days.
- 80% of patients undergo multimodality treatment without abandonment.
- Time from drug approval to availability to the patient <6 months for high priority agents and <year for intermediate priority agents.

Identifying the hidden costs of breast cancer

- Upward trajectory year on year for Universal Health Coverage of breast cancer across the continuum of care, aiming at 100%, to eliminate financial catastrophe and impoverishment for all families experiencing breast cancer.
- Screening for serious health-related suffering at diagnosis and key milestones throughout the breast cancer patient pathway as a research tool with an aim for widespread implementation after validation.
- Minimum of poorest 20%, but aiming at 100%, of patients and families receiving public financing and provision of an essential package of supportive and palliative care across the breast cancer pathway.

Communication and empowerment in breast cancer

- 100% of healthcare professionals in 100% of countries should receive communication skills training.
- 100% of breast cancer clinical research in 100% of countries should partner with patients from research concept to reporting and translation into practice.

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References

1. WHO - Breast Cancer. 2021. <https://www.who.int/news-room/fact-sheets/detail/breast-cancer> (accessed 2023 April).
2. Mailhot Vega RB, Balogun OD, Ishaq OF, Bray F, Ginsburg O, Formenti SC. Estimating child mortality associated with maternal mortality from breast and cervical cancer. *Cancer* 2019; **125**(1): 109-17.
3. Cavallo J. Maternal Deaths From Cancer Worldwide Have Led to Approximately 1 Million New Maternal Orphans. 2022. <https://ascopost.com/news/october-2022/maternal-deaths-from-cancer-worldwide-have-led-to-approximately-1-million-new-maternal-orphans/> (accessed April 2023).
4. UN. Inequality in a rapidly changing world, 2020.
5. Daly B, Olopade OI. A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. *CA Cancer J Clin* 2015; **65**(3): 221-38.
6. Coles CE, Anderson BO, Cameron D, et al. The Lancet Breast Cancer Commission: tackling a global health, gender, and equity challenge. *Lancet* 2022; **399**(10330): 1101-3.
7. Knaul FM, Garcia PJ, Gospodarowicz M, Essue BM, Lee N, Horton R. The Lancet Commission on cancer and health systems: harnessing synergies to achieve solutions. 2021; **398**(10306): 1116.
8. Knaul FM, Farmer PE, Krakauer EL, et al. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report. *The Lancet* 2018; **391**(10128): 1391-454.
9. Arnold M, Morgan E, Rumgay H, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast* 2022; **66**: 15-23.
10. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* 2021; **71**(3): 209-49.
11. Jayasekera J, Mandelblatt JS. Systematic Review of the Cost Effectiveness of Breast Cancer Prevention, Screening, and Treatment Interventions. *J Clin Oncol* 2020; **38**(4): 332-50.
12. Bellanger M, Barry K, Rana J, Regnaud JP. Cost-Effectiveness of Lifestyle-Related Interventions for the Primary Prevention of Breast Cancer: A Rapid Review. *Front Med (Lausanne)* 2019; **6**: 325.
13. Li SX, Milne RL, Nguyen-Dumont T, et al. Prospective Evaluation of the Addition of Polygenic Risk Scores to Breast Cancer Risk Models. *JNCI Cancer Spectr* 2021; **5**(3).
14. Howell A, Anderson AS, Clarke RB, et al. Risk determination and prevention of breast cancer. *Breast Cancer Res* 2014; **16**(5): 446.
15. Dorling L, Carvalho S, Allen J, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. *N Engl J Med* 2021; **384**(5): 428-39.
16. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. *N Engl J Med* 2021; **384**(5): 440-51.
17. Mavaddat N, Michailidou K, Dennis J, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2019; **104**(1): 21-34.
18. Parkin DM, Boyd L, Walker L. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British journal of cancer* 2011; **105**(2): S77-S81.
19. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995; **87**(22): 1681-5.
20. Britt KL, Cuzick J, Phillips K-A. Key steps for effective breast cancer prevention. *Nat Rev Cancer* 2020; **20**(8): 417-36.
21. Zhang B, Shu XO, Delahanty RJ, et al. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. *J Natl Cancer Inst* 2015; **107**(11).

22. Maas P, Barrdahl M, Joshi AD, et al. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. *JAMA Oncol* 2016; **2**(10): 1295-302.
23. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin* 2018; **68**(1): 31-54.
24. Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer* 2018; **118**(8): 1130-41.
25. Parkin DM. 9. Cancers attributable to inadequate physical exercise in the UK in 2010. *Br J Cancer* 2011; **105 Suppl 2**: S38-41.
26. International Agency for Research on Cancer (IARC), World Health Organisation. Cancer Attributable to Alcohol. 2022. <https://gco.iarc.fr/causes/alcohol/> (accessed 27 Oct 2022 2022).
27. International Agency for Research on Cancer (IARC), World Health Organisation. Cancer Attributable to obesity. 2022. <https://gco.iarc.fr/causes/obesity> (accessed 27 Oct 2022 2022).
28. Rumgay H, Shield K, Charvat H, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *Lancet Oncol* 2021; **22**(8): 1071-80.
29. Yin X, Zhang T, Zhang Y, Man J, Yang X, Lu M. The global, regional, and national disease burden of breast cancer attributable to low physical activity from 1990 to 2019: an analysis of the Global Burden of Disease Study 2019. *Int J Behav Nutr Phys Act* 2022; **19**(1): 42.
30. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *PLoS One* 2012; **7**(12): e51446.
31. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. *Int J Cancer* 2009; **124**(3): 698-712.
32. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat* 2010; **123**(3): 641-9.
33. Shi Y, Li T, Wang Y, et al. Household physical activity and cancer risk: a systematic review and dose-response meta-analysis of epidemiological studies. *Sci Rep* 2015; **5**: 14901.
34. Guo W, Fensom GK, Reeves GK, Key TJ. Physical activity and breast cancer risk: results from the UK Biobank prospective cohort. *Br J Cancer* 2020; **122**(5): 726-32.
35. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. *N Engl J Med* 2017; **377**(23): 2228-39.
36. Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V. Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis. *PLoS Med* 2023; **20**(3): e1004188.
37. Cancer CGoHFIB. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet* 2019; **394**(10204): 1159-68.
38. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, Comparative Risk Assessment collaborating g. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet* 2005; **366**(9499): 1784-93.
39. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *Journal of the National Cancer Institute* 2006; **98**(17): 1215-26.
40. Bissell MCS, Kerlikowske K, Sprague BL, et al. Breast Cancer Population Attributable Risk Proportions Associated with Body Mass Index and Breast Density by Race/Ethnicity and Menopausal Status. *Cancer Epidemiol Biomarkers Prev* 2020; **29**(10): 2048-56.
41. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; **10**(11): 1033-4.

42. Ginsburg O, Vanderpuye V, Beddoe AM, et al. Women, power, and cancer: a Lancet Commission. *The Lancet* 2023.
43. Rovira P, Rehm J. Estimation of cancers caused by light to moderate alcohol consumption in the European Union. *Eur J Public Health* 2021; **31**(3): 591-6.
44. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015; **112**(3): 580-93.
45. Choi YJ, Myung SK, Lee JH. Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies. *Cancer Res Treat* 2018; **50**(2): 474-87.
46. Yoo JE, Han K, Shin DW, et al. Association Between Changes in Alcohol Consumption and Cancer Risk. *JAMA Netw Open* 2022; **5**(8): e2228544.
47. Brinton LA, Figueroa JD, Awuah B, et al. Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast Cancer Res Treat* 2014; **144**(3): 467-78.
48. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; **360**(9328): 187-95.
49. Rollins NC, Bhandari N, Hajeerhoy N, et al. Why invest, and what it will take to improve breastfeeding practices? *Lancet* 2016; **387**(10017): 491-504.
50. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; **387**(10017): 475-90.
51. Jung AY, Ahearn TU, Behrens S, et al. Distinct Reproductive Risk Profiles for Intrinsic-Like Breast Cancer Subtypes: Pooled Analysis of Population-Based Studies. *J Natl Cancer Inst* 2022; **114**(12): 1706-19.
52. Chlebowski RT, Rohan TE, Manson JE, et al. Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol* 2015; **1**(3): 296-305.
53. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347**(9017): 1713-27.
54. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **400**(10352): 563-91.
55. International Agency for Research on Cancer (IARC), World Health Organisation. Global Cancer Observatory. Cancer causes. [Available from: <https://gco.iarc.fr/causes/>]
56. Peacey V, Steptoe A, Davidsdottir S, Baban A, Wardle J. Low levels of breast cancer risk awareness in young women: an international survey. *Eur J Cancer* 2006; **42**(15): 2585-9.
57. Peltzer K, Pengpid S. Awareness of breast cancer risk among female university students from 24 low, middle income and emerging economy countries. *Asian Pac J Cancer Prev* 2014; **15**(18): 7875-8.
58. Gupta A, Shridhar K, Dhillon PK. A review of breast cancer awareness among women in India: Cancer literate or awareness deficit? *Eur J Cancer* 2015; **51**(14): 2058-66.
59. Osei-Afriyie S, Addae AK, Oppong S, Amu H, Ampofo E, Osei E. Breast cancer awareness, risk factors and screening practices among future health professionals in Ghana: A cross-sectional study. *PLoS One* 2021; **16**(6): e0253373.
60. Elshami M, Usrof FD, Alser M, et al. Awareness of Palestinian Women About Breast Cancer Risk Factors: A National Cross-Sectional Study. *JCO Glob Oncol* 2022; **8**: e2200087.
61. Sinclair J, McCann M, Sheldon E, Gordon I, Brierley-Jones L, Copson E. The acceptability of addressing alcohol consumption as a modifiable risk factor for breast cancer: a mixed method study within breast screening services and symptomatic breast clinics. *BMJ Open* 2019; **9**(6): e027371.
62. Khushalani JS, Qin J, Ekwueme DU, White A. Awareness of breast cancer risk related to a positive family history and alcohol consumption among women aged 15-44 years in United States. *Prev Med Rep* 2020; **17**: 101029.

63. Grigg J, Manning V, Lockie D, et al. A brief intervention for improving alcohol literacy and reducing harmful alcohol use by women attending a breast screening service: a randomised controlled trial. *Med J Aust* 2023; **218**(11): 511-9.
64. Kushi LH, Byers T, Doyle C, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2006; **56**(5): 254-81; quiz 313-4.
65. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. *Int J Cancer* 2014; **135**(10): 2444-52.
66. Thomson CA, McCullough ML, Wertheim BC, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev Res (Phila)* 2014; **7**(1): 42-53.
67. Bevel MS, Tsai M-H, Parham A, Andrzejak SE, Jones S, Moore JX. Association of Food Deserts and Food Swamps With Obesity-Related Cancer Mortality in the US. *JAMA Oncology* 2023.
68. Wyper GMA, Mackay DF, Fraser C, et al. Evaluating the impact of alcohol minimum unit pricing on deaths and hospitalisations in Scotland: a controlled interrupted time series study. *Lancet* 2023.
69. Gilmore AB, Fooks G, Drope J, Bialous SA, Jackson RR. Exposing and addressing tobacco industry conduct in low-income and middle-income countries. *Lancet* 2015; **385**(9972): 1029-43.
70. Balekrouzou A, Yin P, Pamatika CM, et al. Epidemiology of breast cancer: retrospective study in the Central African Republic. *BMC public health* 2016; **16**(1): 1230.
71. World Health Organisation. WHO Report on the Global Tobacco Epidemic, 2021: Addressing new and emerging products. 2021. <https://www.who.int/publications/i/item/9789240032095>
72. Saenz-de-Miera B, Wu DC, Essue BM, Maldonado N, Jha P, Reynales-Shigematsu LM. The distributional effects of tobacco tax increases across regions in Mexico: an extended cost-effectiveness analysis. *Int J Equity Health* 2022; **21**(1): 8.
73. Wilkinson AL, Scollo MM, Wakefield MA, Spittal MJ, Chaloupka FJ, Durkin SJ. Smoking prevalence following tobacco tax increases in Australia between 2001 and 2017: an interrupted time-series analysis. *Lancet Public Health* 2019; **4**(12): e618-e27.
74. Chipty T. Study of the Impact of the Tobacco Plain Packaging Measure on Smoking Prevalence in Australia. 2016. <https://www.health.gov.au/sites/default/files/study-of-the-impact-of-the-tobacco-plain-packaging-measure-on-smoking-prevalence-in-australia.pdf> (accessed 13 Nov 2022).
75. World Health Organisation. Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. Resolution adopted by the General Assembly January 2022. 2022. https://apps.who.int/gb/ebwha/pdf_files/EB150/B150_7Add1-en.pdf
76. World Health Organisation, UNICEF. Implementation guidance: protecting, promoting, and supporting breastfeeding in facilities providing maternity and newborn services: the revised Baby-friendly Hospital Initiative 2018. 2018. <https://www.who.int/publications/i/item/9789241513807> (accessed 13 Nov 2022).
77. World Health Organisation. WHO Discussion Paper: Draft recommendations for the prevention and management of obesity over the life course, including potential targets. 2021. <https://www.who.int/publications/m/item/who-discussion-paper-draft-recommendations-for-the-prevention-and-management-of-obesity-over-the-life-course-including-potential-targets> (accessed 13 Nov 2022).
78. World Health Organisation. Global action plan on physical activity 2018–2030: more active people for a healthier world. . 2018. <https://apps.who.int/iris/handle/10665/272722> (accessed 13 Nov 2022).
79. World Health Organisation. Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases, and mental health Draft updated menu of policy options and cost-effective interventions for the prevention and control

- of noncommunicable diseases. 2023. https://apps.who.int/gb/ebwha/pdf_files/EB152/B152_6-en.pdf
80. World Health Organisation. Global Information System on Alcohol and Health. 2022. <https://www.who.int/data/gho/data/themes/global-information-system-on-alcohol-and-health> (accessed 13 Nov 2022).
 81. World Health Organisation. Time to deliver: report of the WHO Independent high-level commission on noncommunicable diseases. 2018. <https://apps.who.int/iris/handle/10665/272710>. (accessed 13 Nov 2022).
 82. UNICEF. UNICEF data: monitoring the situation of children and women. Breastfeeding dataset. 2021. <https://data.unicef.org/resources/dataset/breastfeeding/> (accessed 22 Nov 2022).
 83. Jackson-Morris AM, Mutungi G, Maree E, Waqanivalu T, Marten R, Nugent R. 'Implementability' matters: using implementation research steps to guide and support non-communicable disease national planning in low-income and middle-income countries. *BMJ Glob Health* 2022; **7**(4).
 84. Brownson RC, Chiqui JF, Stamatakis KA. Understanding evidence-based public health policy. *Am J Public Health* 2009; **99**(9): 1576-83.
 85. Breda J, Wickramasinghe K, Peters DH, et al. One size does not fit all: implementation of interventions for non-communicable diseases. *BMJ* 2019; **367**: l6434.
 86. World Health Organisation. A guide to implementation research in the prevention and control of noncommunicable diseases. 2016. <https://apps.who.int/iris/bitstream/handle/10665/252626/9789241511803-eng.pdf> (accessed 13 Nov 2022).
 87. Lee JK, Bullen C, Ben Amor Y, et al. Institutional and behaviour-change interventions to support COVID-19 public health measures: a review by the Lancet Commission Task Force on public health measures to suppress the pandemic. *Int Health* 2021; **13**(5): 399-409.
 88. Elghazaly H, Aref AT, Anderson BO, et al. The first BGICC consensus and recommendations for breast cancer awareness, early detection and risk reduction in low- and middle-income countries and the MENA region. *Int J Cancer* 2021; **149**(3): 505-13.
 89. US Department of Health and Human Services. Charter: Advisory Committee on Breast Cancer in Young Women 2022 2022.
 90. Nsaful J, Dedey F, Nartey E, Labi J, Adu-Aryee NA, Clegg-Lampsey JN. The impact of a breast cancer educational intervention in Ghanaian high schools. *BMC Cancer* 2022; **22**(1): 893.
 91. Soto-Perez-de-Celis E, Smith DD, Rojo-Castillo MP, et al. Implementation of a School-Based Educational Program to Increase Breast Cancer Awareness and Promote Intergenerational Transmission of Knowledge in a Rural Mexican Community. *Oncologist* 2017; **22**(10): 1249-56.
 92. World Health Organisation. Regional technical consultation with member states on the working document for development of the action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority: virtual meeting, 25–26 March 2021: meeting report. World Health Organization. Regional Office for Europe. 2021. <https://apps.who.int/iris/handle/10665/341837>.
 93. Mialon M, McCambridge J. Alcohol industry corporate social responsibility initiatives and harmful drinking: a systematic review. *Eur J Public Health* 2018; **28**(4): 664-73.
 94. McCambridge J, Mialon M, Hawkins B. Alcohol industry involvement in policymaking: a systematic review. *Addiction* 2018; **113**(9): 1571-84.
 95. Hammond D. Health warning messages on tobacco products: a review. *Tob Control* 2011; **20**(5): 327-37.
 96. Moodie C, Hoek J, Hammond D, et al. Plain tobacco packaging: progress, challenges, learning and opportunities. *Tob Control* 2022; **31**(2): 263-71.
 97. Greenhalgh EM, Scollo MM. 11A.9 Real-world research on the effects of plain packaging. In: Greenhalgh EM, Scollo MM, Winstanley MH, eds. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2022.

98. Hughes N, Arora M, Grills N. Perceptions and impact of plain packaging of tobacco products in low and middle income countries, middle to upper income countries and low-income settings in high-income countries: a systematic review of the literature. *BMJ Open* 2016; **6**(3): e010391.
99. Giesbrecht N, Reisdorfer E, Rios I. Alcohol Health Warning Labels: A Rapid Review with Action Recommendations. *Int J Environ Res Public Health* 2022; **19**(18).
100. Wilkinson C, Room R. Warnings on alcohol containers and advertisements: international experience and evidence on effects. *Drug Alcohol Rev* 2009; **28**(4): 426-35.
101. Scholes-Balog KE, Heerde JA, Hemphill SA. Alcohol warning labels: unlikely to affect alcohol-related beliefs and behaviours in adolescents. *Aust N Z J Public Health* 2012; **36**(6): 524-9.
102. Tam TW, Greenfield TK. Do Alcohol Warning Labels Influence Men's and Women's Attempts to Deter Others from Driving When Intoxicated? *Hum Factors Ergon Manuf* 2010; **20**(6): 538-46.
103. Coomber K, Martino F, Barbour IR, Mayshak R, Miller PG. Do consumers 'Get the facts'? A survey of alcohol warning label recognition in Australia. *BMC Public Health* 2015; **15**: 816.
104. Petticrew M, Douglas N, Knai C, Durand MA, Eastmure E, Mays N. Health information on alcoholic beverage containers: has the alcohol industry's pledge in England to improve labelling been met? *Addiction* 2016; **111**(1): 51-5.
105. Wagenaar AC, Salois MJ, Komro KA. Effects of beverage alcohol price and tax levels on drinking: a meta-analysis of 1003 estimates from 112 studies. *Addiction* 2009; **104**(2): 179-90.
106. Stockwell T, Zhao J, Giesbrecht N, Macdonald S, Thomas G, Wettlaufer A. The raising of minimum alcohol prices in Saskatchewan, Canada: impacts on consumption and implications for public health. *Am J Public Health* 2012; **102**(12): e103-10.
107. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *J Clin Oncol* 2023; **41**(17): 3116-21.
108. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. *J Clin Oncol* 2019; **37**(19): 1629-37.
109. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* 2007; **99**(4): 283-90.
110. Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol* 2015; **16**(1): 67-75.
111. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *The Lancet* 2020; **395**(10218): 117-22.
112. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; **364**(25): 2381-91.
113. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; **97**(22): 1652-62.
114. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *Journal of Clinical Oncology*; **0**(0): JCO.22.02900.
115. Visvanathan K, Fabian CJ, Bantug E, et al. Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2019; **37**(33): 3152-65.
116. Paluch-Shimon S, Cardoso F, Sessa C, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 2016; **27**(suppl 5): v103-v10.
117. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *J Clin Oncol* 2023: JCO2202900.

118. Cuzick J, Chu K, Keevil B, et al. Effect of baseline oestradiol serum concentration on the efficacy of anastrozole for preventing breast cancer in postmenopausal women at high risk: a case-control study of the IBIS-II prevention trial. *The Lancet Oncology* 2023.
119. Nolan E, Vaillant F, Branstetter D, et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. *Nat Med* 2016; **22**(8): 933-9.
120. Bhulani N, Wood M, Tsai J, et al. A phase 3 study to determine the breast cancer risk reducing effect of denosumab in women carrying a germline BRCA1 mutation (BRCA-P Study). *Journal of Clinical Oncology* 2022; **40**(16_suppl): TPS10616-TPS.
121. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst Rev* 2018; **4**(4): Cd002748.
122. Lacaze PA, Tiller J, Winship I. Population DNA screening for medically actionable disease risk in adults. *Med J Aust* 2022; **216**(6): 278-80.
123. Jackson L, Weedon M, Harrison J, et al. Influence of family history on penetrance of hereditary cancers in a population setting. *medRxiv* 2022: 2022.07.08.22277415.
124. Esserman LJ, Anton-Culver H, Borowsky A, et al. The WISDOM Study: breaking the deadlock in the breast cancer screening debate. *npj Breast Cancer* 2017; **3**(1): 34.
125. Sergeant JC, Warwick J, Evans DG, et al. Volumetric and area-based breast density measurement in the predicting risk of cancer at screening (PROCAS) study. Breast Imaging: 11th International Workshop, IWDM 2012, Philadelphia, PA, USA, July 8-11, 2012 Proceedings 11; 2012: Springer; 2012. p. 228-35.
126. Renehan AG, Pegington M, Harvie MN, et al. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS Study (United Kingdom). *British journal of cancer* 2020; **122**(10): 1552-61.
127. Brentnall AR, Harkness EF, Astley SM, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. *Breast Cancer Research* 2015; **17**(1): 1-10.
128. Velentzis LS, Freeman V, Campbell D, et al. Breast Cancer Risk Assessment Tools for Stratifying Women into Risk Groups: A Systematic Review. *Cancers (Basel)* 2023; **15**(4).
129. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 2004; **91**(8): 1580-90.
130. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med* 2004; **23**(7): 1111-30.
131. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol* 2019; **20**(4): 504-17.
132. Banegas MP, John EM, Slattey ML, et al. Projecting Individualized Absolute Invasive Breast Cancer Risk in US Hispanic Women. *J Natl Cancer Inst* 2017; **109**(2).
133. Matsuno RK, Costantino JP, Ziegler RG, et al. Projecting individualized absolute invasive breast cancer risk in Asian and Pacific Islander American women. *J Natl Cancer Inst* 2011; **103**(12): 951-61.
134. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst* 2007; **99**(23): 1782-92.
135. Park B, Ma SH, Shin A, et al. Korean risk assessment model for breast cancer risk prediction. *PLoS One* 2013; **8**(10): e76736.
136. Wang S, Ogundiran T, Ademola A, et al. Development of a Breast Cancer Risk Prediction Model for Women in Nigeria. *Cancer Epidemiol Biomarkers Prev* 2018; **27**(6): 636-43.
137. Palmer JR, Zirpoli G, Bertrand KA, et al. A Validated Risk Prediction Model for Breast Cancer in US Black Women. *J Clin Oncol* 2021; **39**(34): 3866-77.
138. Han Y, Lv J, Yu C, et al. Development and external validation of a breast cancer absolute risk prediction model in Chinese population. *Breast Cancer Res* 2021; **23**(1): 62.

139. Gallegos-Carrillo K, Krug-Llamas E, Doubova SV, Cervantes-Ocampo M, Vargas-Sánchez HR, Duque-Molina C. [PREVENIMSS: a brief overview of its 20 years, challenges and opportunities]. *Rev Med Inst Mex Seguro Soc* 2022; **60**(Suppl 2): 134-41.
140. Hughes E, Wagner S, Pruss D, et al. Development and Validation of a Breast Cancer Polygenic Risk Score on the Basis of Genetic Ancestry Composition. *JCO Precis Oncol* 2022; **6**: e2200084.
141. Eriksson M, Czene K, Vachon C, Conant EF, Hall P. Long-Term Performance of an Image-Based Short-Term Risk Model for Breast Cancer. *J Clin Oncol* 2023: Jco2201564.
142. Lehman CD, Mercaldo S, Lamb LR, et al. Deep Learning vs Traditional Breast Cancer Risk Models to Support Risk-Based Mammography Screening. *J Natl Cancer Inst* 2022; **114**(10): 1355-63.
143. Yala A, Mikhael PG, Strand F, et al. Multi-Institutional Validation of a Mammography-Based Breast Cancer Risk Model. *J Clin Oncol* 2022; **40**(16): 1732-40.
144. Omoleye OJ, Woodard AE, Howard FM, et al. External Evaluation of a Mammography-based Deep Learning Model for Predicting Breast Cancer in an Ethnically Diverse Population. *Radiology: Artificial Intelligence* 2023; **0**(ja): e220299.
145. Arasu VA, Habel LA, Achacoso NS, et al. Comparison of Mammography Artificial Intelligence Algorithms for 5-year Breast Cancer Risk Prediction. *medRxiv* 2022: 2022.01.05.22268746.
146. Phillips KA, Liao Y, Milne RL, et al. Accuracy of Risk Estimates from the iPrevent Breast Cancer Risk Assessment and Management Tool. *JNCI Cancer Spectr* 2019; **3**(4): pkz066.
147. iPrevent. 2023. <https://www.petermac.org/iprevent> (accessed 22 August 2023).
148. Macdonald C, Saunders CM, Keogh LA, et al. Breast Cancer Chemoprevention: Use and Views of Australian Women and Their Clinicians. *Cancer Prev Res (Phila)* 2021; **14**(1): 131-44.
149. Bellhouse S, Hawkes RE, Howell SJ, Gorman L, French DP. Breast Cancer Risk Assessment and Primary Prevention Advice in Primary Care: A Systematic Review of Provider Attitudes and Routine Behaviours. *Cancers (Basel)* 2021; **13**(16).
150. World Health Organisation, International Agency for Research on Cancer (IARC). Global Cancer Observatory. 2022. <https://gco.iarc.fr/> (accessed 1 Nov 2022 2022).
151. World Health Organisation, UNICEF. Global Breastfeeding Collective 2022 2022. <https://www.globalbreastfeedingcollective.org/global-breastfeeding-scorecard>.
152. World Health Organisation. The Global Health Observatory. 2022. <https://www.who.int/data/gho> (accessed 1 Nov 2022 2022).
153. Young A, Bu W, Jiang W, et al. Targeting the Pro-survival Protein BCL-2 to Prevent Breast Cancer. *Cancer Prev Res (Phila)* 2022; **15**(1): 3-10.
154. Slepicka PF, Cyrill SL, Dos Santos CO. Pregnancy and Breast Cancer: Pathways to Understand Risk and Prevention. *Trends Mol Med* 2019; **25**(10): 866-81.
155. Santucci-Pereira J, George C, Armiss D, et al. Mimicking pregnancy as a strategy for breast cancer prevention. *Breast Cancer Manag* 2013; **2**(4): 283-94.
156. Disis ML, Cecil DL. Breast cancer vaccines for treatment and prevention. *Breast Cancer Res Treat* 2022; **191**(3): 481-9.
157. Andre F, Filleron T, Kamal M, et al. Genomics to select treatment for patients with metastatic breast cancer. 2022; **610**(7931): 348.
158. Veninga V, Voest EE. Tumor organoids: Opportunities and challenges to guide precision medicine. *Cancer Cell* 2021; **39**(9): 1190-201.
159. Mou H, Kennedy Z, Anderson DG, Yin H, Xue W. Precision cancer mouse models through genome editing with CRISPR-Cas9. *Genome Med* 2015; **7**: 53.
160. Smith I. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol* 2020; **21**: 1443-54.
161. A study looking at personalised treatment for early HER2 positive breast cancer (HER2-RADICAL). 2022. <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-personalised-treatment-for-early-her2-positive-breast-cancer-her2-radical> (accessed 2 May 2023).

162. Pembrolizumab vs. Observation in People With Triple-negative Breast Cancer Who Had a Pathologic Complete Response After Chemotherapy Plus Pembrolizumab. 2023. <https://clinicaltrials.gov/ct2/show/NCT05812807> (accessed 2 May 2023).
163. Fisher B, Anderson S, Bryant J. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**(16): 1233–41.
164. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347**(16): 1227–32.
165. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *Eur J Cancer* 2000; **36**(15): 1938–43.
166. Kouwenberg CAE, de Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg* 2020; **146**(1): 1–13.
167. Witmer TJK, Kouwenberg CAE, Bargon CA. Comparing costs of standard Breast-Conserving Surgery to Oncoplastic Breast-Conserving Surgery and Mastectomy with Immediate two-stage Implant-Based Breast Reconstruction. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2022.
168. Abdel-Wahab M, Gondhowiardjo SS, Rosa AA, et al. Global Radiotherapy: Current Status and Future Directions-White Paper. *JCO Glob Oncol* 2021; **7**: 827–42.
169. Earl H, Hiller L, Vallier AL, et al. Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT. *Health Technol Assess* 2020; **24**(40): 1–190.
170. Kirwan CC, Coles CE, Bliss J, Group PPW, Group PPW. It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence. *Clin Oncol (R Coll Radiol)* 2016; **28**(9): 594–6.
171. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSOUND). *Breast* 2012; **21**(5): 678–81.
172. Fine RE, Gilmore RC, Dietz JR, et al. Cryoablation Without Excision for Low-Risk Early-Stage Breast Cancer: 3-Year Interim Analysis of Ipsilateral Breast Tumor Recurrence in the ICE3 Trial. *Ann Surg Oncol* 2021; **28**(10): 5525–34.
173. Morgan J, Potter S, Sharma N, et al. The SMALL Trial: A Big Change for Small Breast Cancers. *Clin Oncol (R Coll Radiol)* 2019; **31**(9): 659–63.
174. Morrow M, Khan AJ. Locoregional Management After Neoadjuvant Chemotherapy. *J Clin Oncol* 2020; **38**(20): 2281–9.
175. Taylor C, McGale P, Probert J, et al. Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993–2015: population based observational cohort study. *Bmj* 2023; **381**: e074684.
176. Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. *Int J Cancer* 2019; **144**(1): 49–58.
177. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013; **108**(11): 2205–40.
178. Larsson S, Clawson J, Howard R. Value-Based Health Care at an Inflection Point: A Global Agenda for the Next Decade. *Catalyst non-issue content* 2023; **4**(1).
179. Fayanju OM. Value-Based Breast Cancer Care: A Multidisciplinary Approach for Defining Patient-Centered Outcomes. *Ann Surg Oncol* 2016; **23**: 2385–90.
180. Egdom LSE. Implementation of Value Based Breast Cancer Care. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2019; **45**: 1163–70.

181. Porter ME. What is value in health care? *N Engl J Med* 2010; **363**(26): 2477-81.
182. Teisberg E, Wallace S, O'Hara S. Defining and Implementing Value-Based Health Care: A Strategic Framework. *Acad Med* 2020; **95**(5): 682-5.
183. Beauchamp A. Systematic development and implementation of interventions to Optimise Health Literacy and Access (Ophelia). *BMC Public Health* 2017; **17**: 230.
184. Beauchamp A. Distribution of health literacy strengths and weaknesses across socio-demographic groups: a cross-sectional survey using the Health Literacy Questionnaire (HLQ). *BMC Public Health* 2015; **15**: 678.
185. Garberis IJ. 11240 Prediction of distant relapse in patients with invasive breast cancer from deep learning models applied to digital pathology slides. *Ann Oncol* 2021; **32**: 921.
186. Torres FS. End-to-End Non-Small-Cell Lung Cancer Prognostication Using Deep Learning Applied to Pretreatment Computed Tomography. *JCO Clin Cancer Inform* 2021; **1141–1150**.
187. Meglio A. Dynamics of Long-Term Patient-Reported Quality of Life and Health Behaviors After Adjuvant Breast Cancer Chemotherapy. *JCO* 2022; **40**: 3190–204.
188. Bayoumy K. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol* 2021; **18**: 581–99.
189. Gresham G. Wearable activity monitors to assess performance status and predict clinical outcomes in advanced cancer patients. *Npj Digit Med* 2018; **1**: 1–8.
190. Hasnain Z. Quantified Kinematics to Evaluate Patient Chemotherapy Risks in Clinic. *JCO Clin Cancer Inform* 2020; **583–601**.
191. Ward WH. Feasibility of Fitness Tracker Usage to Assess Activity Level and Toxicities in Patients With Colorectal Cancer. *JCO Clin Cancer Inform* 2021; **125–133**.
192. Smuck M, Odonkor CA, Wilt JK, Schmidt N, Swiernik MA. The emerging clinical role of wearables: factors for successful implementation in healthcare. *NPJ Digit Med* 2021; **4**: 45.
193. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. *Nat Med* 2022; **28**: 1773–84.
194. 15. ISRCTN - ISRCTN81408940: Tailoring treatment for HER2-positive early breast cancer.
195. Bizot A. Multicenter evaluation of breast cancer patients' satisfaction and experience with oncology telemedicine visits during the COVID-19 pandemic. *Br J Cancer* 2021; **125**: 1486–93.
196. Cadili L. The Breast Cancer Patient Experience of Telemedicine During COVID-19. *Ann Surg Oncol* 2022; **29**: 2244–52.
197. Curigliano G. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Annals of Oncology* 2020; **31**: 1320–35.
198. Dietz JR. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat* 2020; **181**: 487–97.
199. Azambuja E. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. *ESMO Open* 2020; **5**, e000793.
200. Molen DR. The impact of the COVID-19 pandemic on perceived access to health care and preferences for health care provision in individuals (being) treated for breast cancer. *Breast Cancer Res Treat* 2021.
201. Pennell NA. American Society of Clinical Oncology Road to Recovery Report: Learning From the COVID-19 Experience to Improve Clinical Research and Cancer Care. *J Clin Oncol* 2021; **39**: 155–69.
202. Johnson BA. The New Normal? Patient Satisfaction and Usability of Telemedicine in Breast Cancer Care. *Ann Surg Oncol* 2021; **28**: 5668–76.
203. Meneses AdFP, Pimentel FF, Cruz JPF, Candido Dos Reis FJ. Experiences of Women With Breast Cancer Using Telehealth: A Qualitative Systematic Review. *Clin Breast Cancer* 2023; **23**: 101–7.
204. Calip GS. Telemedicine use among patients with metastatic breast cancer during the COVID-19 pandemic: Differences by race, age, and region. *Pharmacoepidemiol Drug Saf* 2023; **32**: 66–72.

205. Uemoto Y. Efficacy of Telemedicine Using Videoconferencing Systems in Outpatient Care for Patients With Cancer: A Systematic Review and Meta-Analysis. *JCO Clin Cancer Inform* 2022; **6**: 2200084.
206. Miziara RA. Teleoncology Orientation of Low-Income Breast Cancer Patients during the COVID-19 Pandemic: Feasibility and Patient Satisfaction. *Rev Bras Ginecol Obstet* 2021; **43**: 840–6.
207. Clinical outcomes in patients with solid tumors living in rural and urban areas followed via telemedicine: experience in a highly complex latin american hospital | BMC Cancer | Full Text.
208. Kunkler IH, Prescott RJ, Lee RJ, et al. TELEMAM: a cluster randomised trial to assess the use of telemedicine in multi-disciplinary breast cancer decision making. *Eur J Cancer* 2007; **43**(17): 2506–14.
209. Beaver K. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. *BMJ* 2009; **338**: 3147.
210. Stavrou E. Breast Medical Oncologists' Perspectives of Telemedicine for Breast Cancer Care: A Survey Study. *JCO Oncol Pract* 2022; **18**: 1447– 53.
211. Malek Pascha VA, Sun L, Gilardino R, Legood R. Telemammography for breast cancer screening: a cost-effective approach in Argentina. *BMJ Health Care Inform* 2021; **28**: 100351.
212. Johnston K. From the technology came the idea': safe implementation and operation of a high quality teleradiology model increasing access to timely breast cancer assessment services for women in rural Australia. *BMC Health Serv Res* 2020; **20**: 1103.
213. Krzyzanowska MK. Remote, proactive, telephone based management of toxicity in outpatients during adjuvant or neoadjuvant chemotherapy for early stage breast cancer: pragmatic, cluster randomised trial. *BMJ* 2021; **375**: 066588.
214. Mir O. Intervention combining nurse navigators (NNs) and a mobile application versus standard of care (SOC) in cancer patients (pts) treated with oral anticancer agents (OAA): Results of CapRI, a single-center, randomized phase III trial. *JCO* 2020; **38**: 2000–.
215. Absolom K. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. *JCO* 2021; **39**: 734–47.
216. Basch E. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016; **34**: 557–65.
217. Basch E. Effect of Electronic Symptom Monitoring on Patient-Reported Outcomes Among Patients With Metastatic Cancer: A Randomized Clinical Trial. *JAMA* 2022; **327**: 2413–22.
218. Maguire R. Real time remote symptom monitoring during chemotherapy for cancer: European multicentre randomised controlled trial (eSMART. *BMJ* 2021; **374**: 1647.
219. Harbeck N, Fasching PA, Wuerstlein R, et al. Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HR+ HER2- metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial. *Ann Oncol* 2023; **34**(8): 660-9.
220. Maio M. The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. *Ann Oncol* 2022; **33**: 878–92.
221. Patt D. Implementation of Electronic Patient-Reported Outcomes for Symptom Monitoring in a Large Multisite Community Oncology Practice: Dancing the Texas Two-Step Through a Pandemic. *JCO Clin Cancer Inform* 2021; **5**: 615–21.
222. Alfano CM, Oeffinger K, Sanft T, Tortorella B. Engaging TEAM Medicine in Patient Care: Redefining Cancer Survivorship From Diagnosis: American Society of Clinical Oncology Educational Book; 2022.
223. Chan RJ. The efficacy, challenges, and facilitators of telemedicine in post-treatment cancer survivorship care: an overview of systematic reviews. *Ann Oncol* 2021; **32**: 1552–70.
224. Singleton AC. Electronic Health Interventions for Patients With Breast Cancer: Systematic Review and Meta-Analyses. *JCO* 2022; **40**: 2257–70.

225. Abrahams HJG. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: A randomized controlled trial. *Cancer* 2017; **123**: 3825–34.
226. Zachariae R. Internet-Delivered Cognitive-Behavioral Therapy for Insomnia in Breast Cancer Survivors: A Randomized Controlled Trial. *JNCI: Journal of the National Cancer Institute* 2018; **110**: 880–7.
227. Akechi T. Smartphone Psychotherapy Reduces Fear of Cancer Recurrence Among Breast Cancer Survivors: A Fully Decentralized Randomized Controlled Clinical Trial (J-SUPPORT 1703 Study. *JCO* 2023; **41**: 1069–78.
228. Compen F. Face-to-Face and Internet-Based Mindfulness-Based Cognitive Therapy Compared With Treatment as Usual in Reducing Psychological Distress in Patients With Cancer: A Multicenter Randomized Controlled Trial. *JCO* 2018; **36**: 2413–21.
229. Bray VJ. Evaluation of a Web-Based Cognitive Rehabilitation Program in Cancer Survivors Reporting Cognitive Symptoms After Chemotherapy. *JCO* 2017; **35**: 217–25.
230. Goodwin PJ. The LISA randomized trial of a weight loss intervention in postmenopausal breast cancer. *NPJ Breast Cancer* 2020; **6**, 6.
231. Santa-Maria CA. The Effects of a Remote-based Weight Loss Program on Adipocytokines, Metabolic Markers, and Telomere Length in Breast Cancer Survivors: the POWER-Remote Trial. *Clin Cancer Res* 2020; **26**: 3024–34.
232. Webb J, Fife-Schaw C, Ogden J. A randomised control trial and cost-consequence analysis to examine the effects of a print-based intervention supported by internet tools on the physical activity of UK cancer survivors. *Public Health* 2019; **171**: 106–15.
233. Lozano-Lozano M. Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: Randomized controlled trial. *Ann Phys Rehabil Med* 2020; **63**: 316–24.
234. Abernethy A. The Promise of Digital Health: Then, Now, and the Future. *NAM Perspect* 2022; 10 31478 202206.
235. Leach CR. Cancer health self-efficacy improvement in a randomized controlled trial. *Cancer* 2022; **128**: 597–605.
236. Cheikh-Moussa K, Mira JJ, Orozco-Beltran D. Improving Engagement Among Patients With Chronic Cardiometabolic Conditions Using mHealth. *Critical Review of Reviews JMIR Mhealth Uhealth* 2020; **8**, e15446.
237. Atasoy H, Greenwood BN, McCullough JS. The Digitization of Patient Care: A Review of the Effects of Electronic Health Records on Health Care Quality and Utilization. *Annual Review of Public Health* 2019; **40**: 487–500.
238. Hammer RD. Digital Tumor Board Solutions Have Significant Impact on Case Preparation. *JCO Clinical Cancer Informatics* 2020; **757–768**.
239. Nobori A. Electronic Health Record–Integrated Tumor Board Application to Save Preparation Time and Reduce Errors. *JCO Clinical Cancer Informatics* 2022; **e2100142**.
240. Bayard S, Fasano G, Tamimi RM, Oh PS. Leveraging Electronic Health Records to Address Breast Cancer Disparities. *Curr Breast Cancer Rep* 2022; **14**: 199–204.
241. Wardley A. Flexible care in breast cancer. *ESMO Open* 2021; **6**: 100007.
242. Arora S, Ryals C, Rodriguez JA, Byers E, Clewett E. Leveraging Digital Technology to Reduce Cancer Care Inequities: American Society of Clinical Oncology Educational Book; 2022.
243. Irwin KE. Developing a Virtual Equity Hub: Adapting the Tumor Board Model for Equity in Cancer Care. *The Oncologist* 2022; **27**: 518–24.
244. Struminger BB, Arora S. Leveraging Telehealth to Improve Health Care Access in Rural America: It Takes More Than Bandwidth. *Ann Intern Med* 2019; **171**: 376–7.
245. Estes F. Implementation of a virtual multicenter gastrointestinal tumor board to reduce cancer disparities in Argentina. *World J Clin Oncol* 2022; **13**: 423–8.

246. Fokom Domgue J. Development, Implementation, and Evaluation of a Distance Learning and Telementoring Program for Cervical Cancer Prevention in Cameroon. *JAMA Netw Open* 2022; **5**: 2240801.
247. Paterson C. The Role of Telehealth During the COVID-19 Pandemic Across the Interdisciplinary Cancer Team: Implications for Practice. *Semin Oncol Nurs* 2020; **36**: 151090.
248. Kickbusch I. The Lancet and Financial Times Commission on governing health futures 2030: growing up in a digital world. *Lancet* 2021; **398**: 1727–76.
249. Cykert S. A Multi-faceted Intervention Aimed at Black-White Disparities in the Treatment of Early Stage Cancers: The ACCURE Pragmatic Quality Improvement trial. *Journal of the National Medical Association* 2020; **112**: 468–77.
250. Gerbasi A. DeepMiCa: Automatic segmentation and classification of breast MlcroCALcifications from mammograms. *Comput Methods Programs Biomed* 2023; **235**: 107483.
251. Zhou W. Improved breast lesion detection in mammogram images using a deep neural network. *Diagn Interv Radiol* 2023.
252. Koch HW, Larsen M, Bartsch H, Kurz KD, Hofvind S. Artificial intelligence in BreastScreen Norway: a retrospective analysis of a cancer-enriched sample including 1254 breast cancer cases. *Eur Radiol* 2023.
253. Albusayli R. Artificial intelligence-based digital scores of stromal tumour-infiltrating lymphocytes and tumour-associated stroma predict disease-specific survival in triple-negative breast cancer. *J Pathol* 2023; **260**: 32–42.
254. Inan OT. Digitizing clinical trials. *npj Digit. Med* 2020; **3**: 1–7.
255. Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L. Strategies to Advance Equity in Cancer Clinical Trials. *American Society of Clinical Oncology Educational Book* 2022; (42): 127-37.
256. Presti D. Factors associated with enrolment in clinical trials among women with early-stage breast cancer. *ESMO Open* 2022; **7**: 100513.
257. Frérot M. Factors influencing inclusion in digestive cancer clinical trials: A population-based study. *Digestive and Liver Disease* 2015; **47**: 891–6.
258. Ousseine YM, Bouhnik A-D, Mancini J. Health Literacy and Clinical Trial Participation in French Cancer Patients: A National Survey. *Curr Oncol* 2022; **29**: 3118–29.
259. Horvat L, Horey D, Romios P, Kis-Rigo J. Cultural competence education for health professionals. *Cochrane Database Syst Rev* 2014; **CD009405**.
260. Barrett NJ. An Assessment of the Feasibility and Utility of an ACCC-ASCO Implicit Bias Training Program to Enhance Racial and Ethnic Diversity in Cancer Clinical Trials. *JCO Oncology Practice* 2023; **22**(00378).
261. Guerra C. Increasing Racial and Ethnic Equity, Diversity, and Inclusion in Cancer Treatment Trials: Evaluation of an ASCO-Association of Community Cancer Centers Site Self-Assessment. *JCO Oncology Practice* 2023; **22**(00560).
262. Beck JT. Artificial Intelligence Tool for Optimizing Eligibility Screening for Clinical Trials in a Large Community Cancer Center. *JCO Clinical Cancer Informatics*; 2020: 50–9.
263. Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L. Strategies to Advance Equity in Cancer Clinical Trials: American Society of Clinical Oncology Educational Book; 2022.
264. Delorme J. Natural Language Processing for Patient Selection in Phase I or II Oncology Clinical Trials. *JCO Clin Cancer Inform* 2021; **5**: 709–18.
265. Tan RKJ. Digital approaches to enhancing community engagement in clinical trials. *npj Digit Med* 2022; **5**: 1–8.
266. Perez MV. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *New England Journal of Medicine* 2019; **381**: 1909–17.
267. Offodile AC, Seitz AJ, Peterson SK. Digital Health Navigation: An Enabling Infrastructure for Optimizing and Integrating Virtual Care Into Oncology Practice. *JCO Clinical Cancer Informatics* 2021; (5): 1151-4.

268. Lord SJ, Bahlmann K, O'Connell DL, et al. De novo and recurrent metastatic breast cancer - A systematic review of population-level changes in survival since 1995. *EClinicalMedicine* 2022; **44**: 101282.
269. NZ BCF. I'm still here". Insights into living – and dying – with advanced breast cancer in New Zealand. 2018. <https://www.breastcancerfoundation.org.nz/what-we-do/advocacy/abcinnz> (accessed November 2022).
270. Debiassi M, Reinert T, Kaliks R, et al. Estimation of Premature Deaths From Lack of Access to Anti-HER2 Therapy for Advanced Breast Cancer in the Brazilian Public Health System. *J Glob Oncol* 2017; **3**(3): 201-7.
271. Li J, Wang S, Wang Y, et al. Disparities of Trastuzumab Use in Resource-Limited or Resource-Abundant Regions and Its Survival Benefit on HER2 Positive Breast Cancer: A Real-World Study from China. *Oncologist* 2017; **22**(11): 1333-8.
272. Blackwell K, Gligorov J, Jacobs I, Twelves C. The Global Need for a Trastuzumab Biosimilar for Patients With HER2-Positive Breast Cancer. *Clin Breast Cancer* 2018; **18**(2): 95-113.
273. Ferrant G, OECD. Unpaid Care Work: The missing link in the analysis of gender gaps in labour outcomes. 2014. https://www.oecd.org/dev/development-gender/Unpaid_care_work.pdf (accessed January 8 2023).
274. Trogdon JG, Liu X, Reeder-Hayes KE, Rotter J, Ekwueme DU, Wheeler SB. Productivity costs associated with metastatic breast cancer in younger, midlife, and older women. *Cancer* 2020; **126**(18): 4118-25.
275. Alliance AG. ABC Hub. 2022. <https://www.abcgloballiance.org/abc-hub> (accessed January 8 2023).
276. Matos L, Borges M, Oliveira AT, et al. OR46 THE IMPACT ON PRODUCTIVITY COSTS OF REDUCING UNEMPLOYMENT IN PATIENTS WITH ADVANCED BREAST CANCER: A MODEL ESTIMATION BASED ON A PORTUGUESE NATIONWIDE OBSERVATIONAL STUDY. *The Breast* 2023; **71**: S28.
277. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). *Breast* 2018; **39**: 131-8.
278. McKenzie F, Zietsman A, Galukande M, et al. Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer - disparities in outcomes (ABC-DO) study. *Int J Cancer* 2018; **142**(8): 1568-79.
279. Benitez Fuentes JD, Morgan E, de Luna Aguilar A, et al. Global Stage Distribution of Breast Cancer at Diagnosis: A Systematic Review and Meta-Analysis. *JAMA Oncol* 2023.
280. McCormack V, McKenzie F, Foerster M, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *Lancet Glob Health* 2020; **8**(9): e1203-e12.
281. Gogia A, Deo SVS, Sharma D, et al. Clinicopathologic Characteristics and Treatment Outcomes of Patients With Up-Front Metastatic Breast Cancer: Single-Center Experience in India. *J Glob Oncol* 2019; **5**: 1-9.
282. Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. *Eur J Cancer* 2020; **129**: 60-70.
283. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**(4): 519-30.
284. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med* 2022; **386**(10): 942-50.
285. Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. *Ann Oncol* 2021; **32**(8): 1015-24.
286. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017; **28**(10): 2340-66.

287. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *J Clin Oncol* 2015; **33**(23): 2563-77.
288. Caswell-Jin JL, Sun, L., Munoz, D., Lu, Y., Li, Y., Huang, H., et al. . Contributions of screening, early-stage treatment, and metastatic treatment to breast cancer mortality reduction by molecular subtype in U.S. women, 2000-2017. *J Clin Oncol* 2022; **40**.
289. Temel JS, Greer JA, El-Jawahri A, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *J Clin Oncol* 2017; **35**(8): 834-41.
290. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**(1): 96-112.
291. Dans M, Kutner JS, Agarwal R, et al. NCCN Guidelines(R) Insights: Palliative Care, Version 2.2021. *J Natl Compr Canc Netw* 2021; **19**(7): 780-8.
292. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; **31**(12): 1623-49.
293. Cavallo J. Understanding oncologists' perceptions about palliative care and the barriers preventing its use. 2022. <https://ascopost.com/issues/may-25-2022/understanding-oncologists-perceptions-about-palliative-care-and-the-barriers-preventing-its-use/> (accessed January 8 2023).
294. de Ligt KM, de Rooij, B. H., Hedayati, E., Karsten, M. M., Smaardijk, V. R., Velting, M., Saunders, C., Travado, L., Cardoso, F., Lopez, E., Carney, N., Wengström, Y., Ives, A., Velikova, G., Sousa Fialho, M. D. L., Seidler, Y., Stamm, T. A., Koppert, L. B., van de Poll-Franse, L. V., on behalf of the Innovative Medicines Initiative Health Outcomes Observatory (H2O) consortium. International development of a patient-centered core outcome set for assessing health-related quality of life in metastatic breast cancer patients. *JAMA Oncology* 2022.
295. Jencks MK, editor. A view from the front line. 1st edition ed. London; 1995.
296. Coalition BBCA. Striving for better care. 2022. <https://www.breastcancer.org.nz/content/striving-better-care> (accessed January 8 2023).
297. Kuper-Hommel MJJ, Little Z, Gautier A. New Zealand experience with implementation of the ESO-ESMO consensus guidelines for advanced breast cancer-report of achievements and lessons learned. *Breast* 2022; **63**: 108-12.
298. Jonker L, Fisher SJ. The correlation between National Health Service trusts' clinical trial activity and both mortality rates and care quality commission ratings: a retrospective cross-sectional study. *Public Health* 2018; **157**: 1-6.
299. Wells JC, Sharma S, Del Paggio JC, et al. An Analysis of Contemporary Oncology Randomized Clinical Trials From Low/Middle-Income vs High-Income Countries. *JAMA Oncol* 2021; **7**(3): 379-85.
300. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. *Cancer Control* 2016; **23**(4): 327-37.
301. Kwiatkowski K, Coe K, Bailar JC, Swanson GM. Inclusion of minorities and women in cancer clinical trials, a decade later: Have we improved? *Cancer* 2013; **119**(16): 2956-63.
302. Biganzoli L, Cardoso F, Beishon M, et al. The requirements of a specialist breast centre. *Breast* 2020; **51**: 65-84.
303. Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: An update from the EUSOMA working group. *Eur J Cancer* 2017; **86**: 59-81.
304. Cardoso F, McCartney, A., Ponti, A., Marotti, L., Vrieling, C., Eniu, A., Sousa, B., Ripamonti, C., Travado, L., Spitz, S., Gustafsson, E., Rubio, I., Biganzoli, L. EUSOMA/ABC Global Alliance quality indicators for metastatic breast cancer care. *Eur J Cancer* 2023; **under submission**.
305. Ricci-Cabello I, Vasquez-Mejia A, Canelo-Aybar C, et al. Adherence to breast cancer guidelines is associated with better survival outcomes: a systematic review and meta-analysis of observational studies in EU countries. *BMC Health Serv Res* 2020; **20**(1): 920.

306. Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. *J Clin Oncol* 2004; **22**(18): 3685-93.
307. Song CV, Yip CH, Mohd Taib NA, et al. Association Between Adherence to Clinical Practice Guidelines for Adjuvant Therapy for Breast Cancer and Survival in a Resource-Limited Setting. *JCO Glob Oncol* 2022; **8**: e2100314.
308. Trapani D, Douillard JY, Winer EP, et al. The Global Landscape of Treatment Standards for Breast Cancer. *J Natl Cancer Inst* 2021; **113**(9): 1143-55.
309. Fatima. 2023.
310. Foerster M, McCormack V, Anderson BO. Treatment guideline concordance, initiation, and abandonment in patients with non-metastatic breast cancer from the African Breast Cancer-Disparities in Outcomes (ABC-DO) cohort in sub-Saharan Africa: a prospective cohort study. *Lancet Oncol* 2022; **23**(6): 729–38.
311. Bestvina CM, Zullig LL, Yousuf Zafar S. The implications of out-of-pocket cost of cancer treatment in the USA: a critical appraisal of the literature. *Future Oncol* 2014; **10**(14): 2189-99.
312. Nyblade L, Stockton M, Travasso S, Krishnan S. A qualitative exploration of cervical and breast cancer stigma in Karnataka, India. *BMC Womens Health* 2017; **17**(1): 58.
313. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005; **10 Suppl 3**: 20-9.
314. van Brakel WH, Cataldo J, Grover S, et al. Out of the silos: identifying cross-cutting features of health-related stigma to advance measurement and intervention. *BMC Med* 2019; **17**(1): 13.
315. Weiss MG, Ramakrishna J, Somma D. Health-related stigma: rethinking concepts and interventions. *Psychol Health Med* 2006; **11**(3): 277-87.
316. Scambler G. Stigma and disease: changing paradigms. *Lancet* 1998; **352**(9133): 1054-5.
317. Link BG, Phelan, J. C. Conceptualizing Stigma. *Annu Rev Sociol* 2001; **27**: 363–85.
318. Pescosolido BA, Martin JK, Lang A, Olafsdottir S. Rethinking theoretical approaches to stigma: a Framework Integrating Normative Influences on Stigma (FINIS). *Soc Sci Med* 2008; **67**(3): 431-40.
319. Weiss MG. Stigma and the social burden of neglected tropical diseases. *PLoS Negl Trop Dis* 2008; **2**(5): e237.
320. Heijnders M, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. *Psychol Health Med* 2006; **11**(3): 353-63.
321. ABC-SG. Project PINK BLUE. 2022. <https://projectpinkblue.org/abc-sg/>.
322. Alliance MBCG. We're changing the face of breast cancer. 2023. <https://mbcglobalalliance.org/>.
323. Villarreal-Garza C, Mesa-Chavez F, Lopez-Martinez EA, et al. Gaps in Knowledge and Understanding of Patients With Metastatic Breast Cancer in Mexico. *Cancer control : journal of the Moffitt Cancer Center* 2020; **27**(1): 1073274820920637.
324. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**(1): 7–30.
325. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**(6): 394–424.
326. Duggan C, Trapani D, Ilbawi A. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. *Lancet Oncol* 2021; **2021**.
327. Anderson BO, Cazap E, El Saghir NS. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus. *Lancet Oncol* 2010; **12**(4): 387–98.
328. Allemani C, Matsuda T, Carlo V. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**(10125): 1023–75.

329. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening--viewpoint of the IARC Working Group. *N Engl J Med* 2015; **372**(24): 2353-8.
330. Harford J, Azavedo E, Fischietto M. Guideline implementation for breast healthcare in low- and middle-income countries: breast healthcare program resource allocation. *Cancer* 2008; **113**(8 Suppl): 2282-96.
331. Berry DA, Cronin KA, Plevritis SK. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005; **353**(17): 1784-92.
332. Anderson BO, Ilbawi AM, Fidarova E. The Global Breast Cancer Initiative: a strategic collaboration to strengthen health care for non-communicable diseases. *Lancet Oncol* 2021; **22**(5): 578-81.
333. Duggan C, Dvaladze A, Rositch AF, et al. The Breast Health Global Initiative 2018 Global Summit on Improving Breast Healthcare Through Resource-Stratified Phased Implementation: Methods and overview. *Cancer* 2020; **126** Suppl 10(Suppl 10): 2339-52.
334. Shyyan R, Sener SF, Anderson BO. Guideline implementation for breast healthcare in low- and middle-income countries: diagnosis resource allocation. *Cancer* 2008; **113**(8 Suppl): 2257-68.
335. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999; **353**(9159): 1119-26.
336. Bukowski A, Gioia S, Chavarri-Guerra Y. Patient Navigation to Improve Access to Breast Cancer Care in Brazil. *J Glob Oncol* 2017; **3**(5): 433-7.
337. Gray E. ESMO Open Cancer Horizons. 2021.
338. van Maaren MC, Rachet B, Sonke GS, et al. Socioeconomic status and its relation with breast cancer recurrence and survival in young women in the Netherlands. *Cancer Epidemiol* 2022; **77**: 102118.
339. Dasgupta P, Baade PD, Youlden DR, et al. Variations in outcomes by residential location for women with breast cancer: a systematic review. *BMJ Open* 2018; **8**(4): e019050.
340. Goel N, Lubarsky M, Hernandez A, et al. Unmet Social Needs on Breast Cancer Screening Utilization and Stage at Presentation. *JAMA Netw Open* In review.
341. Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya. Washington, DC: The World Bank; 2022.
342. Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K. Access to pathology and laboratory medicine services: a crucial gap. *The Lancet* 2018; **391**(10133): 1927-38.
343. Steakley L. Using the Coca-Cola supplier network to distribute medicines in Africa. 2013. <https://scopeblog.stanford.edu/2013/04/26/using-the-coca-cola-supplier-network-to-distribute-medicines-in-africa/> (accessed 15 September 2023).
344. Mugabe M, Andrici J, Ho K. Comparing the Gene Xpert Breast Cancer RUO mRNA Assay with ER and HER2 Immunohistochemistry (IHC) for Rapid Biomarker Analysis. *Mod Pathol* 2017; **30**(S2).
345. Wu NC, Wong W, Ho KE. Comparison of central laboratory assessments of ER, PR, HER2, and Ki67 by IHC/FISH and the corresponding mRNAs (ESR1, PGR, ERBB2, and MKi67) by RT-qPCR on an automated, broadly deployed diagnostic platform. *Breast Cancer Res Treat* 2018; **172**(2): 327-38.
346. Kimambo A, Ng D. Validation of the GeneXpert Breast Cancer STRAT4 Assay for Rapid Analysis of Breast Cancer Biomarker Status From Fine-Needle Aspiration Biopsies in Tanzania (GX-BCB): Preliminary Results. *American Journal of Clinical Pathology* 2018; **150**(suppl_1).
347. Denny L, Sanjose S, Mutebi M. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *The Lancet* 2017; **389**(10071): 861-70.
348. Black E, Richmond R. Improving early detection of breast cancer in sub-Saharan Africa: why mammography may not be the way forward. *Global Health* 2019; **15**(3).
349. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. *World J Clin Oncol* 2015; **6**(6): 281-90.

350. Symmans WF, Peintinger F, Hatzis C. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; **25**(28): 4414–22.
351. Symmans WF, Yau C, Chen YY. Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for High-risk Breast Cancer: An Analysis of Data From the I-SPY2 Randomized Clinical Trial. *JAMA Oncol* 2021; **7**(11): 1654–63.
352. Yau C, Osdoit M, Noordaa M. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol* 2022; **23**(1): 149–60.
353. Miller ME, Patil N, Li P. Hospital System Adoption of Magnetic Seeds for Wireless Breast and Lymph Node Localization. *Ann Surg Oncol* 2021; **28**(6): 3223–9.
354. Serventi F, Musyoka A, Saunders J. NOHA: A Promising Biomarker for Determining Estrogen Receptor Status Among Patients With Breast Cancer in Resource-Constrained Settings. *JCO Glob Oncol* 2022; **8**:e2200192.
355. Banys-Paluchowski M, Fehm TN, Grimm-Glang D, Rody A, Krawczyk N. Liquid Biopsy in Metastatic Breast Cancer: Current Role of Circulating Tumor Cells and Circulating Tumor DNA. *Oncol Res Treat* 2022; **45**(1-2): 4–11.
356. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. *New England Journal of Medicine* 2019; **380**(20): 1929–40.
357. Fleming KA, Naidoo M, Wilson M. An Essential Pathology Package for Low- and Middle-Income Countries. *American Journal of Clinical Pathology* 2017; **147**(1): 15–32.
358. Wu G, Zaman MH. Low-cost tools for diagnosing and monitoring HIV infection in low-resource settings. *Bull World Health Organ* 2012; **90**(12): 914–20.
359. Letter Q. Quality Glossary of Terms, Acronyms & Definitions with Letter Q | ASQ.
360. Proctor E, Silmere H, Raghavan R. Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda. *Adm Policy Ment Health* 2011; **38**(2): 65–76.
361. Autier P, Hery C, Haukka J, Boniol M, Byrnes G. Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. *J Clin Oncol* 2009; **27**(35): 5919–23.
362. Chávarri-Guerra Y, Villarreal-Garza C, Liedke PE, et al. Breast cancer in Mexico: a growing challenge to health and the health system. *Lancet Oncol* 2012; **13**(8): e335–43.
363. Tamez-Salazar J, Mireles-Aguilar T, de la Garza-Ramos C, et al. Prioritization of Patients with Abnormal Breast Findings in the Alerta Rosa Navigation Program to Reduce Diagnostic Delays. *Oncologist* 2020; **25**(12): 1047–54.
364. Perez-Bustos AH, Orozco-Urdaneta M, Erazo R, et al. A patient navigation initiative to improve access to breast cancer care in Cali, Colombia. *Cancer Rep (Hoboken)* 2022; **5**(9): e1564.
365. Imkampe A, Bendall S, Chianakwalam C. Two-week rule: Has prioritisation of breast referrals by general practitioners improved? *The Breast* 2006; **15**(5): 654–8.
366. Cortes J, Perez-García JM, Llombart-Cussac A, et al. Enhancing global access to cancer medicines. *CA Cancer J Clin* 2020; **70**(2): 105–24.
367. IQVIA/MIDAS. Geographical breakdown (by main markets) of sales of new medicines launched during the period 2016-2021. . 2022. <https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-economy/geographical-breakdown-of-sales-of-new-medicines> (accessed 13 December 2023).
368. Miljkovic MD, Tuia JE, Olivier T, Haslam A, Prasad V. Association Between US Drug Price and Measures of Efficacy for Oncology Drugs Approved by the US Food and Drug Administration From 2015 to 2020. *JAMA Intern Med* 2022; **182**(12): 1319–20.
369. Tay-Teo K, Ilbawi A, Hill SR. Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. *JAMA Netw Open* 2019; **2**(1): e186875.

370. CRUK. Outcome-based payment for cancer drugs. 2023. <https://www.cancerresearchuk.org/about-us/we-develop-policy/our-policy-on-access-to-cancer-treatments/outcome-based-payment-for-cancer-drugs>. (accessed 13 December 2023).
371. Sleeman KE, Gomes B, Brito M, Shamieh O, Harding R. The burden of serious health-related suffering among cancer decedents: Global projections study to 2060. *Palliative medicine* 2021; **35**(1): 231–5.
372. Hubinette M, Dobson S, Scott I, Sherbino J. Health advocacy. *Med Teach* 2017; **39**(2): 128–35.
373. Maxwell GL. The state of advocacy in cancer. *Gynecol Oncol* 2015; **139**(3): 573–9.
374. Janamian T, Greco M, Cosgriff D, Baker L, Dawda P. Activating people to partner in health and self-care: use of the Patient Activation Measure. *Med J Aust* 2022; **10**(Suppl 10).
375. Morhason-Bello IO, Odedina F, Rebbeck TR, et al. Challenges and opportunities in cancer control in Africa: a perspective from the African Organisation for Research and Training in Cancer. *Lancet Oncol* 2013.
376. Odedina FT, Asante-Shongwe K, Kandusi EJ. The African cancer advocacy consortium: shaping the path for advocacy in Africa. *Infect Agents Cancer* 2013; **8**(Suppl 1): 8.
377. Connor S. Global Atlas of Palliative Care. 2021-04-30 2021. <http://www.thewhpc.org/resources/global-atlas-on-end-of-life-care> (accessed 3 January 2023).
378. Sun H, Lv H, Zeng H, Niu L, Yan M. Distress Thermometer in breast cancer: systematic review and meta-analysis. *BMJ supportive & palliative care* 2022; **12**(3): 245–52.
379. Chen X, Wu C, Bai D, et al. Health-related quality of life in breast cancer patients in Asia: A meta-analysis and systematic review. *Frontiers in oncology* 2022; **12**: 954179.
380. Gonzalez L, Bardach A, Palacios A, et al. Health-Related Quality of Life in Patients with Breast Cancer in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. *The oncologist* 2021; **26**(5): 794– 806.
381. Rezagholi P, Abdi K, Barzanji A, et al. Prevalence of depression in Iranian women with breast cancer: a systematic review and meta-analysis. *Przegląd epidemiologiczny* 2022; **76**(1): 29–36.
382. Leysen L, Lahousse A, Nijs J, et al. Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2019; **27**(12): 4401–33.
383. Liu L, Wu Y, Cong W, Hu M, Li X, Zhou C. Experience of women with breast cancer undergoing chemotherapy: a systematic review of qualitative research. Quality of life research : an international journal of quality of life aspects of treatment. *care and rehabilitation* 2021; **30**(5): 1249–65.
384. Roberts F, Andrewes T. Exploring the psychological impacts of a gestational cancer diagnosis on women: a literature review. British journal of nursing: Mark Allen Publishing; 2022.
385. Fortin J, Leblanc M, Elgbeili G, Cordova MJ, Marin MF, Brunet A. The mental health impacts of receiving a breast cancer diagnosis: A meta-analysis. *British journal of cancer* 2021; **125**(11): 1582–92.
386. Durosini I, Triberti S, Savioni L, Sebri V, Pravettoni G. The Role of Emotion-Related Abilities in the Quality of Life of Breast Cancer Survivors: A Systematic Review. *International journal of environmental research and public health* 2022; **19**(19): 12704.
387. Maheu C, Singh M, Tock WL, et al. Fear of Cancer Recurrence, Health Anxiety, Worry, and Uncertainty: A Scoping Review About Their Conceptualization and Measurement Within Breast Cancer Survivorship Research. *Frontiers in psychology* 2021; **12**: 644932.
388. Lim E, Humphris G. The relationship between fears of cancer recurrence and patient age: A systematic review and meta-analysis. *Cancer reports*. 2020.
389. Samuel CA, Mbah OM, Elkins W, et al. Calidad de Vida: a systematic review of quality of life in Latino cancer survivors in the USA. Quality of life research : an international journal of quality of life aspects of treatment. *care and rehabilitation* 2020; **29**(10): 2615–30.

390. Zomkowski K, Souza B, Silva F, Moreira GM, Souza Cunha N, Sperandio FF. Physical symptoms and working performance in female breast cancer survivors: a systematic review. *Disability and rehabilitation* 2018; **40**(13): 1485–93.
391. Wang K, Yee C, Tam S, et al. Prevalence of pain in patients with breast cancer post-treatment: A systematic review. 2018.
392. Adler SR, Coulter YZ, Stone K, Glaser J, Duerr M, Enochy S. End-of-Life Concerns and Experiences of Living With Advanced Breast Cancer Among Medically Underserved Women. *Journal of pain and symptom management* 2019; **58**(6): 959–67.
393. Matsuoka J, Kunitomi T, Nishizaki M, Iwamoto T, Katayama H. Advance care planning in metastatic breast cancer. *Chinese clinical oncology* 2018; **7**(3): 33.
394. Accordino MK, Wright JD, Vasan S, et al. Association between survival time with metastatic breast cancer and aggressive end-of-life care. *Breast cancer research and treatment* 2017; **166**(2): 549–58.
395. Roberson PNE, Cortez G, Freeman T, Lloyd J, Tasman J, Woods SB. Relationship quality and psychophysiological distress for underserved breast cancer patients and their caregiver before treatment. *Psycho-oncology* 2022; **31**(11): 1904–12.
396. Overcash J, Johnston M, Sinnott LT, Williams N. Influence of Patient Functional Status and Depression on Strain in Caregivers. *Clinical journal of oncology nursing* 2022; **26**(4): 406–12.
397. Dumitra S, Jones V, Rodriguez J, et al. Disparities in managing emotions when facing a diagnosis of breast cancer: Results of screening program of couples distress. *Surgery* 2018; **S0039-6060(17)30861-9**.
398. Selamat Din SH, Nik Jaafar NR, Zakaria H, Mohamed Saini S, Ahmad SN, Midin M. Anxiety Disorders in Family Caregivers of Breast Cancer Patients Receiving Oncologic Treatment in Malaysia. *Asian Pac J Cancer Prev* 2017; **18**(2): 465–71.
399. Elfgen C, Montagna G, Schmid SM, Bierbauer W, Gütha U. Metastatic Breast Cancer as a Chronic Disease: Evidence-Based Data on a Theoretical Concept. *Breast Care* 2020; **15**: 281–8.
400. Tang WZ, Yusuf A, Jia K, et al. Correlates of stigma for patients with breast cancer: a systematic review and meta-analysis. *Support Care Cancer* 2022; **31**: 55.
401. Trusson D, Pilnick A. The Role of Hair Loss in Cancer Identity: Perceptions of Chemotherapy-Induced Alopecia Among Women Treated for Early-Stage Breast Cancer or Ductal Carcinoma in Situ. *Cancer Nurs* 2017; **40**: 9– 16.
402. Melhem SJ, Nabhani-Gebara S, Kayyali R. Latency of breast cancer stigma during survivorship and its influencing factors: A qualitative study. *Front Oncol* 2023; **14**: 13.
403. Lee MC, Bhati RS, Rottenthaler EE, Reagan AM, Karver SB, Reich RR. Therapy choices and quality of life in young breast cancer survivors: a short-term follow-up. *Am J Surg* 2013; **206**(5): 625–31.
404. Silvestris E, Dellina M, Cafforio P, Paradiso AV, Cormio G, D’Oronzio S. Breast cancer: an update on treatment-related infertility. *J Cancer Res Clin Oncol* 2020; **146**: 647–57.
405. Mungrue K, Ramdath J, Ali S, et al. Challenges to the control of breast cancer in a small developing country. *Breast cancer : basic and clinical research* 2014; **8**: 7–13.
406. Pace LE, Dusengimana JM, Hategekimana V, et al. Benign and Malignant Breast Disease at Rwanda's First Public Cancer Referral Center. *The oncologist* 2016; **21**(5): 571–5.
407. Pace LE, Mpunga T, Hategekimana V, et al. Delays in Breast Cancer Presentation and Diagnosis at Two Rural Cancer Referral Centers in Rwanda. *The oncologist* 2015; **20**(7): 780–8.
408. Tieman JT, Nourian MM, Agbenorku P, et al. Developing a Breast Reconstruction Program in a Resource-Constrained Ghanaian Teaching Hospital: Needs Assessment and Implementation. *Annals of plastic surgery* 2021; **86**(2): 129–31.
409. Ortega CCF, Veiga DF, Camargo K, Juliano Y, Sabino Neto M, Ferreira LM. Breast Reconstruction May Improve Work Ability and Productivity After Breast Cancer Surgery. *Annals of plastic surgery* 2018; **81**(4): 398–401.

410. Roy N, Villavisanis DF, Taub PJ. Mitigating Financial Toxicity in Breast Cancer From Diagnosis to Treatment and Reconstruction. *Clinical breast cancer* 2023; **23**(1): 32– 6.
411. Quincey K, Williamson I, Winstanley S. 'Marginalised malignancies': A qualitative synthesis of men's accounts of living with breast cancer. *Soc Sci Med* 2016; **149**: 17–25.
412. Bhadelia A, Greaves N, Doubova S, Knaul F. Understanding the Value of Alleviating Health-Related Suffering and Palliative Care Centered in Lived Experience: The SAVE Toolkit. 2023. <https://doi.org/10.21203/rs.3.rs-3716807/v1>.
413. Doubova S BA, Pérez-Moran D, Martinez-Vega IP, García-Cervantes N, Knaul FM. Dimensions of suffering and the need for palliative care: experiences and expectations of patients living with cancer and diabetes and their caregivers in Mexico – a qualitative study. *BMJ Open* 2023; **13**(12): e075691.
414. Essue BM, Oliveira Cd, Bushnik T, et al. The Burden of Health-Related Out-of-Pocket Cancer Costs in Canada: A Case-Control Study Using Linked Data. *Current Oncology* 2022; **29**(7): 4541-57.
415. Iraragorri N, de Oliveira C, Fitzgerald N, Essue B. The Out-of-Pocket Cost Burden of Cancer Care-A Systematic Literature Review. *Curr Oncol* 2021; **28**(2): 1216-48.
416. Iraragorri N, de Oliveira C, Fitzgerald N, Essue B. The Indirect Cost Burden of Cancer Care in Canada: A Systematic Literature Review. *Appl Health Econ Health Policy* 2021; **19**(3): 325-41.
417. Essue BM, Laba M, Knaul F, et al. Economic Burden of Chronic Ill Health and Injuries for Households in Low- and Middle-Income Countries. In: Jamison DT, Gelband H, Horton S, et al., eds. *Disease Control Priorities: Improving Health and Reducing Poverty*. Washington (DC): The International Bank for Reconstruction and Development / The World Bank © 2018 International Bank for Reconstruction and Development / The World Bank.; 2017.
418. Jan S, Kimman M, Peters SA, Woodward M. Financial catastrophe, treatment discontinuation and death associated with surgically operable cancer in South-East Asia: Results from the ACTION Study. *Surgery* 2015; **157**(6): 971-82.
419. Fact Sheet: Breast cancer. World Health Organization. 2021. <https://www.who.int/news-room/fact-sheets/detail/breast-cancer> (accessed 3 January 2023).
420. Knaul FM. Closing the cancer divide: An equity imperative: Harvard Global Equity Initiative; 2012.
421. Tawfik B, Jaffe SA, Mohler L, et al. Developing a survivorship care plan (SCP) delivery process for patients and primary care providers serving poor, rural, and minority patients with cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*; 2021. p. 5021-8.
422. Yeoh Z-Y, Jaganathan M, Rajaram N, et al. Feasibility of Patient Navigation to Improve Breast Cancer Care in Malaysia. *Journal of Global Oncology* 2018; **4**(4): 1-13.
423. Ghaffari F, Ghahramanian A, Zamanzadeh V, et al. Patient-centred communication for women with breast cancer: Relation to body image perception. *Journal of clinical nursing* 2020; **29**(23-24): 4674-84.
424. Gakunga R, Kinyanjui A, Ali Z, et al. Identifying Barriers and Facilitators to Breast Cancer Early Detection and Subsequent Treatment Engagement in Kenya: A Qualitative Approach. *The oncologist*; 2019. p. 1549-56.
425. Kathrikolly TR, Nair S, Poobalan AS, Shetty RS, Tripathee S, Mac Lennan SJ. Increasing Engagement for Breast Cancer Screening and Treatment: The "ICANTREAT" Community of Expertise Initiative. *Asian Pac J Cancer Prev* 2020; **21**(12): 3655-9.
426. Guerra RL, Castaneda L, de Albuquerque RdCR, et al. Patient Preferences for Breast Cancer Treatment Interventions: A Systematic Review of Discrete Choice Experiments. *The patient* 2019; **12**(6): 559-69.
427. Raisa A, Roberto AJ, Love RR, Steiness HLS, Salim R, Krieger JL. Pot Song as a Novel Cancer Communication Intervention: Lessons Learned from Developing, Implementing, and Evaluating a Culturally Grounded Intervention for Breast Cancer Education in Rural Bangladesh. *Journal of cancer education : the official journal of the American Association for Cancer Education* 2021.

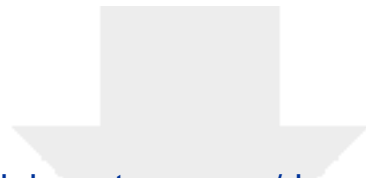
428. Schliemann D, Htay MNN, Dahlui M, et al. Impact of a mass media campaign on breast cancer symptoms awareness and screening uptake in Malaysia: findings from a quasi-experimental study. *BMJ open*; 2020. p. e036503.
429. Odigie VI, Yusufu LMD, Dawotola DA, et al. The mobile phone as a tool in improving cancer care in Nigeria. *Psycho-oncology* 2012; **21**(3): 332-5.
430. Gutnik L, Moses A, Stanley C, Tembo T, Lee C, Gopal S. From Community Laywomen to Breast Health Workers: A Pilot Training Model to Implement Clinical Breast Exam Screening in Malawi. *PloS one* 2016; **11**(3): e0151389.
431. Zhou Q, Shen J-C, Liu Y-Z, Lin G-Z, Dong H, Li K. Effects of Doctor-patient Communication on Quality of Life among Breast Cancer Patients in Southern China. *Asian Pacific Journal of Cancer Prevention* 2014; **15**(14): 5639-44.
432. Noyan MA, Sertoz OO, Elbi H, Kayar R, Yilmaz R. Variables affecting patient satisfaction in breast surgery: a cross-sectional sample of Turkish women with breast cancer. *International journal of psychiatry in medicine*; 2006. p. 299-313.
433. Wako Z, Mengistu D, Dinegde NG, Asefa T, Wassie M. Adherence to Adjuvant Hormonal Therapy and Associated Factors Among Women with Breast Cancer Attending the Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2019: A Cross-sectional Study. *Breast cancer (Dove Medical Press)* 2021; **13**: 383-92.
434. Yap ML, Zubizarreta E, Bray F, Ferlay J, Barton M. Global Access to Radiotherapy Services: Have We Made Progress During the Past Decade? *Journal of global oncology: American Society of Clinical Oncology*; 2016. p. 207-15.
435. Agyemang LS, Foster C, McLean C, Fenlon D, Wagland R. The cultural and structural influences that 'hide' information from women diagnosed with breast cancer in Ghana: an ethnography. *BMC women's health*; 2021. p. 364.
436. Geng C, Lu G-J, Zhu J, Li Y-Y. Patients' awareness about their own breast cancer characteristics. *World journal of clinical cases*; 2021. p. 7043-52.
437. Daniel S, Venkateswaran C, Singh C, Hutchinson A, Johnson MJ. "So, when a woman becomes ill, the total structure of the family is affected, they can't do anything..." Voices from the community on women with breast cancer in India: a qualitative focus group study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*; 2022. p. 951-63.
438. Scheel JR, Parker S, Hippe DS, et al. Role of Family Obligation Stress on Ugandan Women's Participation in Preventive Breast Health. *The oncologist*; 2019. p. 624-31.
439. Lambert M, Mendenhall E, Kim AW, Cubasch H, Joffe M, Norris SA. Health system experiences of breast cancer survivors in urban South Africa. *Women's health (London, England)*; 2020. p. 1745506520949419.
440. Brinton L, Figueroa J, Adjei E, et al. Factors contributing to delays in diagnosis of breast cancers in Ghana, West Africa. *Breast cancer research and treatment*; 2017. p. 105-14.
441. Sajjad S, Gul R, Gowani A, Ali A, Chagani S. Developing the Reliability and Validity of an Urdu Version-Self-Efficacy Scale for Breast Cancer Patients in Pakistan. *Journal of nursing measurement* 2021; **29**(2): 239-53.
442. Mandrik O, Yaumenenka A, Herrero R, Jonker MF. Population preferences for breast cancer screening policies: Discrete choice experiment in Belarus. *PloS one* 2019; **14**(11): e0224667.
443. Whelan T, Levine M, Willan A, et al. Effect of a decision aid on knowledge and treatment decision making for breast cancer surgery: a randomized trial. *JAMA* 2004; **292**(4): 435-41.
444. Hawley ST, Li Y, An LC, et al. Improving Breast Cancer Surgical Treatment Decision Making: The iCanDecide Randomized Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2018. p. 659-66.
445. Lyman GH, Greenlee H, Bohlke K, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. *Journal of Clinical Oncology: American Society of Clinical Oncology*; 2018. p. 2647-55.

446. Hawley ST, Kidwell K, Zahrieh D, et al. STUDY PROTOCOL Improving patient-centered communication in breast cancer: a study protocol for a multilevel intervention of a shared treatment deliberation system (SharES) within the NCI community oncology research program (NCORP) (Alliance A231901CD). 2023.
447. Wallner LP, Martinez KA, Li Y, et al. Use of Online Communication by Patients With Newly Diagnosed Breast Cancer During the Treatment Decision Process. *JAMA Oncology* 2016; **2**(12): 1654-6.
448. Liu Y, Malin JL, Diamant AL, Thind A, Maly RC. Adherence to Adjuvant Hormone Therapy in Low-income Women with Breast Cancer: The Role of Provider-Patient Communication \$watermark-text \$watermark-text \$watermark-text. *Breast Cancer Res Treat* 2013; **137**(3): 829-36.
449. Kerr J, Engel J, Schlesinger-Raab A, Sauer H, Hölzel D. Communication, quality of life and age: results of a 5-year prospective study in breast cancer patients. *Annals of Oncology: Elsevier*; 2003. p. 421-7.
450. Seror V, Cortaredona S, Bouhnik AD, et al. Young breast cancer patients' involvement in treatment decisions: the major role played by decision-making about surgery. *Psycho-oncology* 2013; **22**(11): 2546-56.
451. Mott N, Wang T, Miller J, et al. Medical Maximizing–Minimizing Preferences in Relation to Low-Value Services for Older Women with Hormone Receptor-Positive Breast Cancer: A Qualitative Study. *Annals of Surgical Oncology: Ann Surg Oncol*; 2021. p. 941-9.
452. Lantz PM, Janz NK, Fagerlin A, et al. Satisfaction with Surgery Outcomes and the Decision Process in a Population-Based Sample of Women with Breast Cancer. *Health Services Research* 2005; **40**(3): 745.
453. Martinez KA, Kurian AW, Hawley ST, Jagsi R. How can we best respect patient autonomy in breast cancer treatment decisions? *Breast cancer management* 2015; **4**(1): 53-64.
454. Khoshnazar TAK, Rassouli M, Akbari ME, et al. Communication Needs of Patients with Breast Cancer: A Qualitative Study. *Indian Journal of Palliative Care: Scientific Scholar*; 2016. p. 402.
455. Shim EJ, Park JE, Yi M, Jung D, Lee KM, Hahm BJ. Tailoring communications to the evolving needs of patients throughout the cancer care trajectory: A qualitative exploration with breast cancer patients. *BMC Women's Health* 2016; **16**(1): 1-8.
456. Ward ZJ, Scott AM, Hricak H, Atun R. Global costs, health benefits, and economic benefits of scaling up treatment and imaging modalities for survival of 11 cancers: a simulation-based analysis. *The Lancet Oncology*; 2021. p. 341-50.
457. Caverly TJ, Hayward RA. Dealing with the Lack of Time for Detailed Shared Decision-making in Primary Care: Everyday Shared Decision-making. *Journal of General Internal Medicine: Journal of General Internal Medicine*; 2020. p. 3045-9.
458. Street RL, Mazor KM, Arora NK. Assessing Patient-Centered Communication in Cancer Care: Measures for Surveillance of Communication Outcomes. *Journal of Oncology Practice* 2016; **12**(12): 1198.
459. Banerjee SC, Manna R, Coyle N, et al. The implementation and evaluation of a communication skills training program for oncology nurses. *Translational behavioral medicine: Transl Behav Med*; 2017. p. 615-23.
460. Bylund CL, Banerjee SC, Bialer PA, et al. A rigorous evaluation of an institutionally-based communication skills program for post-graduate oncology trainees. *Patient education and counseling: Patient Educ Couns*; 2018. p. 1924-33.
461. Kissane DW, Bylund CL, Banerjee SC, et al. Communication skills training for oncology professionals. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2012. p. 1242-7.
462. Bylund CL, Brown RF, Bialer PA, Levin TT, Lubrano Di Ciccone B, Kissane DW. Developing and implementing an advanced communication training program in oncology at a comprehensive cancer center. *Journal of cancer education : the official journal of the American Association for Cancer Education: J Cancer Educ*; 2011. p. 604-11.

463. Bylund CL, Brown R, Gueguen JA, Diamond C, Bianculli J, Kissane DW. The implementation and assessment of a comprehensive communication skills training curriculum for oncologists. *Psycho-oncology* 2010; **19**(6): 583-93.
464. Langewitz W, Denz M, Keller A, Kiss A, Rütimann S, Wössmer B. Spontaneous talking time at start of consultation in outpatient clinic: cohort study. *BMJ (Clinical research ed)*: *BMJ*; 2002. p. 682-3.
465. Decise D, Gheran MP, Kimhi E, et al. Putting words into practice. *Breast* 2020; **49**: 171-3.
466. Fallowfield L, Boyle FM, Travado L, et al. Gaps in Care and Support for Patients With Advanced Breast Cancer: A Report From the Advanced Breast Cancer Global Alliance. *JCO Glob Oncol* 2021; **7**: 976-84.
467. Weeks JC, Catalano PJ, Cronin A, et al. Patients' Expectations about Effects of Chemotherapy for Advanced Cancer. *New England Journal of Medicine*: *New England Journal of Medicine (NEJM/MMS)*; 2012. p. 1616-25.
468. Weeks JC, Cook EF, O'Day SJ, et al. Relationship Between Cancer Patients' Predictions of Prognosis and Their Treatment Preferences. *JAMA: American Medical Association*; 1998. p. 1709-14.
469. Smith-Uffen MES, Johnson SB, Martin AJ, et al. Estimating survival in advanced cancer: a comparison of estimates made by oncologists and patients. *Supportive Care in Cancer*: Springer; 2020. p. 3399-407.
470. Chen CH, Kuo SC, Tang ST. Current status of accurate prognostic awareness in advanced/terminally ill cancer patients: Systematic review and meta-regression analysis. *Palliative medicine*: *Palliat Med*; 2017. p. 406-18.
471. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA: JAMA*; 2008. p. 1665-73.
472. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*: *J Clin Oncol*; 2012. p. 4387-95.
473. Kaplowitz SA, Campo S, Chiu WT. Cancer patients' desires for communication of prognosis information. *Health communication*: *Health Commun*; 2002. p. 221-41.
474. Back AL, Arnold RM. Discussing prognosis: "How much do you want to know?" Talking to patients who are prepared for explicit information. *Journal of Clinical Oncology*: *J Clin Oncol*; 2006. p. 4209-13.
475. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. *British journal of cancer*: *Br J Cancer*; 2001. p. 48-51.
476. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Annals of internal medicine*: *Ann Intern Med*; 2001.
477. Baile WF, Lenzi R, Parker PA, Buckman R, Cohen L. Oncologists' attitudes toward and practices in giving bad news: an exploratory study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*: *J Clin Oncol*; 2002. p. 2189-96.
478. Fenton JJ, Duberstein PR, Kravitz RL, et al. Impact of Prognostic Discussions on the Patient-Physician Relationship: Prospective Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*: *J Clin Oncol*; 2018. p. 225-30.
479. Vasista A, Stockler MR, Martin A, Lawrence NJ, Kiely BE. Communicating prognostic information: what do oncologists think patients with incurable cancer should be told? *Internal medicine journal*: *Intern Med J*; 2020. p. 1492-9.
480. Fallowfield LJ, Jenkins VA, Beveridge HA. Truth may hurt but deceit hurts more: communication in palliative care. *Palliative medicine*: *Palliat Med*; 2002. p. 297-303.
481. Barnett MM. Does it hurt to know the worst?--psychological morbidity, information preferences and understanding of prognosis in patients with advanced cancer. *Psycho-oncology*: *Psychooncology*; 2006. p. 44-55.

482. Enzinger AC, Zhang B, Schrag D, Prigerson HG. Outcomes of Prognostic Disclosure: Associations With Prognostic Understanding, Distress, and Relationship With Physician Among Patients With Advanced Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2015. p. 3809-16.
483. Hagerty RG, Butow PN, Ellis PM, et al. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2005. p. 1278-88.
484. Gattellari M, Voigt KJ, Butow PN, Tattersall MHN. When the treatment goal is not cure: are cancer patients equipped to make informed decisions? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2002. p. 503-13.
485. Nahm SH, Stockler MR, Martin AJ, et al. Using three scenarios to explain life expectancy in advanced cancer: attitudes of patients, family members, and other healthcare professionals. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer: Support Care Cancer*; 2022. p. 7763-72.
486. Kiely BE, McCaughan G, Christodoulou S, et al. Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer: Support Care Cancer*; 2013. p. 369-76.
487. Kiely BE, Martin AJ, Tattersall MHN, et al. The median informs the message: Accuracy of individualized scenarios for survival time based on oncologists' estimates. *Journal of Clinical Oncology: American Society of Clinical Oncology*; 2013. p. 3565-71.
488. Stockler MR, Tattersall MHN, Boyer MJ, Clarke SJ, Beale PJ, Simes RJ. Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer. *British Journal of Cancer: Nature Publishing Group*; 2006. p. 208.
489. 3 SCENARIOS FOR SURVIVAL. 2019. <https://ctc.usyd.edu.au/3scenarios/> (accessed 30 August 2023).
490. CancerSurvivalRates. 2022. <https://cancersurvivalrates.com/> (accessed 30 August 2023).
491. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2010. p. 1203-8.
492. WHO traditional medicine strategy: 2014-2023. 2013. <https://web.archive.org/web/20230430163013/https://www.who.int/publications/i/item/9789241506096> (accessed 30 April 2023).
493. Witt CM, Balneaves LG, Cardoso MJ, et al. A Comprehensive Definition for Integrative Oncology. *JNCI Monographs* 2017; **2017**(52).
494. Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How Many Cancer Patients Use Complementary and Alternative Medicine: A Systematic Review and Metaanalysis. *Integrative Cancer Therapies* 2012; **11**(3): 187-203.
495. Spence D, Brown K, Smith S, et al. Jamaican Cultural and Spiritual Guidance in Caring for Cancer Patients, Jamaica. *Global Perspectives in Cancer Care: Religion, Spirituality, and Cultural Diversity in Health and Healing*: Oxford University Press; 2022: 0.
496. Abrams D, Weil A. *Integrative Oncology*: Oxford University Press; 2014.
497. About Herbs, Botanicals & Other Products. 2023. <https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs> (accessed 1 May 2023).
498. Yonas MA, Jones N, Eng E, et al. The art and science of integrating Undoing Racism with CBPR: challenges of pursuing NIH funding to investigate cancer care and racial equity. *Journal of urban health : bulletin of the New York Academy of Medicine* 2006; **83**(6): 1004-12.

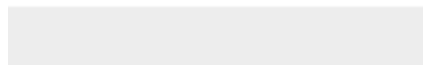
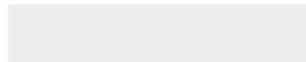
499. Baker SL, Black KZ, Dixon CE, et al. Expanding the Reach of an Evidence-Based, System-Level, Racial Equity Intervention: Translating ACCURE to the Maternal Healthcare and Education Systems. *Frontiers in public health: Front Public Health*; 2021.
500. Enard KR, Nicks SE, Campbell BA, McClure SM. In pursuit of equity: partnering to improve breast and prostate cancer outcomes among African Americans. *Cancer causes & control : CCC: Cancer Causes Control*; 2021. p. 473-82.
501. Rodriguez NM, Casanova F, Pages G, et al. Community-based participatory design of a community health worker breast cancer training intervention for South Florida Latinx farmworkers. *PloS one: PLoS One*; 2020.
502. Lynch KA, Bernal C, Romano DR, et al. Navigating a newly diagnosed cancer through clinician-facilitated discussions of health-related patient values: a qualitative analysis. *BMC palliative care* 2022; **21**(1).
503. Desai AV, Michael CL, Kuperman GJ, et al. A Novel Patient Values Tab for the Electronic Health Record: A User-Centered Design Approach. *Journal of medical Internet research: J Med Internet Res*; 2021.
504. Kamen CS, Reichelt M, Dadgostar P, et al. Sexual and gender minority cultural humility training for oncology settings: An example of iterative adaptation and implementation. *Frontiers in health services: Front Health Serv*; 2022.



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Supplementary Materials

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The Lancet Breast Cancer Commission Report

Executive summary

The Lancet Breast Cancer Commission, a diverse multidisciplinary international group, are unanimous in our determination to ~~try and~~ improve the lives of all people everywhere globally who live with or who are at risk of breast cancer. ~~irrespective of where they live.~~ We came together in July 2021 and are committed to raising the standard of breast cancer care to close, whilst closing the equity gap in that care which exists between and within countries. Over a 2-year period, we brainstormed ideas, scoped the literature, obtained funding for dedicated pilot research which has provided to provide new data, and produced this Commission report with a single purpose: to reduce the impact that increase prevention and improve outcomes for every individual affected by breast cancer has on society today and in the future.

Lancet Breast Cancer The Commission new findings

Our Lancet Breast Cancer Commission report highlights that, despite tremendous advances in learned quickly that the key issues regarding breast cancer research and treatment in recent decades leading to a 40% reduction in reach for beyond biomedical determinants. We considered the abundance of evidence that breast cancer mortality in some high-income countries (HICs), there remain gross inequities was inextricably linked with many groups being systematically left behind, ignored, and even forgotten. Our findings suggest this is mistaken as people with breast cancer are indispensable to our socioeconomical fabric and culture.

We show that the number of people living with metastatic breast cancer (MBC) is currently unknown as cancer registries do not record relapse. Many patients with MBC feel abandoned, isolated, alone, and may not receive appropriate care, both in high and low-middle income countries: this should and can be tackled. With adequate evidence-based resources and a shift in the current negative societal attitudes toward the disease, it may be possible to cure some patients with MBC, treat most, alleviate the suffering of all, and forget or abandon no-one.

We have identified that the hidden costs of breast cancer and associated suffering are considerable, varied, and with far-reaching impact. Costs and suffering can be financial, physical, psychological, emotional, gender, ethnicity, and social; justice themes, and when these impact on children, families, local communities, and wider society. These can occur at all stages of breast cancer and are evident even within health services that are free at the point of delivery. Exposing and reducing both costs and suffering provides incentive for policymakers to invest in prevention, early detection, cost-effective therapy, and optimal management of breast cancer.

We demonstrate that improving patient communication and decision making in breast cancer improves quality of life and body image, but factors intersect it produces perhaps the starkest examples of disparity and inequity. However, we also adherence to therapy which can impact on survival. Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, there discovered great reason for hope and concluded that lessons learnt from this condition, could be an opportunity to regain power and emerge stronger than before, with people exercising empowerment in also provide a positive "beacon" for other areas of their lives.

Lancet Breast Cancer Commission reinforces and builds on existing evidence

We acknowledge that early detection of breast cancer is of fundamental importance and should be available to all individuals wherever they live. We encourage broadening breast cancer early detection efforts in low- and middle-income countries (LMICs) from a narrow focus on mammographic

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screening, which may be unaffordable or unachievable in limited resource settings, to include breast cancer 'early diagnosis' as recommended by the World Health Organisation (WHO).

Every country that successfully reduced national breast cancer mortality rates between 1990 and 2020 now has at least 60% of invasive breast cancers at stages I or II. Recent evidence shows that awareness and education focusing on finding and treating symptomatic (palpable) breast cancers when they are first discoverable promotes stage-shifting toward or even surpassing this 60% threshold, a finding that is especially relevant for women younger than screening age, as well as older women living in regions where limited healthcare access prevents more progressive early detection efforts to be employed.

Lancet Breast Cancer Commission roadmap for change

We have developed an inclusive evidence-based roadmap to address these urgent breast cancer, and wider health and social challenges. The roadmap is divided into 6 themes:

Prevent - breast~~The result of this work has culminated in 6 specific key messages. These warn of the consequences of inaction, together with a positive, aspirational vision of what could be achieved with global solidarity (see Panel 1: Summary of the Lancet Breast Cancer Commission key messages):~~

1. Breast cancer prevention

Breast cancer is the most common cancer worldwide and, by 2040, the annual incidence of new breast cancers is predicted to be over 3 million cases per year, with the incidence rising most rapidly in low- and middle-income countries. The mindset that this upward trajectory is inevitable and therefore acceptable should must be changed as action now can prevent many of these future breast cancers.

We emphasise that breast ~~Breast~~ cancer risk factor education is vital but should be combined with alongside policy change to support sustained behaviour change and decrease health inequalities. Policy makers should must reject commercial marketing for products that increase breast cancer risk. Co-ordinated approaches ~~Approaches~~ to systematically identify individuals at increased risk of breast cancer and to offer them evidence-based prevention interventions, are proposed as should be an aspirational goal to and be developed through ongoing research.

2. Personalise - Breast cancer treatment innovation through science and clinical research~~technology~~

Innovation through science and digital health can facilitate equitable and prompt access to the right breast cancer treatment at the right time for each individual whilst respecting personal needs and preferences. Better targeting of existing treatments through development of validated biomarkers is needed to identify those people who benefit the most and to reduce treatment burden for those likely to have more toxicity than gain. We identify the ~~There is~~ need to develop and facilitate novel, efficient, patient-centred, translational clinical trials and enable a research culture and infrastructure to ensure these can be undertaken done across the globe.

Digital health technology can facilitate personalised breast cancer care ~~innovation~~ through integration of multi-modal complex datasets; promote flexible, coordinated care particularly for vulnerable patients; democratise access to research; and decentralise trial participation. We suggest that, if ~~if~~ used optimally, digital health ~~innovative advances in breast cancer science and~~ technology can alleviate inequities in breast cancer ~~inequalities~~ rather than drive them, and these principles can be applied to other health conditions.

Include - our Commission report places MBC as a central theme and urges for inclusion of this important group. We justify why optimal MBC management

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3.—Optimal management of metastatic breast cancer

Many patients with metastatic breast cancer (MBC) feel abandoned, isolated, and alone and some do not receive appropriate care: this should and can be tackled. The number of people living with MBC is unknown and high-quality cancer registry data needs to be collected worldwide. Stigma and inequity for those with MBC must be addressed. With adequate resources and a shift in attitudes, it may be possible to cure some of these patients, treat most, alleviate the suffering of all and forget no one.

The dedicated section on MBC justifies why its optimal management is valuable to individuals, families, and society. We show it includes results of the Commission's international health care professionals survey, which suggests that there is a growing belief that patients with some subtypes of MBC can be treated as chronic illnesses for many years, and some patients may even be cured.

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In addition to collecting data on cancer incidence and stage at presentation, we call for high-quality data on cancer relapse worldwide to include not just those with MBC, but other metastatic cancers. We recommend that stigma around MBC can be addressed through education and awareness of all stakeholders and society.

4.—We must Collaborate to close the equity gap through global early diagnosis, treatment frameworks, and innovative technology. Women with low incomes Breast cancer global gaps and inequities

Poorer women and those from minoritised populations in all countries, often have their breast cancer diagnosed at late-stage with a breast cancer and are at high-risk of dying from their cancer. The early diagnosis This inequity gap will widen without intervention. Equitable access to early diagnosis and treatment is a fundamental need for all individuals to improve breast cancer survival and quality-of-life.

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In collaboration with the WHO Global Breast Cancer Initiative, we call for action to deliver “stage-shifting”, as a sustained decline in breast-cancer mortality rates is achieved by diagnosing at least 60% of invasive cancers at stage I-II. We show that tools Tools to achieve this 60% threshold can be achieved through population-based mammographic screening programmes when they are feasible to establish and operate operated sustainably, but early detection approaches should must in practice be adapted to local context and resources. We suggest that technology Technology innovations could can catalyse the speed and efficacy of early breast cancer diagnosis and treatment implementation globally, and these should be combined with an integrated health systems policy, education, and advocacy, are needed. These pioneering approaches in breast cancer could also be used as a model for other cancers.

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5.—Hidden costs of breast cancer

Costs of breast cancer and associated suffering are immense, and society and policymakers currently see only the tip of an iceberg: these should be exposed and quantified in order to be reduced. Costs include financial, emotional, social, and economic costs; these impact on children, families, local communities, and wider society and can occur at all stages of breast cancer, from risk prevention, early diagnosis, and MBC.

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New Identify - the hidden data from this Commission show that even within health services that are free at the point of delivery, those affected by breast cancer face substantial additional costs and serious these may particularly impact the poorest in society. Serious health-related suffering of breast cancer goes unmeasured in global health metrics, so its alleviation is not prioritised by policymakers. Our Commission calls for new and Exposing and reducing costs and suffering provides a major incentive for policymakers to invest in prevention, early detection, cost effective therapy, and optimal

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~~management of breast cancer. New validated health economic tools to capture the myriad of costs and serious health related suffering are required to determine what value society places on relief of these costs and suffering experienced by patients, caregivers, and families experiencing related to breast cancer.~~

~~We also indicate the urgency of developing metrics, and to measure the full benefits that patients and society places on alleviating suffering related to breast cancer, of addressing these costs. These novel tools could influence policy makers to set new priorities for breast and other cancers to guarantee that, in addition, supportive and palliative care is should be available to all and at every stage of across the breast cancer pathway, alongside financial protection to prevent catastrophic and impoverishing health expenditure from direct and indirect health care costs and lost family income continuum.~~

~~6. Communicate - being female is the greatest risk factor for breast cancer and women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings. As such, our Communication and empowerment~~

~~The final theme section focuses on communication and empowerment related to breast cancer. We suggest and suggests that prioritising patient autonomy regarding medical treatment is paramount to close the gender equity gap and will have broader impacts for the physical, social, and financial wellbeing of women globally. Being female is the greatest risk factor for breast cancer and women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings.~~

We propose a framework to improve communication and aid decision making for those with breast cancer. Placing patients at the centre of clinical communication, and empowering them to exercise their voices, become fully informed, and choose their level of involvement in decisions about their care, is an achievable and worthwhile goal worldwide. ~~Improving patient communication and decision making in breast cancer improves quality of life and body image, but also adherence to therapy which can impact survival.~~ Health communication training should be person-centred and include: eliciting

- ~~Eliciting~~ patients' core values and preferences for information; explaining
- ~~Explaining~~ goals of care; risk
- ~~Risk~~ benefit communication; skills
- ~~Skills~~ to help estimate and explain prognosis and share serious news; skills
- ~~Skills~~ to empathically but honestly respond to questions; and consideration
- ~~Consideration~~ of local cultural traits and individual differences.

~~Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, there could be an opportunity to regain power and emerge stronger than before, with women exercising empowerment in other areas of their lives.~~

Measurable indicators of change and future work

~~Our inclusive report describes a road map for change, which is evidence-based and includes new compelling data. It is inclusive and designed for everyone with any connection to with breast cancer but is particularly aimed at policymakers. We have suggested detailed measurable indicators of progress in of this road map, with targets and suggested responsible groups. These indicators are designed to be actionable, auditable, and to facilitate lobbying for change.~~

Our work with the Lancet Breast Cancer Commission will not end with ~~this the publication of the report~~, as it has catalysed lasting partnerships between co-authors, as well as with other Commissions and key international organisations and patient groups. As a result, we have on-going collaborative research and will continue to strive to raise the bar and close the equity gap for breast cancer.

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Panel 1 - Summary of the Lancet Breast Cancer Commission key messages

The Lancet Breast Cancer Commission report shows glaring inequities, with **6 key messages:**

1. ~~Action now could prevent many groups with breast cancer being of the 3 million per year new breast cancers predicted by 2040 through a united global policy change to minimise modifiable risk factors, with an aspirational goal to systematically left behind identify and forgotten. This is a global blunder. People with help all those at increased risk of developing breast cancer.~~

~~Innovation through breast cancer are indispensable to our socioeconomical fabric science and culture. digital health can facilitate equitable~~

New findings:

2. ~~The number of people living with metastatic breast cancer (MBC) is unknown and many do not receive appropriate care. prompt access to the right treatment at the right time for each individual whilst respecting personal needs and preferences.~~

3. ~~With adequate resources and a shift in attitudes, it may be possible to cure some patients with MBC metastatic breast cancer, treat most, alleviate the suffering of all, and forget or abandon no one.~~

Hidden

4. ~~Poorer women everywhere are often diagnosed with advanced stage disease and are at high risk of dying from breast cancer costs and this equity gap can be closed through global early diagnosis and treatment frameworks and innovative technology.~~

5. ~~Costs of breast cancer and associated suffering can be financial, physical, psychological, emotional, and social; these impact children, families, communities, and wider are immense with society. Exposing and reducing costs and suffering provides incentive for policymakers to invest in prevention, early detection, cost-effective therapy only seeing the tip of an iceberg these should be exposed, quantified, and optimal management of breast cancer. then reduced for all.~~

6. ~~Improving patient communication in breast Breast cancer improves quality of life and body image, but also adherence to therapy which can impact survival. Breast cancer robs many is a disease described by patients as robbing them of power, but through good person-centred communication and facilitating patient autonomy, there could be provide an opportunity to regain power, and emerge stronger than before, and exercise empowerment in other areas of their lives.~~

Roadmap for change

An inclusive roadmap addresses these urgent breast cancer challenges through 6 themes:

- Society should **prevent** as many as possible of the 3 million new breast cancers per year that are predicted to occur by 2040 through a united global policy change to minimise modifiable risk factors, as well as coordinated, systematic personalised risk prevention programmes.
- Health systems and clinicians should **personalise** the right treatment at the right time for each individual whilst respecting personal needs and preferences.
- We call for high-quality cancer registry data on cancer relapse to be collected worldwide, to **include** not just those with MBC, but other metastatic cancers.
- **Collaboration** is key to close the equity gap through global early diagnosis, treatment frameworks and innovative technology.

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- We should **identify** what value society places on relief of the hidden costs and suffering related to breast cancer, and to measure the benefits of addressing these costs.
- Placing patients at the centre of clinical **communication** and empowering them to exercise their voices about their breast cancer care is an achievable and worthwhile worldwide goal.

Introduction

Scientific advances that have dramatically improved what is possible for breast cancer prevention and treatment, contrast starkly with the reality of failure to deliver good care to most patients with breast cancer around the world. The Lancet Breast Cancer Commission calls for raised awareness and change to ensure the translation of evidence into policy and practice for breast cancer care and prevention.

In 2020, over 2.3 million women were diagnosed with breast cancer, and breast cancer caused 685,000 deaths globally.¹ In addition, around 1% of the total incidence of breast cancer occurs in men. Breast cancer is now the world's most prevalent cancer; at the end of 2020, 7.8 million women were alive having been diagnosed in the previous 5 years, with an unknown number of people living with metastatic breast cancer.¹

Breast cancer affects people in every country, but large geographical variations exist around the world. For example, annual incidence rates range from <40 per 100,000 females in some Asian and African countries, to over 80 per 100,000 in Australia/New Zealand, Northern America, and parts of Europe. Economic transitioning countries carry a disproportionate share of breast cancer deaths. The breast cancer burden is predicted to increase to more than 3 million new cases per year (an increase of 40%) and more than 1 million deaths per year (an increase of 50%) by 2040. In low human development index (HDI) countries, the numbers of new cases and deaths are anticipated to double by 2040¹, and in medium HDI countries the incidence and mortality are predicted to increase by 70% and 60% respectively.

~~Ignoring individuals with metastatic breast cancer (MBC) is a mistake.~~ In 2020, 4.4 million women died from cancer worldwide, leaving behind 1.04 million maternal orphans, and 25% of these orphans lost their mother to breast cancer.² Importantly, there is a strong inverse correlation between the HDI and the number of new maternal orphans per 100 female cancer deaths.³ It is estimated that for every 100 women who die of breast or cervical cancer in African countries, between 14 and 30 children will die as a result.² Thus, the chronic social disruption and financial harm of breast cancer will continue to disproportionately impact low and middle-income countries (LMICs) for generations to come. In addition, deep gender, ethnic, and socioeconomic divides exist both within and between countries.⁴ Breast cancer represents one of the most significant examples of the gender, racial, and ethnic inequities in oncology.⁵

Despite these stark statistics, biomedical advances have produced dramatic improvements in breast cancer outcomes over the last 30 years, and this has contributed to falling mortality rates, but mostly in higher income countries. A crucial pivotal point for breast cancer has been reached globally, whereby either current inequities both between and within countries widen irreparably, or society unites to ensure equitable access to evidence-based breast cancer prevention and care as a fundamental right for all.

The Lancet Breast Cancer Commission – structure and aim

It is against this background that the Lancet Breast Cancer Commission convened in July 2021. Its aim is to provide a new perspective on an old and seemingly insurmountable global problem and identify key areas for change to influence global policy and ultimately improve lives of those affected by breast cancer.⁶ The Commission is multidisciplinary and diverse in terms of geographical distribution (high-,

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middle- and low-income countries are represented), gender, ethnicity, professional role, career-level and includes patient advocate commissioners with lived experience of early and metastatic breast cancer (see supplementary material 2 for all those involved). The first commission meeting identified 5 workstreams, each with 2 co-chairs, to co-ordinate scoping and evidence synthesis with assistance from early career researchers around 12 key questions identified by the group.⁶ Main meetings were held quarterly over 2 years. The vast majority were virtual, with one 2-day meeting in Cambridge in summer 2022. Workstream meetings were held in between, and work that was carried out consisted of literature reviews, an international healthcare professionals' survey, and new research projects, some of which were funded specifically to produce new data to inform the Commission report. The Breast Cancer Commission is collaborating with other key groups including the Lancet Commission on Cancer And Health Systems,⁷ and Lancet Commission on Global Access to Palliative Care and Pain Relief,⁸ the WHO Global Breast Cancer Initiative, and the ABC Global Alliance.

The Lancet Breast Cancer Commission—a new narrative for change

The Commission decided to re-think the approach to breast cancer. Instead of focusing on breast cancer as a problem, the Commission raised the question:

What is distinctive about breast cancer and what can we learn from it?

Breast cancer is a disease that can affect any person, but it is disproportionately common among women, who constitute a group whose fundamental human rights have historically been accorded lesser respect than men. This is the case in high-, middle-, and low-income settings alike, and recent experience suggests that this continues to be true.⁹ The Commission seeks to emphasise how its recommendations may go beyond the specific setting of breast cancer to transform culture in ways that lead to the more equitable empowerment of all individuals in making decisions related to their own health and beyond. By treating breast cancer as an index condition or even a positive “beacon”, we may learn how better to improve women's health and the health of all members of marginalised groups in our society. Therefore, this report deliberately has the patient with breast cancer at its centre, and focuses on ways to empower individuals, in the context of growing recognition of the social determinants of health.

Building upon this foundation, the Commission proposed a second related question:

How can we influence positive change for those affected by breast cancer, and ultimately for other health conditions?

Given these two underpinning questions, the Commission report is divided into 6 main sections:

- 1—Breast cancer prevention
- 2—Breast cancer treatment innovation through science and technology
- 3—Optimal management of metastatic breast cancer
- 4—Breast cancer global gaps and inequities
- 5—Hidden costs of breast cancer
- 6—Communication and empowerment

Each section starts with a summary and ends with suggested measurable indicators for change. Any forward-looking document runs the risk of being seen as platitudinous rather than radical: gilding the surface of what happens rather than getting to the roots of the problem. The commissioners felt it important therefore that their work led to real change for the sake of breast cancer patients, past, present, and future, worldwide. We decided to include a set of indicators that would reflect specific changes that we felt are needed to empower real change. These indicators were drafted by the leads of the six final themes, focussed not only on what the indicator could be, but also who or what should

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be responsible for ensuring their delivery, and were based on the appraisal of evidence accumulated during the two years, and then shared with the whole commissioning group for comments and revisions. Whilst they are therefore in essence 'expert opinion', they are based on hundreds of years' collective understanding of breast cancer as a global and system problem, and aimed at being broad, practical, and adaptable to specific contexts. The specific numerical targets were drafted in the same way and chosen as being likely to engineer real change for patients, whilst acknowledging that there are always challenges in changing systems.

Individuals with or at risk of breast cancer are referred to variously as 'individuals', 'patients'~~"individuals"~~, "~~patients~~" and sometimes 'women'~~"women"~~ throughout the report, but the Commission acknowledges that definitions are much broader, for example including men and transgender people who may experience considerable stigma and inequity (*see supplementary material 3 developed through the Commission - Towards Breast Cancer Care Equity: Considerations for Sexual and Gender Minority Persons*). A glossary of terms used within the report is also available in *supplementary material 1*.

~~The~~In summary, the Commission report is *not* a textbook chapter or review of the biomedical management of breast cancer but, in response to the very real inadequacies and inequities in global breast cancer care, it is a call to action on specific important global challenges, each coupled with the opportunities for positive change. We propose this compelling evidence-based narrative to start the journey of positive change for all those affected by breast cancer, now and in the future. ▲

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| Theme

Section 1: Breast Cancer Prevention

Panel 2 - Summary for breast cancer prevention

- Action now could prevent as many as possible of the 3 million per year new breast cancers per year that are predicted to occur by 2040.
- Breast cancer risk factor education is vital but should be combined alongside policy change to support sustained behaviour change and decrease health inequalities.
- Governments and policy makers should have the will, courage, and integrity to reject lobbying from vested interest groups that profit from exposing populations to breast cancer risk factors.
- Approaches to systematically identify individuals at increased risk of breast cancer and to offer them evidence-based prevention interventions, should be implemented and refined through on-going research.

Worldwide, women have on average, a 1 in 12 risk of breast cancer by age 75, and the incidence is rising.^{10,11} With the current trajectory, by 2040, an estimated 3 million individuals will be diagnosed each and every year.¹⁰ This upward trajectory is neither acceptable nor inevitable: action now can prevent many of these future cancers. Prevention potentially offers the most cost-effective strategy for breast cancer control and would reduce the impact of breast cancer on individuals and all aspects of society.^{11,12,13}

There are two complementary approaches to primary prevention:

- i) Population prevention - minimising risk factor exposure for all women, regardless of their personal breast cancer risk. Understanding to what extent each risk factor contributes to the number of individuals with breast cancer in a population, can inform the focus of education programs in partnership with policy change to drive population prevention.
- ii) Personalised prevention through targeted delivery of intensified prevention interventions. First, identifying the 20-30%^{14,15} of women at substantially higher than average risk of breast cancer using existing tools; refining these tools and their implementation through on-going research and development. Based on an individual's risk, offering proven interventions to substantially reduce breast cancer risk, such as inexpensive medications or, for those at very high risk, preventive surgery.

Breast Cancer Risk Factors

The most important risk factor for breast cancer is being a woman, and risk generally increases with increasing age. At least 5% of breast cancer is attributable to rare inherited pathogenic variants in major breast cancer predisposition genes, of which half are due to *BRCA1* and *BRCA2*.^{16,17} Women with pathogenic variants in these genes are at substantially increased risk for breast cancer and can be identified by genetic testing. There are other more common genetic variants that individually increase breast cancer risk very little, but clustering of several variants in one individual can lead to larger increases in breast cancer risk.¹⁸ The polygenic risk score summarises a person's risk of breast cancer attributable to their individual profile of these common variants.¹⁸ Other established breast cancer risk factors include: family history of breast cancer, a history of radiation exposure (involving breast), non-invasive breast conditions such as atypical hyperplasia and lobular carcinoma in situ, being taller, reproductive history, and modifiable risk factors such as alcohol consumption, being overweight, physical inactivity, limited or no breast feeding in parous women, exogenous female hormone use, and breast density (modifiable with the use of medications).¹⁸⁻⁴⁰¹⁹⁻⁴¹

See Panel 3 → Major Potentially Modifiable Breast Cancer Risk Factors.

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Panel 3 - Major Potentially Modifiable Breast Cancer Risk Factors

Post-menopausal overweight and obesity:

- Associated with post-menopausal breast cancer, especially in oestrogen receptor (ER) and progesterone receptor (PR) positive tumours.^{25,28,31-33}
- Worldwide, 110,000 breast cancers were attributable to obesity in 2012^{27,28}, mostly in North America, Western and Eastern Europe and Latin America.^{27,28}
- The percentage of breast cancers attributable to obesity is around 8-13% in some HIC^{25,39}, and is up to 28% in post-menopausal African American women.^{40,41}

Alcohol:

- Alcohol is a well-established carcinogen.^{41,42,43}
- There is no 'safe'/'safe' consumption threshold: 13% of all cancer attributable to alcohol in Europe in 2017 was due to 'light-moderate'/'moderate' consumption (20g/2 standard drinks per day), of which half were breast cancers.⁴⁴
- Compared with non-drinkers, relative risk of breast cancer is 9%, 13%-23% and 60% higher in women who consume up to 15g (2 units), 12.5-50g (1.5-6 units) or 50g+ (6+ units) of alcohol per day, respectively.^{44,45,46}
- 98,300 breast cancers (i.e. 4% of all breast cancers globally and 8%-16% in some HICs) were attributable to alcohol in 2020.^{25,27,29}
- Cessation or a sustained reduction in consumption reduces cancer incidence.^{46,47}

Breastfeeding:

- The percentage of breast cancer cases attributable to not breast-feeding in the UK is 4.7%²⁵, but is not well defined in LIC and LMIC.⁴⁷
- The relative risk of breast cancer decreases by 4.3% for every 12 months of breastfeeding.⁴⁸, but is not well defined in LIC and LMIC.⁴⁸
- The relative risk of breast cancer decreases by 4.3% for every 12 months of breastfeeding.⁴⁹
- Reduces the risk of triple negative breast cancer, an aggressive subtype that is more common in younger women and those with African ancestry.⁵⁰⁻⁵²

Physical Inactivity:

- Is associated with an increased risk of breast cancer, independent of body size.³³
- Between 2%-10% of breast cancers are attributable to physical inactivity in HICs.³⁸
- Is associated with an increased risk of breast cancer, independent of body size.³⁴
- Between 2%-10% of breast cancers are attributable to physical inactivity in HICs.³⁹
- Breast cancer disability-adjusted life years (DALYs) attributable to low physical activity are highest in HICs, but LICs have the fastest increase in low physical activity-associated DALYs.³⁰

Exogenous Hormone Use (HRT):

- Combined oestrogen-progestogen HRT increases breast cancer risk, which increases with longer duration of use. For current users of combined HRT for 1-4 years, relative risk is 1.60.^{12,53} This excess risk is not seen for oestrogen only HRT⁵³ but unopposed oestrogen should not be used by women with a uterus because of the increased risk of uterine cancer.^{11,42}
- The relative risk of breast cancer in current users of combined oral contraceptives is 1.24.⁵³ This risk declines after cessation with no excess risk 10 years later.⁵³ Risk is similar with other forms of hormonal contraception. The relative risk of breast cancer in current users of combined oral contraceptives is 1.24.⁵⁴ This risk declines after cessation with no excess risk 10 years later.⁵⁴ Risk is similar with other forms of hormonal contraception.^{36,37}

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- The percentage of breast cancer attributable to HRT and hormonal contraceptives in the UK is 2.1% and 0.8% respectively.²⁵

Population breast cancer prevention

Up to one quarter of breast cancers in HICs could be prevented by modifying risk factors (Figure 2).^{19,24-28} The proportion of breast cancer attributable to each risk factor varies by world region and socio-demographic index (SDI).^{55,56} Deriving global population attributable risk estimates is difficult due to limited epidemiological studies in LIC and LMIC^{47,48}, however it is estimated that 21% of breast cancer deaths worldwide could be attributed to alcohol, post-menopausal overweight and obesity, and physical inactivity.^{38,39}

Population-wide approaches to breast cancer prevention have mainly focused on education to motivate individual responsibility in reducing exposure to risk factors. There is low community awareness about modifiable risk factors for breast cancer in most countries.⁵⁷⁻⁶³ Educational interventions can increase knowledge about risk factors⁶⁴, however knowledge alone is not generally sufficient for sustained behaviour change.

There is evidence that some breast cancer prevention strategies work for some people. For example, women who followed the American Cancer Society guidelines on weight control, physical activity, alcohol intake and diet⁶⁵ had 22-31% lower risk of breast cancer compared to women who were less adherent.^{66,67} Reliance on individual responsibility, while empowering for some, may be perceived as a 'blame culture' for others. Changing health behaviour to reduce the risk of breast cancer may be more challenging for women struggling with other health and social problems. For example, a small proportion of women are unable to breastfeed and must have access to formula milk. Another example. For example, there is ~~thea~~ positive dose-response relationship between obesity-related cancer mortality in the US and 'food deserts' (fewer healthy food resources) and 'food swamps' (higher access to fast food). The same study demonstrated higher rates of poverty and non-hispanic Black residents in regions with high obesity-related cancer mortality, demonstrating the complex intersection between cancer, ethnicity, and poverty.^{67,68}

In contrast, policy and legislative change have the potential to reach an entire population and, in some cases (such as taxation), can have the greatest impact in disadvantaged groups, reducing deprivation-based inequalities in harms attributable to risk factors.⁶⁹⁻⁷³ Increased tobacco tax has consistently resulted in immediate and sustained reduction in the prevalence of smoking in both HIC and LICs⁷²⁻⁷⁴, when coupled with other policies which increase the financial and social cost of smoking. In addition, the introduction of plain paper packaging of tobacco products in Australia was associated with a 25% reduction in cigarette smokers over the subsequent 3 years.^{74,75}

A key aspiration of this Commission is to help policymakers recognise that the current predicted upward trajectory of breast cancer incidence can be modulated by policies that reduce risk factor exposure at the population level. Development and delivery of such policies will require governments to demonstrate strong political will and integrity in resisting lobbying by industries that might be adversely affected by the policy changes. Implementation of education strategies will be needed to support and enhance policy changes. The top targets are alcohol consumption, obesity, physical inactivity, and inadequate breastfeeding (see Figure 2: Approximate proportion of breast cancers in high income countries due to more readily modifiable breast cancer risk factors).

Public health policy

There are existing World Health Organisation (WHO) endorsed recommendations to reduce harmful alcohol use⁷⁵, inadequate breast-feeding⁷⁶, overweight and obesity⁷⁷, and physical inactivity.⁷⁸ The WHO provides policymakers a list of recommended cost-effective interventions to address these risk

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factors.⁷⁹ Examples of recurring policy recommendations include a focus on taxation, marketing regulation, and restrictions on the availability of alcohol and certain foods. There are existing World Health Organisation (WHO) endorsed recommendations to reduce harmful alcohol use⁷⁶, inadequate breast feeding⁷⁷, overweight and obesity⁷⁸ and physical inactivity.⁷⁹ The WHO provides policymakers a list of recommended cost-effective interventions to address these risk factors.⁸⁰ Examples of recurring policy recommendations include a focus on taxation, marketing regulation and restrictions on the availability of alcohol and certain foods.^{76,78,80} Implementation of these policies is variable.^{80,81,82} Tracking how effectively these policies have been implemented is hampered by inadequate data collection on the prevalence of breast cancer risk factors in some regions, such as adequate breast feeding.^{82,83} For improved policy implementation, there needs to be adequate data collection to understand the effectiveness of proposed interventions in different local contexts.⁸⁴

Common barriers to public health policy implementation include lack of prioritisation, perceived insufficient evidence base, the power and influence of industry over governments, variation in complex political and policy systems, and lack of resources.^{85,86} Obesity, alcohol consumption, and inadequate breast feeding are all heavily influenced by the food (including baby milk formula) and alcohol industries. Policies and legislation that limit the influence of these industries and reduce exposure of the population to risk factors is essential, as well as policies which promote protective behaviours, such as breast feeding or expressing at work.

Many of the alcohol and food industry strategies to increase consumption resemble those of the tobacco industry, so successful tobacco policies can be used to inform harm reduction policy agendas (*Panel 4 - Public health policy case study: comparing and contrasting approaches to tobacco and alcohol*). Like tobacco policies, prioritisation of sustainable, high-impact, and cost-effective alcohol and food policies supported by legislation addressing affordability and availability is needed. Restrictions on advertising and sponsorship, and penalties for false advertising should be enforced. Warning labels and public education campaigns should be independent of industry influence. Regarding physical inactivity, governments should prioritise urban planning that promote physical activity, such as providing adequate walking paths and open spaces.

Role of education in facilitating successful policy implementation

Education at a community level is important so that policies have 'social validity' and are acceptable.^{86,87} Policies that are not well understood are often unpopular and are difficult to implement, as seen during the COVID-19 pandemic where differences in public communication could potentially explain some of the observed differences in adherence to government recommended interventions across different countries.⁸⁸ Therefore, multisector and multi-stakeholder action and partnership are needed^{86,87} from politicians, celebrities (such as sporting heroes), civil organisations, and healthcare providers to encourage successful policy change at a population level.

Existing recommendations call for breast cancer awareness campaigns to target everyone.⁸⁹ The U.S. Education and Awareness Requires Learning Young (EARLY) Act aims to develop age-appropriate education initiatives for young women and their healthcare professionals to increase knowledge regarding breast cancer.^{89,90} Introducing teaching on breast cancer in the high school health education curriculum may increase awareness and knowledge about breast cancer risk factors^{91,92}, through intergenerational transmission of knowledge.⁹² Other educational methods are required, particularly where there is limited access to high school education. This could include cooperation with local authorities, faith leaders and traditional healers, as well as using social media, and engaging celebrities as ambassadors to convey the importance of breast cancer awareness.

Panel 4 - Public health policy case study: comparing and contrasting approaches to tobacco and alcohol

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	Tobacco	Alcohol
WHO recommendations	~~6 “MPOWER” tobacco control strategies:~~⁷¹ ~~6 “MPOWER” tobacco control strategies:~~⁷² M: Monitor tobacco use and prevention policies. P: Protect people from tobacco smoke. O: Offer help to quit smoking. W: Warn about the dangers of tobacco. E: Enforce bans on tobacco advertising, promotion and sponsorship. R: Raise taxes on tobacco.	WHO recommended policies:^{75,92-94,96,93-95} • Make alcohol less affordable. • Ban or restrict alcohol marketing. • Raise public awareness on risks of alcohol and cancer – 5 facts information sheet – includes message that cancers due to alcohol are preventable. • Enforce drink driving laws. • Provide interventions for hazardous drinking.
Barriers to reduction in risk factor exposure	Tobacco use is reducing in countries implementing most MPOWER measures, but: • Over 80% of the world’s 1.3 billion tobacco users live in LIC and LMIC.^{71,72} • 41 of 49 countries yet to adopt a single MPOWER measure are LIC and LMIC.^{71,72} Lack of policy adoption facilitates market expansion through aggressive marketing, low prices, 3rd party advocacy to influence policy makers, branding tobacco industry activities as corporate social responsibility initiatives.^{69,70}	WHO recommended policies:^{75,92-94,96,93-95} Barriers to alcohol control as health priority: • Influence of alcohol industry in policy making. • Lack of political will and investment. • Limited capacity to develop and implement control interventions. • Lack of robust studies and data collection. Alcohol regulation barriers: • Industry self-regulation. • Lack of international regulation. • Differences in cultural norms and context between countries. • Informally/illegally produced products challenge regulation. • Digital marketing more challenging to regulate. • Inappropriate branding alcohol industry activities as corporate social responsibility initiatives.⁹³⁻⁹⁵
Public health policy implementation	<u>Packaging</u> <u>Health warnings on cigarettes have led to lower initiation and increased cessation rates of smoking.</u>⁹⁵ ~~Health warnings on cigarettes have led to lower initiation and increased cessation rates of smoking.~~⁹⁶ Plain paper packaging of cigarettes in HIC reduces appeal of tobacco	<u>Packaging</u> Health warnings on alcoholic beverages are generally subject to voluntary action by the industry and have not been associated with a consistent change in alcohol consumption.^{99-104,100-105} Learning from tobacco control, policymakers should consider regulation

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	products, decreases uptake, and increases cessation of cigarette smoking. ^{97,98} Available evidence suggests same behavioural effect possible in LMIC. ^{98,99}	of alcohol packaging that is independent of industry influence.
	Taxation and price regulation: Taxation has consistently been demonstrated to reduce cigarette consumption.^{72,74,103,104}	Taxation and price regulation: ~~A 10% increase in alcohol price is associated with an average decrease of 5% in consumption.¹⁰⁵~~ ~~A 10% increase in alcohol price is associated with an average decrease of 5% in consumption.¹⁰⁶~~ 10% increase in minimum alcohol price in Canada was associated with 8% reduction in consumption within 2 years¹⁰⁷, and reduced alcohol-related: - deaths by 32% - hospital admissions by 9% - traffic violations by 19% - crime by 9% ~~Introduction of minimum unit pricing for alcohol in Scotland in 2018 was associated with reduced deaths and hospitalisations, especially in the lowest socioeconomic groups.⁶⁸~~Introduction of minimum unit pricing for alcohol in Scotland in 2018 was associated with reduced deaths and hospitalisations, especially in the lowest socioeconomic groups.⁶⁹

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Systematic risk assessment and personalised prevention

Current practice in HIC involves selective risk assessment and genetic testing of women who typically have already developed breast cancer with certain additional criteria such as young age or family history or Ashkenazi heritage or triple negative breast cancer subtype. Germline mutations resulting in the highest breast cancer risk (e.g. *BRCA* mutations) are present in a small percentage of women. However, a much larger group of women are at moderately increased risk of breast cancer and these women typically receive no personalised risk assessment, nor are they offered tailored prevention strategies, unless they seek out information or testing. Effective medical and surgical interventions can reduce risk in women who are at substantially greater than population risk for developing breast cancer. Medications inexpensive medications (tamoxifen, including a low dose option^{107,108}, raloxifene or aromatase inhibitors) taken daily for 3 to 5 years reduce the relative risk of breast cancer by 30%-60%¹⁰⁸⁻¹¹⁶ and should be considered for women at increased risk. Tamoxifen is an affordable option

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in LMIC and LIC countries. These medications approximately halve the risk of hormone receptor positive breast cancer in randomised trials that tested the intervention across diverse populations.^{108-113,117} Further research is needed to ascertain which patients are likely to benefit most from preventative breast cancer medicines and what is the lowest efficacious dose to give the least side effects.¹¹⁸ For hormone receptor negative breast cancer prevention, trials of the RANK ligand inhibitor, denosumab, are underway.^{118,119} Bilateral mastectomy reduces the relative risk of breast cancer by over 90%, and should be accessible for those at very high risk, such as those with high penetrance pathogenic variants in breast cancer predisposition genes.¹²¹⁻¹²⁹ However, it is important that these women are supported to feel empowered to make their own informed decision considering both potential benefits and risks (see section 6: Communication and Empowerment).

If a woman is unaware that her breast cancer risk is substantially elevated above that of the general population, then she misses the opportunity to access proven prevention strategies. Therefore, the first step in personalised breast cancer prevention is high-quality risk assessment. Proactive, systematic breast cancer risk assessment for all women (rather than just for those who request it or who are diagnosed with cancer), followed by personalised advice about effective, evidence-based preventive interventions for those at increased risk, should become an integral part of high-quality care. This is an aspirational goal that health systems and policymakers should start moving towards by using the existing assessment tools available locally. These may range from basic to more sophisticated methods depending on local infrastructure and resource, that can be developed and refined over time. Engagement of health services researchers and implementation scientists will be required to elucidate the most appropriate implementation pathways for each health care setting, taking into account health system structure and resources and sociocultural setting.

How systematic risk assessment could be achieved

Risk assessment would need to commence at a young age (e.g. 25 – 30 years) to facilitate identification of, and preventive interventions for, those who are at high risk for early-onset breast cancer (e.g. carriers of *BRCA1* pathogenic variants). Comprehensive risk assessment of all genetic and non-genetic risk factors may not be necessary when assessing risk in very young women; systematic population-based assessment of high penetrance genetic factors alone may be an appropriate first risk assessment step. This might consist of offering testing to all young women for major breast cancer predisposition genes. Studies are already examining the feasibility and acceptability of this type of genetic risk assessment in young people.¹²²⁻¹²⁴ Women with a pathogenic *BRCA1* or *BRCA2* variant and a history of breast cancer in a first degree relative are at higher risk than those without an affected first degree relative.^{123, 122} Therefore, in resource-poor settings where population genetic testing is not feasible, initial assessment of family cancer history to triage those for genetic testing might be another approach. However, not all women have an informative family structure (e.g. due to adoption, genocide, young maternal death from non-cancer causes, lack of cancer work up and/or diagnosis for family members, etc) so reliance on family history could lead to inequities.

At subsequent timepoints in an individual's life trajectory, more comprehensive risk assessment considering other genetic and non-genetic risk factors will be needed, particularly to identify women at moderate risk of breast cancer. This is a much larger group than women at very high risk. A potential subsequent timepoint for more comprehensive risk assessment could be at age 40 or when an individual considers that her childbearing is complete and risk-reducing medication such as tamoxifen could be considered. Earlier opportunities for risk assessment could be at the time of maternity care and or cervical screening. Targeted prevention interventions, such as risk-reducing medications, in women at moderate risk could potentially substantially reduce population breast cancer incidence. Risk assessment would need to occur at regular intervals, perhaps every 10 years to account for i) changing risk factors in an individual that alter the risk assessment and ii) advances in medical knowledge that might inform risk assessment. Systematic risk assessment using risk assessment

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algorithms that have been validated in the relevant population could be embedded in broader routine health care, specifically in i) primary care and ii) cancer screening and early detection programs. Countries that already have population-wide mammographic screening programmes could consider incorporating routine risk assessment, linked to prevention interventions and advice, within these programmes.¹²³⁻¹²⁵ This would be opportune as mammographic density is an important risk factor for breast cancer.^{127,126}

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There are several tools, based on mathematical algorithms, available to estimate a woman's breast cancer risk according to her risk factor profile. No one algorithm or tool is best in all circumstances.¹²⁷ Algorithms such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model (BOADICEA)¹²⁸ and the Breast Cancer Intervention Study model (IBIS)^{130,129} which integrate both genetic and non-genetic risk factors tend to perform best in most settings.¹³⁰

The optimal validated algorithm for systematic breast cancer risk assessment will vary between settings, depending on the ethnic and age characteristics of the population being assessed and the availability of risk factor information in each setting. It should be easy to use and affordable. Validated risk assessment tools can be adapted and calibrated to evaluate performance in the local context. For example, the BCRAT tool has been validated for use in white women, Black/African American women, Hispanic women and for Asian and Pacific Islander women in the United States.¹³¹⁻¹³³ Risk assessment tools have been adapted for Korean, Nigerian, Chinese and Mexican populations, as well as for Black and mammographically screened populations in the United States.^{56,123,134-138} Recent attempts at using genetic ancestral composition to expand polygenic risk assessment to women of diverse ancestries are a step towards improving equity in breast cancer risk assessment.¹³⁹ In women undergoing age-based population mammographic screening, risk estimation tools that incorporate mammographic density are likely to be valuable, although only likely to be feasible if automated measures of mammographic density are available.^{141,140} There is increasing research regarding use of artificial intelligence-based risk models which incorporate mammographic data to address this issue.¹⁴¹⁻¹⁴⁴ Risk assessment tools that also provide tailored risk management advice based on local guidelines, the woman's absolute risk level, and other factors that affect risk management decisions are also desirable.^{145,146,147}

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Research needed to support systematic risk assessment and personalised risk management

To successfully implement proactive and systematic breast cancer risk assessment to drive delivery of targeted preventive interventions, stakeholders and funders will need to understand the potential benefits and invest in on-going research. Implementation of evidence-based access to genetic testing for breast cancer risk will be important. In addition, there should be evidence that systematic breast cancer risk assessment is clinically effective in preventing or downstaging breast cancer, results in behaviour change and risk-appropriate uptake of preventives. Currently there is very little prescribing of preventive medications; workforce education is a major barrier. Clinician capability and knowledge has been identified as a major barrier to the discussion of, and prescribing of, risk-reducing medications.^{148,149} This will need to be addressed, and resources prioritised for successful widespread implementation of preventive medications that can bridge the current large evidence-implementation gap. Research will also need to demonstrate that systematic risk assessment does not significantly increase anxiety and show it can be implemented in a variety of healthcare systems. Therefore, there is a need for greater investment in breast cancer prevention research, including in non-European populations. Thought must be given to the downstream workforce issues in terms of capability, opportunity, and motivation to implement prevention strategies (e.g. prescribing risk-reducing medications) for those at increased risk. Clinician capability and knowledge has been identified as a major barrier to the discussion of, and prescribing of, risk-reducing medications.^{147,148} Improved education and professional support for healthcare workers is needed, especially in community and primary health.

A measure of progress is the proportion of women who undergo personalised risk assessment, access to genetic testing for major breast cancer predisposition genes, and the uptake of risk appropriate prevention interventions. In countries with high quality collection of administrative data this could be assessed through data linkage. Monitoring the change in the prevalence of key modifiable risk factors such as alcohol, obesity, and breast feeding, using existing tools such as the Global Cancer Observatory, the Global Health Observatory, and the Global Breastfeeding Collective Scorecards may be another marker of progress, emphasising the need for countries to adequately collect these data.¹⁴⁹⁻¹⁵¹ Moreover, reductions in the sale of alcohol and baby milk formula would also indicate progress.

Future work and potential wider impact

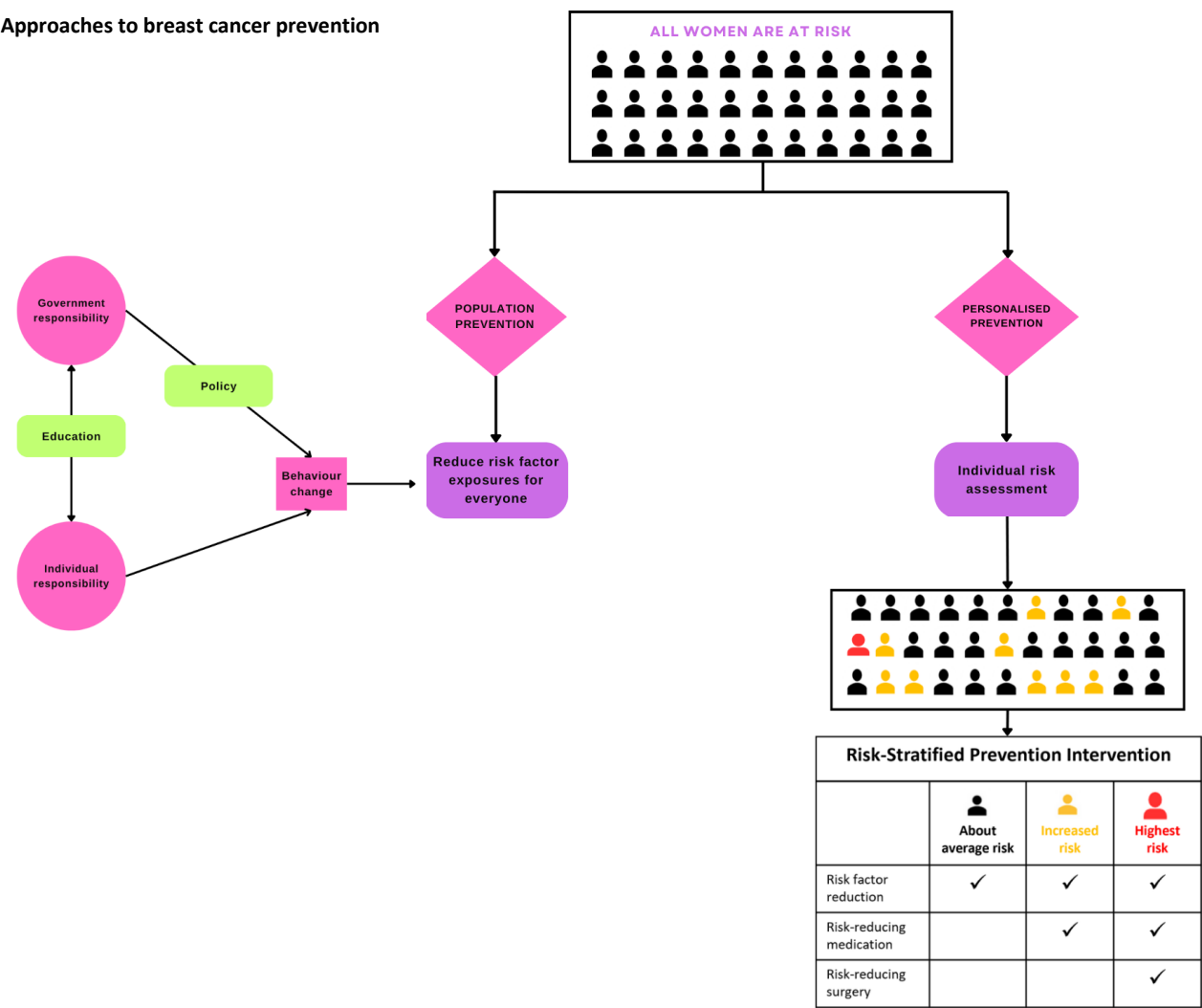
As an immediate action, equitable access to effective resources and interventions is vital for successful breast cancer prevention globally. Research into novel prevention strategies should be prioritised. This would include medications which target molecular pro-survival signals^{117,152}, medications that mimic the breast cancer protection mechanisms from pregnancy and lactation^{153,154}, and vaccines that boost the immune system.^{156,155}

Many breast cancer risk factors such as alcohol, post-menopausal obesity or overweight, physical inactivity, and limited or no breastfeeding also predispose to other non-communicable diseases. For example, breast feeding is well recognised to be beneficial to both maternal and child health.^{50,67} Modification of the prevalence of these risk factors may have wider reaching benefits for other health conditions. Successful implementation of personalised prevention approaches in breast cancer could also pave the way for similar approaches to other cancers such as colorectal cancer.

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Figure 1: Approaches to breast cancer prevention



Prevention of breast cancer requires a dual approach.

- 1) ~~There are two complementary approaches to primary prevention: i) population prevention to minimise-minimising risk factor exposure for all women, regardless of their personal breast cancer risk. This can be achieved by policies that reduce exposure to harmful BC risk and ii) personalised precision prevention through targeted interventions for women at substantially higher than average risk of the disease based on their risk factors, such as alcohol and obesity, and that increase exposure to protective factors such as physical activity and breastfeeding. Education of-Systematic and proactive risk assessment of all women in the population can facilitate the ability of governments to legislate what may otherwise be unpopular policies. Education can also lead to risk factor optimisation by individuals, but sustained behaviour change is difficult to achieve with education alone.~~
- 2) **personalised prevention** based on a woman's risk of breast cancer. This requires identification of ~~is necessary to be able to identify~~ those at increased risk, preferably through proactive, systematic risk assessment of all individuals, not just those that ask for it. This should be followed by risk-stratified prevention interventions based on the individual's risk. Over 20% of women in most populations are likely to be at increased risk and should consider use of risk reducing so they don't miss the opportunity to reduce their risk with proven prevention strategies such as inexpensive medications (such as tamoxifen, raloxifene, anastrozole or exemestane) and those at highest risk (such as those with germline pathogenic variants that greatly increase risk), can consider risk reducing surgery (bilateral mastectomy).

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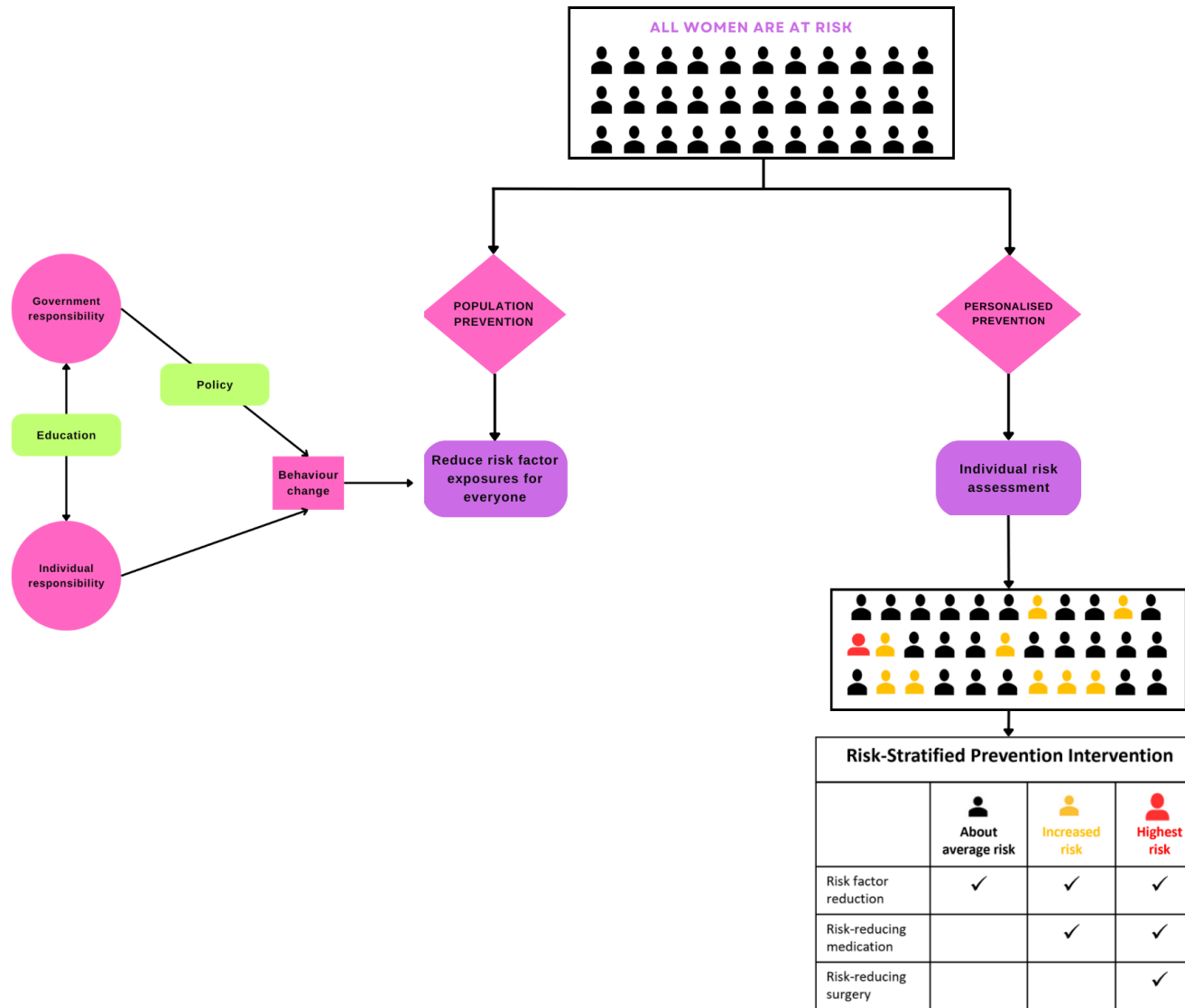
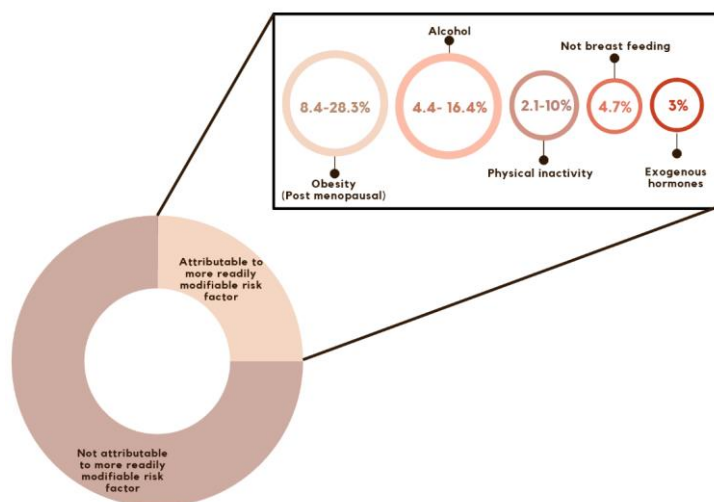


Figure 2: Approximate population attributable risks in high income countries of more readily modifiable breast cancer risk factors



Panel 5 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
ThemeSection 1: Breast cancer prevention						
Alcohol and commercial milk formula.	Effectively control alcohol and commercial milk formula advertising and sponsorship.	Alcohol use and using commercial milk formula rather than breastfeeding are important modifiable causes of breast cancer globally.	Legislation.	Ministries of Health in Collaboration with Commerce.	95% of countries legislating fully the UNICEF Code for advertising and promotion of commercial milk formula products & adhering to the WHO 'Best buys' with respect to alcohol advertising.	Close current loopholes in advertising.
Parental leave and supportive work environment for breastfeeding and expressing.	Ensure adequate publicly funded parental leave and provision of paid breaks and nursing facilities on return to work.	Working women should be supported to breastfeed if they choose. Supporting breastfeeding reduces breast cancer risk and provides other important health benefits to mothers and children.	Legislation.	Ministries of Health.	Statutory access to at least 18 weeks, and preferably 26 weeks of parental leave at 100% pay. Mandatory provision of paid breaks and nursing-expressing facilities on return to work.	
Non-alcoholic sugar sweetened beverages (SSBs).	Limit consumption of SSBs.	SSBs contribute to weight gain and obesity that increase non communicable disease (NCD).	Measure change in the total volume of sugar sold from soft drinks.	Ministries of Health.	Tax SSBs to raise the retail price at least 20%.	Tax according to sugar content may encourage reformulation

						and shift to lower sugar content drinks.
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Section 2: Personalising breast cancer treatment innovation through science and technology

Panel 6 - Summary for personalising breast cancer treatment innovation through science and technology

Breast innovation through breast cancer research science and digital health can facilitate equitable and prompt access to the right breast cancer treatment at the right time for each individual whilst respecting personal needs and preferences.

- Better targeting of existing treatments through development of validated accessible biomarkers is needed to identify those people that benefit the most and to reduce treatment burden for those likely to have more toxicity than gain.
- Development and facilitation of novel, efficient, patient-centred, translational clinical trials to enable a research culture and infrastructure across the globe are required.
- Digital health can facilitate innovation through integration of multi-modal complex datasets; promote flexible, coordinated care particularly for vulnerable patients; democratise access to research and decentralise trial participation.
- If used optimally, digital health innovative advances in breast cancer science and technology can alleviate inequalities in breast cancer rather than drive them — these principles can be applied to other health conditions.

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Personalised breast cancer treatment

There have been extraordinary advances in breast cancer discovery biology and translational and clinical research in the last decade. However, without action now, the cost of treatment and research will become unaffordable to all but the privileged few and will increase the equity gap. The Commission has an aspirational goal for all people with breast cancer to access personalised treatment as a universal right, as well as fostering greater patient diversity in clinical trials. For this aspiration to become reality, there must be a substantial shift in how breast cancer treatment and research is undertaken globally. For example, future regulation of clinical trials should be ensure that these are risk-adapted and fit for purpose, else breast cancer clinical trials will not be feasible or affordable aside from those motivated and conducted by pharmaceutical companies, and this needs to be recognised by funding agencies and regulators. The Commission proposes that the framework underpinning this aspirational goal can be applied to other cancers and wider range of health conditions.

Panel 7 - Personalised breast cancer treatment requires the following approaches:

1. **Precision** – determining and exploiting the molecular characteristics of each breast cancer and tumour microenvironment by identifying validated accessible biomarkers and adapting treatment to response and/or resistance is necessary for early interventions.
2. **Optimisation** – determining the best cancer-related outcome, with the least toxicity and minimal treatment burden for everyone. Optimisation considers patient co-morbidity, needs and personal preferences, and seeks to reduce breast cancer death in high-risk cancers and allow the safe reduction of treatment burden in good prognosis disease where many people may currently be overtreated.
3. **Innovation** – ensuring equity of access with the best use of resources for treatment and clinical trials. Innovation is accelerated through interaction with disciplines outside medicine.
4. **Understanding** – of the role of prognostic biomarkers (common) which determine the risk of disease recurrence (e.g. nodal involvement, stage) and of predictive biomarkers (uncommon) which inform an individual person's likely sensitivity to treatment (e.g. ER and HER2).

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To date, in spite of considerable world-wide efforts true predictive biomarkers such as ER and HER2, are rare with benefit for treatment largely determined by absolute risk dictated by the many individual

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and composite factors affecting prognosis. Modelling tumour biology at an individual level will enable mechanisms of cancer progression and drug resistance to be deciphered and permit identification of specific therapeutic targets. Proof of concept has been carried out with genomics, including the identification of *BRCA*, *HER2*, and *PIK3CA* alterations, but this approach is limited.¹⁵⁶ A more detailed understanding of spatial biology including spatial measurements of gene and protein expression, and single cell analysis are now possible. This will enhance prediction of response to treatments and early indications of metastatic dissemination potential, allowing more precise and potentially earlier treatment of micro-metastatic disease. However, improved model systems are required to predict which patients will benefit from specific As treatments ~~evolve~~, including newer targeted agents such as antibody-drug conjugates, as well as to identify those unlikely to benefit (or indeed suffer harm) from treatment. Living there is a need to better define which targeted agents are most effective within individuals. ~~Other promising technology to deliver precision medicine is living~~ diagnostic tools including. ~~As a result of~~ ex-vivo models such as organoids, spheroids, and patient-derived xenografts, mean that it is now possible to define which proteins are involved in the progression of cancer and to refine treatment accordingly.¹⁵⁷ This is currently being assessed by drug exposure ex-vivo, but ongoing efforts are testing whether gene editing of living models could model cancer biology in each patient.¹⁵⁹ Once refined, there will be a need to consider the optimum way of integrating the information gained from these models into healthcare systems to support the care of individual patients.¹⁵⁸

Given the rare nature of many molecular aberrations in cancers, it is possible that many may not appear targetable, or that they are so rare in breast cancer that a clinical trial to test the efficacy of an intervention is not possible. There is a need to rethink drug development and clinical trial design in the era of molecular medicine, whilst acknowledging the global inequalities in access to research. The use of 'pan-cancer' trials may help with understanding of the similarities and differences of molecular markers within and across tumour types. These trials need to integrate both genomics (germline and somatic) and, where relevant, other 'omics'. Biological differences in diverse ethnic populations and the tumour microenvironment for different sub-types and at different stages of breast cancer need to be considered in clinical trial design to enable bespoke treatments.

Combining precision oncology with optimisation and value-based care

The role of the Early Breast Cancer Trialists Collaborative Group (EBCTCG), which has undertaken meta-analyses of worldwide evidence from randomised clinical trials for 40 years, has enabled precise estimation of breast cancer treatment effects long beyond the time of a trial's primary endpoint analysis. These seminal analyses have enabled dissection of treatment effects within subgroups and across follow-up period and, with the exception of *ER* and *HER2*, have shown remarkably consistent relative benefits of treatment across different clinical and prognostic patient groups. This leads to an understanding that it will be the absolute potential gain informed by prognosis, which impacts optimised treatment decisions and the concept of precision approaches to treatment choice. Precision approaches have great potential value in the early disease setting, where many patients at present are over-treated, resulting in a significant burden of therapy which is also costly. Optimisation of treatment aims to maintain excellent outcomes whilst reducing financial, physical, and psychological costs. Treatment de-intensification may be achieved by using prognostic biomarkers at the start of the therapeutic pathway to identify patients likely to have very good outcomes due to an intrinsically non-aggressive cancer. More recently, biomarkers have been used to assess dynamic responses to initial therapy and inform whether subsequent treatment components can be safely reduced. One model of this approach is the 'pre-operative window' study, where short duration treatments may be used to identify responsive tumours and improve prediction of outcomes.¹⁶⁰ ~~One model of this approach is the 'pre-operative window' study, where short duration treatments may be used to identify responsive tumours and improve prediction of outcomes.~~¹⁵⁹ Another model of use is a full course of neoadjuvant systemic therapy with ~~and~~ the pathological response to that treatment assessed at surgery. Patients without a pathological complete response have been shown to benefit

from escalation of further therapies (e.g. anti-body drug conjugates or a different chemotherapy agent), whilst those with an excellent response may require less adjuvant therapy to maintain the same excellent oncological outcomes. This approach is being tested in HER2-positive breast cancer in ongoing clinical trials such as HER2-RADICAL (UK) and OPTIMICE (USA).^{161,162,160,161}

Despite the rapid advances described previously, most patients with breast cancer continue to be treated with a standardised approach, with primary surgery followed by adjuvant systemic therapies and radiotherapy. This approach does not consider breast cancer as a highly heterogenous disease, with a very broad spectrum of risk, ranging from early, low-risk screen-detected disease with favourable biology through to highly aggressive, life-threatening tumours. Furthermore, such a conventional approach does not use all the potentially available information, such as more refined measures of risk or evidence of response to a particular therapy,⁷ and can lead to suboptimal treatment choices at all points on this risk continuum. This underscores the need for diagnostic precision and optimisation of treatment. However, EBCTCG analyses (*see supplementary material 4: proportional benefits of systemic therapy in reducing distant recurrence rates*) demonstrate that widespread global use of a 5-year course of the endocrine therapy tamoxifen or several months of anthracycline chemotherapy alone reduces breast cancer recurrence and ultimate survival substantially at a modest treatment cost and substantial personal and societal gain.

In many patients with early-stage disease and favourable biology, it is likely that loco-regional therapy alone is curative. There has been a belief that more breast cancer therapy results in improved outcomes, however evidence suggests that in many instances less may be enough. An example is the similar oncological outcomes of breast conserving surgery plus radiotherapy to those of more extensive mastectomy surgery^{162,163}, with the former approach providing improved aesthetic outcomes, better quality of life and increased cost-effectiveness.¹⁶⁴⁻¹⁶⁶ The use of breast conserving approaches, however, is dependent on timely and equitable access to adjuvant radiotherapy. This is not currently available to all across the world and those without access are also denied the potential proven overall survival advantages associated with radiotherapy.¹⁶⁷ Hypofractionation, i.e. giving larger radiotherapy doses in fewer treatments, is another form of optimisation as it decreases the treatment burden for patients, whilst maintaining efficacy with similar or reduced side effects, and is also more cost-effective (*see Supplementary material 5: Case study – Hypofractionated breast radiation therapy*). Allowing all patients informed choice and equitable access to optimal loco-regional treatment is dependent on improved and integrated infrastructure. Optimisation of systemic treatments in early breast cancer include immunotherapy in triple negative breast cancer and reduced duration adjuvant trastuzumab in HER2-positive disease.¹⁶⁸ *See Supplementary material 6: Case Study – Immunotherapy in early TNBC.*

Implementation of stage-shifting strategies (*see ThemeSection 4*) is likely to increase the proportion of patients where loco-regional therapy will be curative, but this will take some years. Subsequent use of improved precision approaches will allow the identification of patients where treatment may be further de-escalated/optimised. Examples include the omission of radiotherapy in very low-risk disease^{170,169}, or de-escalation of surgery by either omission of surgical axillary staging or minimally invasive treatment of the primary tumour.¹⁷⁰⁻¹⁷² Thus, optimisation of treatment is dependent on access to a full range of both diagnostic and therapeutic modalities.

Despite efforts to increase early diagnosis, there will remain a group of individuals with high-risk tumours where treatment optimisation will require escalation of therapy. In this context, neoadjuvant systemic therapy is increasingly used as a standard of care. As previously discussed, this approach provides an opportunity to test reducing therapies in those with a complete pathological response. However, it also enables treatment escalation or alternative treatment strategies in those patients

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with significant residual disease. Furthermore, this approach may provide an opportunity to tailor loco-regional treatment of the breast and axilla based on response.^{174,173}

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To ensure optimised treatment, a multidisciplinary approach from diagnosis is essential. Information regarding tumour molecular characteristics is needed to determine an individual's level of risk and therefore their optimal treatment sequence. This information will allow the patient to see the right specialist at the right point in their treatment pathway. All patients with breast cancer need access to multidisciplinary teams and tumour boards at the point of diagnosis to facilitate optimal treatment planning, and often this is required later to determine subsequent therapies based on initial response or management of recurrence.

It is essential that this multidisciplinary approach of optimal care is applied to all individuals with breast cancer without discrimination of subpopulations. An example is the management of older patients with breast cancer. More than 35% of women diagnosed with invasive breast cancer in the UK are 65 years or older.¹⁷⁴ This proportion is increasing globally because of population demographics and the management of older patients presents a number of challenges.¹⁷⁵ Older patients have the highest breast cancer mortality, when adjusted for tumour characteristics and stage, than any age group, experience greater variation in care and are not eligible for systematic breast screening because of their exclusion from the formative trials.^{174,176} Unfortunately, the mistaken notion that older patients have indolent disease is still all too prevalent. Simple and reliable assessments of co-morbidity and fitness are now routinely available and would allow more consistent care and facilitate ongoing national audit which should remain a priority for this large and growing patient group.

Value-based approaches^{178,177} have a goal of delivering the best possible outcomes for less cost.^{179,180} Value in breast cancer care can be defined as the summation of quality, outcome, cost, and patient preference. Porter and Teisberg introduced the value-based healthcare (VBHC) concept as a strategy to rein in health care expenditure while maintaining or even improving outcome.^{181,182} The VBHC framework consists of understanding the health needs of the patient, designing solutions to improve outcome, integrating learning teams, measuring outcome, and expanding partnerships.^{178,179}

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However, in many countries the business model of healthcare continues to be followed, contributing to both between- and within-country inequities. Currently, those with breast cancer in rich countries are often overtreated, but in low- and middle-income countries, patients with breast cancer may get little or no care, and indeed in the poorest countries may not even receive a diagnosis. Adopting value-based healthcare for breast cancer has the potential to optimise care in rich countries, to give much needed guidance to low- and middle-income countries to improve outcomes without bankruptcy, and help those countries with minimal provision currently to kick-start breast cancer care from ground zero. Sharing technologies and making the outcomes of research freely available will help to establish and maintain value-based breast cancer care and the acceleration of technological change will facilitate this.

Technology enabled breast cancer management

Technology can facilitate the integration of multi-modal data inputs from complex and large datasets to set-up personalised treatment and follow-up. Figure 3 depicts a vision for technology-enabled breast cancer treatment and research. In this vision, data is collected digitally from multiple sources: patient generated data, the environment including the social determinants of health inequities, biological tumour omics and classical clinical, pathological, and treatment data and integrated in a multimodal data model¹⁸³⁻¹⁹² with real-time interpretation and large-scale interoperability. This should allow data exchange within all stakeholders of the oncology healthcare system (patients, providers and researchers at hospital, primary care, and supportive care network) to inform personalised risk-stratified pathways of care that could reduce treatment toxicity, improve survival and quality of life and potentially reduce healthcare costs and burden and inform innovative health policies.^{193,194}

Several specific digital health applications can facilitate the implementation of this future vision and already impact clinical care and research in several aspects. We provide examples below (see Panel 8 - Digital health – terms and applications). Different types of data include: digital pathology¹⁸⁰ and digital imaging¹⁸¹; omics data such as genomics, proteomics, metabolomics; microbiome information; patient-generated data including quality of life and symptom burden.¹⁸² Passive behavioural and physiological data can be collected from wearable devices and biosensors.¹⁸³⁻¹⁸⁷ Classical clinical, pathological, and treatment data alongside social determinants of health such as health literacy can all be integrated in this multimodal data model^{188,189} (see Figure 3: Vision for technology-enabled breast cancer treatment and research). Real-time interpretation of multimodal data can generate and inform personalised risk-stratified pathways of care that could reduce treatment toxicity, improve survival and quality of life and potentially reduce healthcare costs and burden.^{190,191} Such approaches must also consider patient preferences, priorities, and individual circumstances in addition to tumour biology to ensure a truly personalised approach. On-going research is exploring machine learning to convert complex and large datasets into algorithms to further aid prognostication and prediction of response to treatments.

Digital health innovations for breast cancer care and research

Many dimensions of daily life have been revolutionised by digital technology. Healthcare delivery is now facing a rapid change from traditional processes towards the integration of digital health interventions (see Panel 8: Digital health – terms and applications). The COVID pandemic accelerated this integration with expansion of telemedicine and remote monitoring solutions.¹⁹² Digital therapeutics are being approved and commercialised¹⁹³ primarily for chronic diseases management with the majority focusing on behavioural change promotion.¹⁹³ Areas such as cardiovascular health^{183,194,195} adopted fully decentralised practice changing trials by using digital health solutions¹⁹⁶, enrolling 419,297 patients in just 8 months.

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Panel 8 - Digital health - general terms and applications:

- Telemedicine - medical care by healthcare professionals delivered through telecommunication.
- Remote monitoring – real time- monitoring of patient's symptoms or vital signs using technology devices.
- Electronic medical records - digital patient charts allowing data storage, access, and sharing within information governance frameworks.
- mHealth - technology for health through mobile devices.
- Biosensors - capturing physiological and/or behavioural data for patient and medical purposes.
- Digital therapeutics – evidence-based software interventions to prevent, manage, or treat a medical disorder.
- Advanced analytic techniques - evaluating datasets with AI to predict medical events (response, relapse, toxicity).

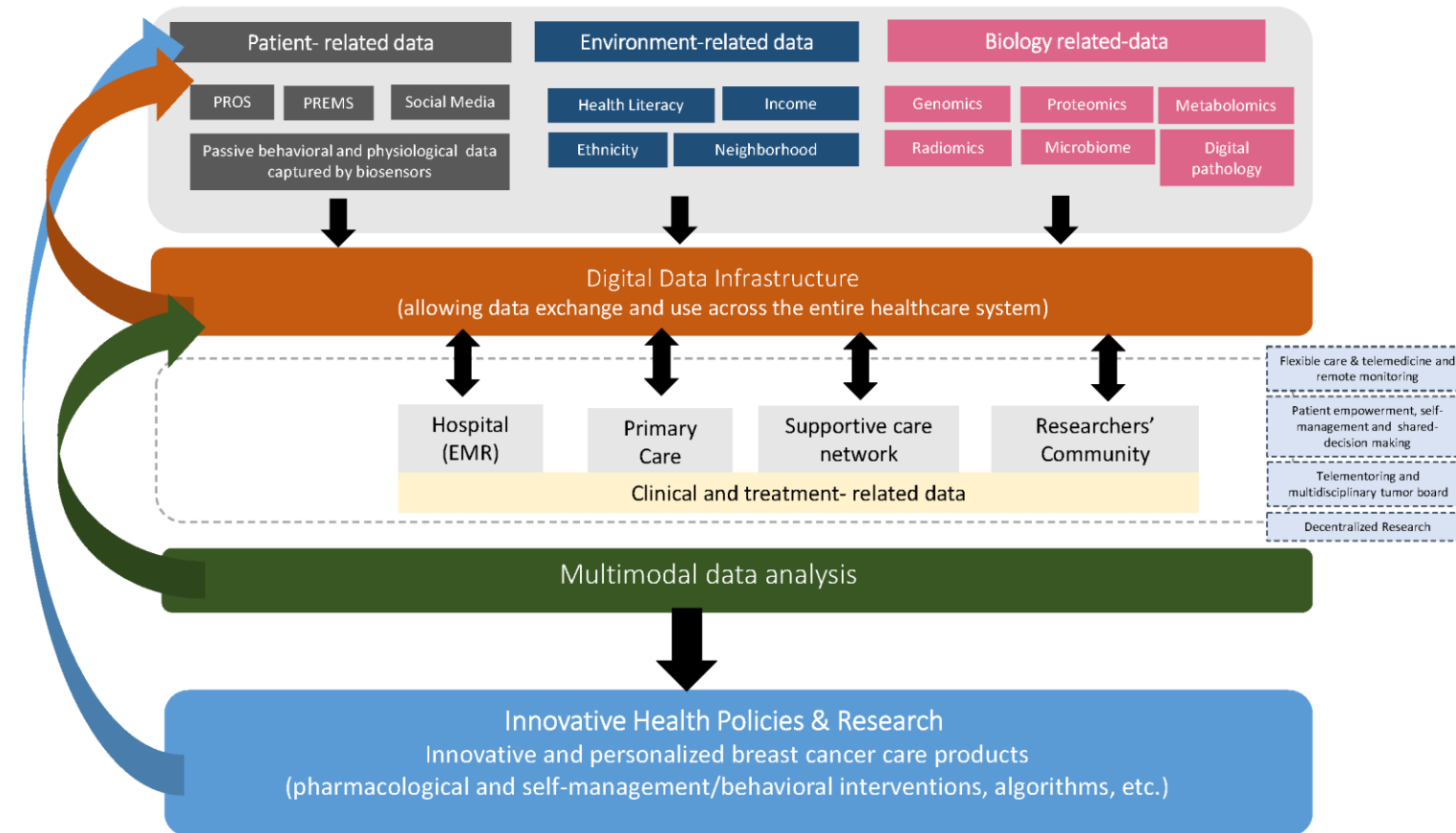
Improving organisation, quality of care and efficiency of healthcare systems through digital health

Telemedicine and teleradiology. Telemedicine was rapidly implemented in breast cancer care¹⁹⁷⁻²⁰¹ during the pandemic. This enabled prioritisation of in-patient care for critical patients, paving the way for decentralised care.^{199,202,203} The level of patient satisfaction was high^{197,198,204} and positive experience²⁰³ was reported among patients across the breast cancer continuum^{195,204}, and within high²⁰⁵ and low^{206,207} and positive experience²⁰⁵ was reported among patients across the breast cancer continuum^{197,206}, and within high²⁰⁷ and low^{208,209} resources settings and remote rural areas.¹⁹⁶ Telemedicine has been used in some MDTs for years¹⁹⁸ resources settings and remote rural areas.¹⁹⁸ Telemedicine has been used in some MDTs for years²¹⁰, and telephone-led consultations for follow-up breast cancer care have also been used in some settings for decades. A randomised study^{209,211} showed that telemedicine was well perceived with no detrimental effect on anxiety or the ability to detect relapses. Telemedicine is seen as a valuable tool to enhance breast cancer care by oncologists^{210,212} and teleradiology can provide timely diagnostic assessment and efficient breast cancer screening in areas with scarce local radiology support.^{211,212,213,214}

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Figure 3: Vision for technology-enabled breast cancer treatment and research



- **Remote monitoring.** A breast cancer cluster randomised trial among 20 Canadian centres with 2158 patients receiving chemotherapy demonstrated that nurse-led telephone-based management was associated with lower rates of grade 3 toxicity, although no statistically significant impact was found in hospitalisation rates or patient reported outcomes.^{213,245} Several randomised clinical trials have confirmed the benefit of using patient reported outcomes (PROs) as early warning monitoring to avoid or reduce severe treatment related toxicities and increasing quality of life for oncological patients with early and metastatic disease receiving systemic therapy, including patients with breast cancer.²¹⁶⁻²²⁰ Although remote monitoring is already recommended in oncology^{220,224} and deployed in some healthcare systems^{221,222}, global real-world implementation is still slow. Efforts regarding awareness, training, are needed to ensure workforce development and integration with electronic medical records, policy, re-imbursement are needed to ensure re-organisation of care to allow real time response to patients ePROs in routine practice.

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Rehabilitation and self-symptom management. Delivering comprehensive breast cancer survivorship care, including management of long-term physical and psychosocial consequences of cancer and its treatment, is complex, costly and insufficiently implemented (see Themes 3, 5 and 6).²²² Digital health offers an opportunity to facilitate comprehensive survivorship care and self-management support. Randomised clinical studies have demonstrated that digital support increases quality of life and self-management for patients with breast cancer during the post-treatment follow-up phase.^{223,224} Examples include use of digital cognitive behavioural therapy for fatigue²²⁵, insomnia²²⁶, fear of recurrence²²⁷, and emotional distress.²²⁸ Cognitive rehabilitation after chemotherapy through digital health solutions has also proved promising.²²⁹ Health promotion such as physical activity and weight management programmes can be successfully delivered with digital health solutions.

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- **Facilitating the communication within healthcare systems.** Use of electronic health records improves patient safety, operational efficiency, and quality of care.^{237,238} For example, electronic health record ~~integrating tumour~~^{integrated tumor} board applications save preparation time and reduce errors.²³⁸⁻²⁴⁰ Electronic health records may also increase patient engagement through automated mammography scheduling, screening reminders, determining eligibility for genetic testing and counselling, identifying patients who would benefit from weight management, and determining clinical trial eligibility.^{240,241} Technology can create virtual mapping and linking of the patient's residency with community mobile healthcare professionals and comprehensive cancer centres enabling more flexible care (e.g. anti-HER2 subcutaneous therapies).^{241,242}

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Telementoring. Telementoring can enhance training to increase numbers of healthcare practitioners, especially in underserved areas (such as the Project ECHO- Extension for Community Healthcare Outcomes).²⁴² It can support virtual multidisciplinary team meetings (MDM).^{193,243}

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Digital health as a care equaliser

Effort and careful planning is needed to expand access to technology, but also to ensure that the digital divide does not exacerbate breast cancer care disparities.^{248,249}

- Technology can be transformative in care and research if health infrastructure is tailored according to the patient's ability to cope and adopt digital devices.^{234,235} In oncology, randomised clinical trials have demonstrated that using low complexity digital health devices to perform weekly symptom monitoring was feasible among patients with lower educational levels, and low eHealth literacy. This led to reduced emergency visits and improvements in quality of life.^{216,217,248,249} In the cluster randomised clinical trial PRO-TECT^{217,249}, weekly symptom monitoring with electronic patient reported outcomes was implemented in 52 community-based oncology practices in the United States. The trial included around 20% of patients who had never used email before and 30% with financial difficulties. The option of assessing the symptoms through an automated telephone rather than internet was chosen by 36% of the patients and was associated with older age and lower education. The Accountability for Cancer Care through Undoing Racism and Equity (ACCURE) Pragmatic Quality Improvement Trial led to the elimination of black-white treatment gaps in patients with early stage breast and lung cancer.^{249,250} The digital health intervention was composed of i) an automated warning system from patients' electronic health records automatically sending alerts when an appointment is missed; ii) a proactive navigator monitoring the warning system and addressing care barriers; iii) dissemination of race and ethnic feedback to clinical teams on treatment completion rates coupled with a health equity training.
- Machine learning algorithms may be used to decrease breast cancer care disparities, especially in low-income settings. Promising results have been reported for analysing breast cancer mammograms to automate or improve the sensitivity of breast cancer screening²⁵¹⁻²⁵³ and in digital pathology slides to provide timely breast cancer diagnosis. Further work uses AI-algorithms applied in digital pathology for evaluating tumour infiltrating lymphocytes and its correlation with outcomes^{253,254}, and a molecular profile and risk of relapse to inform decision making and guide treatments.^{185,480} It is important to ensure that datasets used to train AI-algorithms are representative of the real world breast cancer patient population otherwise there is a risk that such models will not be applicable in clinical practice or may widen inequalities gaps for groups of patients that are usually excluded from research and also face difficulties in accessing care.

Digital health as a tool to enhance research

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Digital technology can improve participant access, engagement, trial-related measurements, and interventions. It can enable concealed randomised interventions allocation, and has the potential to transform clinical trials whilst lowering their cost.²⁵⁴²⁵⁵ Efficient and generalisable research calls for a representation of all patient groups.²⁵⁵²⁵⁶ Nevertheless, groups often facing disparities and difficulties in healthcare are particularly under-represented in oncology research.²⁵⁷⁻²⁵⁹ Barriers include low understanding of research, unconscious bias from researchers, out of pocket costs, and accessibility issues. For further information, see *Supplementary material 7: Opportunities and challenges for digital health in breast cancer care*. Strategies to reduce inequities in access to cancer research include:

- Digital education programmes to improve cultural competence, promote self-assessment and reduce unconscious bias.²⁶⁰⁻²⁶²
- Automated clinical trial eligibility screening²⁶³⁻²⁶⁵ and matching algorithms.
- Decentralised tools for patient consent, inclusion, study conduct, electronic patient-reported outcomes (ePROs), and digital capturing of study endpoints.²⁵⁴²⁵⁵
- Activating community engagement and foster co-design and participatory research.²⁶⁵²⁶⁶ Incorporation of ePROs co-developed with patients can capture patient experience and outcomes optimally.²⁵⁴²⁵⁵
- Set-up of global clinical trials and equal research collaborations between high and LMICs through innovative digital networks with fully digital clinical trials.²⁶⁶¹⁹⁶
- Digital navigation support.²⁶⁷

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Panel 9 - Take home messages for digital health and breast cancer

- Digital health has been used in breast cancer care to a limited extent over many years, but its use expanded and accelerated during the COVID-19 pandemic.
- Digital health has potential to improve efficiency of healthcare systems, reduce breast cancer care delivery barriers and costs, promote patient empowerment and self-management.
- The use of electronic patient reported outcomes (ePROs) in routine clinical care improves symptom management and quality of life and offers patients an opportunity to participate in their care.
- Digital technology may enable multimodal data integration to inform personalised treatment and follow up plans.
- Digitally enabled clinical trials simplify and accelerate research workflows and can increase community engagement and reach.
- Digital health can promote care equity, especially if technology innovations are co-designed with patients and navigation is provided.
- Digital literacy and social determinants of health, contextual patient factors, confidentiality and information governance, and the healthcare organisation all need to be considered when implementing digital health.
- Policy level actions are required to increase broadband access and to promote large scale digital navigation for populations frequently excluded from healthcare innovations.

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Panel 10 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
ThemeSection 2: Personalising breastBreast cancer innovation through science and technology						
Breast cancer diagnosis.	Ensure high-quality breast cancer receptor testing at diagnosis.	Ensuring all patients with breast cancer have access to accurate tumour subtyping to enable appropriate treatment sequencing and selection of endocrine/targeted/chemo-therapies.	Facility records, National audit, national and international certification procedures for breast units.	Facility, Ministry of Health.	>80% (aiming for 95%) of patients have access to accurate tumour subtyping.	Need to ensure global collection of these data.
Multidisciplinary meeting (MDM) review at diagnosis.	Ensure MDM review, linking with expert team members virtually where appropriate.	All patients with a new diagnosis of breast cancer should have their case discussed by a multidisciplinary team to allow optimal treatment planning.	Facility records, national and international certification procedures for breast units.	Facility, Ministry of Health.	>80% (aiming for 95%) patients with new diagnosis to be discussed at MDM.	
Range of treatment for breast cancer.	Appropriate access to appropriate range of surgical, radiotherapy and systemic treatments.	All patients with breast cancer should have access to a full range of treatment modalities to allow equitable treatment choices globally and ensure optimal outcomes.	Facility records, national and international certification procedures for breast units.	Ministry of Health.	100% of patients with breast cancer to have access to full range of treatment modalities.	Integrated Cancer Health System with Regional Infrastructure based on burden of disease in each country.
Breast cancer clinical trials.	Increase global leadership and participation with clinical breast cancer research.	Ensure that patients participating in clinical trials are representative of the global breast cancer patient population and that	Clinical trial registries, PubMed Global patient ID.	Policy makers research funders, higher education institutes.	At least 10% (aiming for >25%) of participants of international breast cancer	Ensure clinical trials are representative and generalisable globally; to

		research leadership includes HICs and LMICs.			trials are from LMICs. At least 10% (aiming for >25%) of all breast cancer trials are led/co-led by LMIC researchers.	build research capacity, infrastructure and expertise globally.
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ThemeSection 3: Optimal **inclusive** management of metastatic breast cancer

Panel 11 - Summary for metastatic breast cancer

Many patients with metastatic breast cancer (MBC) feel abandoned, isolated, and alone and some do not receive appropriate care – this can and should be tackled.

- The number of people living with MBC is unknown - high-quality cancer registry data needs to be collected worldwide.
- Optimal management of MBC is valuable to individuals and society – stigma and inequity for those with MBC must be addressed.
- There is a growing belief that some subtypes of metastatic breast cancer can be treated as chronic diseases for many years.
- With adequate resources and a shift in attitudes, it may be possible to cure some of these patients, treat most, alleviate the suffering of all and forget or abandon no-one.

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Where are we now and where do we want to get to?

In many regions of the world, people with metastatic breast cancer (MBC) are unseen. We do not know globally how many people have MBC²⁶⁸ and this knowledge gap prevents adequate allocation of resources and intensifies stigma and inequity associated with the disease. These patients often have restricted access to treatments despite proven overall survival (OS) benefits, as well as experiencing limitations to supportive care.²⁶⁹⁻²⁷² As a result, individuals with MBC can feel abandoned and stigmatised not only by policymakers and society, but also by healthcare providers and sometimes even the advocacy community. There is an urgent need to address this.

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A diagnosis of MBC should not stop a person's contribution to society, either as part of the work force or in unpaid caring roles, and ~~also~~ more broadly by contributing to cultural life. Breast cancer predominantly affects women and, globally, women compared with men spend up to 10 times more of their time on unpaid care work.²⁷³ It has been estimated that in 2015 MBC was associated with \$6.6 billion in lost productivity in the US alone, mostly due to days missed at work and home due to illness and premature mortality.²⁷⁴ Inadequate or absent treatment not only has a devastating impact on the patient, their families, and local communities, but also creates an economic disadvantage worldwide (see Panel 12 → *Economic modelling for patients with MBC in Portugal*). Even with the best possible treatments²⁷⁵, 20-30% of those with early breast cancer relapse, so optimal treatment of patients with MBC is valuable to both the individual and society.

A shift in attitudes of policy makers and the public needs to occur to create a world where all patients with MBC are recognised and receive individualised treatment, with an honest but positive approach (see ThemeSection 6). This is important so that patients with MBC feel empowered and are supported to continue to contribute to local communities and wider society.

Panel 12 - Economic modelling study for patients with metastatic breast cancer in Portugal²⁷⁶

The ABC Global Alliance and Centre for Evidence Based Medicine (CEMBE) jointly developed a project aiming to show that allowing women living with MBC to continue to work would be beneficial not only to the patient and her family, but also to the state and to society in general.

Breast cancer is the most common malignancy among women in Portugal, with an incidence rate of 156 per 100,000 women. Given that most diagnoses occur in women aged between 20 and 64 years, studying the impact of breast cancer on the women's labour market is of major economic and social relevance.

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This study quantified the productivity costs (i.e. losses) of nonemployment due to MBC in Portugal and evaluated potential labour market policies designed to promote employment in this group. The analysis was based on (i) an original cumulative incidence model that allows estimation of the prevalence of working-aged women with MBC in 2019, and on (ii) an observational study that characterised the employment status and working conditions of patients with MBC in Portugal. To determine productivity costs, the human capital approach was adopted.

A total of 2,151 working age women were estimated to have MBC in 2019, with productivity costs amounting to €28,676,754 over the period 2019-2021. In addition, unemployment subsidies and disability pensions were estimated to be €3,468,866, with a total cost of over €32m. The 3-year period was chosen in view of the median overall survival (OS) of MBC being 3 years.

The researchers modelled the impact of a subsidised, part-time employment scheme designed to encourage women with MBC to continue working. The estimated increased cost of this policy for the government was €11,951,048 over the three-year period 2019-2021. However, a reduction of €14,338,377 in productivity costs (losses), led to a cost-saving of nearly €2.5m over the same 3-year period.

The authors call for changes in labour market laws to enable all patients with metastatic cancers, the right to choose part-time and/or flexible working, without first acquiring employer permission.

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Four key themes are identified as crucial areas to be addressed: data collection, individualised management with global equity in access to therapies, multidisciplinary management driven by guidelines, and targeting stigma.

1) Data

It currently is impossible to know the prevalence of MBC since most cancer registries record information on initial diagnosis and death but not on recurrences.^{268,275} This is made more difficult by an increasingly mobile global population, which makes longitudinal tracking challenging. Data protection regulations and laws, although clearly important, render sharing of patient information and cross-checking between databases virtually impossible. In addition, not all cancer registries collect stage at diagnosis.

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In HICs, only about 5-10% of patients with breast cancer are metastatic at initial diagnosis, whereas in LMICs, those with de novo Stage III/IV may reach 50-60%.^{276,277} Distinguishing between Stage III (locally advanced) and IV (metastatic) disease in LMICs is problematic given that the definitive diagnosis of Stage IV requires costly imaging and, in some cases metastatic biopsy, to determine distant disease. These investigations often require out-of-pocket payment by patients. As a result, de novo metastatic disease often goes undetected. This is supported by the unusually rapid decline and very poor 3-year overall survival seen in the African Breast Cancer-Disparities in Outcomes (ABC-DO) study.²⁷⁸

In HICs, some national or regional registries have been developed that are specifically dedicated to MBC (see *Supplementary material 8: Table of existing MBC databases*), a development mostly by patient advocates. However, in LMICs data for MBC are largely absent and any reports are primarily single centre analyses.²⁷⁹ Data collection in LMICs needs to be made possible by encouraging the establishment of cancer registries funded by government or non-government agencies. For HICs, the solution is complex and will require waivers regarding sharing of information between databases and the development of 'big data' analytical processes (see [ThemeSection 2 – digital health](#)). IARC (the International Agency for Research on Cancer) and the ABC Global Alliance are defining the essential

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data to be collected and strategies to overcome data collection difficulties for MBC. Getting data collection right will mean MBC can be a beacon of change for global health systems.

2) MBC management should be individualised with equitable access to evidence-based therapies

Cancer directed therapies and overall survival

Outcomes of MBC have improved considerably in the last decade, and patients should not be denied access to life-extending therapies. The median overall survival of MBC has remained at around 2 to 3 years for decades²⁸⁰ but has recently reached 5 years for two of its three main subtypes (HER2 positive and ER positive/HER2 negative), representing approximately 85% of MBC patients.²⁸¹⁻²⁸³ Some patients may now live up to 10 years or longer with metastatic disease, with some subgroups beginning to be considered as having a 'chronic disease'. MBC is a spectrum of disease, both at a molecular level (see [ThemeSection 2](#)) and in terms of disease burden. This includes potentially curable oligometastatic disease, long-term remissions or stabilisations, and more rapidly progressive disease (often the triple negative subtype). Therefore, management of MBC must be individualised, but not just based on biology, but also on patient characteristics, preferences, and toxicities of treatment.

The use of validated tools such as the ESMO Magnitude of Clinical Benefit Scale (MCBS)²⁸⁴ or the ASCO Framework of Value²⁸⁵ allow for cost-effective prioritisation of existing therapies based on their clinical value. Furthermore, the development and use of biomarkers that could allow the identification of patients who derive most benefit, as well as those who do not benefit from these therapies, is crucial to optimise resources and should be a research priority (see [ThemeSection 2](#)).

Active management of MBC impacts mortality

The advances in MBC treatments in the past decade have been shown to reduce mortality in the general population by the model-based analysis (CISNET: Cancer and Intervention Surveillance Modeling Network²⁸⁸); [Caswell Jin, #374](#)) and have contributed between 20-24% of the mortality reduction seen overall (see *Supplementary material 9: Table of therapies known to extend OS or progression-free survival (PFS) in MBC*).

Continuum of care

Supportive and palliative care are crucial parts of the management of MBC and should be incorporated from diagnosis (including supportive care for early breast cancer), through the whole breast cancer journey (see [ThemesSections 5 and 6](#)). Early integration of supportive/palliative care has been shown to improve quality of life and reduce depression.²⁸⁶ and there needs to be better education for clinicians, patients and the wider public (see [ThemesSection 5 and 6](#)). Definitions have been extensively discussed and proposed by the Lancet Commission on Global Access to Palliative Care and Pain Relief⁸ (see glossary). The importance of early supportive/palliative care involvement has been highlighted in ASCO guidelines, and NCCN Clinical Practice guidelines and in the ABC Guidelines.²⁸⁷⁻²⁸⁹ These fundamental aspects of MBC care are often neglected and there needs to be a transition from traditional siloed care into integrated, patient-centered, holistic management.

In a survey of 240 US oncologists, only 17% said that they refer patients to palliative care upon diagnosis of metastatic disease, despite two-thirds of respondents agreeing that earlier introduction of palliative care leads to better outcomes.²⁹³²⁹⁰ In addition, 14% of oncologists reported that they only refer patients to palliative care once all standard of care treatment options are exhausted.²⁹³²⁹⁰ Resistance from patients and their families is also a problem, often due to stigma and the perception that palliative care only means end-of-life care. Nearly 40% of the survey respondents reported that this is the main barrier to patients receiving appropriate and timely palliative care.²⁹³²⁹⁰ There is a lack of palliative care resources, especially in LMICs but also in HICs, and oncologists and primary care physicians need to focus on symptom control as well as cancer treatments (also see Sections 5 and 6).

Quality of life measurement

The balance between efficacy and toxicity, between survival and quality of life (QoL) or relief of serious health-related suffering (SHS, see [ThemeSection 5](#)) is delicate and very personal in the metastatic setting. An additional hurdle is the fact that QoL measurement tools have all been developed for the early cancer setting, and do not accurately capture the most important aspects of the metastatic setting. To overcome this, the EORTC Quality of Life Group has partnered with the ABC Global Alliance and is currently developing a new QoL tool specifically dedicated to MBC, which after validation will be incorporated into clinical trials and clinical practice. In addition, the EU-funded multinational Innovative Medicines Initiative Health Outcomes Observatory (H2O) consortium has recently published core outcome sets for assessing health-related quality of life in patients with metastatic breast cancer, which is in line with the EORTC-ABC Global Alliance work.²⁹⁴²⁹⁴ These initiatives will make the evaluation of QoL in MBC more accurate in the future.

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Communication

Communicating well with patients throughout their disease journey and giving realistic hope is also extremely important (see [ThemeSection 6](#)). Maggie Jencks, a patient with MBC who was fundamental in setting up 'Maggie's centres' in the UK, wrote '*however bad the prognosis, it will still help the patient to know that the median may not be the message*'.²⁹⁵²⁹² Suggestions on how to improve patient-HCP communication are given in section 6 - Communication and empowerment.

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Equitable access to treatment for MBC

It is crucial to address the global inequities between and within countries, in access to all therapies for MBC (including but not limited to medicines), as well as to supportive care and clinical trials. An example of inequity in access is with trastuzumab use in HER2-positive MBC. Despite the development of highly successful anti-HER2 therapies and trastuzumab being included in the WHO's list of essential medicines, it is often not funded in the metastatic setting. In Brazil, an analysis carried out in 2016 projected that an additional 600 patients with MBC would be alive at 2 years if trastuzumab was available to them, and this figure increased to 768 patients with the addition of pertuzumab.²⁷⁰ Inequitable access is not an issue restricted to LICs; there are often discrepancies in funding within Middle and HICs. An observational study of HER2-positive patients in China carried out in 2017 reported that 27% of those with metastatic disease did not receive trastuzumab at all regardless of local resources.²⁷¹ Observational studies in HER2-positive metastatic patients between 2000 and 2015 have demonstrated that 27-54% in Europe, 12% in the US and 27.1-49.2% in China did not receive trastuzumab or other anti-HER2 therapy as first- and/or subsequent-line treatment.²⁷² A fundamental barrier to accessing trastuzumab is cost, and the availability of effective and safe biosimilars should allow greater use of anti-HER2 therapies.²⁷² Unfortunately, to date price reductions have not been enough to make trastuzumab more available in LMICs.

Panel 13 - Inequity within HICs - New Zealand as a case study

In 2018, the first study of the incidence, treatment, and survival of MBC in New Zealand was carried out.²⁶⁹ Prior to this, the New Zealand Ministry of Health only tracked outcomes for patients with curable breast cancer or de novo metastatic breast cancer and patients with relapsed disease were not counted.²⁶⁹

The study revealed that the median survival after a diagnosis of MBC was 16 months, which was considerably worse than comparable countries (2-3 years).²⁶⁹ There was substantial inequity in outcomes within New Zealand, with five-year survival of MBC significantly worse in the Maori population (5%) than the non-Maori (15%).²⁶⁹ Despite evidence to show that quality of life and survival improved with more lines of treatment given, only 15% of patients with MBC received more than 3 lines of therapy, and 10-30% received no treatments at all.²⁶⁹ There was a lack of awareness or adherence to international guidelines for the treatment of MBC, no national MBC guidelines, and

the possibility for treating oligometastases with curative intent was underexplored.²⁶⁹ There was also restricted access to many therapies proven to be effective in MBC.²⁶⁹ Importantly, for the HER2-positive subtype, only one line of HER2 directed therapy could be used, since trastuzumab use beyond progression was not allowed and there was no access to any of the newer anti-HER2 therapies. This led to a 15-month median survival in patients with this MBC subtype, which in other HICs reaches 5 years. In this subtype, the most important therapeutic approach is to continue to block the HER2 pathway, since leaving it unblocked leads to a much faster death.

Since then, 3 new treatments, including one additional anti-HER2 therapy, have been funded in New Zealand after extensive petitioning, but still many others, including the use of trastuzumab beyond progression, are not publicly funded.^{296,293} Furthermore, national guidelines for the management of MBC have been developed.²⁹⁴ Five areas of focus for change to improve these outcomes were identified: drugs, symptom management, medical care, support, and investing in the future.²⁶⁹ The progress made in New Zealand is an outstanding example of recognising the deficit of MBC data locally, analysing and reporting outcomes, and using this information to drive change in order to improve and extend lives for people with MBC.

Panel 14 – Inequity in access to clinical trials

Clinical trials can be beneficial to participating and future patients, but also increase the quality of care within health services.²⁹⁵ Inequity in access to research studies is a problem for patients with all stages of breast cancer including MBC. Randomised clinical trials in oncology are conducted predominantly in HICs and there is often publication and funding bias against trials carried out in LMICs.²⁹⁶ Patient access to oncological clinical trials remains inadequate, particularly to racial and ethnic minority populations, and it is well documented that many ethnic groups are underrepresented.^{297,298} Other patient populations that tend to be underrepresented include older people, patients with several co-morbidities, those of low socio-economic status, and those living in rural areas.^{300,297} This reduces the generalisability of trial findings and creates disparity in access to high-quality care.^{300,297} This disparity stems from interlinked practices and policies and from barriers at individual (patient and healthcare professional), interpersonal, and system levels.^{300,297} In order to overcome this, multilevel interventions are needed to increase world-wide access to trials and stimulate diverse enrollment, including the use of education, training and high-quality communication.^{300,297} (See *ThemeSection 2 for enabling equitable access to clinical trials through digital health and technology*)

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3) Multidisciplinary management and the use of evidence-based guidelines

Multidisciplinary care

In early breast cancer, multidisciplinary specialised care and management according to high quality guidelines has contributed greatly to the decrease in mortality, together with screening, early diagnosis and new therapies. The same oncology principles should be applied to MBC management and care. Multidisciplinary management improves health outcomes and quality of life in patients with MBC, for example by offering specialised loco-regional therapies and access to clinical trials, as well as early involvement of palliative care teams and psychosocial support.²⁹⁹

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The European Society of Breast Cancer Specialists (EUSOMA) established multidisciplinary care as one of its mandatory high-quality indicators.³⁰⁰ Through a collaboration between EUSOMA and the ABC Global Alliance, new quality indicators specifically dedicated to MBC have been established and will soon be incorporated in the certification process.^{304,301} The EUSOMA requirements for a specialist breast centre state that at least 50% of metastatic cases must be discussed at a multidisciplinary meeting (MDM) as a minimum, but with the aim of discussing every patient with MBC and ideally at

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each point of progression.²⁹⁹ These indicators also recommend that the core team members for a metastatic MDM include a medical oncologist, radiation oncologist, radiologist, breast care nurse, nuclear medicine physician, palliative care specialist, and data manager.²⁹⁹ The ABC international consensus guidelines also emphasise that multidisciplinary input is crucial for the management of MBC and should include at least medical, radiation and surgical oncologists, imaging experts, pathologists, gynaecologists, psycho-oncologists, social workers, specialised oncology nurses, and palliative care specialists.²⁸⁹ There are no specific recommendations for what a metastatic MDM should consist of in the ESMO, ASCO or NCCN breast cancer guidelines. Telemedicine could accelerate widespread implementation of multidisciplinary meetings for MBC (See [ThemeSection 2 – Digital Health](#)).

Guidelines

There is often variation in adherence to guidelines by healthcare professionals, both in LMICs and HICs, despite evidence that adherence to clinical guidelines is associated with improved outcomes in breast cancer. For example, a systematic review in the European Union, and a cohort study in Canada both showed that adherence to guidelines is associated with improved disease-free survival and overall survival.^{302,303} The same applies to resource-limited settings; a study in Malaysia found similar improved outcomes in breast cancer survival when treatment was in line with locally adapted management guidelines.³⁰⁴ However, most breast cancer management guidelines available are not context appropriate.³⁰⁵ Therefore, observation of resource-adapted guidelines and support for patients to avoid treatment abandonment, be that for financial or toxicity reasons, should be a priority in MBC management and will translate to improved outcomes (see [ThemeSection 4 – WHO 3 pillars](#)). There is evidence that treating according to high quality guidelines is cost-effective and would contribute to avoiding unnecessary costs and optimisation of resources in cancer care.^{309,306} Even when guidelines are implemented, treatment abandonment is a huge problem in LMICs and in marginalised and hard-to-reach populations in HICs, sometimes due to toxicities, but frequently secondary to financial reasons and lack of social support.^{307,308} This is another strong argument for improved treatment access and support for patients (see [ThemeSection 4 – WHO 3 pillars](#)). Despite the ready availability of many high-quality guidelines in the management of breast cancer, analyses using information within national datasets routinely demonstrate marked care variation. Pursuing small incremental improvements from new drugs in clinical trials is of limited value if they are not used. The translation of evidence into practice is often difficult particularly in LMICs but is a priority.

4) Stigma

Patients with MBC experience stigma from society, policymakers, healthcare professionals, and some patient advocacy groups. This is isolating and can have a huge impact on the physical, social, and emotional functioning of a patient with MBC, leading to worse outcomes.³⁰⁹ (see [ThemeSection 5](#)) Misconceptions among the general population and healthcare providers, regarding the nature and expected outcomes of MBC, substantially contribute to this. Stigma is responsible for prejudice against these patients within the health system, as well as socially and professionally, which generates isolation, loneliness, and feelings of guilt. Stigma is a major driver of poor health outcomes globally as it can lead to reduced help-seeking, social withdrawal, and can be a barrier to therapy adherence.³⁰⁹ As a result, patients are dying earlier due to inadequate care. Education and awareness of all stakeholders and public is paramount: these issues must be highlighted repeatedly, until things are changed.

Characterisation of MBC as a ‘rapidly fatal disease’ contributes to stigma and abandonment. Furthermore, characterisation of EBC as ‘curable if everything is done well’ creates misconceptions about those who develop metastatic disease, even though approximately 30% of patients with early disease will develop MBC despite optimal therapy.^{313,310} Slogans such as ‘early detection saves lives’, although extremely important for creating awareness, can promote myths that patients with MBC did not, for example, get a screening mammogram or self-examine. There is a difficult balance between

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generating breast cancer awareness and avoiding attributing blame to the individual with MBC. Stigma is accentuated within societies that do not typically acknowledge or discuss mortality, and this can be a very negative experience for patients with MBC.

Quantifying MBC stigma

The Decade Report, an analysis of the MBC status and evolution between 2005 and 2015, included a general population survey analysing awareness of MBC, which consisted of 14,315 participants from 14 countries.²⁷⁶ The results emphasised that public understanding of MBC was limited. Across all countries, 14-61% of respondents agreed with the statement 'there is no point in treating advanced or metastatic breast cancer'.²⁷⁶ 18-49% of participants indicated that 'people with advanced or metastatic breast cancer should not talk about it with anyone other than their physician'.²⁷⁶ Two extreme misconceptions exist among the general population regarding MBC: some believe it is equal to early breast cancer and therefore curable, while others believe it is a terminal illness for which there is no hope. These findings illustrate the striking myths that can fuel stigma and isolation in MBC. Furthermore, the misconception that MBC is a rapid terminal illness leads to prejudicial policy decisions in many LMICs and some HICs, where limited resources are usually dedicated to early detected cancers, cutting short the survival, and increasing the suffering of MBC patients.

Cross-cutting features of health-related stigma and identifying interventions

Stigma has been studied in many medical conditions outside of cancer, for example, HIV and mental health, but often a siloed, disease-specific measurement and intervention approach is suggested.³¹¹ The concept of 'health-related stigma' could facilitate generic stigma assessment tools and interventions rather than disease-specific, which would be a highly beneficial and cost-effective approach from a health systems perspective.^{314,315,311,312}

There are multiple theoretical models describing the cross-cutting elements of health-related stigma.^{311,313-316} It has been shown that a patient-centred but multi-component approach, directed at many socio-ecological levels, is required if stigma is to be effectively addressed.^{320,317} The ABC Global Alliance has created a tool-kit to address unmet needs for hard-to-reach populations and this includes examples of community-based initiatives that target stigma.²⁷⁵ For example, Project PINK BLUE was set up in Nigeria in 2016 to address stigma and misunderstanding around breast cancer.^{321,318} The aim of this initiative is to support, empower, and educate people with breast cancer by providing educational materials, financial and telephone support, monthly support groups, and patient navigators.^{321,318} Another example is the Male Breast Cancer Global Alliance that was created to address stigma and raise awareness for male breast cancer, with initiatives including breast self-examination cards, support calls and an annual conference.^{322,319}

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Panel 15 - Lancet Breast Cancer Commission Healthcare Practitioner survey

We carried out a bespoke web-based survey for healthcare professionals (HCP) globally, to study views and perceptions regarding MBC within the healthcare community (*see supplementary material 10 for full survey results*). Our survey obtained~~This analysis includes~~ a total of 382 responses. 46% of participants were from Europe with limited representation from North America, Africa, and the Middle East. Most of the respondents (70%) were oncologists with more than 10 years of professional activity, and three-quarters of them had > 50% of their clinical practice devoted to breast cancer.

When asked how many lines of treatment patients receive on average, HR-positive and HER2-positive patients were reported to receive more treatment lines (5 or more and 4 or more, respectively). Patients with triple negative breast cancer received the least treatment with an average of three lines of therapy. These results probably reflect the biology of the disease and the available treatment alternatives within these subtypes.

80% of respondents considered MBC an incurable disease, and when asked whether MBC would become curable within the next decade, most were undecided or disagreed. However, 55% agreed that it may become curable for certain subtypes and, importantly, 75% agreed that MBC will become a chronic disease.

More than 70% of health care professionals reported that they inform patients with MBC that their disease is incurable. They considered they had received adequate communication training and felt confident in communicating difficult issues with patients, such as poor prognosis and death. This does not reflect what patients report. For example, a survey of 185 MBC patients in Mexico revealed that only 52% of patients were aware that their disease was incurable, 31% were not sure, and 17% thought it was curable.³²³ This shows the lack of understanding that some patients have regarding their disease, despite most healthcare professionals feeling confident in their communication skills.³²⁰ ~~This shows the lack of understanding that some patients have regarding their disease, despite most healthcare professionals feeling confident in their communication skills.~~ This communication gap needs urgent attention if we aim to improve the overall management and the outcomes of MBC (*see section 6 – communication and empowerment*). When asked to rank objectives for MBC patients, 72% of our survey respondents stated quality of life as the most important. Progression free survival and overall survival were also highly ranked, whereas improving communication was felt as being of lower priority. Only 18% were very familiar with the ABC Global Alliance 10 Actions for change, which is an important global initiative to address urgent and actionable gaps in management of patients with MBC.²⁷⁵

This survey of HCPs reflects the negative views associated with MBC that contribute to the stigma patients experience. At the same time, a significant proportion of physicians consider recent treatment advances will have a positive impact on the disease. This may be a good starting point to begin to change the overall negative perception of the disease and consider that not all MBC patients are destined to have poor outcomes.

Potential wider impact outside of MBC

By using breast cancer as a model cancer, we hope that our suggestions for reducing discrepancies and stigma, and improving MBC care, can be applied as a framework for positive change to other cancers. Updating cancer registries is integral to more accurate outcome data collection and better allocation of resources, and this is also important across all tumour types. We strongly urge a shift in mindset and aims when treating people with MBC, as this will be valuable not only to the individual and their family, but also to society.

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Panel 16 - Lancet Breast Cancer Commission proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target
ThemeSection 3: Optimal inclusive management of metastatic breast cancer ~~is valuable to individuals and society~~					
Data collection on metastatic breast cancer (MBC).	Improvements in cancer registry data collection: stage at diagnosis including de novo metastatic disease and breast cancer relapse data.	Knowing the actual number of people living with MBC would allow a better allocation of resources.	Cancer registries.	Ministry of Health.	Minimum of 70% of cancer registries, aiming at 100%.
Multidisciplinary meeting (MDM) review for MBC.	MBC cases discussed at a multidisciplinary meeting (MDM).	Improve outcomes: survival and quality of life.	Facility records, national and international certification procedures for breast units.	Ministry of Health.	Minimum of 50%, aiming at 95% MBC cases discussed at MDM.
MBC outcomes.	Improvements in median overall survival (OS) of MBC.	Improve outcome.	Cancer registries, Facility records, national and international certification procedures for breast units.	Facility, Ministry of Health.	~~Record the number~~ Doubling of people with MBC and double the median OS in a decade.
End of life care.	Number of patients with breast cancer dying in pain: morphine use as an indicator of suffering.	Improved QoL and reduced suffering.	Pharmacy registries.	Ministry of Health.	Aiming for less than 5% of patients at end of life without access to morphine.
Essential breast cancer	Updates and uptake in WHO	Improve outcomes for MBC.	WHO EML updates, National regulators data.	Ministry of Health.	All MBC patients have access to life saving cancer medicines.

medicines for MBC are affordable globally.	essential medicines to promote equal access.				
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ThemeSection 4: Tackling breastBreast cancer global-gaps and inequities though global collaboration

Panel 17 - Summary for tackling breast cancer global-gaps and inequities though global collaboration

Poorer women and minoritised populations often have late-stage breast cancer and are at high-risk of dying from cancer - this equity gap will widen without global collaborative intervention.

- Equitable access to early diagnosis and treatment is a fundamental need for all individuals to improve breast cancer survival and quality-of-life.
- In collaboration with the WHO Global Breast Cancer Initiative, we call for action to deliver 'stage-shifting' – as a sustained decline in breast-cancer mortality rates is achieved by diagnosing at least 60% of invasive cancers at stage I-II.
- Tools to achieve this 60% threshold can be adapted to local context and resources.
- Technology innovations can catalyse the speed and efficacy of early diagnosis and treatment implementation globally.
- Integrated health systems policy, education, and advocacy are needed – pioneering approaches in breast cancer and can be used as a model for other cancers.

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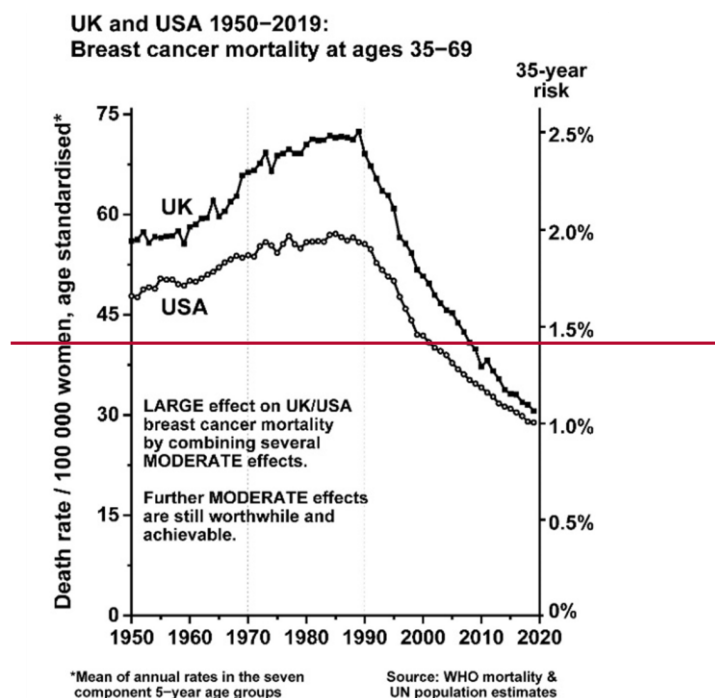
In the early 1990s, many high-income countries witnessed a sea change in diagnosis and coordinated multidisciplinary evidence-based treatment as exemplified by the initiation of the Early Breast Cancer Trialist Collaborative Group. These changes have demonstrated declines in breast cancer mortality rates of around 2% per year or greater (see Figure 4), translating to an overall 40% reduction in breast cancer age-standardised mortality rates (ASMR) over 3 decades.^{324,325} The 40% improvement in age-adjusted breast cancer mortality has not yet been achieved in most low- and middle-income countries.³²⁶ In LMICs, advanced stage at diagnosis and limited diagnostic and treatment capacities contribute to lower breast-cancer survival rates.^{279,327} 5-year breast cancer survival rates exceed 90% in high-income countries, compared to 66% in India and 40% in South Africa.³²⁸ To address this inequity, translation of what has worked well in high-income countries to less well-resourced settings is required, but tailored to local context.

According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to assert that mammographic screening reduces breast-cancer mortality in women 50–74 years of age and limited evidence supporting the same benefit in women ages 45 – 49.³²⁹ While the evidence for the net benefits of mammographic screening is well established for women 50 years of age and above, the obstacles to translation of these findings to implementable strategies in LMICs are significant.³³⁰

Learning from past failures in breast cancer management globally

Since the early 1990s, many high-income countries have demonstrated declines in breast cancer mortality rates of around 2% per year or greater (see Figure 4), translating to an overall 40% reduction in breast cancer age-standardised mortality rates (ASMR) over 3 decades.^{321,322} The 40% improvement in age-adjusted breast cancer mortality has not yet been achieved in most low- and middle-income countries.³²³ In LMICs, advanced stage at diagnosis and limited diagnostic and treatment capacities contribute to lower breast cancer survival rates.³²⁴ 5-year breast cancer survival rates exceed 90% in high-income countries, compared to 66% in India and 40% in South Africa.³²⁵ To address this inequity, translation of what has worked well in high-income countries to less well-resourced settings is required, but tailored to local context.

Figure 4: An example of the fall in breast cancer mortality in two high income countries in the last three decades. Graph produced by the Early Breast Cancer Trialists Collaborative Group and shown with their permission.



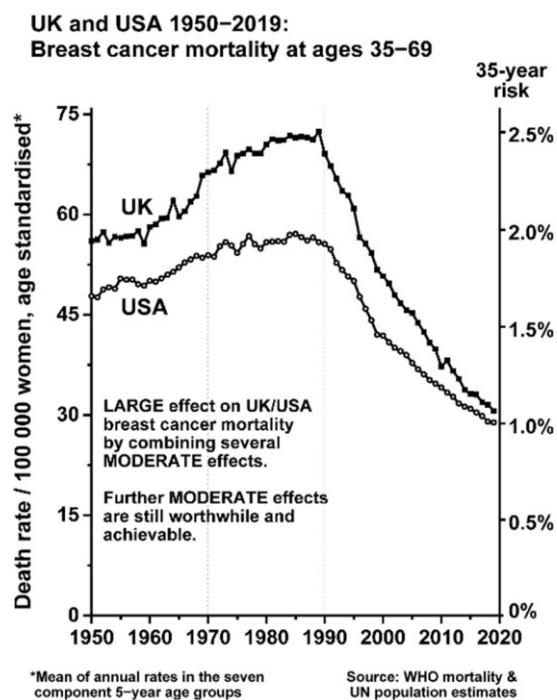
According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to assert that mammographic screening reduces breast cancer mortality in women 50-74 years of age and limited evidence supporting the same benefit in women ages 45-49.³²⁶ While the evidence for the net benefits of mammographic screening is well established for women 50 years of age and above, the obstacles to translation of these findings to implementable strategies in LMICs are significant.³²⁷

In order to reduce breast cancer mortality, early detection including both early clinical diagnosis and screening programmes (see supplementary material 11); and effective multimodality treatment are needed.^{331,328} (see Panel 18 - World Health Organization (WHO) Global Breast Cancer Initiative (GBCI) Pillars and Early breast cancer detection). The infrastructure and processes used for breast cancer management are similar for other adult solid tumours such as colorectal, prostate, and lung cancers. If breast cancer can be managed effectively in a limited resource setting, then improved management of other malignancies is more likely to follow.

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Figure 4: An example of the fall in breast cancer mortality in two high-income countries in the last three decades. Graph produced by the Early Breast Cancer Trialists Collaborative Group and shown with their permission.



Panel 18 - World Health Organization (WHO) Global Breast Cancer Initiative (GBCI) Pillars

A population-based analysis demonstrated two health-system characteristics were significantly associated with lower age-standardised mortality rates (ASMR): higher levels of universal health coverage (UHC) levels (funding) and increased numbers of public cancer centres per 10,000 cancer patients (access).³²⁶³²³

In 2021, the GBCI was set up, with the aim of reducing breast cancer mortality by 2.5% per year and potentially preventing 2.5 million premature deaths over 20 years.³³²³²⁹ To achieve this target, GBCI (Figure 1) suggests three sequential care intervals or 'pillars' for effective management³³⁰:

Pillar 1: Health promotion for early detection (pre-diagnostic interval)

Individuals enter the pre-diagnostic interval either by presenting with a breast symptom, such as a lump or breast change; or presenting without symptoms to a screening programme if available. Analysis carried out by GBCI shows that not all countries that achieve a sustained breast cancer mortality reduction have population-based mammographic screening programs.³²⁶³³³ These findings encourage a focus on early detection programs that vary based on the needs assessment of individual countries. Stage shifting is required to increase the fraction of patients initially diagnosed with early-stage disease. Early detection begins with breast-health awareness and the establishment of early diagnosis programs, which identify people with symptoms and signs of possible malignancy and link them to diagnostic services. Breast cancer screening is not appropriate until the required infrastructure and quality-control measures are fully functional. All healthcare systems require the capacity to diagnose symptomatic breast findings in a timely manner, regardless of whether they have mammographic-screening programs.

Pillar 1 key process indicator (KPI): at least 60% of invasive cancers diagnosed at stages I or II.

Pillar 2: Timely breast diagnostics (diagnostic interval)

Breast diagnosis requires clinical evaluation, breast imaging, and tissue sampling from suspicious lesions (triple assessment). The optimal imaging and sampling methodologies will vary, depending on the availability of equipment and trained staff.³³⁴³³⁵ Treatment delays beyond 90 days lead to lower rates of breast cancer survival.³³⁵³³² In 2012, Brazil established the '60 days law' - all cancer patients should start treatment within 60 days of diagnosis.³³⁶³³³

Pillar 2 KPI: diagnostic process to take place within 60 days.

Pillar 3: Comprehensive breast cancer management (treatment interval)

Effective treatment requires a multidisciplinary approach from radiology, pathology, surgical oncology, medical oncology, radiation oncology, and supportive oncology. However, these treatment strategies are usually only effective when the entire treatment course is given. Treatment abandonment, in which the patient begins treatment but fails to complete it for reasons other than a clinical decision to stop, is a common problem in LMICs. In the African Breast Cancer Disparities in Outcomes (ABC-DO) study of 5 sub-Saharan African countries, less than 50% of patients started and completed their treatment course.³¹⁰³⁰⁷

Pillar 3 KPI: >80% of individuals to complete multimodality treatment without abandonment.

Most HICs have lower rates of later-stage diagnosis and better outcomes, however there can be differences in breast cancer mortality within most HICs, with evidence from the USA (See Panel 19 – Breast cancer stage disparities in Miami), Scotland³³⁷³³⁴, The Netherlands³³⁵, and Australia.³³⁹³³⁶ All countries across the globe should set out on this journey but they will not all start from the same place. For further reading see stage shifting strategies with and without *functioning screening programmes and future directions are outlined in supplementary materials 12-14.*

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Panel 19 – Case history – breast cancer stage disparities in Miami³⁴⁰

Panel 19 – Case history – breast cancer stage disparities in Miami

Background:

Unmet Social Needs are direct mediators of health outcomes. We aimed to evaluate if 1) city-funded screening mammography is associated with utilisation of screening mammography, 2) Unmet Social Needs are associated with utilisation of screening mammography, and 3) Unmet Social Needs are associated with later-stage disease at diagnosis.

Methods:

Prospective cohort study of stage I-IV breast cancer patients recruited from 2020-2023 at both an underserved safety-net hospital (SNH) and a National Cancer Institute-designated Academic Cancer Center (ACC) who completed the Health Leads Social Needs Screening Toolkit. Univariable and multivariable logistic regression was utilised to evaluate the following primary outcomes: 1) routine screening mammography and 2) AJCC 8th edition clinical stage at presentation.

Findings:

Of the 322 women who completed the Health Leads Social Needs Screening Toolkit, 76% with access to city-funded screening mammography completed a screening mammogram. Patients who presented to the SNH were more likely to present with late-stage disease compared to early-stage disease (31% vs 18%, $p=.04$). On multivariable logistic regression, independent predictors of not completing a screening mammography were having an increasing number of Unmet Social Needs (OR 0.74 95% CI 0.55-~~0.99~~~~1.00~~, $p=0.047$) and increasing age at diagnosis (OR 0.92 95% CI 0.89-0.96, $p<0.001$). Moreover, increasing Unmet Social Needs (OR 1.38 95% CI 1.01-1.89, $p=.04$) was an independent predictor of late-stage at diagnosis, above and beyond screening mammography.

Interpretation:

Our prospective cohort study found that access to screening mammography did not translate to utilisation of screening mammography, increasing Unmet Social Needs significantly predicted lower rates of screening mammography, and having increasing Unmet Social Needs significantly predicted late-stage diagnosis. This effect transcended recruitment site (SNH vs. ACC), indicating that patients in any hospital setting may benefit from Unmet Social Needs screening to overcome access to care barriers associated with late-stage disease at diagnosis.

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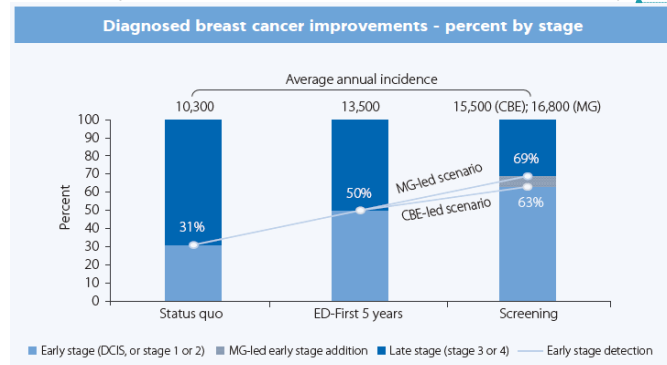
Panel 20 - Case study: economic evaluation of breast cancer control in Kenya, 2022

In 2020, the Kenyan Ministry of Health partnered with the World Bank to create an investment case for combatting non-communicable diseases. Working in collaboration with WHO and GBCI, the GBCI group developed a health-system model to predict breast cancer outcomes and related implementation costs. The resulting Kenya model for early detection proposes a 15-year implementation plan, using a phased implementation approach. During the first five years, health-system strengthening focuses on the establishment of diagnostic services to work-up clinically detectable breast changes, thereby establishing early diagnosis services. In years 6 to 15, Kenya plans to establish screening programs based on a combination of clinical breast examination-led screening and mammogram-led screening, utilising the infrastructure and programming established during the first five years. The following predictions and cost estimates were projected based on the Kenya-specific baseline data and examines outcomes as measured by stage shifting projected to 15-years (Figure 5A), breast cancer survival rates projected to 40-years (Figure 5B), and project associated costs for each development strategy (Figure 6).^{341,342}

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Figure 5A: The Kenya Model for early detection and predicted stage shifting over a 15-year period (2022–2037), Kenya

Source: Reproduced with permission of the publisher from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya*³⁴¹³³⁷

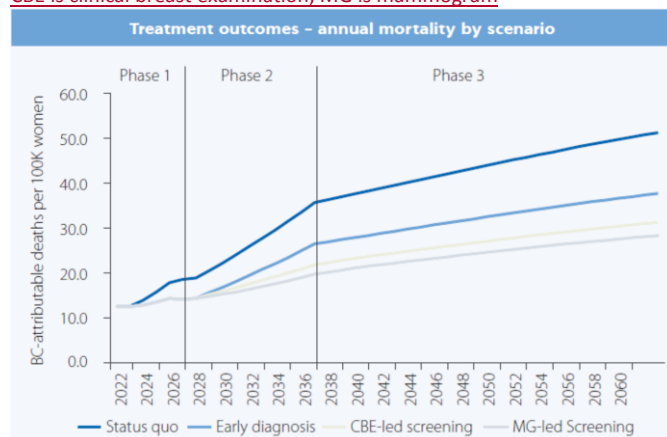


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Figure 5B: Predicted breast cancer mortality reductions over 40 years (2022–2062), Kenya

Source: Reproduced with permission of the publisher from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya*³⁴¹³³⁷

CBE is clinical breast examination; MG is mammogram



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Figure 6: Predicted breast cancer programme and service-delivery costs over a 15-year period (2022–2037), Kenya

Source: Based on data from *Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya* with the permission of the publisher³⁴¹. CBE is Clinical Breast

15-year programme and service delivery costs (KES (discounted) and approximate US\$)								
Cost type	Early diagnosis only			CBE-led total 15-years			MG-led total 15-years	
Health-system strengthening	KES 8.54 billion (US\$ 69.99 million)			KES 14.56 billion (US\$*118.78 million)			KES 15.94 billion (US\$*127.52 million)	
Direct treatment	KES 11.46 billion (US\$*93.73 million USD)			KES 16.74 billion (US\$*136.95 million)			KES 38.41 billion (US\$*311.39 million USD)	
Screening	00			KES 1.67 billion (US\$*13.66 million)			KES 19.97 billion (US\$*163.57 million)	
Diagnosis	KES 1.46 billion (US\$*11.98 million)			KES 3.46 billion (US\$*28.33 million)			KES 5.34 billion (US\$*43.72)	
Treatment	KES 7.42 billion (US\$*60.80 million)			KES 8.77 billion (US\$*71.82 million)			KES 9.77 billion (US\$*80.02 million)	
Palliative	KES 2.56 billion (US\$*21.03 million)			KES 2.83 billion (US\$*23.23 million)			KES 2.96 billion (US\$*24.22 million)	
Total	KES 19.99 billion (US\$*163.71 million)			KES 31.30 billion (US\$*256.31 million)			KES 53.63 billion (US\$*439.12 million)	

Examination; MG is Mammogram.³³⁷

15-year programme and service delivery costs (KES (discounted) and approximate US\$)						
Cost type	Early diagnosis only		CBE-led total 15-years		MG-led total 15-years	
Health-system strengthening	KES 8.54 billion (US\$ 69.99 million)		KES 14.56 billion (US\$*118.78 million)		KES 15.94 billion (US\$*127.52 million)	
Direct treatment	KES 11.46 billion (US\$*93.73 million USD)		KES 16.74 billion (US\$*136.95 million)		KES 38.41 billion (US\$*311.39 million USD)	
Screening	00		KES 1.67 billion (US\$*13.66 million)		KES 19.97 billion (US\$*163.57 million)	
Diagnosis	KES 1.46 billion (US\$*11.98 million)		KES 3.46 billion (US\$*28.33 million)		KES 5.34 billion (US\$*43.72)	
Treatment	KES 7.42 billion (US\$*60.80 million)		KES 8.77 billion (US\$*71.82 million)		KES 9.77 billion (US\$*80.02 million)	
Palliative	KES 2.56 billion (US\$*21.03 million)		KES 2.83 billion (US\$*23.23 million)		KES 2.96 billion (US\$*24.22 million)	
Total	KES 19.99 billion (US\$*163.71 million)		KES 31.30 billion (US\$*256.31 million)		KES 53.63 billion (US\$*439.12 million)	

Adapting technologies

Technologies for early breast cancer diagnosis and treatment to local settings

Diagnostic services coupled with treatment provision are the foundation for high quality and effective healthcare delivery³⁴². ~~Through adapting³⁴⁸, allowing the right treatment to be delivered to the right patient in a timely manner. Traditionally, technological innovations in diagnosis and treatment for breast cancer have increased healthcare disparities, often widening the gap between health systems with different resource levels both between and within countries. However, advances in technology to local settings there is a also have the potential to ‘leapfrog’ ahead of existing methods and move, thereby reducing disparities, and moving~~ closer to equity across all contexts if a framework of ‘smart leapfrogging’ is adopted. ~~(see also section 2 – digital health as a care equaliser).~~ Adapting to local context using local knowledge and innovation is also required. A striking example of this is the use of Coca-Cola lorries to deliver essential medicines in rural Zambia, given that Coca-Cola drinks were readily available in in remote villages, but anti-diarrhoea kits were not.^{343,349}

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Leapfrogging technologies fall into two categories: 1) novel technology that augments or bypasses an existing technology or addresses a previously unmet need, and 2) innovation achieved through the reorganisation or reframing of current practices or resources. An example of the first category is automated systems that measure RNA levels to determine breast cancer biomarker status, which may have the potential to bypass immunohistochemistry (IHC) and fluorescence in situ hybridisation (FISH) where it is currently absent, unreliable, or only available in tertiary care facilities.³⁴⁰⁻³⁴² An example of the second category is the shift to virtual multidisciplinary tumour boards using existing teleconferencing software during the coronavirus disease 2019 (COVID-19) pandemic, which increased access to expert multidisciplinary care to non-tertiary care settings and enabled remote patient consultations (see [Theme section 2 – digital health](#)).

The key principles of smart leapfrogging include defining the specific local context by carrying out a situational analysis to identify gaps that act as critical barriers to equitable access to care, identifying an innovation or technology that may fill the gap and add value to the local context. A limitation in the development and validation of novel technologies is that specific tools can be tested in isolation, without considering how they fit into the healthcare system.

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Technologies or innovations shown to be highly effective in high-resource settings may not have the same performance characteristics in a resource-constrained setting, while others might have greater impact.³⁴³⁻³⁴⁵ For example, the systematic measurement of breast residual cancer burden (RCB) and stage after neoadjuvant chemotherapy provides prognostic information that helps treatment decisions for subsequent adjuvant therapies. There is negligible cost for measuring residual cancer burden as it is an adaptation of usual pathology practice.³⁴⁶⁻³⁴⁸ However, a prerequisite for a neoadjuvant systemic therapy approach requires a functioning healthcare system to coordinate analysis of results and deliver multimodal therapies in a timely fashion and safer manner. ~~Another promising example of a leapfrogging technology is the use of artificial intelligence (AI-based) digital platforms in both radiology and pathology (See section 2 – technology enabled breast cancer management). The applications of AI may range from cancer detection, characterisation, and prediction of biomarker status.³⁴⁹⁻³⁵² However, these technologies may be helpful as training tools or for task shifting but do not replace existing standards of care. Moreover, the training sets need to be representative of the intended population. Nevertheless, AI-based approaches might bypass existing practice methods, in the right practice environment and clinical utility setting.~~

Novel technologies have been proposed as potential methods for screening, monitoring treatment response, predicting disease progression or relapse, or guiding therapy, which will have wider implications beyond breast cancer diagnosis. A surgical example is the use of magnetic markers that can serve as a non-radioactive and wireless alternative for localisation of sentinel lymph nodes and non-palpable breast lesions, respectively.³⁵³ With standard metal clips, image-guided wire localisation

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is required. By contrast, with magnetic markers, the surgeon can find the correct region without special assistance from the radiologist. Whole slide imaging and digital pathology can also be used to increase access to expert assessments of response to neoadjuvant therapy in regions where pathology services are limited, allowing for a more personalised and cost-effective therapeutic approach. Moreover, several blood-based technologies (i.e. liquid biopsies) that leverage a broad scope of technologies have emerged, ranging from detection of tumour biomarkers using low-cost methods such as enzyme-linked immunosorbent assays (ELISA), to high complexity methods such as sequencing and methylation profiling of circulating tumour DNA (ctDNA) and cell-free DNA (cfDNA).^{354,355} For example, the United States Food and Drug Administration and European Medicines Agency have approved the use of alpelisib in patients with PIK3CA-mutated metastatic breast cancer, detected either in ctDNA or tissue.^{355,356} These blood-based methods are still under investigation, and it is unclear what clinical role they will play in the future. ~~Future studies are needed to investigate how technologies (e.g. smart phones, genomic profiling, or artificial intelligence) could reduce breast cancer inequities in risk assessment, screening, diagnosis, treatment, and monitoring, patient education, and navigation (see section 2 – digital health as a care equaliser).~~

Panel 21 - Smart leapfrogging

Key principles

- Conduct needs assessment/situational analysis to identify gaps and specify local context.
- Identify root causes of the gaps.
- Find or adapt technologies to address gap & able to integrate within health system.
- Assess the value added.
- Determine whether partnerships would be beneficial.

Characteristics of an innovative and leap frogging technology^{357,358}

1. Integration into broader health system:
 - Addresses a specified evidence-to-practice clinical gap.
 - Health system can provide sufficient human resources, education and training, reliable supplies and procurement, maintenance.
 - Clinically relevant turnaround time to guide therapeutic decision-making.
2. Assay characteristics:
 - Robust performance characteristics (sensitivity, specificity, predictive values, precision, and accuracy).
 - Easy to perform and maintain.
 - Easy to interpret and communicate.
 - Cost-effective.
 - Clinically relevant turnaround time to guide clinical decision-making.
3. Quality management and outcome metrics:
 - Well documented structure, processes, roles, responsibilities, and procedures required to achieve effective quality implementation and maintenance (see *Quality System Essentials Table*).³⁵⁹
 - Well defined implementation outcomes that are also linked to service and client outcomes. (see *Proctor's Conceptual Framework for Implementation Outcomes*)³⁶⁰

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Patient navigation and equitable access to medications

Access to high-quality breast cancer care may be hampered by delays in diagnosis and treatment.^{361,362} Prioritisation of patients scheduled for diagnostic evaluation according to suspicion of malignancy based on image findings and/or symptoms can reduce health system interval delays. This strategy has been employed by navigation programs in Mexico³⁶³ and Colombia³⁶⁴ that have been successful at reducing the time to diagnosis of breast cancer. In Mexico, the 'Alerta Rosa' program introduced a

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triage system to stratify and prioritise patients for imaging studies and appointments with breast specialists to accelerate access to diagnostic procedures and treatment. In Colombia, the 'Breast Cancer Early Detection Pilot Program' focused on evaluating care barriers and coordinating timely referrals for early breast cancer detection and prompt access to treatment. A comparable approach was developed in the United Kingdom, which established national referral guidelines requiring that every patient with suspicion of breast cancer should receive a specialist consultation within two weeks of referral by their general practitioner. Adherence to these guidelines resulted in a significant improvement in adequate patient prioritisation and reduction in health system waiting times.³⁶⁵

Equitable access to medications is essential across the breast cancer continuum

This is discussed in Panel 22 - Equitable access to ~~medicines~~^{medications} and explored further in a case study on immunotherapy in supplementary material 6. See also ~~Theme~~^{Section} 3 – metastatic breast cancer.

Panel 22 - Equitable access to medicines

Access to medicines is a complex and multidimensional problem, with cost being a major barrier to optimal treatment. Access is a worldwide problem, but underserved populations are routinely consistently worse affected. Potential strategies to address drug access include establishing universal health coverage for essential cancer medicines (for both early and metastatic cancers), fair drug pricing, and optimising regulatory demands and improving global supply.³⁶⁶⁺ Treating patients according to context-adapted high-quality guidelines is another important strategy to optimise care and avoids unnecessary waste of resources.⁰

Access to medications released to the market over the last 5 years represents one of the more telling discrepancies clearly related to the different cancer outcomes seen in different regions of the world.³⁶⁷⁺ While the US, Western Europe, and Japan consume approximately 90% of all new medications, the rest of the world population accounts for only the remaining 10%.³⁶⁷⁺ Too frequently, we are seeing a complete dissonance between the price of new cancer medicines and the benefit seen in registration clinical trials. Recent analyses indicate no association between medicine prices and the magnitude of benefit on end points such as progression-free survival, overall survival or objective response rate, suggesting that cancer medicines are priced based on what the market can stand, not the clinical benefits they provide.³⁶⁸⁺ Addressing this inappropriate process in a transparent way is fundamental for the future of breast and other cancer care, as it leads to differential medicine access within HICs, as well as the rest of the world.

The recurrent argument that prices should cover not only the few medications that make it to the market but all the other failed experiments as well, has been questioned by an analysis indicating that cancer medicines have generated returns far in excess of officially reported research and development costs.³⁶⁹⁺ This challenging scenario has led to increasing interest in alternative pricing strategies including different versions of value-based pricing, a discussion that should be encouraged. Affordability of a particular country or region should also be considered. Outcome-based payment is being explored in certain scenarios.³⁷⁰⁺ Different prices according to the different benefits a medicine may have on different indications has been proposed. Also, Food and Drug Administration accelerated approvals could be priced at lower levels to be adjusted after confirmatory evidence is generated.³⁶⁸⁺ Regulators should be more active in withdrawing approval when benefits are not confirmed within clinical trials or when 'real world data' fails to demonstrate benefits.

Furthermore, payers should not be influenced by pharmaceutical industries and should use an objective assessment tool – such as the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale²⁸⁴ or the American Society of Clinical Oncology (ASCO) Framework of

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Value³⁷¹³⁶⁶ – to prioritise cancer medicines that should be approved in each country. Medicines that provide the highest benefit should be approved faster than the ones that provide only marginal benefit. This is crucial in countries with limited resources but, in view of the uncontrolled rise in costs, it is important in HICs as well. ~~Improving~~ Ultimately, to improve access to cancer medicines ~~to and the currently discrepant breast cancer outcomes observed in different regions of the world, a transparent strategic discussion involving all populations interested players is a universal and urgent unmet need.~~ needed.

See *Panel 13 - Inequity within HICs - New Zealand* as a case study, as a breast cancer specific example of improving equity of access to HER2-directed therapies.

Patient advocacy to improve equity in breast cancer detection and care

Health advocacy has been defined in the medical profession as activities related to ensuring access to care, to navigating health systems, mobilising resources and to addressing health inequities, influencing health policy and creating system change.³⁷² Cancer advocacy relates to the application of these strategies to the cancer care continuum and has been largely led by civil society organisations in many countries.³⁷³ Historically, advocacy has been powerful in bringing about global change in disease and healthcare, but it is not clearly understood by many and lacks a robust evidence base. Even so, it plays a fundamental role within every society and drives the evolution of breast cancer care globally. For example, advocacy efforts could be aligned to the GCBI pillars to facilitate achieving the three major KPIs.

~~Historically, advocacy has been powerful in bringing about global change in disease and healthcare, but it is not clearly understood by many and lacks a robust evidence base. Even so, it plays a fundamental role within every society and drives the evolution of breast cancer care globally. For example, advocacy efforts could be aligned to the GCBI pillars to facilitate achieving the three major KPIs.~~

Self-advocacy or patient activation is an important overarching theme in the literature.³⁷⁴³⁶⁷ Patients should be empowered to feel control over their body, health, and decision making, for example, regarding breast cancer treatment options (see ~~Theme~~*Section 6: Communication and empowerment*). With the understanding of the disease process, self-advocacy may help to push for supporting timely diagnosis and could enhance treatment adherence and completion of care (pillars II and III).

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A 'structured' advocacy approach can address awareness and early detection concerns, and treatment and survivorship needs. This organised approach to advocacy can touch on legal, educational, research and policy aspects of care. A proposal by the African coalition of cancer advocates (ACAC) suggests 6 key areas of prioritisation for comprehensive cancer advocacy: political, education, research, fundraising, support, and community outreach.^{368,369} These key tenets must however be contextualised to different settings. See *supplementary material 15* for more information on structured advocacy.

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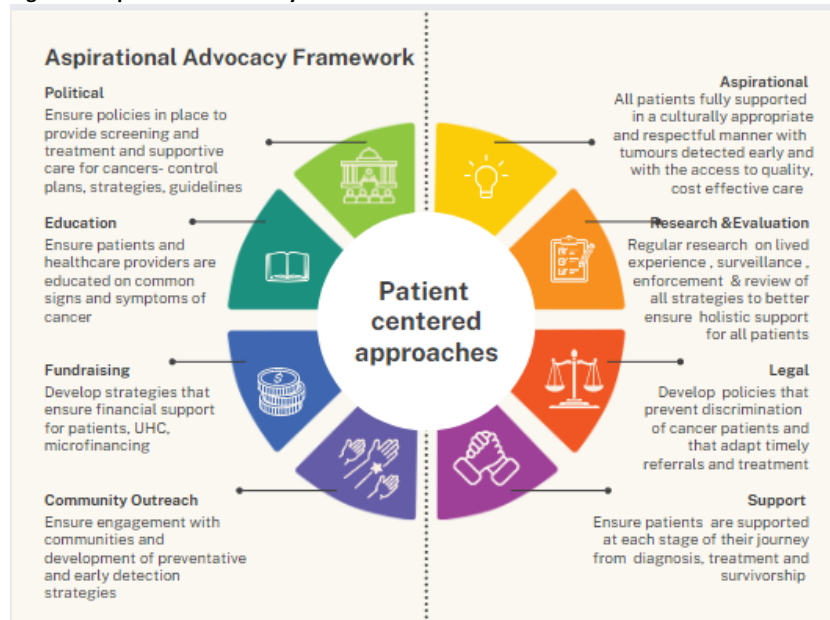
Innovative approaches and strategies need to be considered to enable advocacy to bridge global gaps in care. Advocacy must be contextual but should also leverage existing networks. Developing a cadre of advocates that will engage all stakeholders including policymakers about concerns along the care continuum whether financial, legal or supportive, and provide funding for care is important. Advocates should prompt researchers to ask the relevant questions for their communities, to empower and improve the lived experience of cancer patients and their care givers. This may mark the first steps towards achieving equitable care in many settings. The additive effects of the outputs of these advocacy efforts must be assessed along with the GCBI pillars and targets.

In rethinking approaches to cancer advocacy, we propose an ‘aspirational’ advocacy framework (See *Figure 7*) which builds on experiences from breast cancer advocacy to form a broader relationship around equity and health. It is important to widen the focus to go beyond the individual need and to target broader platforms in civil society, for example, women’s rights. Here, aspirational advocacy could contribute more broadly to women’s empowerment, health systems strengthening, anti-poverty efforts, and address violence against women with measurable outcomes. Education of women in LMICs is paramount to develop preventative aspects of breast cancer care as early as possible. This highlights the importance of younger females remaining in formal education settings to enable this transfer of information.

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Figure 7: Aspirational Advocacy



Panel 23 - Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Section 4: Tackling breast cancer gaps, global gap and inequities through global collaboration						
Stage-shifting.	Ensuring prompt diagnosis of breast cancer.	Decrease breast cancer mortality rates and prolong life.	Cancer registries.	Ministries of Health.	60% of all invasive cancers are at stage 1-2 at diagnosis.	WHO Global Breast Cancer Initiative (GBCI) Pillar 1 Key Performance indicator (KPI).
Timely and appropriate treatment.	Evaluation, imaging, tissue sampling and pathology.	Improve breast cancer outcomes.	Facility records, National audit.	Ministries of Health.	Evaluation, imaging, tissue sampling and pathology within 60 days.	WHO GBCI Pillar 2 KPI.
Treatment abandonment as defined by WHO Global Breast Cancer Initiative.	Optimising multimodality treatment without abandonment.	Improve breast cancer outcomes.	Facility records, National audit, national and international certification procedures for breast units.	Ministries of Health.	80% of patients undergo multimodality treatment without abandonment.	WHO GBCI Pillar 3 KPI.
Access to medicines.	Reduce inequalities in access to medicines between and within countries.	Improve breast cancer outcomes.	Time for Harmonization of Global Clinical Trials to decrease time from Food and Drug Administration and European Medicines Agency (FDA/EMA) approval to availability to the patient globally.	Ministries of Health National regulatory bodies.	Time from FDA/EMA approval to availability to the patient less than 6 months for high priority agents, less than 1 year for intermediate priority agents.	Use an objective assessment tool to prioritise cancer medicines for approval in each country.

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Section 5: Identifying the hidden costs of breast cancer

Panel 24 - Summary for hidden costs of breast cancer

Costs of breast cancer and associated suffering are immense - society and policymakers currently see only the tip of an iceberg. These should be exposed and quantified in order to be reduced.

- Costs include financial, emotional, social, and economic costs; these impact on children, families, local communities, and wider society.
- Even within health services that are free at the point of delivery, those affected by breast cancer face additional costs that may particularly impact on the poorest in society.
- Serious health-related suffering goes unmeasured in global health metrics, so its alleviation is not prioritised by policy makers.
- Exposing and reducing costs provides a major incentive for policymakers to invest in prevention, early detection, cost-effective therapy, and optimal management of breast cancer.
- Initial estimates of hidden costs of suffering from breast cancer provided can catalyse new priority-setting tools for breast and other cancers and this research is pivotal and in process as part of the Lancet Commission on Cancer and Health Systems.

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The burden of suffering:

Both health systems in general and cancer systems must acknowledge serious health-related suffering (SHS) and, therefore, the value of alleviating this suffering by better investing in appropriate supportive and palliative care.^{8,370} Yet, the alleviation of SHS which is paramount to patients and their families goes unmeasured in global health metrics and is therefore undervalued.

~~Absent~~

~~The Lancet Commission on~~ Palliative Care and Pain Relief⁸ showed that because they are absent in priority setting, many key interventions for alleviating suffering are not considered in either covered health care packages or in universal health coverage.

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~~The Lancet Commission on~~ The Commission Global Access to Palliative Care and Pain Control Relief⁸ estimated that ~~well~~ over 61 million people per year experience SHS and one-quarter of this is due to cancer. ~~While much~~ Much of this could be relieved with better access to palliative care and pain relief.⁸ ~~Yet~~ between 80 and 90% of this global need is unmet due to a lack of available workforce, necessary training, health system investment, and equitable access to palliative care medicines.^{8,371} SHS can affect patients throughout the breast cancer trajectory and hence the measure is relevant not only for imminently dying patients (year of death measured by mortality), but also at earlier stages (before year of death). Hence, to ~~To~~ accurately count the number of people and their days with SHS (SHS days per year), both mortality and data needs to be differentiated from prevalence data are required. A decedent is a person who dies in a given year and can only experience SHS in that year. Non-decedents are people who do not die in that year but may also have SHS. By 2060, it is projected that 16.3 million people each year will die from cancer and will experience SHS. Importantly, breast cancer is predicted to account for the highest proportion of cancer decedent SHS in all countries, but particularly in low and lower-middle income countries.^{371,366}

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All people with breast cancer experience suffering at some point in their cancer journey, regardless of stage of illness. This affects their quality of life, relationships, self-perceptions, and independence.³⁷²⁻

³⁷⁶ Patients may face physical, psychological, spiritual, and existential distress over a long period.³⁷⁷⁻³⁸⁸

This begins with the realities of diagnosis and continues with fears associated with prognostic uncertainty and the possibility of death. Treatments have collateral physical and psychological impact, and this is added to by the long-term challenges of survivorship (see CASCARA Panel 26) with fear of recurrence and possible debilitating symptoms. Families and caregivers of people with breast cancer may also experience extended periods of social suffering and financial hardship.³⁸⁹⁻³⁹² This includes not

only out-of-pocket costs for healthcare, but also loss of income of the person with breast cancer and their caregivers, and with the added possibility and vulnerability of orphaned children.

Serious health related suffering (SHS) specific to breast cancer

As part of follow up work for the Lancet Commission on Global Access to Palliative Care and Pain Relief⁸, the measurement of SHS is being updated with a disease-specific approach. In collaboration with the Lancet Commission on Cancer and Health Systems⁷, a pilot study was undertaken on breast cancer with expert providers and patient advocate groups. The group of 14 experts were invited to participate in a three-part process; an online survey, a focus group, and a structured one-to-one interview. Their collective experience was from Jamaica, Haiti, Rwanda, Mexico, Brazil, India, Lebanon, Portugal, United States of America, United Kingdom, Malaysia, and South Africa ~~and they. They~~ represented breast surgery, medical oncology, radiation oncology, physiotherapy, palliative medicine, and the patient and patient advocacy experience.

The findings showed that SHS is not restricted to metastatic breast cancer but is highly relevant for early-stage disease and for survivorship, though these groups had lower SHS burden compared those with metastatic disease. Non-decedents include patients with early cancer, but also patients with metastatic disease, whose life-expectancy even in LMICs can be several years, and they may continue to suffer from high SHS burden throughout that time. Non-decedents also include patients in survivorship who most probably will not die of breast cancer. Adjuvant systemic therapies (e.g. hormonal therapies and more recently CDK4/6 inhibitors) are used for years into survivorship and can cause toxicity. Patients may also suffer ongoing sequelae from curative surgery, chemotherapy, or radiotherapy. These patients may have a high prevalence of SHS symptoms such as pain or fatigue, and reproductive health challenges. Indeed, the expectation that they are 'symptom-free' within a few years post-treatment veils their need for supportive care.

The expert group agreed that ~~half a year of SHS - about on average, there were~~ 175 days ~~- is experienced by patients of reported SHS~~ in the last ~~12 months~~ year of life. The typical patient was estimated to need access to about 60mg of opioid morphine equivalent per day in their last year of life to sufficiently manage pain and breathlessness. The expected lifespan for people living with metastatic or locally advanced breast cancer (non-decedents) was estimated to be about 4 years, with an average of close to 70 SHS days per year. The group considered that for both those who died of their breast cancer and those living with the disease, approximately two-thirds of SHS days each year are likely preventable through improved access to care. It is important to note that these estimates refer to a typical patient and mask inequities across and within countries.

The term 'survivor' was challenged by experts and more strongly by patients (*see CASCARA panel below*). In alignment with a person-first language, the term survivorship was preferred which would include disease-free patients following curative therapy, those still undergoing adjuvant therapies, and those with metastatic disease. Survivorship is also a depersonalised term that refers to a health state rather than a nominal patient. ~~This is aligned with an ongoing change of concept for some types of breast cancer, which is perceived now less as a life-limiting disease, and more as a chronic illness.~~³⁹⁹ (*see Themes* ~~This is aligned with an ongoing change of concept for some types of breast cancer, which is perceived now less as a life limiting disease, and more as a chronic illness.~~³⁹³ (*see Sections 3 and 6*).

There was also some reluctance to use the term palliative care in people with early breast cancer. Whereas experts working in resource-poor settings tended to accept a much broader range of palliative care, experts from high income countries found it difficult to accept the term when treating people with early breast cancer. A broader terminology using 'supportive and palliative care' was found to be acceptable to all experts.

Breast cancer can cause significant social stigma (*see also ThemeSection 3*) and suffering, for example from a feeling of disfigurement and issues with body image, reduced sexual quality of life with diminished feelings of sexual attraction and femininity.³⁹⁴⁻³⁹⁸ Social stigma, secondary or associative

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stigma experienced by family members, and self-stigma or internalised shame can result from discriminatory sociocultural beliefs and practices that reinforce gender roles. These include value-setting based on women's reproductive capacity or potential marital status and the impact of illness on these.³⁷ Due to the prevalence of pre-menopausal breast cancer in LMICs^{71,399-401}, these types of suffering are of particular concern. Women in resource-limited settings are also less likely to have access to reconstructive surgery and assistance with protecting fertility.⁴⁰²⁻⁴⁰⁴ Men with breast cancer, though a minority, suffer from social stigma related to the diagnosis of what is perceived as a 'women's disease'.^{411,405} See also [Themesection 2 - Male Breast Cancer Global Alliance](#).

The expert panel recommended adding sexual, reproductive, and gynaecological health items to the SHS assessment. Patients are often reluctant to raise these problems in their medical consultations, requiring that healthcare professionals actively address them sensitively (see [Themesection 6](#)). Although these results are based on a small sample of professionals, our exploratory analysis provides a preliminary quantification of suffering, that is primarily based on the provider perspective, to initiate the discussion on the need to assess and treat SHS in patients with breast cancer.

[The effort to strengthen measurement of the disease-specific burden of SHS is complementary to ongoing research on the value of suffering alleviation to patients, caregivers, and health systems. This is a component of the linked work with the Lancet Commission on Cancer And Health Systems and in follow-up to the Lancet Commission on Palliative Care and Pain Relief \(see Panel 25\).](#)

Panel 25 - Dimensions of suffering and the value of alleviating suffering [among patients with breast cancer](#): case report from Mexico

The research agenda set out in The Lancet Commission on Global Access to Palliative Care and Pain Relief report⁸ called for in-depth work on the dimensions of suffering as an input into developing [more inclusive, effective and patient-responsive](#) indicators for priority setting. ~~(for example as Suffering Adjusted Life Years, SALYs).~~ As part of the exploratory phase ~~of and~~ a multi-country study to identify the dimensions of suffering and the need for palliative care⁴¹², qualitative research was undertaken at the Mexican National Social Security Institute (IMSS) consisting of in-depth interviews with 14 women with breast cancer, receiving care at the IMSS pain clinic in Mexico City and approaching end of life.

The thematic analysis identified two main themes:

- SHS as a multifaceted phenomenon,
- Relief of SHS requiring a joint effort from the patient, family, and health services.

The first theme encompassed intrapersonal SHS (physical and emotional SHS increasing over time due to disease progression), interpersonal SHS (family suffering, psychological, and economic suffering due to job loss and health services scarcities, social suffering, and cultural influence on the SHS perception) as well as differences in SHS according to age and socioeconomic level. The second theme was about SHS relief and included intrapersonal and interpersonal strategies to alleviate SHS, and health services response. The women expressed the importance of SHS relief for everyone and acknowledged the need for a joint effort from the person living with the disease, their family, and health services, including more palliative care services, pain clinics, and innovations to alleviate SHS. [The findings are consistent with research on SHS associated with various cancer types and diabetes, including some patients with breast cancer.](#)⁴¹³ Furthermore, ~~these~~ findings are part of ongoing research to understand the meaning of SHS and the value of alleviating SHS in monetary and non-monetary terms across sociocultural, socioeconomic, and health system contexts.

Hidden financial costs from breast cancer

A diagnosis of breast cancer can threaten financial well-being even in countries and for populations that have financial protection through public or private health and disability insurance.⁴⁰⁶⁻⁴¹⁰ More systematic monitoring of family income loss, cost-related non-adherence, treatment withdrawal and quality of life would allow identification of these hidden costs and calculation of the true cost of breast cancer to societies.

With the Lancet Commission on Cancer And Health Systems⁷, the The Lancet Breast Cancer Commission, initiated a collaboration working in alliance with the Lancet Commission on Cancer And Health Systems are collaborating with partners in several countries to generate country-level, context relevant cost and cost burden data to better inform priority setting for cancer control. Exploratory pilot research in the UK, a country with Universal Health Coverage for cancer care (the National Health Service), was carried out through the (see Panel 26: The CASCARA (Costs And Supportive CARE in bReast cAncer) study (see Panel 26 - CASCARA participant quotes)

The CASCARA (Costs And Supportive CARE in bReast cAncer) Study

CASCARA is a UK pilot study scoping the economic burden, financial toxicity, and supportive care needs amongst individuals with breast cancer in a high-income country with a National Health Service that is free at the point of use. Online anonymous population-based surveys were designed by researchers from the Lancet Breast Cancer Commission and The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU) in collaboration with volunteers with lived experience of primary and metastatic breast cancer. A patient survey and a carers survey were designed, and these were open from 24/01/2023 to 03/03/2023. Individuals with lived experience of primary or metastatic breast treated in the UK were eligible to complete the CASCARA survey and were asked to provide information relating to their most recent episode disease-. This included patients and carers, which may include family and friends. Survey participants were recruited via two main routes. The first was from the Breast Cancer Now Patient Forum. The second was through other charity groups including Macmillan, Cancer Research UK, and Maggie's (Cancer Support Centres). Completion and submission of the survey were taken as consent for participation.

The CASCARA patient survey had 606 responses. 470 and 136 participants reported experience of primary and metastatic breast cancer respectively. 24% of participants had their diagnosis within the last year and 25% of participants had their diagnosis more than 5 years ago. 35% of the participants were aged 41-50 at diagnosis and 33% were aged 51-60. 96% of participants described their ethnicity as White. 69% of participants had a postgraduate degree, degree, or professional qualification. CASCARA carer survey had 30 responses. 70% of participants reported themselves as partner of a patient, 50% were aged 51-60, and 40% were female. 97% described their ethnicity as White, 63% had a postgraduate degree, degree, or professional qualification.

For participants reporting with early breast cancer, 77% of them were in employment at diagnosis and 61% were still in employment at the time of survey completion. With income presented in bracketed ranges (e.g. <£12.5k, £12.5k-£25k, etc), 25% of participants reported a decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=27.5-40) hours compared with 30 (IQR=18-37) hours at the time of survey completion. For those with metastatic breast cancer, 79% were in employment at diagnosis and 40% were still in employment at the time of survey completion. 38% reported decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=28.5-40) hours compared with 24 (IQR=12-37) hours at the time of survey completion. 47% of carers

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reported change in their employment because of their caring role for the person with breast cancer. 23% of carers reported decrease in income. 27% of carers took compassionate/carer's leave.

20% of participants with early breast cancer and 25% of those with metastatic breast cancer reported difficulty in covering costs of travel for treatment. 27% with early breast cancer and 35% with metastatic breast cancer reported having financial problems. A small proportion of participants also reported loss and change of home, not able to keep up with mortgage or rent, attending foodbanks.

48% of participants reported people dependent upon them, with 41% of participants having dependent children. For those with early breast cancer, 33% could not fulfil their caring responsibilities at diagnosis and 8% at the time of survey completion. For participants with metastatic breast cancer, 41% could not fulfil their caring responsibilities at diagnosis and 26% at the current time. 29% with early breast cancer and 32% with metastatic breast cancer had their family and friends fulfilling their caring responsibilities at diagnosis, whilst 6% with early breast cancer and 21% with metastatic disease needed support from family and friends at the time of survey completion. 33% of carers reported having other people dependent upon them, with 27% of carers having dependent children. 20% could not fulfil their other caring responsibilities at the time the patient was diagnosed, 10% of carers had some or all caring responsibilities left undone and 10% had received support from family and friends.

Nearly all participants reported physical or well-being issues related to breast cancer. For participants with early breast cancer, common issues (>60%) included fatigue (83%), menopausal symptoms (75%), anxiety (71%), pain (67%), loss of confidence (65%), impact on sexual health (62%), memory problems (61%), and concerns regarding body image (60%). For those with metastatic breast cancer, common issues (>60%) included fatigue (88%), menopausal symptoms (78%), memory problems (70%), pain (70%), impact on sexual health (68%), anxiety (66%), loss of confidence (66%), reduced mobility (63%), concerns regarding body image (60%).

51% of participants reporting experience of primary breast cancer and 67% of those metastatic breast cancer disliked the term 'cancer survivor'. 33% of participants reporting experience of primary breast cancer and 47% of those metastatic breast cancer disliked the term 'palliative care'. 79% of participants never heard of the term 'supportive care'. 59% of participants reporting experience of primary breast cancer and 55% of those metastatic breast cancer agreed that 'supportive care' includes all supportive care needs.

CASCARA provides exploratory evidence which is hypothesis-generating for future research. Given the web-based questionnaire dissemination model and limited time frame, the study was limited in its ability to recruit a representative sample of those in the UK affected by breast cancer. Respondents appear to report higher educational attainment levels and higher financial security than would be expected if this sample was truly representative of UK population affected breast cancer, yet continued suffering and unmet was reported.

Subsequent research will form part of the Lancet Commission on Cancer And Health Systems report with a focus on countries and settings where national health insurance is lacking. *(see Panel 27: Linking to the Lancet Commission on Cancer And Health Systems).*

Panel 26 → The CASCARA (Costs And Supportive CARE in bReast cAncer) Study – participant quotes
CASCARA is a UK pilot study scoping the economic burden, financial toxicity, and supportive care needs amongst individuals with breast cancer in a high-income country with a National Health Service that is free at the point of use. Participants had

Study Design

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Online anonymous population-based surveys were designed by researchers from the opportunity to write free text related to the different Lancet Breast Cancer Commission and The Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU) in collaboration with volunteers with lived experience of primary and metastatic breast cancer. A patient survey domains and some quotes are illustrated here and a carers survey were designed, and these were open from 24/01/2023 to 03/03/2023.

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Inclusion Criteria

Individuals with lived experience of primary or metastatic breast treated in the UK were eligible to complete the CASCARA survey. This included patients and carers, which may include family and friends.

Recruitment Process

Survey participants were recruited via two main routes. The first was from the Breast Cancer Now Patient Forum. The second was through other charity groups including Macmillan, Cancer Research UK, and Maggie's (Cancer Support Centres). Completion and submission of the survey were taken as consent for participation.

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Results

Population

CASCARA patient survey had 606 responses. 470 and 136 participants reported experience of primary and metastatic breast cancer respectively. 24% of participants had their diagnosis within the last year and 25% of participants had their diagnosis more than 5 years ago. 35% of the participants were aged 41-50 at diagnosis and 33% were aged 51-60. 96% of participants described their ethnicity as White. 69% of participants had a postgraduate degree, degree, or professional qualification.

CASCARA carer survey had 30 responses. 70% of participants reported themselves as partner of a patient, 50% were aged 51-60, and 40% were female. 97% described their ethnicity as White, 63% had a postgraduate degree, degree, or professional qualification.

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Employment

For participants with early breast cancer, 77% of them were in employment at diagnosis and 61% were still in employment at the time of survey completion. With income presented in bracketed ranges (e.g. <£12.5k, £12.5k-£25k, etc), 25% of participants reported a decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=27.5-40) hours compared with 30 (IQR=18-37) hours at the time of survey completion. For those with metastatic breast cancer, 79% were in employment at diagnosis and 40% were still in employment at the time of survey completion. 38% reported decrease in income bracket. Of those reporting to be in employment at diagnosis, the median working hours per week were 37 (IQR=28.5-40) hours compared with 24 (IQR=12-37) hours at the time of survey completion.

"Extreme fatigue impacts how much work I can do. Brain fog has led to me making numerous little mistakes."

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47% of carers reported change in their employment because of their caring role for the person with breast cancer. 23% of carers reported decrease in income. 27% of carers took compassionate/carer's leave.

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"I lost my job when I started chemotherapy as I could not cope very well."

"Treatment causes too many side effects to hold down work. Daughter became the main priority as a single parent."

"I am struggling with fatigue and menopause symptoms so needed to reduce my working hours."

"I need to take time off for hospital appointments. I need to play a more active part in school pick up/drop off/homework/after schools."

Financial situation

20% of participants with early breast cancer and 25% of those with metastatic breast cancer reported difficulty in covering costs of travel for treatment. 27% with early breast cancer and 35% with metastatic breast cancer reported having financial problems. A small proportion of participants also reported loss and change of home, not able to keep up with mortgage or rent, attending foodbanks.

'Losing your home and business shatters all future plans.'

"I really struggled to pay for all the things I needed such as new bras, clothing (front fastening shirts and pyjamas) wig, heating when in the house more, etc. I had to scrap any idea of future holidays and also had to get a second job where I

Caring
48% of participants reported people dependent upon them, with 41% of participants having dependent children. For those with early breast cancer, 33% could not fulfil their caring responsibilities at diagnosis and 8% at the time of survey completion. For participants with metastatic breast cancer, 41% could not fulfil their caring responsibilities at diagnosis and 26% at the current time.

29% with early breast cancer and 32% with metastatic breast cancer had their family and friends fulfilling their caring responsibilities at diagnosis, whilst 6% with early breast cancer and 21% with metastatic disease needed support from family and friends at the time of survey completion. *could earn a bit more."*

"Can't mend a leaking roof. Stopped all nice things such as treats, days out as can't even afford cinema. Cannot afford gym membership need to pay back family who loaned us money to live during treatment."

"I've had to cut back on making memories as I can't afford it with rising cost of travel for treatment."

Caring

'My husband had to take unpaid leave for multiple months.'

33% of carers reported having other people dependent upon them, with 27% of carers having dependent children. 20% could not fulfil their other caring responsibilities at the time the patient was diagnosed, 10% of carers had some or all caring responsibilities left undone and 10% had received support from family and friends.

"My partner has had to reduce his working hours to cover childcare and that has also impacted

Supportive Care Needs

Nearly all participants reported physical or well being issues related to breast cancer. For participants with early breast cancer, common issues (>60%) included fatigue (83%), menopausal symptoms (75%), anxiety (71%), pain (67%), loss of confidence (65%), impact on sexual health (62%), memory problems (61%), and concerns regarding body image (60%). For those with metastatic breast cancer, common issues (>60%) included fatigue (88%), menopausal symptoms (78%), memory problems (70%), pain (70%), impact on sexual health (68%), anxiety (66%), loss of confidence (66%), reduced mobility (63%), concerns regarding body image (60%).
on his income."

"My mother now needs care and we are paying for home help to support where I am unable to physical do things."

"My son is often left on his iPad or watching TV while I sleep in the afternoon."

Supportive Care Needs

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‘Once you have completed active treatment you are considered “well”.’

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“After radiotherapy finished I was left on my own.”

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“It took me a long time to ask for help with sexual dysfunction.”

“Because I’m in my 30s I’ve had a lot of pushback from people telling me I don’t need the help as much as older patients. I’ve also had problems as I’ve lived longer than expected with stage 4. Most help dried up after 6 months.”

Attitudes to Terminology

51% of participants reporting experience of primary breast cancer and 67% of those metastatic breast cancer disliked the term ‘cancer survivor’.

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“Cancer survivor”:

‘I’m not a survivor as I still need monitoring. I see myself as have lived through cancer and it’s changed my life forever. I’m now a different person with a different perspective and I will live with its consequences forever. It’s the gift that keeps on giving!’

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‘I hate the whole “battle” analogies of cancer. It’s a disease not a battle. Also “cancer survivor” is derogatory to stage 4 patients, as the implication is that they have somehow failed.’

33% of participants reporting experience of primary breast cancer and 47% of those metastatic breast cancer disliked the term ‘palliative care’.

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“Palliative care”

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‘I associate this term with end of life, although I now know this not to be correct.’

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‘I find it hard to shake off the “end-of-life” meaning. I think a new name should be found, but the services should be available to all breast cancer patients who need them.’

79% of participants never heard of the term ‘supportive care’. 59% of participants reporting experience of primary breast cancer and 55% of those metastatic breast cancer agreed that ‘supportive care’ includes all supportive care needs.

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Strategies to tackle SHS and hidden costs from breast cancer

Using the reported figure of 685,000⁴¹⁹ patients worldwide dying each year from breast cancer, and applying the expert group average of suffering days in the last year of life gives an estimated SHS decedent total of over 120 million days each year. In addition, the 7.8 million non-decedent patients with breast cancer⁴¹⁹ accumulate over 520 million additional SHS days.

~~Behind these numbers are patients suffering from pain, dyspnea, fatigue, and other distressing symptoms, who might benefit from supportive or palliative care, but in many regions of the world, and especially for those living in poverty, there is no access to this care. Unfortunately, the poorest in society have the worst palliative and psychosocial services. Meeting this need requires large scale, global capacity building in palliative care and psychosocial services as a component of comprehensive breast cancer management, and training efforts should begin immediately. Yet, the cancer divide differences in access to effective screening, diagnosis, and treatment options within resource constrained health systems fuelled by poverty and inequity compounds rather than complements the need for palliative care.~~⁴²⁰ A first step is to recognise and quantify the costs and suffering

associated with breast cancer and develop validated tools to incorporate these into global health metrics (see Panel 27 – proposed measurable indicators of change).

					Panel 27—Lancet Breast Cancer Commission proposed measurable indicators of change				
Theme					Definition	Rationale	Data sources	Responsible entity	
Theme 5: Identifying the hidden costs of breast cancer									
Physical, psychological, social, spiritual, and financial-related serious health-related suffering (SHS) in breast cancer care.					Screen patients at intervals throughout the breast cancer trajectory for SHS.	Making the hidden costs of serious health-related suffering (SHS) visible in individual health care plans.	Facility records Third-party and government records Patient self-reports and develop specific patient-reported outcome measures.	Health care facilities, Ministries of Health.	
Breast cancer health care costs.	Identify the proportion of each phase of the breast cancer trajectory covered by insurance and proportion of the population with access to this insurance.	Making the hidden costs of financial toxicity visible and identifying which groups are affected and when.	Expansion of national cancer registries.	Ministries of Health.	Upward trajectory year Panel 27—Linking to the Lancet Commission on year for Universal Cancer and Health Coverage of Systems Recognising the high-yield opportunities for collaboration,	Research needed on: out-of-pocket spending on all aspects of breast cancer measured over the breast cancer trajectory.	Formatted Table		
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					The Lancet Breast Cancer Commission and the Lancet Commission on Cancer And Health Systems⁷ identified and took forward collaborative research endeavors. The objective was to make a stronger case for investing in breast cancer worldwide and provide a base for work on a broad set of cancers for the Lancet Commission on Cancer and Health Systems. The work is ongoing as the exploratory research that informed the work on breast cancer in this report is being extended by the	
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					Lancet Commission on Cancer And Health Systems in comparative research across cancers and focusing on health system strengthening. It also builds out the research agenda set forth in the report of the Lancet Commission on Global Access to Palliative Care and Pain Control⁸. The focus of this ongoing research is on reducing the economic burden, financial toxicity, and suffering from cancer worldwide to provide empirical evidence for an economics of hope set forward
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					as a core concept of the Lancet Commission on Cancer And Health Systems.² The approach includes a strong equity focus as often individuals and households most experiencing financial toxicity, pain and suffering, and the overall economic burden of cancer are from marginalised and minoritised communities. Using breast cancer as the pilot condition for the exploratory research was deliberate and is proving to yield important results that are guiding field work on cervical,	
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					colorectal, and paediatric cancers, among others. Breast cancer primarily affects women, both young and old, providing key insights into gender and age-related priorities, particularly with respect to the multi-faceted range of suffering. Further, interventions to alleviate the burden of breast cancer span the continuum of care, <u>aiming at 100%, to eliminate financial catastrophe from primary prevention to end of life and encompass an important survivorship</u>	
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					component, providing key inputs into the cancer and health systems research focused on refining universal health coverage models and on next steps in measuring serious health-related suffering as put forward in The Lancet Commission on Global Access to Palliative Care and Pain Control.⁸ Breast cancer as a choice of pilot is particularly poignant since there is extensive evidence on the experience of abandonment and stigma faced by patients with breast cancer, providing insight into the layers of social exclusion	
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					associated with poverty, gender, and age, which form barriers along the entire continuum of care. Priority setting for health, including cancer, relies upon robust economic evidence. Traditional economic evaluation techniques (i.e. cost-effectiveness and cost-utility analysis) focus narrowly on health gains to individual patients and have overlooked other benefits such as alleviating suffering, protecting patients from financial hardship and	
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					impoverishment, <u>for all, reducing abandonment of care, and the impact on families experiencing breast cancer and communities.</u> Understanding and measuring these limitations for the specific case of breast cancer provides a model to elucidate and estimate the broader impacts for individuals and families associated with many types of cancer diagnosis. <u>Minimum of poorest 20%, but aiming at 100%, of patients and families receiving public financing and provision of an essential package of</u>	
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					<u>supportive and palliative care across the breast cancer pathway.</u> Existing metrics focus almost exclusively on mortality and morbidity as avoidable outcomes and fail to measure the high value placed by patients, their caregivers, and loved ones on the alleviation of pain and suffering and improving their overall quality of life. A better understanding of this is core to an effectively applying people-centred approaches in providing care and designing health systems. Melding data on value with	
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					existing measures of need or burden is providing novel inputs into a cost of inaction framework that better elucidates the benefits of increased and more efficacious investment in cancer systems. As part of work spanning two Lancet Commissions, the breast cancer specific results reported here should be taken as illustrative of the multiplicity of hidden costs of cancer overall. The ongoing research that will be presented as part of the Lancet Commission on Cancer And Health Systems⁷
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					includes a broader conceptualisation of the burden and costs associated with other cancers and population groups including men, new tools for measuring the value of alleviating pain and suffering, and a fuller accounting of the costs of inaction; these are all key inputs into applying the economics of hope concept to cancer.	
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Theme 6: Communication

~~Strategies to tackle SHS and empowerment in hidden costs from breast cancer~~

~~685,000⁴¹¹ patients worldwide die each year from breast cancer, and the expert group average of suffering days in the last year of life gives an estimated SHS decedent total of over 120 million days each year. In addition, the 7.8 million non-decedent patients with breast cancer⁴¹² accumulate over 520 million additional SHS days. Behind these numbers are patients suffering from pain, dyspnea, fatigue, and other distressing symptoms, who might benefit from supportive or palliative care, but in many regions of the world, and especially for those living in poverty, there is no access to this care. Unfortunately, the poorest in society have the worst palliative and psychosocial services. Meeting this need requires large-scale, global capacity building in palliative care and psychosocial services as a component of comprehensive breast cancer management, and training efforts should begin immediately. Yet, the cancer divide – differences in access to effective screening, diagnosis, and treatment options within resource-constrained health systems fuelled by poverty and inequity – compounds rather than complements the need for palliative care. A first step is to recognise and quantify the costs and suffering associated with breast cancer and develop validated tools to incorporate these into global health metrics (see Panel 28 – proposed measurable indicators of change).~~

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Panel 28—Lancet Breast Cancer Commission proposed measurable indicators of change						
Theme	Definition	Rationale	Data sources	Responsible entity	Target	Comments
Section 5: Hidden costs of breast cancer						
Physical, psychological, social, spiritual, and financial—related serious health-related suffering (SHS) in breast cancer care.	Panel 28Screen patients at intervals throughout the breast cancer trajectory for SHS.—Summary for communication and empowerment Being female is the greatest risk factor for breast cancer—women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings. We propose that a framework to improve	Making the hidden costs of serious health-related suffering (SHS) visible in individual health care plans.	Facility records Third-party and government records Patient self-reports and develop specific patient-reported outcome measures.	Health care facilities, Ministries of Health.	Introduce screening for SHS at diagnosis and at intervals throughout the breast cancer trajectory as research tool, with aim to implement as standard of care after validation.	Aim to implement suffering-intensity-adjusted life years, a new metric under development for health system performance assessment and quality assurance.

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	communication and decision making for those with breast cancer can be used for women to take control over other aspects of their lives. ● Placing patients at the centre of clinical communication, and empowering them to exercise their voices, become fully informed, and choose their own level of involvement in decisions about their care, is an achievable and worthwhile					
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	goal worldwide- ● Improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival. ● Healthcare professional education should include person-centred and culturally sensitive communication skills training.					
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	especially when patient literacy or numeracy is limited, or other barriers to participation in decision-making exist. Health communication training should include eliciting patients' core values and preferences for information, explaining goals of care, risk-benefit communication, skills to help estimate					
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	and explain prognosis and share serious news, and empathically but honestly respond to questions. • Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return					
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	~~power and emerge stronger than before.~~					
Breast cancer health care costs.	Identify the proportion of each phase of the breast cancer trajectory covered by insurance and proportion of the population with access to this insurance.	Making the hidden costs of financial toxicity visible and identifying which groups are affected and when.	Expansion of national cancer registries.	Ministries of Health.	% of patients with access to Universal Health Coverage across the continuum of care; % total cost covered by the health care funder.	Research needed on: out-of-pocket spending on all aspects of breast cancer measured over the breast cancer trajectory.

Introduction

Section 6: Communication and methodology

The Lancet Commission group acknowledged that patient empowerment should be defined as: *being fully informed and supported to confidently participate in decisions about your own health and wellbeing, to the extent which you wish*. We define patient-centred communication as acknowledging the unique background and need for information of each individual patient, considering their situation holistically and working with the patient to define and achieve shared goals in their care.

Some commonly held beliefs ('myths') about the limits to patient empowerment were initially discussed by the Commission group, and a literature search on patient empowerment and communication was conducted to challenge these preconceptions, focused on low- and middle-income countries to ensure cross-cultural considerations (see supplementary material 16 for search terms). This literature review informed further group discussion and developed into this Commission report section (see Panel 29 - Commonly held beliefs).

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Panel 29—Commonly held beliefs about patient empowerment and communication in breast cancer and actual results of literature search.	
Common beliefs: 'MYTHS'	Literature search results: 'FACT'
<i>MYTH: Publications on communication and shared decision making are largely from high-income countries and the ideals presented in the literature may only be feasible in high income countries.</i> Outcome from literature review: FALSE	Panel 29 - Summary for communication and empowerment <u>Being female is the greatest risk factor for breast cancer - women constitute a group whose fundamental human rights have historically been accorded lesser respect than men in all settings.</u> <u>We propose that a framework to improve communication and decision making for those with breast cancer can be used for women to take control over other aspects of their lives.</u> • <u>Placing patients at the centre of clinical communication, and empowering them to exercise their voices, become fully informed, and choose their own level of involvement in decisions about their care, is an achievable and worthwhile goal worldwide.</u> • <u>Improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival.</u> • <u>Healthcare professional education should include person-centred and culturally sensitive communication skills training, especially when patient literacy or numeracy is limited, or other barriers to participation in decision-making exist.</u> • <u>Health communication training should include: eliciting patients' core values and preferences for information, explaining goals of care, risk-benefit communication, skills to help estimate and explain prognosis and share serious news, and empathically but honestly respond to questions.</u> <u>Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return power and emerge stronger than before. FACT: Patient decision making and communication research in low- and middle-income countries does exist, although there is more from high income countries.</u>

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	<u>- Many different interventions for supporting patient choice have been published in low and middle-income countries, with the overarching theme of adapting communication methods to the socio-economic and cultural circumstances being key to improving patient-clinician dialogue and empowerment.</u>⁴²¹⁻⁴³⁰ ◆
MYTH: The extra healthcare professional time invested in inviting patients to share decision making does not meaningfully benefit patients. Outcome from literature review: FALSE	FACT: Evidence supports that improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival.⁴³¹⁻⁴³³
MYTH: Little can be done to improve patient involvement in decision making in low- and middle-income countries. Outcome from literature review: FALSE	FACT: Individual and system-level barriers exist to both patient choice of treatment in breast cancer, and patient involvement in decision making.^{423,422,423,434-440} Multiple interventions to overcome barriers to patient choice and involvement in decision making have been successfully trialled in low- and high-income countries.^{425,427-430,441-444}
MYTH: Most alternative treatment is detrimental to patient outcomes. Outcome from literature review: FALSE	FACT: There is evidence that some traditional, complementary, and integrative therapies can be beneficial for symptom management in patients with breast cancer and can be used safely alongside (but not instead of) conventional therapy.⁴⁴⁵

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Introduction and methodology

The Lancet Commission group acknowledged that patient empowerment should be defined as: *being fully informed and supported to confidently participate in decisions about your own health and wellbeing, to the extent which you wish.* We define patient-centred communication as acknowledging the unique background and need for information of each individual patient, considering their situation holistically and working with the patient to define and achieve shared goals in their care.

Some commonly held beliefs ('myths') about the limits to patient empowerment were initially discussed by the Commission group, and a literature search on patient empowerment and communication was conducted to challenge these preconceptions, focused on low- and middle-income countries to ensure cross-cultural considerations (see supplementary material 16 for search terms). This literature review informed further group discussion and developed into this Commission report section (see Panel 30—Commonly held beliefs).

Where are we now?

There is wide global variation in levels of empowerment demonstrated by patients with breast cancer. At one end of the spectrum, involving women in treatment decisions is recognised as crucial, not only to protect individuals' autonomy and dignity, but also because it strengthens the foundation for gender equity beyond the specific context of breast cancer. For example, patient and public involvement and engagement (PPIE) is mandatory for clinical research funding applications in some countries. At the other end of the spectrum, women in many parts of the world have extremely limited bodily, social, and financial autonomy; free choice is unavailable to them not just in breast cancer treatment decisions, but also in their reproductive rights, their family finances, access to education, and myriad other social and political domains.⁴² These stark differences in patient empowerment can occur between countries, but also within a single country, as highlighted by the controversial US Supreme Court ruling which led to the overturning of rights to reproductive autonomy in some states.

Communication, patient empowerment, and patient choice are all inextricably linked. Potential barriers to patient involvement in decision making and choice of treatment are manifold and can occur both at an individual level and system level (see Panel 30 – What are some of the barriers to patient choice of treatment and patient involvement in decision making?).

Panel 30 – Commonly held beliefs about patient empowerment and communication in breast cancer and actual results of literature search.

Common beliefs: 'MYTHS'

MYTH: Publications on communication and shared decision making are largely from high-income countries and the ideals presented in the literature may only be feasible in high-income countries.

Outcome from literature review: FALSE

Literature search results: 'FACT'

Panel 30 - What are some of the barriers to patient choice of treatment and patient involvement in FACT: Patient decision making?

Individual level

- Lack of literacy and numeracy skills.
- Lack of health education.
- Lack of understanding of prognosis and likelihood of cure.
- Social or geographic isolation.
- Family or faith community objections to treatment or patient involvement.
- Unwillingness to engage with conventional medicine due to preference for traditional healers and remedies.
- Inability or difficulty discussing prognosis, advance care planning, and preferences for end-of-life care.
- Language and communication barriers (e.g. lack of health professional or interpreter speaking same language or dialect, hearing or vision impaired patients). research in low- and middle-income countries does exist, although there is more from high-income countries.
- Undiagnosed or untreated mental health issues or emotional distress (e.g. anxiety, depression).

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	• <u>Fear of disclosure of illness due to cultural norms, fear of becoming a burden to others, stigma.</u> • <u>Poor health professional communication skills (e.g. eliciting patient values, goals, preferences, shared decision-making, discussing prognosis, empathic communication).</u> • <u>Healthcare professional beliefs that patients are unable to process the information needed to be involved in decision making.</u> • <u>Healthcare professional inability or unwillingness to culturally adapt services.</u> <u>System level</u> • <u>Geographical inaccessibility of treatments.</u> • <u>Healthcare resource constraints, including infrastructure and healthcare professional time and specialty knowledge limitations.</u> • <u>High out-of-pocket costs for patients.</u> • <u>Economic, political, or climate-related crises.</u> • <u>Unequal patient-provider power dynamics.</u> • <u>Insufficient psychosocial services at all levels of care.</u> • <u>Pervasive biomedical models that prevent tailored services and care plans.</u> –Many different interventions for supporting patient choice have been published in low and middle income countries, with the overarching theme of adapting communication methods to the socio-economic and cultural circumstances being key to improving patient-clinician dialogue and empowerment.⁴¹²⁻⁴²¹
MYTH: The extra healthcare professional time invested in inviting patients to share decision making does not meaningfully benefit patients. Outcome from literature review: FALSE	FACT: Evidence supports that improving patient communication and decision making in breast cancer improves not only quality of life and body image, but also adherence to therapy which can impact survival.⁴²²⁻⁴²⁴
MYTH: Little can be done to improve patient involvement in decision making in low and middle income countries. Outcome from literature review: FALSE	FACT: Individual and system level barriers exist to both patient choice of treatment in breast cancer, and patient involvement in decision making.^{320,413,414,425-431} Multiple interventions to overcome barriers to patient choice and involvement in decision making have been successfully trialled in low and high income countries.^{416,418-421,432-435}

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MYTH: Most alternative treatment is detrimental to patient outcomes. Outcome from literature review: FALSE	FACT: There is evidence that some traditional, complementary, and integrative therapies can be beneficial for symptom management in patients with breast cancer and can be used safely alongside (but not instead of) conventional therapy.⁴³⁶
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Where are we now?

There is wide global variation in levels of empowerment demonstrated by patients with breast cancer. At one end of the spectrum, involving women in treatment decisions is recognised as crucial, not only to protect individuals' autonomy and dignity, but also because it strengthens the foundation for gender equity beyond the specific context of breast cancer. For example, patient and public involvement and engagement (PPIE) is mandatory for clinical research funding applications in some countries. At the other end of the spectrum, women in many parts of the world have extremely limited bodily, social, and financial autonomy; free choice is unavailable to them not just in breast cancer treatment decisions, but also in their reproductive rights, their family finances, access to education, and myriad other social and political domains. These stark differences in patient empowerment can occur between countries, but also within a single country, as highlighted by the controversial US Supreme Court ruling which led to the overturning of rights to reproductive autonomy in some states.

Communication, patient empowerment, and patient choice are all inextricably linked. Potential barriers to patient involvement in decision making and choice of treatment are manifold and can occur both at an individual level and system level (see Panel). Many different types of interventions to support patient autonomy and choice in breast cancer treatment have been published. Examples include translating and validating symptom scales into local languages (e.g. a self-efficacy scale translated into Urdu in Pakistan⁴⁴¹); hyper-local culturally adapted interventions (e.g. ~~31~~ *What are some of the barriers to patient choice of treatment and patient involvement in decision making?*).

~~performance of a traditional folk play, aimed at raising breast cancer awareness in Bangladesh); and targeted research into population preferences (e.g. discrete choice experiments in Belarus to determine preferences about type of national breast cancer screening programme^{425,442}).~~ Interventions can involve training a small number of trusted community members⁴³⁰ to support patients, or using media and technology to target large numbers to improve breast cancer awareness⁴²⁸, or clinical follow up - for example, using mobile phones to avoid travelling to clinic appointments in Nigeria.⁴²⁹ The use of decision aids to improve breast cancer decision-making has a long history⁴⁴³, although cultural adaptation of such tools to the local circumstances and languages is critical and research thus far into how to do this more widely is lacking. Recently, interactive, tailored decision tools have been developed to promote the quality of patient decisions⁴⁴⁴, and enhancements to harness insights from psychology about emotional support are being evaluated (SHARES trial NCT04549571⁴⁴⁶). Improving the quality of online information is also important, given that many women with breast cancer now access the internet to obtain information.⁴⁴⁷

Where do we want to get to?

~~We assert that centring clinical communication on patients and empowering them and their chosen advocates to be as involved as they wish in decisions about their care, is an achievable and worthwhile goal worldwide.~~

Patient-centred communication is an important goal in breast cancer, effective communication from healthcare professionals has been shown to improve long-term adherence to therapy^{433,448}, whilst poor communication has long-lasting negative effects on multiple quality of life domains including

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function, symptoms, body image, lifestyle and other worries scores.⁴⁴⁹ Feeling involved in decisions can provide a lasting positive impact on quality of life⁴³¹, but patient preferences about treatment options and desired degree of involvement in clinical decision making will vary considerably.^{450,451} A central factor in patient satisfaction with the decision making process is the concordance between patients' preferences about involvement in decisions, and their actual experience of involvement.⁴⁵² Empowering patients requires understanding preferences for degree of decision involvement, along with adequate accessible information to allow patients to apply their own values and preferences, to arrive at a decision that is right for them.⁴⁵³ The opportunity for patients to feel listened to and have their questions answered (regardless of perceived relevance of those questions by the clinician) is also key to patient-centred communication.

We acknowledge that informal support persons (e.g. family, friends, or faith representatives) can often play an involved role in decision making, and that such involvement can be both positive or negative for an individual patient's experience. In general, research suggests that a variety of informal decision support persons are utilised across patients from different backgrounds and can provide a positive impact on the treatment deliberation process. The broad concept of relational autonomy has emerged from feminist philosophy and garnered growing attention in clinical ethics discussions. Nevertheless, whilst every individual will be inherently influenced by their unique cultural context and relationships, we advocate that the choice of whom to involve in decision making or be a 'decision supporter' should remain with the individual patient.

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Recognising both between-country and within-country inequalities, and that available choices for patients about their breast cancer care may be extensive in some settings or extremely limited in others, it is nonetheless always possible to offer some degree of choice to a patient. It is always possible to elicit what matters to a particular patient (what their values are), and to provide them with information in an understandable way that describes their options (even if limited), and to empower the patient to engage in the treatment planning process. Offering someone the opportunity to bring their relative or friend into the consultation is an example of a small choice which costs no additional time or money but improves dignity and autonomy.

Patient-centred communication skills applied by treating healthcare professionals demonstrate a core effect of communication on later quality of life.⁴²³ Helping patients to understand their condition, what their options are and why these options are or are not available, assessing patient preferences and active listening, are all skills which may be applied across national borders and the socioeconomic spectrum. Importantly, such skills can also be learnt and taught, and we propose that education of healthcare providers should include specific examples of risk-benefit communication and evidence-based medical decision making in a context-specific way to facilitate patient empowerment.

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How do we start the journey?

A recent global survey of 382 healthcare professionals conducted by the Lancet Breast Commission group showed that more than 70% of healthcare professionals felt confident they had received adequate communication skills training. This is encouraging, although may not match patient expectations and experience, and it is noteworthy that a substantial minority of professionals did not express confidence in these core skills.^{454,455}

The issue of healthcare professionals' available time for each patient is a difficult one globally. We strongly advocate senior healthcare professionals, researchers, and patient advocates in breast cancer care engaging with policymakers to improve investment in breast cancer care. High-income countries have significantly better overall survival for breast cancer than low- and middle-income countries, and recent modelling suggests scaling up comprehensive breast cancer care to be available globally would not only significantly improve overall survival, but also lead to significant longer term economic

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returns.⁴⁵⁶ Such large-scale investment is a long-term strategy, as training the appropriate staff, including pathologists, radiologists, oncologists and surgeons, radiographers, chemotherapy, and specialist breast cancer nurses takes many years. Additionally, whilst the ideal for patients and staff would be to have as much consultation time as needed, the reality now in both high- and low-income settings necessitates optimisation of existing resources alongside long-term lobbying for increased investment.

~~We encourage healthcare professionals to take a patient-centred approach to communication – to focus on assessing what patients need and empowering them to participate, even in just a few minutes, using established communication techniques.~~^{457,458} We suggest a framework to help develop a patient-centred consultation, acknowledging that this should serve as an iterative and non-linear guide, and be adapted to each consultation. ~~It may not be necessary to include each step or communication skill in every consultation. There are many different ways to achieve the same goal, and any consultation should be culturally adapted to the unique needs of the person with breast cancer, their family (as appropriate), and the local clinical and/or community setting (Panel 31, adapted from work of Bylund et al⁴⁵⁹⁻⁴⁶³). The examples given were developed by native speakers of English for use in settings where English is the native language, and alternative wording may be necessary in different settings.~~

Panel 31—Framework to help develop a patient-centred consultation		
Strategies	Description of Relevant Skills	Example Talking Points
Build rapport and check understanding	introduce yourself and listen to the patient's story of their healthcare problem (published evidence suggests most patients will speak for under 2 minutes if left to spontaneously tell their story).⁴⁶⁴	~~'I've had a look through your notes but I'd like to hear from you what your understanding is about what has happened so far and what you are expecting next.'~~
Set and negotiate agenda for consultation	- State the purpose of the consultation. If there is a decision to be made, that should be made clear. - Specifically ask about the patient's priorities for the consultation and their preferences for information and decision involvement. - Negotiate a consultation that includes goals of both clinician and the patient.	'I am hoping to talk about your options for treatment today. Is there anything else on your mind that you would like to make sure we discuss?' (Negotiate agenda based on patient's response). 'Why don't I begin by discussing treatment options for your breast cancer and then we can address those specific questions you have about possible side effects and your ability to work while you are receiving care. Does that sound like a good plan?' 'Some people like to have lots of information about their illness and some people just want the basics. How much information would you like me to give you today?'
Share information	<u>Identify and clearly describe all relevant options, as well as associated risks and benefits, including active surveillance, a supportive or palliative (comfort-focussed) approach when appropriate, and/or acknowledging what is achievable in that particular healthcare setting.</u> <u>Share best, worst, and most likely case scenarios related to treatment outcomes.</u> Panel 31—What are some of the barriers to patient choice of treatment and patient involvement in decision making? Individual level - Lack of literacy and numeracy skills. - Lack of health education. - Lack of understanding of prognosis and likelihood of cure. - Social or geographic isolation. - Family or faith community objections to treatment or patient involvement. - Unwillingness to engage with conventional medicine due to	~~'At this stage of illness, we have multiple options to treat your breast cancer. There is a type of chemotherapy that has shown excellent outcomes in women with your type of illness. There are some side effects to the treatment, and we will talk more in detail about these as we go through the consent process. Fatigue, nausea, and low blood counts causing an increased risk of infection are the most common side effects. We can try to minimise some of the side effects with additional medications.'~~ ~~'I know you are really struggling with your pain right now and it is keeping you from doing many of the things that are important for you. While we continue with radiation, I would like to focus also on symptom control, make sure we are most effectively treating your pain, and provide you with the support you need.'~~

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	preference for traditional healers and remedies. • Inability or difficulty discussing prognosis, advance care planning, and preferences for end-of-life care. • Language and communication barriers (e.g. lack of health professional or interpreter speaking same language or dialect, hearing or vision impaired patients). • Undiagnosed or untreated mental health issues or emotional distress (e.g. anxiety, depression). • Fear of disclosure of illness due to cultural norms, fear of becoming a burden to others, stigma. • Poor health professional communication skills (e.g. eliciting patient values, goals, preferences, shared decision making, discussing prognosis, empathic communication). • Healthcare professional beliefs that patients are unable to process the information needed to be involved in decision making. • Healthcare professional inability or unwillingness to culturally adapt services. System level • Geographical inaccessibility of treatments. • Healthcare resource constraints, including infrastructure and healthcare professional time and specialty knowledge limitations. • High out-of-pocket costs for patients. • Economic, political, or climate-related crises. • Unequal patient-provider power dynamics. • Insufficient psychosocial services at all levels of care. • Pervasive biomedical models that prevent tailored services and care plans.	
Convey respect for patient +/- family involvement	• Validate their concerns as important and relevant to this decision, and explicitly encourage patients to ask questions.	• 'What are your thoughts about what we have discussed so far?' • 'What questions do you have?'

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	- State that you fully support the patient's right to make the final decision. - Ask the patient about use of non-prescribed therapies, traditional, complementary, and alternative medicines, and lifestyle changes since their diagnosis of breast cancer as well as medical and drug history. - Ask anyone accompanying the patient if there is anything else important they wish to add or have observed as a caregiver.	(To family member or caregiver) 'I know that you are an important part of the patient's (name) life. Is there anything you think is important that we are missing or that you would like to talk about?'
Empathise	- Acknowledge the patient's emotion and experience. - Validate their experience. - Normalise their emotional response.	'It sounds like this has been a hard time. But it also sounds like you have a lot of support from your loved ones.' 'It would be completely reasonable to take some time off from work to focus on your recovery.' 'Lots of people talk about feeling overwhelmed during a time like this.'
Review and recommend	- Clarify if the patient has enough information and offer more time for them to decide, if appropriate. - Consider how much the patient wished to be involved in decision making and offer a treatment recommendation if there is one clear best option from a medical perspective, or if the patient has requested the healthcare professional opinion. - When applicable, review multiple options—including no treatment—and state the rationale for your recommendation. Include key risks and benefits and normalise decisions that differ from recommendation. - In the absence of a treatment recommendation from the healthcare professional, validate and support patient decision making autonomy. In the absence of curative treatment, emphasise continued supportive or palliative care, where available emphasising ongoing supportive aspects of care for patients and their families.	'Today we talked about the treatment options available at this time. Do you have a preference about how you would like to proceed?'

Summarise and agree next steps	- Summarise the consultation verbally and ideally provide a short, written summary which includes all options, states any recommendations, and describes the key trade-offs. - Agree on next steps and appropriate follow up or further discussion. - In settings with limited literacy, aim for diagrams or other follow-up mechanisms such as another appointment or discussion with a community health navigator.	'I will refer you to our chemotherapy unit and they will be in contact with a date for your first treatment. Please have some blood tests done on your way out so we know it's ok to go ahead with the treatment. If you think of any concerns or questions later, please call us.'
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Many different types of interventions to support patient autonomy and choice in breast cancer treatment have been published. Examples include translating and validating symptom scales into local languages (e.g. a self-efficacy scale translated into Urdu in Pakistan⁴³²); hyper-local culturally adapted interventions (e.g. performance of a traditional folk play, aimed at raising breast cancer awareness in Bangladesh); and targeted research into population preferences (e.g. discrete choice experiments in Belarus to determine preferences about type of national breast cancer screening programme^{416,433}). Interventions can involve training a small number of trusted community members⁴²¹ to support patients, or using media and technology to target large numbers to improve breast cancer awareness⁴¹⁹, or clinical follow-up—for example, using mobile phones to avoid travelling to clinic appointments in Nigeria.⁴²⁶ The use of decision aids to improve breast cancer decision making has a long history⁴²⁴, although cultural adaptation of such tools to the local circumstances and languages is critical and research thus far into how to do this more widely is lacking. Recently, interactive, tailored decision tools have been developed to promote the quality of patient decisions⁴³⁵, and enhancements to harness insights from psychology about emotional support are being evaluated (SHARES trial NCT04549571⁴²⁷). Improving the quality of online information is also important, given that many women with breast cancer now access the internet to obtain information.⁴³⁸

Where do we want to get to?

We assert that centring clinical communication on patients and empowering them and their chosen advocates to be as involved as they wish in decisions about their care, is an achievable and worthwhile goal worldwide.

Patient-centred communication is an important goal: in breast cancer, effective communication from healthcare professionals has been shown to improve long-term adherence to therapy^{424,439}, whilst poor communication has long-lasting negative effects on multiple quality of life domains including function, symptoms, body image, lifestyle and other worries scores.⁴⁴⁰ Feeling involved in decisions can provide a lasting positive impact on quality of life⁴²², but patient preferences about treatment options and desired degree of involvement in clinical decision making will vary considerably.^{441,442} A central factor in patient satisfaction with the decision-making process is the concordance between patients' preferences about involvement in decisions, and their actual experience of involvement.⁴⁴³ Empowering patients requires understanding preferences for degree of decision involvement, along with adequate accessible information to allow patients to apply their own values and preferences, to arrive at a decision that is right for them.⁴⁴⁴ The opportunity for patients to feel listened to and have their questions answered (regardless of perceived relevance of those questions by the clinician) is also key to patient-centred communication.

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We acknowledge that informal support persons (e.g. family, friends, or faith representatives) can often play an involved role in decision making, and that such involvement can be both positive or negative for an individual patient's experience. In general, research suggests that a variety of informal decision support persons are utilised across patients from different backgrounds and can provide a positive impact on the treatment deliberation process. The broad concept of relational autonomy has emerged from feminist philosophy and garnered growing attention in clinical ethics discussions. Nevertheless, whilst every individual will be inherently influenced by their unique cultural context and relationships, we advocate that the choice of whom to involve in decision-making or be a 'decision supporter' should remain with the individual patient.

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Recognising both between country and within country inequalities, and that available choices for patients about their breast cancer care may be extensive in some settings or extremely limited in others, it is nonetheless always possible to offer some degree of choice to a patient. It is always possible to elicit what matters to a particular patient (what their values are), and to provide them with information in an understandable way that describes their options (even if limited), and to empower the patient to engage in the treatment planning process. Offering someone the opportunity to bring their relative or friend into the consultation is an example of a small choice which costs no additional time or money but improves dignity and autonomy.

Patient-centred communication skills applied by treating healthcare professionals demonstrate a core effect of communication on later quality of life.⁴⁴⁴ Helping patients to understand their condition, what their options are and why these options are or are not available, assessing patient preferences and active listening, are all skills which may be applied across national borders and the socioeconomic spectrum. Importantly, such skills can also be learnt and taught; and we propose that education of healthcare providers should include specific examples of risk-benefit communication and evidence-based medical decision making in a context-specific way to facilitate patient empowerment.

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How do we start the journey?

A recent global survey of 382 healthcare professionals conducted by the Lancet Breast Commission group showed that more than 70% of healthcare professionals felt confident they had received adequate communication skills training. This is encouraging, although may not match patient expectations and experience, and it is noteworthy that a substantial minority of professionals did not express confidence in these core skills.^{445,446}

The issue of healthcare professionals' available time for each patient is a difficult one globally. We strongly advocate senior healthcare professionals, researchers, and patient advocates in breast cancer care engaging with policymakers to improve investment in breast cancer care. High income countries have significantly better overall survival for breast cancer than low- and middle-income countries, and recent modelling suggests scaling up comprehensive breast cancer care to be available globally would not only significantly improve overall survival, but also lead to significant longer term economic returns.⁴⁴⁷ Such large scale investment is a long term strategy, as training the appropriate staff, including pathologists, radiologists, oncologists and surgeons, radiographers, chemotherapy, and specialist breast cancer nurses takes many years. Additionally, whilst the ideal for patients and staff would be to have as much consultation time as needed, the reality now in both high- and low-income settings necessitates optimisation of existing resources alongside long-term lobbying for increased investment.

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We encourage healthcare professionals to take a patient-centred approach to communication – to focus on assessing what patients need and empowering them to participate, even in just a few minutes, using established communication techniques.^{448,449} We suggest a framework to help develop a patient-centred consultation, acknowledging that this should serve as an iterative and non-linear

~~guide, and be adapted to each consultation.~~ It may not be necessary to include each step or communication skill in every consultation. There are many different ways to achieve the same goal, and any consultation should be culturally adapted to the unique needs of the person with breast cancer, their family (as appropriate), and the local clinical and/or community setting (*Panel 32, adapted from work of Bylund et al.⁴⁵⁰⁻⁴⁵⁴*). The examples given were developed by native speakers of English for use in settings where English is the native language, and alternative wording may be necessary in different settings.

Communication in specific situations

Terminology when discussing breast cancer with patients

We encourage healthcare professionals to choose terminology carefully in their own cultural context.^{465,466} Many patients dislike the term 'survivor' due to fears that the cancer may still later recur, feelings of wanting to return to normal life rather than being defined as a cancer survivor, or connotations of the term 'survivor' with war or other violent events. Similarly, tumour characteristics such as oestrogen receptor or progression status should not be applied to the whole patient—person-centred language is essential. The term 'survivorship,' when used to describe a part of the journey or problems specific to past breast cancer treatment, seems more acceptable to many patients. Whilst it is important to discuss risk of recurrence and long-term modifiable risk factors with patients with breast cancer, some patients may wish to forget their diagnosis and past treatment and not be defined by their previous breast cancer.

Panel 32 - Communication examples Framework to help develop a patient-centred consultation		
Strategies	Description of Relevant Skills	Example Talking Points
Build rapport and check understanding	introduce yourself and listen to the patient's story of their healthcare problem (published evidence suggests most patients will speak for under 2 minutes if left to spontaneously tell their story).⁴⁵⁵ Examples of inappropriate healthcare professional language around breast cancer:	'I've had a look through your notes but I'd like to hear from you what your understanding is about what has happened so far and what you are expecting next.' Examples of more appropriate ways to communicate the same message;
Set and negotiate agenda for consultation	'The patient has progressed' State the purpose of the consultation. If there is a decision to be made, that should be made clear. - Specifically ask about the patient's priorities for the consultation and their preferences for information and decision involvement. - Negotiate a consultation that includes goals of both clinician and the patient.	'The patient has a cancer that has grown and got worse' 'I am hoping to talk about your options for treatment today. Is there anything else on your mind that you would like to make sure we discuss?' (Negotiate agenda based on patient's response): 'Why don't I begin by discussing treatment options for your breast cancer and then we can address those specific questions you have about possible side effects and your ability to work while you are receiving care. Does that sound like a good plan?' 'Some people like to have lots of information about their illness and some people

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		just want the basics. How much information would you like me to give you today?'
'The patient is ER positive'		'The patient has a primary tumour that is ER positive'
'Breast cancer survivor'		'Person who has had breast cancer'
'This patient suffers from breast cancer'		'This patient has breast cancer'
'We will be withdrawing care' Share information	- Identify and clearly describe all relevant options, as well as associated risks and benefits, including active surveillance, a supportive or palliative (comfort focussed) approach when appropriate, and/or acknowledging what is achievable in that particular healthcare setting. - Share best, worst, and most likely case scenarios related to treatment outcomes.	"We will be with you every step of the way and continue to focus on your comfort." "At this stage of illness, we have multiple options to treat your breast cancer. There is a type of chemotherapy that has shown excellent outcomes in women with your type of illness. There are some side effects to the treatment, and we will talk more in detail about these as we go through the consent process. Fatigue, nausea, and low blood counts causing an increased risk of infection are the most common side effects. We can try to minimise some of the side effects with additional medications." "I know you are really struggling with your pain right now and it is keeping you from doing many of the things that are important for you. While we continue with radiation, I would like to focus also on symptom control, make sure we are most effectively treating your pain, and provide you with the support you need."
Convey respect for patient +/- family involvement	"There is nothing left for us to do" Validate their concerns as important and relevant to this decision, and explicitly encourage patients to ask questions.	"Whilst I worry that additional anti-cancer treatments would do more harm than good at this time, we can focus on managing your symptoms and helping you to feel

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	- State that you fully support the patient's right to make the final decision. - Ask the patient about use of non-prescribed therapies, traditional, complementary, and alternative medicines, and lifestyle changes since their diagnosis of breast cancer as well as medical and drug history. - Ask anyone accompanying the patient if there is anything else important they wish to add or have observed as a caregiver.	better' 'What are your thoughts about what we have discussed so far?' 'What questions do you have?' (To family member or caregiver) 'I know that you are an important part of the patient's (name) life. Is there anything you think is important that we are missing or that you would like to talk about?'
Empathise	- Acknowledge the patient's emotion and experience. - Validate their experience. - Normalise their emotional response.	'It sounds like this has been a hard time. But it also sounds like you have a lot of support from your loved ones.' 'It would be completely reasonable to take some time off from work to focus on your recovery.' 'Lots of people talk about feeling overwhelmed during a time like this.'
Review and recommend	- Clarify if the patient has enough information and offer more time for them to decide, if appropriate. - Consider how much the patient wished to be involved in decision making and offer a treatment recommendation if there is one clear best option from a medical perspective, or if the patient has requested the healthcare professional opinion. - When applicable, review multiple options including	'Today we talked about the treatment options available at this time. Do you have a preference about how you would like to proceed?'

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	no treatment—and state the rationale for your recommendation. Include key risks and benefits and normalise decisions that differ from recommendation. ▪ In the absence of a treatment recommendation from the healthcare professional, validate and support patient decision-making autonomy. In the absence of curative treatment, emphasise continued supportive or palliative care, where available emphasising ongoing supportive aspects of care for patients and their families.	
Summarise and agree next steps	▪ Summarise the consultation verbally and ideally provide a short, written summary which includes all options, states any recommendations, and describes the key trade-offs. ▪ Agree on next steps and appropriate follow up or further discussion. ▪ In settings with limited literacy, aim for diagrams or other follow up mechanisms such as another appointment or discussion with a community health navigator.	▪ 'I will refer you to our chemotherapy unit and they will be in contact with a date for your first treatment. Please have some blood tests done on your way out so we know it's ok to go ahead with the treatment. If you think of any concerns or questions later, please call us.'

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such there are specific areas to consider in as oestrogen receptor or progression status should not be applied to the whole patient—person-centred communication in this setting language is essential. The term ‘survivorship,’ when used to describe a part of the journey or problems specific to past breast cancer treatment, seems more acceptable to many patients. Whilst it is important to discuss risk of recurrence and long-term modifiable risk factors with patients with breast cancer, some patients may wish to forget their diagnosis and past treatment and not be defined by their previous breast cancer.

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1) The concept of metastatic cancer and goals of treatment

Patients and their family members should be told that metastatic breast cancer is usually incurable, but it is treatable and can often be controlled with treatment for many years. It is important to explain that treatment aims to slow cancer progression, reduce symptoms, improve quality of life, and prolong survival. Many patients receiving chemotherapy for metastatic cancers may not understand that chemotherapy is unlikely to be curative.⁴⁶⁷ Health care professionals need to help patients make the treatment decisions that are best for them. This requires the patient to understand the goals, logistics and side effects of treatment and the clinician to understand the patient’s individual preferences, values, and goals for her life (for example wanting to: attend a loved one’s wedding; travel; meet a grandchild; avoid any change in appearance). Understanding how a patient prioritises longevity, comfort, and independence is important. The aims of communicating about treatment goals in the metastatic breast cancer setting could not be stated better than by the founder of Maggie’s centres (a UK charity providing cancer support centres near hospitals): ‘Above all what matters is not to lose the joy of living in the fear of dying.’

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2) Prognosis

Prognostic information is vitally important for people living with metastatic breast cancer, for decision making around treatment, finances, work, and for helping patients maximise time with loved ones and prepare for death. Misunderstanding about prognosis is common in people with both early stage and advanced cancer⁴⁶⁸⁻⁴⁷⁰ and is associated with more aggressive and futile treatments at the end of life.^{468,471,472} Patients who want prognostic information may not always ask for this information⁴⁷³ so it is recommended that doctors ask explicitly if, when, and how patients want to talk about prognosis.⁴⁷⁴ It is best not to confront patients with information they do not want. Up to 20% of patients in studies report not wanting to discuss prognosis^{473,475} and decision making does not always require that the patient understand detailed prognostic information.^{468,474}

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Estimating and explaining expected survival time is difficult and doctors require guidance and communication skills training that is tailored to the cultural issues and local resources. Studies of oncologists show many report a reluctance to provide estimates of expected survival time.^{476,477} Factors contributing to this include: not knowing how to estimate survival time; fear of getting the estimate wrong; fear of upsetting the patient; fear of negatively affecting the patient–doctor relationship; requests from family to withhold prognostic information; and lack of time during consultations.⁴⁷⁷⁻⁴⁷⁹ Although prognostic information is upsetting, many patients still find it helpful to know the truth and there is no evidence that increased information about prognosis with sensitive communication is harmful to patients, or that it increases anxiety or distress.^{478,480-484} For patients wanting quantitative information on life expectancy, providing ranges for worst-case, typical, and best-case scenarios is more helpful and conveys more hope than providing a single point estimate of median survival.^{485,486} Most patients with advanced cancer surveyed after requesting and receiving their own expected survival time formatted as 3 scenarios reported that the information made sense, helped them make plans and improved their understanding.⁴⁸⁵ The majority also responded that the information about their prognosis was the same as, or better than, they expected before discussing it with their oncologist. Providing ranges for scenarios helps convey the inherent uncertainty of survival estimates and is more accurate than providing a single point estimate.^{485,487,488} Resources are available

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to help healthcare professionals estimate scenarios for survival time to facilitate conversations about prognosis with their patients.^{489,490}

3) End-of-life care and advanced care planning

Discussing prognosis often facilitates conversations about priorities, wishes, advance care planning, palliative care services, and hospice and end of life care. While these conversations can be difficult, they can also be crucial opportunities to identify new goals of care for the patient and their caregivers beyond disease-directed treatment; these conversations should be part of routine oncological care.⁴⁹¹

Patients with cancer are more likely to receive end-of-life care that is consistent with their preferences when they have had the opportunity to discuss their wishes for end-of-life care with a healthcare practitioner.^{471,491}

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Communicating about traditional, complementary, alternative, and integrative medicine (TCIM)

~~Traditional, complementary, alternative, and integrative medicine are terms often used interchangeably by practitioners of conventional medicine (allopathic medicine), though their meanings may be very different:~~

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- ~~• WHO defines traditional medicine as ‘the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness’.~~⁴⁹²
- ~~• Complementary medicine refers to non-mainstream practices used together with conventional medicine.~~
- ~~• Alternative medicine refers to non-mainstream practices used instead of conventional medicine.~~
- ~~• The Society for Integrative Oncology defines integrative oncology as a field based around a patient-centred, evidence-informed approach to cancer care, that uses lifestyle modifications, mind and body therapies, and natural products from different traditions in tandem with conventional cancer treatments.~~⁴⁹³

~~A 2012 systematic review of TCIM use in the USA, Canada, Europe, and Australia and New Zealand indicated a prevalence of 40% of people with cancer using some form of TCIM.~~⁴⁹⁴ Women with breast cancer are frequent users of TCIM in both HIC and LMICs – up to 80% use TCIM in some Caribbean populations.⁴⁹⁵ Although many cancer patients use TCIM, their oncology providers have limited knowledge or understanding of this area of medicine.⁴⁹⁶

~~Exploring and understanding patient TCIM use is a useful part of building rapport and sharing information in a patient-centred consultation, for example:~~

- ~~• ‘Are you currently receiving, or have you previously received care from other healers in the community or other clinicians in the health system before this appointment?’~~
- ~~• ‘Can you tell me more about these treatments or medicines?’~~

Acknowledging that discussion of TCIM should be nuanced due to potential harmful interactions of some TCIM with chemotherapy and radiotherapy, we encourage clinicians and patients to access evidence-informed information about TCIM, for example:

- ASCO and Society for Integrative Oncology joint Recommendations, see also Panel 33.
- Memorial Sloan Kettering Cancer Center guide to herbs, botanicals and other products

~~Further information and discussion about TCIM can be found in supplementary material 17.~~

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Panel 33 - Society for Integrative Oncology Recommendations - Adapted from ⁴⁹⁷	
Panel 33—Communication examples	
Goal	Recommendation
Anxiety/stress reduction	Music therapy Meditation Stress management Yoga
Examples of inappropriate healthcare professional language around breast cancer: Improvement of depression/mood disorders	Meditation Relaxation Yoga Massage
Quality of life improvement	Music therapy
'The patient has progressed'	Examples of more appropriate ways to communicate the same message: Meditation Yoga 'The patient has a cancer that has grown and got worse'
'The patient is ER positive'	'The patient has a primary tumour that is ER positive'
'Breast cancer survivor'	'Person who has had breast cancer'
'This patient suffers from breast cancer'	'This patient has breast cancer'
Reduction of chemotherapy-induced nausea and vomiting	Acupressure Acupuncture
'We will be withdrawing care'	'We will be with you every step of the way and continue to focus on your comfort'
Pain management	Hypnosis Acupuncture
'There is nothing left for us to do'	Music therapy 'Whilst I worry that additional anti-cancer treatments would do more harm than good at this time, we can focus on managing your symptoms and helping you to feel better'

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How do we measure progress

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A diagnosis of metastatic breast cancer has a lifelong impact on patients receiving it, and as such there are specific areas to consider in patient centred communication in this setting.

1) The concept of metastatic cancer and goals of treatment

Patients and their family members should be told that metastatic breast cancer is usually incurable, but it is treatable and can often be controlled with treatment for many years. It is important to explain that treatment aims to slow cancer progression, reduce symptoms, improve quality of life, and prolong survival. Many patients receiving chemotherapy for metastatic cancers may not understand that chemotherapy is unlikely to be curative.⁴⁵⁸ Health care professionals need to help patients make the treatment decisions that are best for them. This requires the patient to understand the goals, logistics and side effects of treatment and the clinician to understand the patient's individual preferences, values, and goals for her life (for example wanting to: attend a loved one's wedding; travel; meet a grandchild; avoid any change in appearance). Understanding how a patient prioritises longevity, comfort, and independence is important. The aims of communicating about treatment goals in the metastatic breast cancer setting could not be stated better than by the founder of Maggie's centres (a UK charity providing cancer support centres near hospitals): 'Above all what matters is not to lose the joy of living in the fear of dying.'

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2) Prognosis

Prognostic information is vitally important for people living with metastatic breast cancer, for decision making around treatment, finances, work, and for helping patients maximise time with loved ones and prepare for death. Misunderstanding about prognosis is common in people with both early stage and advanced cancer⁴⁵⁹⁻⁴⁶⁴ and is associated with more aggressive and futile treatments at the end of life.^{459,462,463} Patients who want prognostic information may not always ask for this information⁴⁶⁴ so it is recommended that doctors ask explicitly if, when, and how patients want to talk about prognosis.⁴⁶⁵ It is best not to confront patients with information they do not want. Up to 20% of patients in studies report not wanting to discuss prognosis^{464,466} and decision making does not always require that the patient understand detailed prognostic information.^{459,465}

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~~Estimating and explaining expected survival time is difficult and doctors require guidance and communication skills training that is tailored to the cultural issues and local resources. Studies of oncologists show many report a reluctance to provide estimates of expected survival time.^{467,468} Factors contributing to this include: not knowing how to estimate survival time; fear of getting the estimate wrong; fear of upsetting the patient; fear of negatively affecting the patient-doctor relationship; requests from family to withhold prognostic information; and lack of time during consultations.⁴⁶⁸⁻⁴⁷⁰ Although prognostic information is upsetting, many patients still find it helpful to know the truth and there is no evidence that increased information about prognosis with sensitive communication is harmful to patients, or that it increases anxiety or distress.^{469,471-475} For patients wanting quantitative information on life expectancy, providing ranges for worst case, typical, and best case scenarios is more helpful and conveys more hope than providing a single point estimate of median survival.^{476,477} Most patients with advanced cancer surveyed after requesting and receiving their own expected survival time formatted as 3 scenarios reported that the information made sense, helped them make plans and improved their understanding.⁴⁷⁶ The majority also responded that the information about their prognosis was the same as, or better than, they expected before discussing it with their oncologist. Providing ranges for scenarios helps convey the inherent uncertainty of survival estimates and is more accurate than providing a single point estimate.^{476,478,479} Resources are available to help healthcare professionals estimate scenarios for survival time to facilitate conversations about prognosis with their patients.^{480,481}~~

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3) End of life care and advanced care planning

Discussing prognosis often facilitates conversations about priorities, wishes, advance care planning, palliative care services, and hospice and end-of-life care. While these conversations can be difficult, they can also be crucial opportunities to identify new goals of care for the patient and their caregivers beyond disease-directed treatment; these conversations should be part of routine oncological care.⁴⁸²

~~Patients with cancer are more likely to receive end-of-life care that is consistent with their preferences when they have had the opportunity to discuss their wishes for end-of-life care with a healthcare practitioner.^{462,483}~~

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Communicating about traditional, complementary, alternative, and integrative medicine (TCIM)

Traditional, complementary, alternative, and integrative medicine are terms often used interchangeably by practitioners of conventional medicine (allopathic medicine), though their meanings may be very different:

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- WHO defines traditional medicine as ‘the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness’.⁴⁸³
- Complementary medicine refers to non-mainstream practices used together with conventional medicine.
- Alternative medicine refers to non-mainstream practices used instead of conventional medicine.
- The Society for Integrative Oncology defines integrative oncology as a field based around a patient-centred, evidence-informed approach to cancer care, that uses lifestyle modifications, mind and body therapies, and natural products from different traditions in tandem with conventional cancer treatments.⁴⁸⁴

A 2012 systematic review of TCIM use in the USA, Canada, Europe, and Australia and New Zealand indicated a prevalence of 40% of people with cancer using some form of TCIM.⁴⁸⁵ ~~Women with breast cancer are frequent users of TCIM in both HIC and LMICs — up to 80% use TCIM in some Caribbean populations.⁴⁸⁶ Although many cancer patients use TCIM, their oncology providers have limited knowledge or understanding of this area of medicine.⁴⁸⁷~~

Exploring and understanding patient TCIM use is a useful part of building rapport and sharing information in a patient-centred consultation, for example:

- ‘Are you currently receiving, or have you previously received care from other healers in the community or other clinicians in the health system before this appointment?’
- ‘Can you tell me more about these treatments or medicines?’

Acknowledging the potential harmful interactions of some TCIM with chemotherapy and radiotherapy, we encourage clinicians and patients to access evidence-informed information about TCIM, for example:

- ~~ASCO and Society for Integrative Oncology joint Recommendations⁴⁸⁸, see also Panel 34.~~
- ~~Memorial Sloan Kettering Cancer Center guide to herbs, botanicals and other products.⁴⁸⁹~~
- _____

Further information and discussion about TCIM can be found in supplementary material 17.

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Clinician facilitated discussions of patients' core values in the setting of newly diagnosed cancer have shown promise in enhancing individual autonomy and leveraging interpersonal supports.^{502,503} Unfortunately, these discussions are often withheld until the end of life. Integrating these conversations regarding 'who the patient is' and 'what is most important to them as a person' can help ensure person-centred decision making and care planning across the breast cancer continuum, from diagnosis to end of life.

A measurable indicator of change is the inclusion of mandatory training in communication for all healthcare professionals and should be measured by both policymakers (as a measure of quality of professional education) and researchers. Training in understanding one's own cultural beliefs and values, recognising and understanding differences in culture, values and beliefs in others, and recognising one's own inherent biases (sometimes called cultural competence or cultural humility⁵⁰⁴), is important to enable healthcare professionals to communicate effectively with all their patients.

The role of patient advocates is to promote issues that are important to them; engaging with policymakers to ensure empowerment and communication are considered as interventions that improve long term outcomes more affordably than some expensive drugs. The role of policymakers is to mandate and facilitate patient and public involvement in research design and practice in all spheres.

What is the potential wider impact?

Our vision is that empowering patients with breast cancer to be engaged in decisions about their care in all healthcare settings is a step towards wider female empowerment, addressing the lack of bodily, social, and financial autonomy for women in some societies worldwide. As a condition that predominantly affects women, breast cancer constitutes not only a challenge to women's health but an opportunity to identify ways in which provider-level interventions and systems-level changes can facilitate women's power and voice in society more generally. When women are treated with respect and recognised for their key, often underappreciated, role in societies where the division of labour remains gendered, they may begin to identify opportunities in other settings to exercise greater autonomy. Breast cancer is a disease that many patients describe as robbing them of power, but through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return power and emerge stronger than before. This is especially important when women have faced marginalisation based on intersecting identity characteristics such as race or socioeconomic status, in addition to marginalisation based on gender.

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Panel 34 - Lancet Breast Cancer Commission proposed measurable indicators of change Panel 34 - Society for Integrative Oncology Recommendations Adapted from ⁴⁸⁹						
ThemeGoal			DefinitionRecommendation	Rationale	Data sources	Responsible entity
Theme 6: Communication and empowerment in breast cancerAnxiety/stress reduction			Music therapy Meditation Stress management Yoga			
Communication skills training	Proper use of those who are in regulated health care roles receive culturally sensitive person-centred communication skills	Healthcare professional communication is key to empowering patients and developing person-centred care.	Facility records, University regulators.	Universities, healthcare facilities.	100% of healthcare professionals in 100% of countries should receive communication skills training-Improvement of depression/mood disorders	Meditation Relaxation Yoga Massage Music therapy

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Panel 34 - Lancet Breast Cancer Commission proposed measurable indicators of change ~~Panel 34 - Society for Integrative Oncology Recommendations - Adapted from~~ ⁴⁸⁹						
ThemeGoal		DefinitionRecommendation	Rationale	Data sources	Responsible entity	Target
Theme 6: Communication and empowerment in breast cancerAnxiety/stress reduction		Music therapy Meditation Stress management Yoga				
	trainings					
Quality of life improvement		Meditation Yoga				
Patient and public involvement in ethical design of breast cancer research.	Proportion of breast cancer clinical trials which have partnered with Patient and public involvement and engagement	PPIE in research promotes patient empowerment and improves the likelihood of the study being important to patients. Acupuncture	Clinical trials databases, research funding body records.	Ministry of Health, research funding bodies including charities, patient advocacy	100% of breast cancer clinical research in 100% of countries should partner with PPIE from research concept to reporting and translation into practice.	

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Panel 34 - Lancet Breast Cancer Commission proposed measurable indicators of change ~~Panel 34—Society for Integrative Oncology Recommendations—Adapted from~~ ⁴⁸⁹						
ThemeGoal		DefinitionRecommendation	Rationale	Data sources	Responsible entity	Target
Theme 6: Communication and empowerment in breast cancerAnxiety/stress reduction		Music therapy Meditation Stress management Yoga				
		(PPIE)-Reduction of chemotherapy-induced nausea and vomiting				
Pain management		Hypnosis Acupuncture Music therapy				

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Future Directions

Breast Cancer Prevention

Our vision for prevention is to be able to identify those at substantially increased risk of breast cancer in the whole population and offer them precision prevention strategies to reduce that risk, thus reducing breast cancer incidence. To achieve this, risk assessment will need to be equitable, proactive, and systematic, rather than largely opportunistic as is currently the case. A coordinated approach to the prescription of risk-reducing medications and the care of women who take them is required. Currently this is not considered to be in the domain of either primary care or specialists, and lack of clinician knowledge and confidence is a major barrier to uptake.

How do we measure progress in communication and empowerment?

Patient empowerment does not have a universal definition and is more difficult to measure than numeric outcomes like survival. Patient satisfaction with breast cancer care may be a useful surrogate, and should be measured by treating healthcare professionals, ideally both quantitatively and qualitatively. Specifically measuring the degree of involvement of patients in their decision making could also act as a surrogate for patient empowerment. Adherence to proposed therapy is another useful surrogate to include in empowerment focussed research. Community-based participatory research methods will be integral to understanding and creating interventions that meet patients in the context of their cultural needs and preferences, and assist with dismantling care inequities.⁴⁹⁰⁻⁴⁹³ Progress can be measured by global research into societal discussion of breast cancer, asking the question: can we freely talk about symptoms, diagnosis, and treatment of breast cancer in all global spheres?

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Clinician-facilitated discussions of patients' core values in the setting of newly diagnosed cancer have shown promise in enhancing individual autonomy and leveraging interpersonal supports.^{494,495} Unfortunately, these discussions are often withheld until the end of life. Integrating these conversations regarding 'who the patient is' and 'what is most important to them as a person' can help ensure person-centred decision-making and care planning across the breast cancer continuum, from diagnosis to end-of-life.

A measurable indicator of change is the inclusion of mandatory training in communication for all healthcare professionals and should be measured by both policymakers (as a measure of quality of professional education) and researchers. Training in understanding one's own cultural beliefs and values, recognising and understanding differences in culture, values and beliefs in others, and recognising one's own inherent biases (sometimes called cultural competence or cultural humility)^{496,77} is important to enable healthcare professionals to communicate effectively with all their patients.

The role of patient advocates is to promote issues that are important to them; engaging with policymakers to ensure empowerment and communication are considered as interventions that improve long-term outcomes more affordably than some expensive drugs. The role of policymakers is to mandate and facilitate patient and public involvement in research design and practice in all spheres.

What is the potential wider impact?

Our vision is that empowering patients with breast cancer to be engaged in decisions about their care in all healthcare settings is a step towards wider female empowerment, addressing the lack of bodily, social, and financial autonomy for women in some societies worldwide. As a condition that predominantly affects women, breast cancer constitutes not only a challenge to women's health but an opportunity to identify ways in which provider-level interventions and systems-level changes can facilitate women's power and voice in society more generally. When women are treated with respect and recognised for their key, often underappreciated, role in societies where the division of labour remains gendered, they may begin to identify opportunities in other settings to exercise greater autonomy. Breast cancer is a disease that many patients describe as robbing them of power, but

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through good communication and facilitating patient autonomy, the experience could be transformed into an opportunity to return power and emerge stronger than before. This is especially important when women have faced marginalisation based on intersecting identity characteristics such as race or socioeconomic status, in addition to marginalisation based on gender.

Catalysed by this Commission, an implementation pilot has commenced in Australia aimed at solving the existing workforce capability gap in a way that is potentially scalable. It will examine if a nurse practitioner led telehealth service can increase uptake and continuation of risk-reducing medications by providing both assessment and prescription before discharging clients back to their primary healthcare provider for ongoing prescriptions. A hotline and, if required, rapid re-entry into the service will be available to support doctors and women in managing side-effects during the full treatment course. At the same time as these precision prevention approaches, better population prevention is needed. Governments can help by prioritising reduction of exposure of their populations to breast cancer risk factors by adjusting health policies. Implementation of simple preventives (e.g. low dose tamoxifen in women <50years) will require increased workforce and training of primary and secondary health care providers. There is a lot of work to be done in education and training of health care practitioners so that risks, benefits, and uncertainties are clearer for individuals to inform their personal lifestyle choices. Specifically, governments must recognise that the rising rates of breast cancer are a major and expensive public health problem and need to legislate for changes, based on those that have been effective in other areas of public health, to reduce exposure to risk factors.

Personalising breast cancer treatment

The breast cancer communities in HIC are making breakthroughs in terms of personalising breast cancer treatments. Perhaps this is most applicable in the early disease setting where there is an increasing recognition that many women at present are over-treated, resulting in a significant burden of treatment which is costly and unnecessary. Emerging technologies will allow the integration of existing clinical data with new molecular data on germline genomics, tumour genomics, pharmacogenomics, and circulating tumour DNA. The aim is to provide a personalised approach for each patient rather than the more common population approach. Optimisation of treatment can preserve the excellent outcomes that have been achieved whilst reducing rising costs; financial, physical, and psychological. Alongside this, AI and allied technologies can democratise this information making it available to be used by everyone. Recognising that each nation's health care system is subtly or, at times radically, different from its neighbours, the leaders for breast cancer would be responsible for interpreting this new information within their own country and for their own citizens. There is no reason once the technological systems have been developed that they could not be applied to every patient with breast cancer. At this point in the technological revolution, the wider medical community needs to 'hold hands with patients' to facilitate best use of all the information that will soon become available.

Once developed, it would be a second order challenge to get advanced communications technology to speak directly to healthcare personnel and patients throughout the world. Applying new technology of assessment would allow personalised information from patients and their tumours to go into algorithms advising best management. Almost certainly in breast cancer this will reduce treatments in most patients, thus saving money to invest in more targeted treatments for those who need them. This approach will allow LMICs to reap the benefits of advancing technology and communications very quickly.

Optimal inclusive management of metastatic breast cancer

In order to fully understand and address the impact of MBC globally, the first crucial step is to collect high-quality metastatic cancer registry data, including relapses. This will ensure patients with MBC are seen and should also better guide allocation of resources. There is an urgent need to improve equitable access to evidence-based therapies for MBC, as well as to clinical trials, and we urge that patients are managed with an individualised approach, which includes not only tailoring therapies appropriately to tumour biology, but also evaluating quality of life regularly and incorporating supportive and palliative

care from diagnosis and always accounting for patients' preferences. People with MBC should be managed with a multidisciplinary approach and according to high quality context-adapted clinical guidelines, both of which have been shown to improve health outcomes and quality of life. Sadly, MBC remains a stigmatised and poorly understood disease for the general population, policy makers, and even for health care professionals. A change in mentality, moving from a fatalistic to a more optimistic approach to this disease, is needed to truly change the outcomes of patients. We propose measurable indicators of positive change with actionable targets for MBC and we hope that this framework can be applied to other metastatic cancers to induce valuable changes globally.

Tackling breast cancer gaps and inequities through global collaboration

Addressing global inequities cannot be achieved by expecting all countries to play linear catch-up with HICs but must be about an increasing emphasis on the regionalisation of cancer care provision. This requires adoption of approaches to earlier diagnosis and better treatments that are effective in the context where they need to happen. Developing models that encourage the advancement of regional centres of excellence, regional pooled procurement and manufacturing of relevant medications and health related products will ensure greater access at lower costs to all patients. Grassroots advocacy and patient education and empowerment across all regions are needed to ensure that health is acknowledged as a global basic right. Whilst continuing to highlight concerns around health gaps and inequities on a broader global platform, there also needs to be leverage that works to hold regional policy makers and other local stakeholders to account. Investment in developing locality based and contextualised training of a workforce competent across the care continuum is essential. Maintaining links to and support from broader global networks, alongside developing the skill sets necessary to address local and region-specific challenges, will encourage the expansion and retention of the necessary workforce in LMICs. Although innovations and technologies hold promise in mitigating some of these disparities, especially when backed by evidence driven outcomes, they are not a panacea for dysfunctional health systems: deliberate investment in health systems and workforce should remain the bedrock on which innovations rest in all countries of the world. For sustainable global solutions to occur, a multi-faceted approach and persistent commitment is needed; one that harnesses all sectors of society including finance, education, and industry, to address health disparities in breast cancer and other health sectors.

Identifying and responding to the hidden costs of breast cancer

Hidden costs of breast cancer need to be exposed and quantified to be reduced. The hidden costs of breast cancer are myriad and have yet to be fully explored, quantified, and incorporated into the framework of serious health related suffering (SHS) or developed into an inclusive suffering metric that combines physical and psychological, as well as social and spiritual components as experienced by patients, caregivers, and their families. Further, many of the financial costs of breast cancer are overlooked or go unmeasured, including the lost family income of both patients and caregivers. The hidden costs of breast cancer are embedded in and intensified by gender inequity and layer onto poverty and marginalisation. Financial protection and quality service delivery must span the entire breast cancer trajectory, but the design, monitoring and evaluation of these interventions requires a full costing model to identify the necessary financial and non-financial resources required to alleviate more of the breast cancer suffering spectrum. Screening for hidden costs and suffering must be designed to influence priority-setting and resource allocation, around a more informed but also achievable target of suffering reduction. Strategies must be grounded in and tailored to the specific stages of the breast cancer trajectory. Better understanding and responding to the value that patients, and

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their caregivers and families place on the alleviation of the suffering associated with the hidden costs of breast cancer - in addition to the reduction of morbidity and mortality – is core to more efficacious and responsive patient-centered care.

Communication and Empowerment in breast cancer

We envisage that reliable and sustainable skills in person-centered communication will be consistently integrated throughout all patient-provider interactions. This will become fundamental to the training of healthcare professionals in breast cancer care, with emphasis on discussing prognosis and encouraging patient participation in decision making. Communication that prioritises empathy, respect, and inclusion, demonstrates recognition of the dignity of the patient and ensures the provision of truly person-centered care. When patient engagement in research design, conduct and evaluation becomes mandatory globally, this will ensure clinical research delivers meaningful answers to research questions of interest and benefit to patients. Policymakers can invest to provide global minimum numbers of treating healthcare staff per capita, which will improve both global survival rates for breast cancer and patient satisfaction with their level of involvement in treatment decision making. By normalising and honouring patient involvement in breast cancer care and decision making, a powerful message will exist of women publicly exercising their voices and rights as citizens, providing opportunities for wider empowerment of women globally.

Conclusion

The Lancet Breast Cancer Commission has produced an evidenced-based inclusive roadmap to address urgent global breast cancer challenges. But the utility of road maps is when they are used, not admired on a shelf. Therefore, we call society to action to scrutinise current approaches to breast cancer, challenge the status quo, and expose practices that create inequity in every country of the world or waste scarce resources. We implore all stakeholders in breast cancer care to disseminate, implement and adapt our roadmap to facilitate changes to practice and outcomes.

We have shown throughout this commission report that data is a powerful promoter for change. Therefore, it is imperative that our breast cancer targets (See Panel 35) are measured, used to hold policy makers and communities to account, and to lobby for better, equitable approaches to breast cancer. We anticipate a united, collaborative, and evidence-based approach, empowering patients, families, communities, health care providers and policy makers, to evolve and improve this roadmap. We believe that this will prevent the inevitability of the anticipated 3 million new cases of breast cancer a year, mean that breast cancer is no longer the leading cause of cancer death and provide better visibility and treatment for everyone affected by breast cancer regardless of who they are or where they live.

Panel 35—Lancet Breast Cancer Commission proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target
Section 6: Communication and empowerment					
Communication skills training.	Proportion of those who are in regulated	Healthcare professional communicatio	Facility records,	Universities, healthcare facilities.	100% of healthcare professionals in 100% of countries should receive communication skills training.

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Panel 35—Lancet Breast Cancer Commission-proposed measurable indicators of change					
Theme	Definition	Rationale	Data-sources	Responsible entity	Target
Section 6: Communication and empowerment					
	healthcare roles receive culturally sensitive person-centred communication skills training.	n is key to empowering patients and developing person-centred care.	University regulators.		
Patient and public involvement in ethical design of breast cancer research.	Proportion of breast cancer clinical trials which have partnered with Patient and public involvement and engagement (PPIE).	PPIE in research promotes patient empowerment and improves the likelihood of the study being important to patients.	Clinical trials databases; research funding-body records.	Ministry of Health; research funding bodies including charities; patient advocacy	<u>Panel 35 - Summary of the Lancet Breast Cancer Commission suggested targets for change Breast Cancer Prevention</u> 95% of countries legislating fully the UNICEF Code for advertising and promotion of commercial milk formula products & adhering to the WHO 'Best buys' with respect to alcohol advertising. - Statutory access to at least 18 weeks, and preferably 26 weeks of parental leave at 100% pay. - Mandatory provision of paid breaks and nursing-expressing facilities on return to work - Tax sugar sweetened beverages to raise the retail price at least 20%. <u>Personalising breast cancer treatment</u> >80% (aiming for 95%) of patients have access to accurate tumour subtyping

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Panel 35—Lancet Breast Cancer Commission-proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target
Section 6: Communication and empowerment					
					• <u>>80% (aiming for 95%) patients with new diagnosis to be discussed at multidisciplinary meetings.</u> • <u>100% of patients with breast cancer to have access to full range of treatment modalities.</u> • <u>At least 10% (aiming for >25%) of participants of international breast cancer trials are from LMICs.</u> • <u>At least 10% (aiming for >25%) of all breast cancer trials are led/co-led by LMIC researchers.</u> <u>Optimal inclusive management of metastatic breast cancer</u> • <u>Minimum of 70% (aiming at 100%) of cancer registries recording cancer stage and relapse.</u> • <u>Minimum of 50%, aiming at 95% MBC cases discussed at multidisciplinary meetings.</u> • <u>Record the number of people with MBC and aim for doubling the median overall survival in a decade.</u> • <u>Aiming for <5% of patients at end of life without access to morphine.</u> • <u>100% MBC patients have access to life saving cancer medicines.</u> <u>Tackling breast cancer gaps and inequities through global collaboration</u> • <u>60% of all invasive cancers are at stage 1-2 at diagnosis.</u>

Panel 35—Lancet Breast Cancer Commission-proposed measurable indicators of change					
Theme	Definition	Rationale	Data-sources	Responsible entity	Target
Section 6: Communication and empowerment					
					• <u>Evaluation, imaging, tissue sampling and pathology within 60 days.</u> • <u>80% of patients undergo multimodality treatment without abandonment.</u> • <u>Time from drug approval to availability to the patient <6 months for high priority agents and <year for intermediate priority agents.</u> <u>Identifying the hidden costs of breast cancer</u> • <u>Upward trajectory year on year for Universal Health Coverage of breast cancer across the continuum of care, aiming at 100%, to eliminate financial catastrophe and impoverishment for all families experiencing breast cancer.</u> • <u>Screening for serious health-related suffering at diagnosis and key milestones throughout the breast cancer patient pathway as a research tool with an aim for widespread implementation after validation.</u> • <u>Minimum of poorest 20%, but aiming at 100%, of patients and families receiving public financing and provision of an essential package of supportive and palliative care across the breast cancer pathway.</u> <u>Communication and empowerment in breast cancer</u>

Panel 35—Lancet Breast Cancer Commission-proposed measurable indicators of change					
Theme	Definition	Rationale	Data sources	Responsible entity	Target
Section 6: Communication and empowerment					
					100% of healthcare professionals in 100% of countries should receive communication skills training. 100% of breast cancer clinical research in 100% of countries should partner with patients^{PPH} from research concept to reporting and translation into practice.

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Conclusion

Our report is the culmination of a two-year journey that began with an ambitious aspiration to develop a roadmap of improved breast cancer care that could be applied worldwide. As commissioners, perhaps we underestimated the challenge; it was certainly more complex than most of us could have ever imagined. We have encouraged each other not to be overwhelmed by the undoubted magnitude of our task, and focussed on crafting compelling arguments for change, enriched with new pilot data of our own. We were aided by some excellent previous and current Lancet commissions.^{278,497-502} We have formed new partnerships, which have not only added value to this report, but have galvanised collaborations for on-going breast cancer and related research.

Many common themes have emerged from the different sections. Our overarching aim throughout has been, like many of our readers, to drive the optimal care for people diagnosed with breast cancer or at risk for developing it. Prevention is better than cure, and our experts have explored in considerable detail how breast cancer can be prevented. We don't have all the answers yet, but discovery science will provide further data to complete the biology of causes that we will then be able to act upon. We draw attention to continued lobbying worldwide by strong commercial interests, which encourage behaviours that increase rather than prevent breast cancer.

In many ways, breast cancer management reflects the advances developed from cutting edge cancer science, and the further potential of this is covered. As part of this, our piece on optimisation of treatment reminds us that more is not always better; particularly in high income countries but not exclusively, many patients with breast cancer are overtreated. A key insight is that by using the power of technology, we are now able to democratise science to benefit all patients with breast cancer. In this section we also address the challenge that technology solutions may widen the equity gap and suggest ways in which technology can be used to provide more equitable access to breast cancer prevention, early detection, and treatment worldwide. Our section on metastatic breast cancer is comprehensive both in its scope and its call for action to pay due attention to this part of many patients' journey. New work is again included here, this time from a survey of breast cancer specialists from across the world. We believe this section will be useful not only for practitioners with its detailed treatment summary, but also for policymakers with its clear recommendations.

We focus on 'closing the gap for breast cancer' by providing not only examples of success, but also robust metrics that should prove powerful in guiding improvements in breast cancer care, particularly in resource poor countries. A special plea is made for the adoption of 'value-based' care within health systems that are focussed on the best outcomes for people with breast cancer. We call for the recognition of serious health related suffering and other hidden costs from breast cancer; these must become metrics by which we judge the success or otherwise of our breast cancer care. We present new research from the UK, showing that even where universal health coverage is the norm, hidden financial toxicity from breast cancer is considerable. We reflect on empowerment and communication in breast cancer with fresh vision and audacious hope that the advances we advocate in the setting of breast cancer may ultimately serve to elevate the rights, dignity, and status of women and other marginalised groups more generally.

Finally, as commissioners, we believe that our proposed measurable indicators for breast cancer prevention and care are crucial in transforming an academic manuscript into a powerful document that can be used to lobby for change. We hope that policy and decision makers globally, will embrace our aspirational road map, and in doing so will improve the lives not only for those affected by breast cancer, but also for others whereby learnings from breast cancer can also be applied.

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References

1. WHO - Breast Cancer. 2021. <https://www.who.int/news-room/fact-sheets/detail/breast-cancer> (accessed 2023 April).
2. Mailhot Vega RB, Balogun OD, Ishaq OF, Bray F, Ginsburg O, Formenti SC. Estimating child mortality associated with maternal mortality from breast and cervical cancer. *Cancer* 2019; **125**(1): 109-17.
3. Cavallo J. Maternal Deaths From Cancer Worldwide Have Led to Approximately 1 Million New Maternal Orphans. 2022. <https://ascopost.com/news/october-2022/maternal-deaths-from-cancer-worldwide-have-led-to-approximately-1-million-new-maternal-orphans/> (accessed April 2023).
4. UN. Inequality in a rapidly changing world, 2020.
5. Daly B, Olopade OI. A perfect storm: How tumor biology, genomics, and health care delivery patterns collide to create a racial survival disparity in breast cancer and proposed interventions for change. *CA Cancer J Clin* 2015; **65**(3): 221-38.
6. Coles CE, Anderson BO, Cameron D, et al. The Lancet Breast Cancer Commission: tackling a global health, gender, and equity challenge. *Lancet* 2022; **399**(10330): 1101-3.
7. Knaul FM, Garcia PJ, Gospodarowicz M, Essue BM, Lee N, Horton R. The Lancet Commission on cancer and health systems: harnessing synergies to achieve solutions. 2021; **398**(10306): 1116.
8. Knaul FM, Farmer PE, Krakauer EL, et al. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report. *The Lancet* 2018; **391**(10128): 1391-454.
9. ~~Harris LH. Navigating Loss of Abortion Services—A Large Academic Medical Center Prepares for the Overturn of Roe v. Wade. *N Engl J Med* 2022; **386**(22): 2061-4.~~
10. Arnold M, Morgan E, Rumgay H, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast* 2022; **66**: 15-23.
1011. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians* 2021; **71**(3): 209-49.
1112. Jayasekera J, Mandelblatt JS. Systematic Review of the Cost Effectiveness of Breast Cancer Prevention, Screening, and Treatment Interventions. *J Clin Oncol* 2020; **38**(4): 332-50.
1213. Bellanger M, Barry K, Rana J, Regnaud JP. Cost-Effectiveness of Lifestyle-Related Interventions for the Primary Prevention of Breast Cancer: A Rapid Review. *Front Med (Lausanne)* 2019; **6**: 325.
1314. Li SX, Milne RL, Nguyen-Dumont T, et al. Prospective Evaluation of the Addition of Polygenic Risk Scores to Breast Cancer Risk Models. *JNCI Cancer Spectr* 2021; **5**(3).
1415. Howell A, Anderson AS, Clarke RB, et al. Risk determination and prevention of breast cancer. *Breast Cancer Res* 2014; **16**(5): 446.
1516. Dorling L, Carvalho S, Allen J, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. *N Engl J Med* 2021; **384**(5): 428-39.
1617. Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. *N Engl J Med* 2021; **384**(5): 440-51.
1718. Mavaddat N, Michailidou K, Dennis J, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet* 2019; **104**(1): 21-34.
1819. Parkin DM, Boyd L, Walker L. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *British journal of cancer* 2011; **105**(2): S77-S81.
1920. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 1995; **87**(22): 1681-5.
2021. Britt KL, Cuzick J, Phillips K-A. Key steps for effective breast cancer prevention. *Nat Rev Cancer* 2020; **20**(8): 417-36.

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- ~~2122~~. Zhang B, Shu XO, Delahanty RJ, et al. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. *J Natl Cancer Inst* 2015; **107**(11).
- ~~2223~~. Maas P, Barrdahl M, Joshi AD, et al. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. *JAMA Oncol* 2016; **2**(10): 1295-302.
- ~~2324~~. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin* 2018; **68**(1): 31-54.
- ~~2425~~. Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. *Br J Cancer* 2018; **118**(8): 1130-41.
- ~~2526~~. Parkin DM. 9. Cancers attributable to inadequate physical exercise in the UK in 2010. *Br J Cancer* 2011; **105** Suppl 2: S38-41.
- ~~2627~~. International Agency for Research on Cancer (IARC), World Health Organisation. Cancer Attributable to Alcohol. 2022. <https://gco.iarc.fr/causes/alcohol/> (accessed 27 Oct 2022 2022).
- ~~2728~~. International Agency for Research on Cancer (IARC), World Health Organisation. Cancer Attributable to obesity. 2022. <https://gco.iarc.fr/causes/obesity> (accessed 27 Oct 2022 2022).
- ~~2829~~. Rumgay H, Shield K, Charvat H, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. *Lancet Oncol* 2021; **22**(8): 1071-80.
- ~~2930~~. Yin X, Zhang T, Zhang Y, Man J, Yang X, Lu M. The global, regional, and national disease burden of breast cancer attributable to low physical activity from 1990 to 2019: an analysis of the Global Burden of Disease Study 2019. *Int J Behav Nutr Phys Act* 2022; **19**(1): 42.
- ~~3031~~. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *PLoS One* 2012; **7**(12): e51446.
- ~~3132~~. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. *Int J Cancer* 2009; **124**(3): 698-712.
- ~~3233~~. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat* 2010; **123**(3): 641-9.
- ~~3334~~. Shi Y, Li T, Wang Y, et al. Household physical activity and cancer risk: a systematic review and dose-response meta-analysis of epidemiological studies. *Sci Rep* 2015; **5**: 14901.
- ~~3435~~. Guo W, Fensom GK, Reeves GK, Key TJ. Physical activity and breast cancer risk: results from the UK Biobank prospective cohort. *Br J Cancer* 2020; **122**(5): 726-32.
- ~~3536~~. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. *N Engl J Med* 2017; **377**(23): 2228-39.
- ~~3637~~. Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V. Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis. *PLoS Med* 2023; **20**(3): e1004188.
- ~~3738~~. Cancer CGoHFIB. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet* 2019; **394**(10204): 1159-68.
- ~~3839~~. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, Comparative Risk Assessment collaborating g. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet* 2005; **366**(9499): 1784-93.
- ~~3940~~. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *Journal of the National Cancer Institute* 2006; **98**(17): 1215-26.
- ~~4041~~. Bissell MCS, Kerlikowske K, Sprague BL, et al. Breast Cancer Population Attributable Risk Proportions Associated with Body Mass Index and Breast Density by Race/Ethnicity and Menopausal Status. *Cancer Epidemiol Biomarkers Prev* 2020; **29**(10): 2048-56.

4142. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 2009; **10**(11): 1033-4.
4243. Ginsburg O, Vanderpuye V, Beddoe AM, et al. Women, power, and cancer: a Lancet Commission. *The Lancet* 2023.
4344. Rovira P, Rehm J. Estimation of cancers caused by light to moderate alcohol consumption in the European Union. *Eur J Public Health* 2021; **31**(3): 591-6.
4445. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015; **112**(3): 580-93.
4546. Choi YJ, Myung SK, Lee JH. Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies. *Cancer Res Treat* 2018; **50**(2): 474-87.
4647. Yoo JE, Han K, Shin DW, et al. Association Between Changes in Alcohol Consumption and Cancer Risk. *JAMA Netw Open* 2022; **5**(8): e2228544.
4748. Brinton LA, Figueroa JD, Awuah B, et al. Breast cancer in Sub-Saharan Africa: opportunities for prevention. *Breast Cancer Res Treat* 2014; **144**(3): 467-78.
4849. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; **360**(9328): 187-95.
4950. Rollins NC, Bhandari N, Hajeebhoy N, et al. Why invest, and what it will take to improve breastfeeding practices? *Lancet* 2016; **387**(10017): 491-504.
5051. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; **387**(10017): 475-90.
5152. Jung AY, Ahearn TU, Behrens S, et al. Distinct Reproductive Risk Profiles for Intrinsic-Like Breast Cancer Subtypes: Pooled Analysis of Population-Based Studies. *J Natl Cancer Inst* 2022; **114**(12): 1706-19.
5253. Chlebowski RT, Rohan TE, Manson JE, et al. Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol* 2015; **1**(3): 296-305.
5354. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347**(9017): 1713-27.
5455. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **400**(10352): 563-91.
5556. International Agency for Research on Cancer (IARC), World Health Organisation. Global Cancer Observatory. Cancer causes. [Available from: <https://gco.iarc.fr/causes/>]
5657. Peacey V, Steptoe A, Davidsdottir S, Baban A, Wardle J. Low levels of breast cancer risk awareness in young women: an international survey. *Eur J Cancer* 2006; **42**(15): 2585-9.
5758. Peltzer K, Pengpid S. Awareness of breast cancer risk among female university students from 24 low, middle income and emerging economy countries. *Asian Pac J Cancer Prev* 2014; **15**(18): 7875-8.
5859. Gupta A, Shridhar K, Dhillon PK. A review of breast cancer awareness among women in India: Cancer literate or awareness deficit? *Eur J Cancer* 2015; **51**(14): 2058-66.
5960. Osei-Afriyie S, Addae AK, Oppong S, Amu H, Ampofo E, Osei E. Breast cancer awareness, risk factors and screening practices among future health professionals in Ghana: A cross-sectional study. *PLoS One* 2021; **16**(6): e0253373.
6061. Elshami M, Usrof FD, Alser M, et al. Awareness of Palestinian Women About Breast Cancer Risk Factors: A National Cross-Sectional Study. *JCO Glob Oncol* 2022; **8**: e2200087.
6162. Sinclair J, McCann M, Sheldon E, Gordon I, Brierley-Jones L, Copson E. The acceptability of addressing alcohol consumption as a modifiable risk factor for breast cancer: a mixed method study within breast screening services and symptomatic breast clinics. *BMJ Open* 2019; **9**(6): e027371.

6263. Khushalani JS, Qin J, Ekwueme DU, White A. Awareness of breast cancer risk related to a positive family history and alcohol consumption among women aged 15-44 years in United States. *Prev Med Rep* 2020; **17**: 101029.
6364. Grigg J, Manning V, Lockie D, et al. A brief intervention for improving alcohol literacy and reducing harmful alcohol use by women attending a breast screening service: a randomised controlled trial. *Med J Aust* 2023; **218**(11): 511-9.
6465. Kushi LH, Byers T, Doyle C, et al. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2006; **56**(5): 254-81; quiz 313-4.
6566. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. *Int J Cancer* 2014; **135**(10): 2444-52.
6667. Thomson CA, McCullough ML, Wertheim BC, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. *Cancer Prev Res (Phila)* 2014; **7**(1): 42-53.
6768. Bevel MS, Tsai M-H, Parham A, Andrzejak SE, Jones S, Moore JX. Association of Food Deserts and Food Swamps With Obesity-Related Cancer Mortality in the US. *JAMA Oncology* 2023.
6869. Wyper GMA, Mackay DF, Fraser C, et al. Evaluating the impact of alcohol minimum unit pricing on deaths and hospitalisations in Scotland: a controlled interrupted time series study. *Lancet* 2023.
6970. Gilmore AB, Fooks G, Drope J, Bialous SA, Jackson RR. Exposing and addressing tobacco industry conduct in low-income and middle-income countries. *Lancet* 2015; **385**(9972): 1029-43.
7071. Balekrouzou A, Yin P, Pamatika CM, et al. Epidemiology of breast cancer: retrospective study in the Central African Republic. *BMC public health* 2016; **16**(1): 1230.
7172. World Health Organisation. WHO Report on the Global Tobacco Epidemic, 2021: Addressing new and emerging products. 2021. <https://www.who.int/publications/i/item/9789240032095>
7273. Saenz-de-Miera B, Wu DC, Essue BM, Maldonado N, Jha P, Reynales-Shigematsu LM. The distributional effects of tobacco tax increases across regions in Mexico: an extended cost-effectiveness analysis. *Int J Equity Health* 2022; **21**(1): 8.
7374. Wilkinson AL, Scollo MM, Wakefield MA, Spittal MJ, Chaloupka FJ, Durkin SJ. Smoking prevalence following tobacco tax increases in Australia between 2001 and 2017: an interrupted time-series analysis. *Lancet Public Health* 2019; **4**(12): e618-e27.
7475. Chipty T. Study of the Impact of the Tobacco Plain Packaging Measure on Smoking Prevalence in Australia. 2016. <https://www.health.gov.au/sites/default/files/study-of-the-impact-of-the-tobacco-plain-packaging-measure-on-smoking-prevalence-in-australia.pdf> (accessed 13 Nov 2022).
7576. World Health Organisation. Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. Resolution adopted by the General Assembly January 2022. 2022. https://apps.who.int/gb/ebwha/pdf_files/EB150/B150_7Add1-en.pdf
7677. World Health Organisation, UNICEF. Implementation guidance: protecting, promoting, and supporting breastfeeding in facilities providing maternity and newborn services: the revised Baby-friendly Hospital Initiative 2018. 2018. <https://www.who.int/publications/i/item/9789241513807> (accessed 13 Nov 2022).
7778. World Health Organisation. WHO Discussion Paper: Draft recommendations for the prevention and management of obesity over the life course, including potential targets. 2021. <https://www.who.int/publications/m/item/who-discussion-paper-draft-recommendations-for-the-prevention-and-management-of-obesity-over-the-life-course-including-potential-targets> (accessed 13 Nov 2022).
7879. World Health Organisation. Global action plan on physical activity 2018–2030: more active people for a healthier world. . 2018. <https://apps.who.int/iris/handle/10665/272722> (accessed 13 Nov 2022).

7980. World Health Organisation. Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases, and mental health Draft updated menu of policy options and cost-effective interventions for the prevention and control of noncommunicable diseases. 2023. https://apps.who.int/gb/ebwha/pdf_files/EB152/B152_6-en.pdf
8081. World Health Organisation. Global Information System on Alcohol and Health. 2022. <https://www.who.int/data/gho/data/themes/global-information-system-on-alcohol-and-health> (accessed 13 Nov 2022).
8182. World Health Organisation. Time to deliver: report of the WHO Independent high-level commission on noncommunicable diseases. 2018. <https://apps.who.int/iris/handle/10665/272710>. (accessed 13 Nov 2022).
8283. UNICEF. UNICEF data: monitoring the situation of children and women. Breastfeeding dataset. 2021. <https://data.unicef.org/resources/dataset/breastfeeding/> (accessed 22 Nov 2022).
8384. Jackson-Morris AM, Mutungi G, Maree E, Waqanivalu T, Marten R, Nugent R. 'Implementability' matters: using implementation research steps to guide and support non-communicable disease national planning in low-income and middle-income countries. *BMJ Glob Health* 2022; **7**(4).
8485. Brownson RC, Chiqui JF, Stamatakis KA. Understanding evidence-based public health policy. *Am J Public Health* 2009; **99**(9): 1576-83.
8586. Breda J, Wickramasinghe K, Peters DH, et al. One size does not fit all: implementation of interventions for non-communicable diseases. *BMJ* 2019; **367**: l6434.
8687. World Health Organisation. A guide to implementation research in the prevention and control of noncommunicable diseases. 2016. <https://apps.who.int/iris/bitstream/handle/10665/252626/9789241511803-eng.pdf> (accessed 13 Nov 2022).
8788. Lee JK, Bullen C, Ben Amor Y, et al. Institutional and behaviour-change interventions to support COVID-19 public health measures: a review by the Lancet Commission Task Force on public health measures to suppress the pandemic. *Int Health* 2021; **13**(5): 399-409.
8889. Elghazaly H, Aref AT, Anderson BO, et al. The first BGICC consensus and recommendations for breast cancer awareness, early detection and risk reduction in low- and middle-income countries and the MENA region. *Int J Cancer* 2021; **149**(3): 505-13.
8990. US Department of Health and Human Services. Charter: Advisory Committee on Breast Cancer in Young Women 2022 2022.
9091. Nsaful J, Dedey F, Nartey E, Labi J, Adu-Aryee NA, Clegg-Lampsey JN. The impact of a breast cancer educational intervention in Ghanaian high schools. *BMC Cancer* 2022; **22**(1): 893.
9192. Soto-Perez-de-Celis E, Smith DD, Rojo-Castillo MP, et al. Implementation of a School-Based Educational Program to Increase Breast Cancer Awareness and Promote Intergenerational Transmission of Knowledge in a Rural Mexican Community. *Oncologist* 2017; **22**(10): 1249-56.
9293. World Health Organisation. Regional technical consultation with member states on the working document for development of the action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority: virtual meeting, 25–26 March 2021: meeting report. World Health Organization. Regional Office for Europe. 2021. <https://apps.who.int/iris/handle/10665/341837>.
9394. Mialon M, McCambridge J. Alcohol industry corporate social responsibility initiatives and harmful drinking: a systematic review. *Eur J Public Health* 2018; **28**(4): 664-73.
9495. McCambridge J, Mialon M, Hawkins B. Alcohol industry involvement in policymaking: a systematic review. *Addiction* 2018; **113**(9): 1571-84.
9596. Hammond D. Health warning messages on tobacco products: a review. *Tob Control* 2011; **20**(5): 327-37.
9697. Moodie C, Hoek J, Hammond D, et al. Plain tobacco packaging: progress, challenges, learning and opportunities. *Tob Control* 2022; **31**(2): 263-71.

9798. Greenhalgh EM, Scollo MM. 11A.9 Real-world research on the effects of plain packaging. In: Greenhalgh EM, Scollo MM, Winstanley MH, eds. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2022.
9899. Hughes N, Arora M, Grills N. Perceptions and impact of plain packaging of tobacco products in low and middle income countries, middle to upper income countries and low-income settings in high-income countries: a systematic review of the literature. *BMJ Open* 2016; **6**(3): e010391.
99400. Giesbrecht N, Reisdorfer E, Rios I. Alcohol Health Warning Labels: A Rapid Review with Action Recommendations. *Int J Environ Res Public Health* 2022; **19**(18).
100401. Wilkinson C, Room R. Warnings on alcohol containers and advertisements: international experience and evidence on effects. *Drug Alcohol Rev* 2009; **28**(4): 426-35.
101402. Scholes-Balog KE, Heerde JA, Hemphill SA. Alcohol warning labels: unlikely to affect alcohol-related beliefs and behaviours in adolescents. *Aust N Z J Public Health* 2012; **36**(6): 524-9.
102403. Tam TW, Greenfield TK. Do Alcohol Warning Labels Influence Men's and Women's Attempts to Deter Others from Driving When Intoxicated? *Hum Factors Ergon Manuf* 2010; **20**(6): 538-46.
103404. Coomber K, Martino F, Barbour IR, Mayshak R, Miller PG. Do consumers 'Get the facts'? A survey of alcohol warning label recognition in Australia. *BMC Public Health* 2015; **15**: 816.
104405. Petticrew M, Douglas N, Knai C, Durand MA, Eastmure E, Mays N. Health information on alcoholic beverage containers: has the alcohol industry's pledge in England to improve labelling been met? *Addiction* 2016; **111**(1): 51-5.
105406. Wagenaar AC, Salois MJ, Komro KA. Effects of beverage alcohol price and tax levels on drinking: a meta-analysis of 1003 estimates from 112 studies. *Addiction* 2009; **104**(2): 179-90.
106407. Stockwell T, Zhao J, Giesbrecht N, Macdonald S, Thomas G, Wettlaufer A. The raising of minimum alcohol prices in Saskatchewan, Canada: impacts on consumption and implications for public health. *Am J Public Health* 2012; **102**(12): e103-10.
107. [Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *J Clin Oncol* 2023; **41**\(17\): 3116-21.](#)
108408. [DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. *J Clin Oncol* 2019; **37**\(19\): 1629-37.](#)
109. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J Natl Cancer Inst* 2007; **99**(4): 283-90.
109. ~~Cuzick J, Sestak I~~, 110. [Cuzick J, Sestak I, Cawthorn S, et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol* 2015; **16**\(1\): 67-75.](#)
111. [Cuzick J, Sestak I](#), 110. ~~Cuzick J, Sestak I~~, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *The Lancet* 2020; **395**(10218): 117-22.
112444. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011; **364**(25): 2381-91.
113442. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; **97**(22): 1652-62.
113. ~~DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. *J Clin Oncol* 2019; **37**(19): 1629-37.~~
114. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *Journal of Clinical Oncology*; **0**(0): JCO.22.02900.

115. Visvanathan K, Fabian CJ, Bantug E, et al. Use of Endocrine Therapy for Breast Cancer Risk Reduction: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2019; **37**(33): 3152-65.
116. Paluch-Shimon S, Cardoso F, Sessa C, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 2016; **27**(suppl 5): v103-v10.
117. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Recurrence in Breast Noninvasive Neoplasia: A 10-Year Follow-Up of TAM-01 Study. *J Clin Oncol* 2023: JCO2202900.
118. [Cuzick J, Chu K, Keevil B, et al. Effect of baseline oestradiol serum concentration on the efficacy of anastrozole for preventing breast cancer in postmenopausal women at high risk: a case-control study of the IBIS-II prevention trial. *The Lancet Oncology* 2023.](#)
119. Nolan E, Vaillant F, Branstetter D, et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. *Nat Med* 2016; **22**(8): 933-9.
120. Bhulani N, Wood M, Tsai J, et al. A phase 3 study to determine the breast cancer risk reducing effect of denosumab in women carrying a germline BRCA1 mutation (BRCA-P Study). *Journal of Clinical Oncology* 2022; **40**(16_suppl): TPS10616-TPS.
121. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst Rev* 2018; **4**(4): Cd002748.
122. Lacaze PA, Tiller J, Winship I. Population DNA screening for medically actionable disease risk in adults. *Med J Aust* 2022; **216**(6): 278-80.
123. Jackson L, Weedon M, Harrison J, et al. Influence of family history on penetrance of hereditary cancers in a population setting. *medRxiv* 2022: 2022.07.08.22277415.
124. Esserman LJ, Anton-Culver H, Borowsky A, et al. The WISDOM Study: breaking the deadlock in the breast cancer screening debate. *npj Breast Cancer* 2017; **3**(1): 34.
125. Sergeant JC, Warwick J, Evans DG, et al. Volumetric and area-based breast density measurement in the predicting risk of cancer at screening (PROCAS) study. Breast Imaging: 11th International Workshop, IWDM 2012, Philadelphia, PA, USA, July 8-11, 2012 Proceedings 11; 2012: Springer; 2012. p. 228-35.
126. Renehan AG, Pegington M, Harvie MN, et al. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS Study (United Kingdom). *British journal of cancer* 2020; **122**(10): 1552-61.
127. Brentnall AR, Harkness EF, Astley SM, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. *Breast Cancer Research* 2015; **17**(1): 1-10.
128. Velentzis LS, Freeman V, Campbell D, et al. Breast Cancer Risk Assessment Tools for Stratifying Women into Risk Groups: A Systematic Review. *Cancers (Basel)* 2023; **15**(4).
129. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 2004; **91**(8): 1580-90.
130. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med* 2004; **23**(7): 1111-30.
131. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol* 2019; **20**(4): 504-17.
132. Banegas MP, John EM, Slattery ML, et al. Projecting Individualized Absolute Invasive Breast Cancer Risk in US Hispanic Women. *J Natl Cancer Inst* 2017; **109**(2).
133. Matsuno RK, Costantino JP, Ziegler RG, et al. Projecting individualized absolute invasive breast cancer risk in Asian and Pacific Islander American women. *J Natl Cancer Inst* 2011; **103**(12): 951-61.
134. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst* 2007; **99**(23): 1782-92.
135. Park B, Ma SH, Shin A, et al. Korean risk assessment model for breast cancer risk prediction. *PLoS One* 2013; **8**(10): e76736.

136135. Wang S, Ogundiran T, Ademola A, et al. Development of a Breast Cancer Risk Prediction Model for Women in Nigeria. *Cancer Epidemiol Biomarkers Prev* 2018; **27**(6): 636-43.
137136. Palmer JR, Zippoli G, Bertrand KA, et al. A Validated Risk Prediction Model for Breast Cancer in US Black Women. *J Clin Oncol* 2021; **39**(34): 3866-77.
138137. Han Y, Lv J, Yu C, et al. Development and external validation of a breast cancer absolute risk prediction model in Chinese population. *Breast Cancer Res* 2021; **23**(1): 62.
139138. Gallegos-Carrillo K, Krug-Llamas E, Doubova SV, Cervantes-Ocampo M, Vargas-Sánchez HR, Duque-Molina C. [PREVENIMSS: a brief overview of its 20 years, challenges and opportunities]. *Rev Med Inst Mex Seguro Soc* 2022; **60**(Suppl 2): 134-41.
140139. Hughes E, Wagner S, Pruss D, et al. Development and Validation of a Breast Cancer Polygenic Risk Score on the Basis of Genetic Ancestry Composition. *JCO Precis Oncol* 2022; **6**: e2200084.
141140. Eriksson M, Czene K, Vachon C, Conant EF, Hall P. Long-Term Performance of an Image-Based Short-Term Risk Model for Breast Cancer. *J Clin Oncol* 2023: Jco2201564.
142141. Lehman CD, Mercaldo S, Lamb LR, et al. Deep Learning vs Traditional Breast Cancer Risk Models to Support Risk-Based Mammography Screening. *J Natl Cancer Inst* 2022; **114**(10): 1355-63.
143142. Yala A, Mikhael PG, Strand F, et al. Multi-Institutional Validation of a Mammography-Based Breast Cancer Risk Model. *J Clin Oncol* 2022; **40**(16): 1732-40.
144143. Omoleye OJ, Woodard AE, Howard FM, et al. External Evaluation of a Mammography-based Deep Learning Model for Predicting Breast Cancer in an Ethnically Diverse Population. *Radiology: Artificial Intelligence* 2023; **0**(ja): e220299.
145144. Arasu VA, Habel LA, Achacoso NS, et al. Comparison of Mammography Artificial Intelligence Algorithms for 5-year Breast Cancer Risk Prediction. *medRxiv* 2022: 2022.01.05.22268746.
146145. Phillips KA, Liao Y, Milne RL, et al. Accuracy of Risk Estimates from the iPrevent Breast Cancer Risk Assessment and Management Tool. *JNCI Cancer Spectr* 2019; **3**(4): pkz066.
147146. iPrevent. 2023. <https://www.petermac.org/iprevent> (accessed 22 August 2023).
148147. Macdonald C, Saunders CM, Keogh LA, et al. Breast Cancer Chemoprevention: Use and Views of Australian Women and Their Clinicians. *Cancer Prev Res (Phila)* 2021; **14**(1): 131-44.
149148. Bellhouse S, Hawkes RE, Howell SJ, Gorman L, French DP. Breast Cancer Risk Assessment and Primary Prevention Advice in Primary Care: A Systematic Review of Provider Attitudes and Routine Behaviours. *Cancers (Basel)* 2021; **13**(16).
150149. World Health Organisation, International Agency for Research on Cancer (IARC). Global Cancer Observatory. 2022. <https://gco.iarc.fr/> (accessed 1 Nov 2022 2022).
151150. World Health Organisation, UNICEF. Global Breastfeeding Collective 2022 2022. <https://www.globalbreastfeedingcollective.org/global-breastfeeding-scorecard>.
152151. World Health Organisation. The Global Health Observatory. 2022. <https://www.who.int/data/gho> (accessed 1 Nov 2022 2022).
153152. Young A, Bu W, Jiang W, et al. Targeting the Pro-survival Protein BCL-2 to Prevent Breast Cancer. *Cancer Prev Res (Phila)* 2022; **15**(1): 3-10.
154153. Slepicka PF, Cyrill SL, Dos Santos CO. Pregnancy and Breast Cancer: Pathways to Understand Risk and Prevention. *Trends Mol Med* 2019; **25**(10): 866-81.
155154. Santucci-Pereira J, George C, Armiss D, et al. Mimicking pregnancy as a strategy for breast cancer prevention. *Breast Cancer Manag* 2013; **2**(4): 283-94.
156155. Disis ML, Cecil DL. Breast cancer vaccines for treatment and prevention. *Breast Cancer Res Treat* 2022; **191**(3): 481-9.
157156. Andre F, Filleron T, Kamal M, et al. Genomics to select treatment for patients with metastatic breast cancer. 2022; **610**(7931): 348.
158157. Veninga V, Voest EE. Tumor organoids: Opportunities and challenges to guide precision medicine. *Cancer Cell* 2021; **39**(9): 1190-201.

159158. Mou H, Kennedy Z, Anderson DG, Yin H, Xue W. Precision cancer mouse models through genome editing with CRISPR-Cas9. *Genome Med* 2015; **7**: 53.
160159. Smith I. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial. *Lancet Oncol* 2020; **21**: 1443–54.
161160. A study looking at personalised treatment for early HER2 positive breast cancer (HER2-RADiCAL). 2022. <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-personalised-treatment-for-early-her2-positive-breast-cancer-her2-radical> (accessed 2 May 2023).
162161. Pembrolizumab vs. Observation in People With Triple-negative Breast Cancer Who Had a Pathologic Complete Response After Chemotherapy Plus Pembrolizumab. 2023. <https://clinicaltrials.gov/ct2/show/NCT05812807> (accessed 2 May 2023).
163162. Fisher B, Anderson S, Bryant J. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347**(16): 1233–41.
164163. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347**(16): 1227–32.
165164. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. *Eur J Cancer* 2000; **36**(15): 1938–43.
166165. Kouwenberg CAE, de Ligt KM, Kranenburg LW, et al. Long-Term Health-Related Quality of Life after Four Common Surgical Treatment Options for Breast Cancer and the Effect of Complications: A Retrospective Patient-Reported Survey among 1871 Patients. *Plast Reconstr Surg* 2020; **146**(1): 1–13.
167166. Witmer TJK, Kouwenberg CAE, Bargon CA. Comparing costs of standard Breast-Conserving Surgery to Oncoplastic Breast-Conserving Surgery and Mastectomy with Immediate two-stage Implant-Based Breast Reconstruction. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS* 2022.
168167. Abdel-Wahab M, Gondhowiardjo SS, Rosa AA, et al. Global Radiotherapy: Current Status and Future Directions-White Paper. *JCO Glob Oncol* 2021; **7**: 827–42.
169168. Earl H, Hiller L, Vallier AL, et al. Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT. *Health Technol Assess* 2020; **24**(40): 1–190.
170169. Kirwan CC, Coles CE, Bliss J, Group PPW, Group PPW. It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence. *Clin Oncol (R Coll Radiol)* 2016; **28**(9): 594–6.
171170. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSound). *Breast* 2012; **21**(5): 678–81.
172171. Fine RE, Gilmore RC, Dietz JR, et al. Cryoablation Without Excision for Low-Risk Early-Stage Breast Cancer: 3-Year Interim Analysis of Ipsilateral Breast Tumor Recurrence in the ICE3 Trial. *Ann Surg Oncol* 2021; **28**(10): 5525–34.
173172. Morgan J, Potter S, Sharma N, et al. The SMALL Trial: A Big Change for Small Breast Cancers. *Clin Oncol (R Coll Radiol)* 2019; **31**(9): 659–63.
174173. Morrow M, Khan AJ. Locoregional Management After Neoadjuvant Chemotherapy. *J Clin Oncol* 2020; **38**(20): 2281–9.
175174. Taylor C, McGale P, Probert J, et al. Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993–2015: population based observational cohort study. *Bmj* 2023; **381**: e074684.

176175. Pilleron S, Sarfati D, Janssen-Heijnen M, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. *Int J Cancer* 2019; **144**(1): 49-58.
177176. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer* 2013; **108**(11): 2205-40.
178177. Larsson S, Clawson J, Howard R. Value-Based Health Care at an Inflection Point: A Global Agenda for the Next Decade. *Catalyst non-issue content* 2023; **4**(1).
179178. Fayanju OM. Value-Based Breast Cancer Care: A Multidisciplinary Approach for Defining Patient-Centered Outcomes. *Ann Surg Oncol* 2016; **23**: 2385-90.
180179. Egdom LSE. Implementation of Value Based Breast Cancer Care. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2019; **45**: 1163-70.
181. Porter ME. What is value in health care? *N Engl J Med* 2010; **363**(26): 2477-81.
182. Teisberg E, Wallace S, O'Hara S. Defining and Implementing Value-Based Health Care: A Strategic Framework. *Acad Med* 2020; **95**(5): 682-5.
183. Beauchamp A. Systematic development and implementation of interventions to Optimize Health Literacy and Access (Ophelia). *BMC Public Health* 2017; **17**: 230.
184. Beauchamp A. Distribution of health literacy strengths and weaknesses across socio-demographic groups: a cross-sectional survey using the Health Literacy Questionnaire (HLQ). *BMC Public Health* 2015; **15**: 678.
185180. Garberis IJ. 11240 Prediction of distant relapse in patients with invasive breast cancer from deep learning models applied to digital pathology slides. *Ann Oncol* 2021; **32**: 921.
186181. Torres FS. End-to-End Non-Small-Cell Lung Cancer Prognostication Using Deep Learning Applied to Pretreatment Computed Tomography. *JCO Clin Cancer Inform* 2021; **1141-1150**.
187182. Meglio A. Dynamics of Long-Term Patient-Reported Quality of Life and Health Behaviors After Adjuvant Breast Cancer Chemotherapy. *JCO* 2022; **40**: 3190-204.
188183. Bayoumy K. Smart wearable devices in cardiovascular care: where we are and how to move forward. *Nat Rev Cardiol* 2021; **18**: 581-99.
189184. Gresham G. Wearable activity monitors to assess performance status and predict clinical outcomes in advanced cancer patients. *Npj Digit Med* 2018; **1**: 1-8.
190185. Hasnain Z. Quantified Kinematics to Evaluate Patient Chemotherapy Risks in Clinic. *JCO Clin Cancer Inform* 2020; **583-601**.
191186. Ward WH. Feasibility of Fitness Tracker Usage to Assess Activity Level and Toxicities in Patients With Colorectal Cancer. *JCO Clin Cancer Inform* 2021; **125-133**.
192187. Smuck M, Odonkor CA, Wilt JK, Schmidt N, Swiernik MA. The emerging clinical role of wearables: factors for successful implementation in healthcare. *NPJ Digit Med* 2021; **4**: 45.
188. Beauchamp A. Systematic development and implementation of interventions to Optimize Health Literacy and Access (Ophelia). *BMC Public Health* 2017; **17**: 230.
189. Beauchamp A. Distribution of health literacy strengths and weaknesses across socio-demographic groups: a cross-sectional survey using the Health Literacy Questionnaire (HLQ). *BMC Public Health* 2015; **15**: 678.
193190. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. *Nat Med* 2022; **28**: 1773-84.
194191. 15. ISRCTN - ISRCTN81408940: Tailoring treatment for HER2-positive early breast cancer.
195192. Knudsen KE, Willman C, Winn R. Optimizing the Use of Telemedicine in Oncology Care: Postpandemic Opportunities. *Clinical Cancer Research* 2021; **27**: 933-6.
193. Wang C, Lee C, Shin H. Digital therapeutics from bench to bedside. *npj Digit. Med* 2023; **6**: 1-10.
194. Vardas PE, Asselbergs FW, Smeden M, Friedman P. The year in cardiovascular medicine 2021: digital health and innovation. *European Heart Journal* 2022; **43**: 271-9.

195. Zwack CC. The evolution of digital health technologies in cardiovascular disease research. *npj Digit. Med* 2023; **6**: 1–11.
196. Perez MV. Large Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *New England Journal of Medicine* 2019; **381**: 1909–17.
197. Bizot A. Multicenter evaluation of breast cancer patients' satisfaction and experience with oncology telemedicine visits during the COVID-19 pandemic. *Br J Cancer* 2021; **125**: 1486–93.
196198. Cadili L. The Breast Cancer Patient Experience of Telemedicine During COVID-19. *Ann Surg Oncol* 2022; **29**: 2244–52.
197199. Curigliano G. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Annals of Oncology* 2020; **31**: 1320–35.
198200. Dietz JR. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat* 2020; **181**: 487–97.
199201. Azambuja E. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. *ESMO Open* 2020; **5**, e000793.
200202. Molen DR. The impact of the COVID-19 pandemic on perceived access to health care and preferences for health care provision in individuals (being) treated for breast cancer. *Breast Cancer Res Treat* 2021.
201203. Pennell NA. American Society of Clinical Oncology Road to Recovery Report: Learning From the COVID-19 Experience to Improve Clinical Research and Cancer Care. *J Clin Oncol* 2021; **39**: 155–69.
202204. Johnson BA. The New Normal? Patient Satisfaction and Usability of Telemedicine in Breast Cancer Care. *Ann Surg Oncol* 2021; **28**: 5668–76.
203205. Meneses AdFP, Pimentel FF, Cruz JPF, Candido Dos Reis FJ. Experiences of Women With Breast Cancer Using Telehealth: A Qualitative Systematic Review. *Clin Breast Cancer* 2023; **23**: 101–7.
204206. Calip GS. Telemedicine use among patients with metastatic breast cancer during the COVID-19 pandemic: Differences by race, age, and region. *Pharmacoepidemiol Drug Saf* 2023; **32**: 66–72.
205207. Uemoto Y. Efficacy of Telemedicine Using Videoconferencing Systems in Outpatient Care for Patients With Cancer: A Systematic Review and Meta-Analysis. *JCO Clin Cancer Inform* 2022; **6**: 2200084.
206208. Miziara RA. Teleoncology Orientation of Low-Income Breast Cancer Patients during the COVID-19 Pandemic: Feasibility and Patient Satisfaction. *Rev Bras Ginecol Obstet* 2021; **43**: 840–6.
207209. Clinical outcomes in patients with solid tumors living in rural and urban areas followed via telemedicine: experience in a highly complex latin american hospital | BMC Cancer | Full Text.
208210. Kunkler IH, Prescott RJ, Lee RJ, et al. TELEMAM: a cluster randomised trial to assess the use of telemedicine in multi-disciplinary breast cancer decision making. *Eur J Cancer* 2007; **43**(17): 2506-14.
209211. Beaver K. Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. *BMJ* 2009; **338**: 3147.
210212. Stavrou E. Breast Medical Oncologists' Perspectives of Telemedicine for Breast Cancer Care: A Survey Study. *JCO Oncol Pract* 2022; **18**: 1447– 53.
211213. Malek Pascha VA, Sun L, Gilardino R, Legood R. Telemammography for breast cancer screening: a cost-effective approach in Argentina. *BMJ Health Care Inform* 2021; **28**: 100351.
212214. Johnston K. From the technology came the idea': safe implementation and operation of a high quality teleradiology model increasing access to timely breast cancer assessment services for women in rural Australia. *BMC Health Serv Res* 2020; **20**: 1103.

- [213245](#). Krzyzanowska MK. Remote, proactive, telephone based management of toxicity in outpatients during adjuvant or neoadjuvant chemotherapy for early stage breast cancer: pragmatic, cluster randomised trial. *BMJ* 2021; **375**: 066588.
- [214246](#). Mir O. Intervention combining nurse navigators (NNs) and a mobile application versus standard of care (SOC) in cancer patients (pts) treated with oral anticancer agents (OAA): Results of CapRI, a single-center, randomized phase III trial. *JCO* 2020; **38**: 2000–.
- [215247](#). Absolom K. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. *JCO* 2021; **39**: 734–47.
- [216248](#). Basch E. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. *J Clin Oncol* 2016; **34**: 557–65.
- [217249](#). Basch E. Effect of Electronic Symptom Monitoring on Patient-Reported Outcomes Among Patients With Metastatic Cancer: A Randomized Clinical Trial. *JAMA* 2022; **327**: 2413–22.
- [218229](#). Maguire R. Real time remote symptom monitoring during chemotherapy for cancer: European multicentre randomised controlled trial (eSMART). *BMJ* 2021; **374**: 1647.
- [219](#). Harbeck N, Fasching PA, Wuerstlein R, et al. Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HR+ HER2- metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial. *Ann Oncol* 2023; **34**(8): 660-9.
- [220224](#). Maio M. The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. *Ann Oncol* 2022; **33**: 878–92.
- [221222](#). Patt D. Implementation of Electronic Patient-Reported Outcomes for Symptom Monitoring in a Large Multisite Community Oncology Practice: Dancing the Texas Two-Step Through a Pandemic. *JCO Clin Cancer Inform* 2021; **5**: 615–21.
- [222223](#). Alfano CM, Oeffinger K, Sanft T, Tortorella B. Engaging TEAM Medicine in Patient Care: Redefining Cancer Survivorship From Diagnosis: American Society of Clinical Oncology Educational Book; 2022.
- [223224](#). Chan RJ. The efficacy, challenges, and facilitators of telemedicine in post-treatment cancer survivorship care: an overview of systematic reviews. *Ann Oncol* 2021; **32**: 1552–70.
- [224225](#). Singleton AC. Electronic Health Interventions for Patients With Breast Cancer: Systematic Review and Meta-Analyses. *JCO* 2022; **40**: 2257–70.
- [225226](#). Abrahams HJG. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: A randomized controlled trial. *Cancer* 2017; **123**: 3825–34.
- [226227](#). Zachariae R. Internet-Delivered Cognitive-Behavioral Therapy for Insomnia in Breast Cancer Survivors: A Randomized Controlled Trial. *JNCI: Journal of the National Cancer Institute* 2018; **110**: 880–7.
- [227228](#). Akechi T. Smartphone Psychotherapy Reduces Fear of Cancer Recurrence Among Breast Cancer Survivors: A Fully Decentralized Randomized Controlled Clinical Trial (J-SUPPORT 1703 Study). *JCO* 2023; **41**: 1069–78.
- [228229](#). Compen F. Face-to-Face and Internet-Based Mindfulness-Based Cognitive Therapy Compared With Treatment as Usual in Reducing Psychological Distress in Patients With Cancer: A Multicenter Randomized Controlled Trial. *JCO* 2018; **36**: 2413–21.
- [229230](#). Bray VJ. Evaluation of a Web-Based Cognitive Rehabilitation Program in Cancer Survivors Reporting Cognitive Symptoms After Chemotherapy. *JCO* 2017; **35**: 217–25.
- [230231](#). Goodwin PJ. The LISA randomized trial of a weight loss intervention in postmenopausal breast cancer. *NPJ Breast Cancer* 2020; **6**, 6.
- [231232](#). Santa-Maria CA. The Effects of a Remote-based Weight Loss Program on Adipocytokines, Metabolic Markers, and Telomere Length in Breast Cancer Survivors: the POWER-Remote Trial. *Clin Cancer Res* 2020; **26**: 3024–34.

232233. Webb J, Fife-Schaw C, Ogden J. A randomised control trial and cost-consequence analysis to examine the effects of a print-based intervention supported by internet tools on the physical activity of UK cancer survivors. *Public Health* 2019; **171**: 106–15.
233234. Lozano-Lozano M. Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: Randomized controlled trial. *Ann Phys Rehabil Med* 2020; **63**: 316–24.
234235. Abernethy A. The Promise of Digital Health: Then, Now, and the Future. *NAM Perspect* 2022; **10** 31478 202206.
235236. Leach CR. Cancer health self-efficacy improvement in a randomized controlled trial. *Cancer* 2022; **128**: 597–605.
236237. Cheikh-Moussa K, Mira JJ, Orozco-Beltran D. Improving Engagement Among Patients With Chronic Cardiometabolic Conditions Using mHealth. *Critical Review of Reviews JMIR Mhealth Uhealth* 2020; **8**, e15446.
237238. Atasoy H, Greenwood BN, McCullough JS. The Digitization of Patient Care: A Review of the Effects of Electronic Health Records on Health Care Quality and Utilization. *Annual Review of Public Health* 2019; **40**: 487–500.
238239. Hammer RD. Digital Tumor Board Solutions Have Significant Impact on Case Preparation. *JCO Clinical Cancer Informatics* 2020; **757–768**.
239240. Nobori A. Electronic Health Record–Integrated Tumor Board Application to Save Preparation Time and Reduce Errors. *JCO Clinical Cancer Informatics* 2022; **e2100142**.
240241. Bayard S, Fasano G, Tamimi RM, Oh PS. Leveraging Electronic Health Records to Address Breast Cancer Disparities. *Curr Breast Cancer Rep* 2022; **14**: 199–204.
241242. Wardley A. Flexible care in breast cancer. *ESMO Open* 2021; **6**: 100007.
242243. Arora S, Ryals C, Rodriguez JA, Byers E, Clewett E. Leveraging Digital Technology to Reduce Cancer Care Inequities: American Society of Clinical Oncology Educational Book; 2022.
243244. Irwin KE. Developing a Virtual Equity Hub: Adapting the Tumor Board Model for Equity in Cancer Care. *The Oncologist* 2022; **27**: 518–24.
244245. Struminger BB, Arora S. Leveraging Telehealth to Improve Health Care Access in Rural America: It Takes More Than Bandwidth. *Ann Intern Med* 2019; **171**: 376–7.
245246. Estes F. Implementation of a virtual multicenter gastrointestinal tumor board to reduce cancer disparities in Argentina. *World J Clin Oncol* 2022; **13**: 423–8.
246247. Fokom Domgue J. Development, Implementation, and Evaluation of a Distance Learning and Telementoring Program for Cervical Cancer Prevention in Cameroon. *JAMA Netw Open* 2022; **5**: 2240801.
247248. Paterson C. The Role of Telehealth During the COVID-19 Pandemic Across the Interdisciplinary Cancer Team: Implications for Practice. *Semin Oncol Nurs* 2020; **36**: 151090.
248249. Kickbusch I. The Lancet and Financial Times Commission on governing health futures 2030: growing up in a digital world. *Lancet* 2021; **398**: 1727–76.
249250. Cykert S. A Multi-faceted Intervention Aimed at Black-White Disparities in the Treatment of Early Stage Cancers: The ACCURE Pragmatic Quality Improvement trial. *Journal of the National Medical Association* 2020; **112**: 468–77.
250251. Gerbasi A. DeepMiCa: Automatic segmentation and classification of breast MlroCalcifications from mammograms. *Comput Methods Programs Biomed* 2023; **235**: 107483.
251252. Zhou W. Improved breast lesion detection in mammogram images using a deep neural network. *Diagn Interv Radiol* 2023.
252253. Koch HW, Larsen M, Bartsch H, Kurz KD, Hofvind S. Artificial intelligence in BreastScreen Norway: a retrospective analysis of a cancer-enriched sample including 1254 breast cancer cases. *Eur Radiol* 2023.
253254. Albusayli R. Artificial intelligence-based digital scores of stromal tumour-infiltrating lymphocytes and tumour-associated stroma predict disease-specific survival in triple-negative breast cancer. *J Pathol* 2023; **260**: 32–42.

254255. Inan OT. Digitizing clinical trials. *npj Digit. Med* 2020; **3**: 1–7.
255256. ~~Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L.~~ Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L. Strategies to Advance Equity in Cancer Clinical Trials. *American Society of Clinical Oncology Educational Book* 2022; (42): 127–37.
256257. Presti D. Factors associated with enrolment in clinical trials among women with early-stage breast cancer. *ESMO Open* 2022; **7**: 100513.
257258. Frérot M. Factors influencing inclusion in digestive cancer clinical trials: A population-based study. *Digestive and Liver Disease* 2015; **47**: 891–6.
258259. Ousseine YM, Bouhnik A-D, Mancini J. Health Literacy and Clinical Trial Participation in French Cancer Patients: A National Survey. *Curr Oncol* 2022; **29**: 3118–29.
259260. Horvat L, Horey D, Romios P, Kis-Rigo J. Cultural competence education for health professionals. *Cochrane Database Syst Rev* 2014; **CD009405**.
260261. Barrett NJ. An Assessment of the Feasibility and Utility of an ACCC-ASCO Implicit Bias Training Program to Enhance Racial and Ethnic Diversity in Cancer Clinical Trials. *JCO Oncology Practice* 2023; **22**(00378).
261262. Guerra C. Increasing Racial and Ethnic Equity, Diversity, and Inclusion in Cancer Treatment Trials: Evaluation of an ASCO-Association of Community Cancer Centers Site Self-Assessment. *JCO Oncology Practice* 2023; **22**(00560).
262263. Beck JT. Artificial Intelligence Tool for Optimizing Eligibility Screening for Clinical Trials in a Large Community Cancer Center. *JCO Clinical Cancer Informatics*; 2020: 50–9.
263. ~~Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L.~~ 264. ~~Guerra CE, Fleury ME, Byatt LP, Lian T, Pierce L.~~ Strategies to Advance Equity in Cancer Clinical Trials: American Society of Clinical Oncology Educational Book; 2022.
264265. Delorme J. Natural Language Processing for Patient Selection in Phase I or II Oncology Clinical Trials. *JCO Clin Cancer Inform* 2021; **5**: 709–18.
265266. Tan RKJ. Digital approaches to enhancing community engagement in clinical trials. *npj Digit Med* 2022; **5**: 1–8.
266. ~~Perez MV. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. *New England Journal of Medicine* 2019; **381**: 1909–17.~~
267. Offodile AC, Seitz AJ, Peterson SK. Digital Health Navigation: An Enabling Infrastructure for Optimizing and Integrating Virtual Care Into Oncology Practice. *JCO Clinical Cancer Informatics* 2021; (5): 1151–4.
268. Lord SJ, Bahlmann K, O'Connell DL, et al. De novo and recurrent metastatic breast cancer - A systematic review of population-level changes in survival since 1995. *EClinicalMedicine* 2022; **44**: 101282.
269. NZ BCF. I'm still here". Insights into living – and dying – with advanced breast cancer in New Zealand. 2018. <https://www.breastcancerfoundation.org.nz/what-we-do/advocacy/abcinnz> (accessed November 2022).
270. Debiase M, Reinert T, Kaliks R, et al. Estimation of Premature Deaths From Lack of Access to Anti-HER2 Therapy for Advanced Breast Cancer in the Brazilian Public Health System. *J Glob Oncol* 2017; **3**(3): 201–7.
271. Li J, Wang S, Wang Y, et al. Disparities of Trastuzumab Use in Resource-Limited or Resource-Abundant Regions and Its Survival Benefit on HER2 Positive Breast Cancer: A Real-World Study from China. *Oncologist* 2017; **22**(11): 1333–8.
272. Blackwell K, Gligorov J, Jacobs I, Twelves C. The Global Need for a Trastuzumab Biosimilar for Patients With HER2-Positive Breast Cancer. *Clin Breast Cancer* 2018; **18**(2): 95–113.
273. Ferrant G, OECD. Unpaid Care Work: The missing link in the analysis of gender gaps in labour outcomes. 2014. https://www.oecd.org/dev/development-gender/Unpaid_care_work.pdf (accessed January 8 2023).

274. Trogon JG, Liu X, Reeder-Hayes KE, Rotter J, Ekwueme DU, Wheeler SB. Productivity costs associated with metastatic breast cancer in younger, midlife, and older women. *Cancer* 2020; **126**(18): 4118-25.
275. Alliance AG. ABC Hub. 2022. <https://www.abcgloballiance.org/abc-hub> (accessed January 8 2023).
276. Matos L, Borges M, Oliveira AT, et al. OR46 THE IMPACT ON PRODUCTIVITY COSTS OF REDUCING UNEMPLOYMENT IN PATIENTS WITH ADVANCED BREAST CANCER: A MODEL ESTIMATION BASED ON A PORTUGUESE NATIONWIDE OBSERVATIONAL STUDY. *The Breast* 2023; **71**: S28.
277. ~~276.~~ Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). *Breast* 2018; **39**: 131-8.
278. ~~277.~~ McKenzie F, Zietsman A, Galukande M, et al. Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer - disparities in outcomes (ABC-DO) study. *Int J Cancer* 2018; **142**(8): 1568-79.
279. Benitez Fuentes JD, Morgan E, de Luna Aguilar A, et al. Global Stage Distribution of Breast Cancer at Diagnosis: A Systematic Review and Meta-Analysis. *JAMA Oncol* 2023.
280. ~~279.~~ McCormack V, McKenzie F, Foerster M, et al. Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *Lancet Glob Health* 2020; **8**(9): e1203-e12.
281. ~~279.~~ Gogia A, Deo SVS, Sharma D, et al. Clinicopathologic Characteristics and Treatment Outcomes of Patients With Up-Front Metastatic Breast Cancer: Single-Center Experience in India. *J Glob Oncol* 2019; **5**: 1-9.
282. ~~280.~~ Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016. *Eur J Cancer* 2020; **129**: 60-70.
283. ~~281.~~ Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**(4): 519-30.
284. ~~282.~~ Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer. *N Engl J Med* 2022; **386**(10): 942-50.
285. ~~283.~~ Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. *Ann Oncol* 2021; **32**(8): 1015-24.
286. ~~284.~~ Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017; **28**(10): 2340-66.
287. ~~285.~~ Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *J Clin Oncol* 2015; **33**(23): 2563-77.
288. Caswell-Jin JL, Sun, L., Munoz, D., Lu, Y., Li, Y., Huang, H., et al. . Contributions of screening, early-stage treatment, and metastatic treatment to breast cancer mortality reduction by molecular subtype in U.S. women, 2000-2017. *J Clin Oncol* 2022; **40**.
289. ~~286.~~ Temel JS, Greer JA, El-Jawahri A, et al. Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer: A Randomized Clinical Trial. *J Clin Oncol* 2017; **35**(8): 834-41.
290. ~~287.~~ Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**(1): 96-112.
291. ~~288.~~ Dans M, Kutner JS, Agarwal R, et al. NCCN Guidelines(R) Insights: Palliative Care, Version 2.2021. *J Natl Compr Canc Netw* 2021; **19**(7): 780-8.
292. ~~289.~~ Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; **31**(12): 1623-49.

- ~~293~~~~290~~. Cavallo J. Understanding oncologists' perceptions about palliative care and the barriers preventing its use. 2022. <https://ascopost.com/issues/may-25-2022/understanding-oncologists-perceptions-about-palliative-care-and-the-barriers-preventing-its-use/> (accessed January 8 2023).
- ~~294~~~~291~~. de Ligt KM, de Rooij, B. H., Hedayati, E., Karsten, M. M., Smaardijk, V. R., Velting, M., Saunders, C., Travado, L., Cardoso, F., Lopez, E., Carney, N., Wengström, Y., Ives, A., Velikova, G., Sousa Fialho, M. D. L., Seidler, Y., Stamm, T. A., Koppert, L. B., van de Poll-Franse, L. V., on behalf of the Innovative Medicines Initiative Health Outcomes Observatory (H2O) consortium. International development of a patient-centered core outcome set for assessing health-related quality of life in metastatic breast cancer patients. *JAMA Oncology* 2022.
- ~~295~~~~292~~. Jencks MK, editor. A view from the front line. 1st edition ed. London; 1995.
- ~~296~~~~293~~. Coalition BBBCA. Striving for better care. 2022. <https://www.breastcancer.org.nz/content/striving-better-care> (accessed January 8 2023).
- ~~297~~~~294~~. Kuper-Hommel MJJ, Little Z, Gautier A. New Zealand experience with implementation of the ESO-ESMO consensus guidelines for advanced breast cancer-report of achievements and lessons learned. *Breast* 2022; **63**: 108-12.
- ~~298~~~~295~~. Jonker L, Fisher SJ. The correlation between National Health Service trusts' clinical trial activity and both mortality rates and care quality commission ratings: a retrospective cross-sectional study. *Public Health* 2018; **157**: 1-6.
- ~~299~~~~296~~. Wells JC, Sharma S, Del Paggio JC, et al. An Analysis of Contemporary Oncology Randomized Clinical Trials From Low/Middle-Income vs High-Income Countries. *JAMA Oncol* 2021; **7**(3): 379-85.
- ~~300~~~~297~~. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Egely S. Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. *Cancer Control* 2016; **23**(4): 327-37.
- ~~301~~~~298~~. Kwiatkowski K, Coe K, Bailar JC, Swanson GM. Inclusion of minorities and women in cancer clinical trials, a decade later: Have we improved? *Cancer* 2013; **119**(16): 2956-63.
- ~~302~~~~299~~. Biganzoli L, Cardoso F, Beishon M, et al. The requirements of a specialist breast centre. *Breast* 2020; **51**: 65-84.
- ~~303~~~~300~~. Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: An update from the EUSOMA working group. *Eur J Cancer* 2017; **86**: 59-81.
- ~~304~~~~301~~. Cardoso F, McCartney, A., Ponti, A., Marotti, L., Vrieling, C., Eniu, A., Sousa, B., Ripamonti, C., Travado, L., Spitz, S., Gustafsson, E., Rubio, I., Biganzoli, L. EUSOMA/ABC Global Alliance quality indicators for metastatic breast cancer care. *Eur J Cancer* 2023; **under submission**.
- ~~305~~~~302~~. Ricci-Cabello I, Vasquez-Mejia A, Canelo-Aybar C, et al. Adherence to breast cancer guidelines is associated with better survival outcomes: a systematic review and meta-analysis of observational studies in EU countries. *BMC Health Serv Res* 2020; **20**(1): 920.
- ~~306~~~~303~~. Hebert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. *J Clin Oncol* 2004; **22**(18): 3685-93.
- ~~307~~~~304~~. Song CV, Yip CH, Mohd Taib NA, et al. Association Between Adherence to Clinical Practice Guidelines for Adjuvant Therapy for Breast Cancer and Survival in a Resource-Limited Setting. *JCO Glob Oncol* 2022; **8**: e2100314.
- ~~308~~~~305~~. Trapani D, Douillard JY, Winer EP, et al. The Global Landscape of Treatment Standards for Breast Cancer. *J Natl Cancer Inst* 2021; **113**(9): 1143-55.
- ~~309~~~~306~~. Fatima. 2023.
- ~~310~~~~307~~. Foerster M, McCormack V, Anderson BO. Treatment guideline concordance, initiation, and abandonment in patients with non-metastatic breast cancer from the African Breast Cancer-Disparities in Outcomes (ABC-DO) cohort in sub-Saharan Africa: a prospective cohort study. *Lancet Oncol* 2022; **23**(6): 729-38.

- 311308.** Bestvina CM, Zullig LL, Yousuf Zafar S. The implications of out-of-pocket cost of cancer treatment in the USA: a critical appraisal of the literature. *Future Oncol* 2014; **10**(14): 2189-99.
- 312309.** Nyblade L, Stockton M, Travasso S, Krishnan S. A qualitative exploration of cervical and breast cancer stigma in Karnataka, India. *BMC Womens Health* 2017; **17**(1): 58.
- 313340.** O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005; **10 Suppl 3**: 20-9.
- 314344.** van Brakel WH, Cataldo J, Grover S, et al. Out of the silos: identifying cross-cutting features of health-related stigma to advance measurement and intervention. *BMC Med* 2019; **17**(1): 13.
- 315342.** Weiss MG, Ramakrishna J, Somma D. Health-related stigma: rethinking concepts and interventions. *Psychol Health Med* 2006; **11**(3): 277-87.
- 316343.** Scambler G. Stigma and disease: changing paradigms. *Lancet* 1998; **352**(9133): 1054-5.
- 317344.** Link BG, Phelan, J. C. Conceptualizing Stigma. *Annu Rev Sociol* 2001; **27**: 363-85.
- 318345.** Pescosolido BA, Martin JK, Lang A, Olafsdottir S. Rethinking theoretical approaches to stigma: a Framework Integrating Normative Influences on Stigma (FINIS). *Soc Sci Med* 2008; **67**(3): 431-40.
- 319346.** Weiss MG. Stigma and the social burden of neglected tropical diseases. *PLoS Negl Trop Dis* 2008; **2**(5): e237.
- 320347.** Heijnders M, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. *Psychol Health Med* 2006; **11**(3): 353-63.
- 321348.** ABC-SG. Project PINK BLUE. 2022. <https://projectpinkblue.org/abc-sg/>.
- 322349.** Alliance MBCG. We're changing the face of breast cancer. 2023. <https://mbcglobalalliance.org/>.
- 323320.** Villarreal-Garza C, Mesa-Chavez F, Lopez-Martinez EA, et al. Gaps in Knowledge and Understanding of Patients With Metastatic Breast Cancer in Mexico. *Cancer control : journal of the Moffitt Cancer Center* 2020; **27**(1): 1073274820920637.
- 324324.** Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**(1): 7-30.
- 325322.** Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**(6): 394-424.
- 326323.** Duggan C, Trapani D, Ilbawi A. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. *Lancet Oncol* 2021; **2021**.
- 327324.** Anderson BO, Cazap E, El Saghir NS. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus. *Lancet Oncol* 2010; **12**(4): 387-98.
- 328325.** Allemani C, Matsuda T, Carlo V. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**(10125): 1023-75.
- 329326.** Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening--viewpoint of the IARC Working Group. *N Engl J Med* 2015; **372**(24): 2353-8.
- 330327.** Harford J, Azavedo E, Fischietto M. Guideline implementation for breast healthcare in low- and middle-income countries: breast healthcare program resource allocation. *Cancer* 2008; **113**(8 Suppl): 2282-96.
- 331328.** Berry DA, Cronin KA, Plevritis SK. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005; **353**(17): 1784-92.

332329. Anderson BO, Ilbawi AM, Fidarova E. The Global Breast Cancer Initiative: a strategic collaboration to strengthen health care for non-communicable diseases. *Lancet Oncol* 2021; **22**(5): 578–81.
333330. Duggan C, Dvaladze A, Rositch AF, et al. The Breast Health Global Initiative 2018 Global Summit on Improving Breast Healthcare Through Resource-Stratified Phased Implementation: Methods and overview. *Cancer* 2020; **126** Suppl 10(Suppl 10): 2339–52.
334331. Shyyan R, Sener SF, Anderson BO. Guideline implementation for breast healthcare in low- and middle-income countries: diagnosis resource allocation. *Cancer* 2008; **113**(8 Suppl): 2257–68.
335332. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet* 1999; **353**(9159): 1119–26.
336333. Bukowski A, Gioia S, Chavarri-Guerra Y. Patient Navigation to Improve Access to Breast Cancer Care in Brazil. *J Glob Oncol* 2017; **3**(5): 433–7.
337334. Gray E. ESMO Open Cancer Horizons. 2021.
338335. van Maaren MC, Rachet B, Sonke GS, et al. Socioeconomic status and its relation with breast cancer recurrence and survival in young women in the Netherlands. *Cancer Epidemiol* 2022; **77**: 102118.
339336. Dasgupta P, Baade PD, Youlden DR, et al. Variations in outcomes by residential location for women with breast cancer: a systematic review. *BMJ Open* 2018; **8**(4): e019050.
340. Goel N, Lubarsky M, Hernandez A, et al. Unmet Social Needs on Breast Cancer Screening Utilization and Stage at Presentation. *JAMA Netw Open* In review.
341337. Tackling NCDs in Kenya: economic evaluation of breast and cervical cancer control interventions in Kenya. Washington, DC: The World Bank; 2022.
342338. Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K. Access to pathology and laboratory medicine services: a crucial gap. *The Lancet* 2018; **391**(10133): 1927–38.
343339. Steakley L. Using the Coca-Cola supplier network to distribute medicines in Africa. 2013. <https://scopeblog.stanford.edu/2013/04/26/using-the-coca-cola-supplier-network-to-distribute-medicines-in-africa/> (accessed 15 September 2023).
344340. Mugabe M, Andrici J, Ho K. Comparing the Gene Xpert Breast Cancer RUO mRNA Assay with ER and HER2 Immunohistochemistry (IHC) for Rapid Biomarker Analysis. *Mod Pathol* 2017; **30**(S2).
345341. Wu NC, Wong W, Ho KE. Comparison of central laboratory assessments of ER, PR, HER2, and Ki67 by IHC/FISH and the corresponding mRNAs (ESR1, PGR, ERBB2, and MKi67) by RT-qPCR on an automated, broadly deployed diagnostic platform. *Breast Cancer Res Treat* 2018; **172**(2): 327–38.
346342. Kimambo A, Ng D. Validation of the GeneXpert Breast Cancer STRAT4 Assay for Rapid Analysis of Breast Cancer Biomarker Status From Fine-Needle Aspiration Biopsies in Tanzania (GX-BCB): Preliminary Results. *American Journal of Clinical Pathology* 2018; **150**(suppl_1).
347343. Denny L, Sanjose S, Mutebi M. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *The Lancet* 2017; **389**(10071): 861–70.
348344. Black E, Richmond R. Improving early detection of breast cancer in sub-Saharan Africa: why mammography may not be the way forward. *Global Health* 2019; **15**(3).
349345. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. *World J Clin Oncol* 2015; **6**(6): 281–90.
350346. Symmans WF, Peintinger F, Hatzis C. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007; **25**(28): 4414–22.
351347. Symmans WF, Yau C, Chen YY. Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for High-risk Breast Cancer: An Analysis of Data From the I-SPY2 Randomized Clinical Trial. *JAMA Oncol* 2021; **7**(11): 1654–63.

352348. Yau C, Osdoit M, Noordaa M. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol* 2022; **23**(1): 149–60.
349. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts H. Artificial intelligence in radiology. *Nat Rev Cancer* 2018; **18**(8): 500–10.
350. Jackson CR, Sriharan A, Vaickus LJ. A machine learning algorithm for simulating immunohistochemistry: development of SOX10 virtual IHC and evaluation on primarily melanocytic neoplasms. *Mod Pathol* 2020; **33**(9): 1638–48.
351. Conde-Sousa E, Vale J, Feng M, et al. HEROHE Challenge: Predicting HER2 Status in Breast Cancer from Hematoxylin Eosin Whole Slide Imaging. *J Imaging* 2022; **8**(8).
352. Lu MY, Chen TY, Williamson DFK, et al. AI-based pathology predicts origins for cancers of unknown primary. *Nature* 2021; **594**(7861): 106–10.
353. Miller ME, Patil N, Li P. Hospital System Adoption of Magnetic Seeds for Wireless Breast and Lymph Node Localization. *Ann Surg Oncol* 2021; **28**(6): 3223–9.
354. Serventi F, Musyoka A, Saunders J. NOHA: A Promising Biomarker for Determining Estrogen Receptor Status Among Patients With Breast Cancer in Resource-Constrained Settings. *JCO Glob Oncol* 2022; **8**:e2200192.
355. Banys-Paluchowski M, Fehm TN, Grimm-Glang D, Rody A, Krawczyk N. Liquid Biopsy in Metastatic Breast Cancer: Current Role of Circulating Tumor Cells and Circulating Tumor DNA. *Oncol Res Treat* 2022; **45**(1–2): 4–11.
356. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. *New England Journal of Medicine* 2019; **380**(20): 1929–40.
357. Fleming KA, Naidoo M, Wilson M. An Essential Pathology Package for Low- and Middle-Income Countries. *American Journal of Clinical Pathology* 2017; **147**(1): 15–32.
358. Wu G, Zaman MH. Low-cost tools for diagnosing and monitoring HIV infection in low-resource settings. *Bull World Health Organ* 2012; **90**(12): 914–20.
359. Letter Q. Quality Glossary of Terms, Acronyms & Definitions with Letter Q | ASQ.
360. Proctor E, Silmere H, Raghavan R. Outcomes for Implementation Research: Conceptual Distinctions, Measurement Challenges, and Research Agenda. *Adm Policy Ment Health* 2011; **38**(2): 65–76.
361. Autier P, Hery C, Haukka J, Boniol M, Byrnes G. Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. *J Clin Oncol* 2009; **27**(35): 5919–23.
362. Chávarri-Guerra Y, Villarreal-Garza C, Liedke PE, et al. Breast cancer in Mexico: a growing challenge to health and the health system. *Lancet Oncol* 2012; **13**(8): e335–43.
363. Tamez-Salazar J, Mireles-Aguilar T, de la Garza-Ramos C, et al. Prioritization of Patients with Abnormal Breast Findings in the Alerta Rosa Navigation Program to Reduce Diagnostic Delays. *Oncologist* 2020; **25**(12): 1047–54.
364. Perez-Bustos AH, Orozco-Urdaneta M, Erazo R, et al. A patient navigation initiative to improve access to breast cancer care in Cali, Colombia. *Cancer Rep (Hoboken)* 2022; **5**(9): e1564.
365. Imkampe A, Bendall S, Chianakwalam C. Two-week rule: Has prioritisation of breast referrals by general practitioners improved? *The Breast* 2006; **15**(5): 654–8.
366. Cortes J, Perez-García JM, Llombart-Cussac A, et al. Enhancing global access to cancer medicines. *CA Cancer J Clin* 2020; **70**(2): 105–24.
367. Sleeman KE, Gomes B, Brito M, Shamieh O, Harding R. The burden of serious health-related suffering among cancer decedents: Global projections study to 2060. *Palliative medicine* 2021; **35**(1): 231–5.
367. IQVIA/MIDAS. Geographical breakdown (by main markets) of sales of new medicines launched during the period 2016-2021. . 2022. <https://www.efpia.eu/publications/data-center/the-pharma-industry-in-figures-economy/geographical-breakdown-of-sales-of-new-medicines> (accessed 13 December 2023).

368. Miljkovic MD, Tuia JE, Olivier T, Haslam A, Prasad V. Association Between US Drug Price and Measures of Efficacy for Oncology Drugs Approved by the US Food and Drug Administration From 2015 to 2020. *JAMA Intern Med* 2022; **182**(12): 1319-20.
369. Tay-Teo K, Ilbawi A, Hill SR. Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies. *JAMA Netw Open* 2019; **2**(1): e186875.
367370. CRUK. Outcome-based payment for cancer drugs. 2023. <https://www.cancerresearchuk.org/about-us/we-develop-policy/our-policy-on-access-to-cancer-treatments/outcome-based-payment-for-cancer-drugs>. (accessed 13 December 2023).
371. Sleeman KE, Gomes B, Brito M, Shamieh O, Harding R. The burden of serious health-related suffering among cancer decedents: Global projections study to 2060. *Palliative medicine* 2021; **35**(1): 231–5.
372. Hubinette M, Dobson S, Scott I, Sherbino J. Health advocacy. *Med Teach* 2017; **39**(2): 128-35.
373. Maxwell GL. The state of advocacy in cancer. *Gynecol Oncol* 2015; **139**(3): 573-9.
374. Janamian T, Greco M, Cosgriff D, Baker L, Dawda P. Activating people to partner in health and self-care: use of the Patient Activation Measure. *Med J Aust* 2022; **10**(Suppl 10).
375368. Morhason-Bello IO, Odedina F, Rebbeck TR, et al. Challenges and opportunities in cancer control in Africa: a perspective from the African Organisation for Research and Training in Cancer. *Lancet Oncol* 2013.
376369. Odedina FT, Asante-Shongwe K, Kandusi EJ. The African cancer advocacy consortium: shaping the path for advocacy in Africa. *Infect Agents Cancer* 2013; **8**(Suppl 1): 8.
370. 377Biparva J, Akbar. Global quality of life in breast cancer: systematic review and meta-analysis. *BMJ supportive & palliative care* 2022.
371. Connor S. Global Atlas of Palliative Care. 2021-04-30 2021. <http://www.thewhpca.org/resources/global-atlas-on-end-of-life-care> (accessed 3 January 2023).
378372. Sun H, Lv H, Zeng H, Niu L, Yan M. Distress Thermometer in breast cancer: systematic review and meta-analysis. *BMJ supportive & palliative care* 2022; **12**(3): 245–52.
379373. Chen X, Wu C, Bai D, et al. Health-related quality of life in breast cancer patients in Asia: A meta-analysis and systematic review. *Frontiers in oncology* 2022; **12**: 954179.
380374. Gonzalez L, Bardach A, Palacios A, et al. Health-Related Quality of Life in Patients with Breast Cancer in Latin America and the Caribbean: A Systematic Review and Meta-Analysis. *The oncologist* 2021; **26**(5): 794–806.
381375. Rezagholi P, Abdi K, Barzanji A, et al. Prevalence of depression in Iranian women with breast cancer: a systematic review and meta-analysis. *Przegląd epidemiologiczny* 2022; **76**(1): 29–36.
382376. Leysen L, Lahousse A, Nijs J, et al. Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2019; **27**(12): 4401–33.
383377. Liu L, Wu Y, Cong W, Hu M, Li X, Zhou C. Experience of women with breast cancer undergoing chemotherapy: a systematic review of qualitative research. Quality of life research : an international journal of quality of life aspects of treatment. *care and rehabilitation* 2021; **30**(5): 1249–65.
384378. Roberts F, Andrewes T. Exploring the psychological impacts of a gestational cancer diagnosis on women: a literature review. British journal of nursing: Mark Allen Publishing; 2022.
385379. Fortin J, Leblanc M, Elgbeili G, Cordova MJ, Marin MF, Brunet A. The mental health impacts of receiving a breast cancer diagnosis: A meta-analysis. *British journal of cancer* 2021; **125**(11): 1582–92.
386380. Durosini I, Triberti S, Savioni L, Sebri V, Pravettoni G. The Role of Emotion-Related Abilities in the Quality of Life of Breast Cancer Survivors: A Systematic Review. *International journal of environmental research and public health* 2022; **19**(19): 12704.

387381. Maheu C, Singh M, Tock WL, et al. Fear of Cancer Recurrence, Health Anxiety, Worry, and Uncertainty: A Scoping Review About Their Conceptualization and Measurement Within Breast Cancer Survivorship Research. *Frontiers in psychology* 2021; **12**: 644932.
388382. Lim E, Humphris G. The relationship between fears of cancer recurrence and patient age: A systematic review and meta-analysis. *Cancer reports*. 2020.
389383. Samuel CA, Mbah OM, Elkins W, et al. Calidad de Vida: a systematic review of quality of life in Latino cancer survivors in the USA. *Quality of life research : an international journal of quality of life aspects of treatment. care and rehabilitation* 2020; **29**(10): 2615–30.
390384. Zomkowski K, Souza B, Silva F, Moreira GM, Souza Cunha N, Sperandio FF. Physical symptoms and working performance in female breast cancer survivors: a systematic review. *Disability and rehabilitation* 2018; **40**(13): 1485–93.
391385. Wang K, Yee C, Tam S, et al. Prevalence of pain in patients with breast cancer post-treatment: A systematic review. 2018.
392386. Adler SR, Coulter YZ, Stone K, Glaser J, Duerr M, Enocht S. End-of-Life Concerns and Experiences of Living With Advanced Breast Cancer Among Medically Underserved Women. *Journal of pain and symptom management* 2019; **58**(6): 959–67.
393387. Matsuoka J, Kunitomi T, Nishizaki M, Iwamoto T, Katayama H. Advance care planning in metastatic breast cancer. *Chinese clinical oncology* 2018; **7**(3): 33.
394388. Accordino MK, Wright JD, Vasan S, et al. Association between survival time with metastatic breast cancer and aggressive end-of-life care. *Breast cancer research and treatment* 2017; **166**(2): 549–58.
395389. Roberson PNE, Cortez G, Freeman T, Lloyd J, Tasman J, Woods SB. Relationship quality and psychophysiological distress for underserved breast cancer patients and their caregiver before treatment. *Psycho-oncology* 2022; **31**(11): 1904–12.
396390. Overcash J, Johnston M, Sinnott LT, Williams N. Influence of Patient Functional Status and Depression on Strain in Caregivers. *Clinical journal of oncology nursing* 2022; **26**(4): 406–12.
397391. Dumitra S, Jones V, Rodriguez J, et al. Disparities in managing emotions when facing a diagnosis of breast cancer: Results of screening program of couples distress. *Surgery* 2018; **50039-6060**(17)30861-9.
398392. Selamat Din SH, Nik Jaafar NR, Zakaria H, Mohamed Saini S, Ahmad SN, Midin M. Anxiety Disorders in Family Caregivers of Breast Cancer Patients Receiving Oncologic Treatment in Malaysia. *Asian Pac J Cancer Prev* 2017; **18**(2): 465–71.
399393. Elfgen C, Montagna G, Schmid SM, Bierbauer W, Gütha U. Metastatic Breast Cancer as a Chronic Disease: Evidence-Based Data on a Theoretical Concept. *Breast Care* 2020; **15**: 281–8.
400394. Tang WZ, Yusuf A, Jia K, et al. Correlates of stigma for patients with breast cancer: a systematic review and meta-analysis. *Support Care Cancer* 2022; **31**: 55.
401395. Trusson D, Pilnick A. The Role of Hair Loss in Cancer Identity: Perceptions of Chemotherapy-Induced Alopecia Among Women Treated for Early-Stage Breast Cancer or Ductal Carcinoma in Situ. *Cancer Nurs* 2017; **40**: 9–16.
402396. Melhem SJ, Nabhani-Gebara S, Kayyali R. Latency of breast cancer stigma during survivorship and its influencing factors: A qualitative study. *Front Oncol* 2023; **14**: 13.
403397. Lee MC, Bhati RS, Rottenthaler EE, Reagan AM, Karver SB, Reich RR. Therapy choices and quality of life in young breast cancer survivors: a short-term follow-up. *Am J Surg* 2013; **206**(5): 625–31.
404398. Silvestris E, Dellina M, Cafforio P, Paradiso AV, Cormio G, D’Oronzo S. Breast cancer: an update on treatment-related infertility. *J Cancer Res Clin Oncol* 2020; **146**: 647–57.
405399. Mungrue K, Ramdath J, Ali S, et al. Challenges to the control of breast cancer in a small developing country. *Breast cancer : basic and clinical research* 2014; **8**: 7–13.
406400. Pace LE, Dusengimana JM, Hategekimana V, et al. Benign and Malignant Breast Disease at Rwanda’s First Public Cancer Referral Center. *The oncologist* 2016; **21**(5): 571–5.

- ~~407401.~~ Pace LE, Mpunga T, Hategekimana V, et al. Delays in Breast Cancer Presentation and Diagnosis at Two Rural Cancer Referral Centers in Rwanda. *The oncologist* 2015; **20**(7): 780–8.
- ~~408402.~~ Tieman JT, Nourian MM, Agbenorku P, et al. Developing a Breast Reconstruction Program in a Resource-Constrained Ghanaian Teaching Hospital: Needs Assessment and Implementation. *Annals of plastic surgery* 2021; **86**(2): 129–31.
- ~~409403.~~ Ortega CCF, Veiga DF, Camargo K, Juliano Y, Sabino Neto M, Ferreira LM. Breast Reconstruction May Improve Work Ability and Productivity After Breast Cancer Surgery. *Annals of plastic surgery* 2018; **81**(4): 398–401.
- ~~410404.~~ Roy N, Villavisanis DF, Taub PJ. Mitigating Financial Toxicity in Breast Cancer From Diagnosis to Treatment and Reconstruction. *Clinical breast cancer* 2023; **23**(1): 32– 6.
- ~~411405.~~ Quincey K, Williamson I, Winstanley S. 'Marginalised malignancies': A qualitative synthesis of men's accounts of living with breast cancer. *Soc Sci Med* 2016; **149**: 17–25.
- ~~412.~~ Bhadelia A, Greaves N, Doubova S, Knaul F. Understanding the Value of Alleviating Health-Related Suffering and Palliative Care Centered in Lived Experience: The SAVE Toolkit. 2023. <https://doi.org/10.21203/rs.3.rs-3716807/v1>.
- ~~413.~~ Doubova S BA, Pérez-Moran D, Martínez-Vega IP, García-Cervantes N, Knaul FM. Dimensions of suffering and the need for palliative care: experiences and expectations of patients living with cancer and diabetes and their caregivers in Mexico – a qualitative study. *BMJ Open* 2023; **13**(12): e075691.
- ~~414406.~~ Essue BM, Oliveira Cd, Bushnik T, et al. The Burden of Health-Related Out-of-Pocket Cancer Costs in Canada: A Case-Control Study Using Linked Data. *Current Oncology* 2022; **29**(7): 4541-57.
- ~~415407.~~ ~~Iragorri N, de Oliveira C, Fitzgerald N, Essue B.~~ Iragorri N, de Oliveira C, Fitzgerald N, Essue B. The Out-of-Pocket Cost Burden of Cancer Care-A Systematic Literature Review. *Curr Oncol* 2021; **28**(2): 1216-48.
- ~~416408.~~ ~~Iragorri N, de Oliveira C, Fitzgerald N, Essue B.~~ Iragorri N, de Oliveira C, Fitzgerald N, Essue B. The Indirect Cost Burden of Cancer Care in Canada: A Systematic Literature Review. *Appl Health Econ Health Policy* 2021; **19**(3): 325-41.
- ~~417409.~~ Essue BM, Laba M, Knaul F, et al. Economic Burden of Chronic Ill Health and Injuries for Households in Low- and Middle-Income Countries. In: Jamison DT, Gelband H, Horton S, et al., eds. *Disease Control Priorities: Improving Health and Reducing Poverty*. Washington (DC): The International Bank for Reconstruction and Development / The World Bank © 2018 International Bank for Reconstruction and Development / The World Bank.; 2017.
- ~~418449.~~ Jan S, Kimman M, Peters SA, Woodward M. Financial catastrophe, treatment discontinuation and death associated with surgically operable cancer in South-East Asia: Results from the ACTION Study. *Surgery* 2015; **157**(6): 971-82.
- ~~419441.~~ Fact Sheet: Breast cancer. World Health Organization. 2021. <https://www.who.int/news-room/fact-sheets/detail/breast-cancer> (accessed 3 January 2023).
- ~~420.~~ Knaul FM. Closing the cancer divide: An equity imperative: Harvard Global Equity Initiative; 2012.
- ~~421442.~~ Tawfik B, Jaffe SA, Mohler L, et al. Developing a survivorship care plan (SCP) delivery process for patients and primary care providers serving poor, rural, and minority patients with cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*; 2021. p. 5021-8.
- ~~422443.~~ Yeoh Z-Y, Jaganathan M, Rajaram N, et al. Feasibility of Patient Navigation to Improve Breast Cancer Care in Malaysia. *Journal of Global Oncology* 2018; **4**(4): 1-13.
- ~~423444.~~ Ghaffari F, Ghahramanian A, Zamanzadeh V, et al. Patient-centred communication for women with breast cancer: Relation to body image perception. *Journal of clinical nursing* 2020; **29**(23-24): 4674-84.

- [424415](#). Gakunga R, Kinyanjui A, Ali Z, et al. Identifying Barriers and Facilitators to Breast Cancer Early Detection and Subsequent Treatment Engagement in Kenya: A Qualitative Approach. *The oncologist*; 2019. p. 1549-56.
- [425416](#). Kathrikolly TR, Nair S, Poobalan AS, Shetty RS, Tripathee S, Mac Lennan SJ. Increasing Engagement for Breast Cancer Screening and Treatment: The "ICANTREAT" Community of Expertise Initiative. *Asian Pac J Cancer Prev* 2020; **21**(12): 3655-9.
- [426417](#). Guerra RL, Castaneda L, de Albuquerque RdCR, et al. Patient Preferences for Breast Cancer Treatment Interventions: A Systematic Review of Discrete Choice Experiments. *The patient* 2019; **12**(6): 559-69.
- [427418](#). Raisa A, Roberto AJ, Love RR, Steiness HLS, Salim R, Krieger JL. Pot Song as a Novel Cancer Communication Intervention: Lessons Learned from Developing, Implementing, and Evaluating a Culturally Grounded Intervention for Breast Cancer Education in Rural Bangladesh. *Journal of cancer education : the official journal of the American Association for Cancer Education* 2021.
- [428419](#). Schliemann D, Htay MNN, Dahlui M, et al. Impact of a mass media campaign on breast cancer symptoms awareness and screening uptake in Malaysia: findings from a quasi-experimental study. *BMJ open*; 2020. p. e036503.
- [429420](#). Odigie VI, Yusufu LMD, Dawotola DA, et al. The mobile phone as a tool in improving cancer care in Nigeria. *Psycho-oncology* 2012; **21**(3): 332-5.
- [430421](#). Gutnik L, Moses A, Stanley C, Tembo T, Lee C, Gopal S. From Community Laywomen to Breast Health Workers: A Pilot Training Model to Implement Clinical Breast Exam Screening in Malawi. *PloS one* 2016; **11**(3): e0151389.
- [431422](#). Zhou Q, Shen J-C, Liu Y-Z, Lin G-Z, Dong H, Li K. Effects of Doctor-patient Communication on Quality of Life among Breast Cancer Patients in Southern China. *Asian Pacific Journal of Cancer Prevention* 2014; **15**(14): 5639-44.
- [432423](#). Noyan MA, Sertoz OO, Elbi H, Kayar R, Yilmaz R. Variables affecting patient satisfaction in breast surgery: a cross-sectional sample of Turkish women with breast cancer. *International journal of psychiatry in medicine*; 2006. p. 299-313.
- [433424](#). Wako Z, Mengistu D, Dinege NG, Asefa T, Wassie M. Adherence to Adjuvant Hormonal Therapy and Associated Factors Among Women with Breast Cancer Attending the Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2019: A Cross-sectional Study. *Breast cancer (Dove Medical Press)* 2021; **13**: 383-92.
- [434425](#). Yap ML, Zubizarreta E, Bray F, Ferlay J, Barton M. Global Access to Radiotherapy Services: Have We Made Progress During the Past Decade? *Journal of global oncology: American Society of Clinical Oncology*; 2016. p. 207-15.
- [435426](#). Agyemang LS, Foster C, McLean C, Fenlon D, Wagland R. The cultural and structural influences that 'hide' information from women diagnosed with breast cancer in Ghana: an ethnography. *BMC women's health*; 2021. p. 364.
- [436427](#). Geng C, Lu G-J, Zhu J, Li Y-Y. Patients' awareness about their own breast cancer characteristics. *World journal of clinical cases*; 2021. p. 7043-52.
- [437428](#). Daniel S, Venkateswaran C, Singh C, Hutchinson A, Johnson MJ. "So, when a woman becomes ill, the total structure of the family is affected, they can't do anything..." Voices from the community on women with breast cancer in India: a qualitative focus group study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*; 2022. p. 951-63.
- [438429](#). Scheel JR, Parker S, Hippe DS, et al. Role of Family Obligation Stress on Ugandan Women's Participation in Preventive Breast Health. *The oncologist*; 2019. p. 624-31.
- [439430](#). Lambert M, Mendenhall E, Kim AW, Cubasch H, Joffe M, Norris SA. Health system experiences of breast cancer survivors in urban South Africa. *Women's health (London, England)*; 2020. p. 1745506520949419.

440431. Brinton L, Figueroa J, Adjei E, et al. Factors contributing to delays in diagnosis of breast cancers in Ghana, West Africa. *Breast cancer research and treatment*; 2017. p. 105-14.
441432. Sajjad S, Gul R, Gowani A, Ali A, Chagani S. Developing the Reliability and Validity of an Urdu Version-Self-Efficacy Scale for Breast Cancer Patients in Pakistan. *Journal of nursing measurement* 2021; **29**(2): 239-53.
442433. Mandrik O, Yaumenenka A, Herrero R, Jonker MF. Population preferences for breast cancer screening policies: Discrete choice experiment in Belarus. *PLoS one* 2019; **14**(11): e0224667.
443434. Whelan T, Levine M, Willan A, et al. Effect of a decision aid on knowledge and treatment decision making for breast cancer surgery: a randomized trial. *JAMA* 2004; **292**(4): 435-41.
444435. Hawley ST, Li Y, An LC, et al. Improving Breast Cancer Surgical Treatment Decision Making: The iCanDecide Randomized Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2018. p. 659-66.
445436. Lyman GH, Greenlee H, Bohlke K, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. *Journal of Clinical Oncology: American Society of Clinical Oncology*; 2018. p. 2647-55.
446437. Hawley ST, Kidwell K, Zahrieh D, et al. STUDY PROTOCOL Improving patient-centered communication in breast cancer: a study protocol for a multilevel intervention of a shared treatment deliberation system (SharES) within the NCI community oncology research program (NCORP) (Alliance A231901CD). 2023.
447438. Wallner LP, Martinez KA, Li Y, et al. Use of Online Communication by Patients With Newly Diagnosed Breast Cancer During the Treatment Decision Process. *JAMA Oncology* 2016; **2**(12): 1654-6.
448439. Liu Y, Malin JL, Diamant AL, Thind A, Maly RC. Adherence to Adjuvant Hormone Therapy in Low-income Women with Breast Cancer: The Role of Provider-Patient Communication \$watermark-text \$watermark-text \$watermark-text. *Breast Cancer Res Treat* 2013; **137**(3): 829-36.
449440. Kerr J, Engel J, Schlesinger-Raab A, Sauer H, Hölzel D. Communication, quality of life and age: results of a 5-year prospective study in breast cancer patients. *Annals of Oncology: Elsevier*; 2003. p. 421-7.
450441. Seror V, Cortaredona S, Bouhnik AD, et al. Young breast cancer patients' involvement in treatment decisions: the major role played by decision-making about surgery. *Psycho-oncology* 2013; **22**(11): 2546-56.
451442. Mott N, Wang T, Miller J, et al. Medical Maximizing–Minimizing Preferences in Relation to Low-Value Services for Older Women with Hormone Receptor-Positive Breast Cancer: A Qualitative Study. *Annals of Surgical Oncology: Ann Surg Oncol*; 2021. p. 941-9.
452443. Lantz PM, Janz NK, Fagerlin A, et al. Satisfaction with Surgery Outcomes and the Decision Process in a Population-Based Sample of Women with Breast Cancer. *Health Services Research* 2005; **40**(3): 745.
453444. Martinez KA, Kurian AW, Hawley ST, Jagsi R. How can we best respect patient autonomy in breast cancer treatment decisions? *Breast cancer management* 2015; **4**(1): 53-64.
454445. Khoshnazar TAK, Rassouli M, Akbari ME, et al. Communication Needs of Patients with Breast Cancer: A Qualitative Study. *Indian Journal of Palliative Care: Scientific Scholar*; 2016. p. 402.
455446. Shim EJ, Park JE, Yi M, Jung D, Lee KM, Hahm BJ. Tailoring communications to the evolving needs of patients throughout the cancer care trajectory: A qualitative exploration with breast cancer patients. *BMC Women's Health* 2016; **16**(1): 1-8.
456447. Ward ZJ, Scott AM, Hricak H, Atun R. Global costs, health benefits, and economic benefits of scaling up treatment and imaging modalities for survival of 11 cancers: a simulation-based analysis. *The Lancet Oncology*; 2021. p. 341-50.
457448. Caverly TJ, Hayward RA. Dealing with the Lack of Time for Detailed Shared Decision-making in Primary Care: Everyday Shared Decision-making. *Journal of General Internal Medicine: Journal of General Internal Medicine*; 2020. p. 3045-9.

458449. Street RL, Mazor KM, Arora NK. Assessing Patient-Centered Communication in Cancer Care: Measures for Surveillance of Communication Outcomes. *Journal of Oncology Practice* 2016; **12**(12): 1198.
459450. Banerjee SC, Manna R, Coyle N, et al. The implementation and evaluation of a communication skills training program for oncology nurses. *Translational behavioral medicine: Transl Behav Med*; 2017. p. 615-23.
460451. Bylund CL, Banerjee SC, Bialer PA, et al. A rigorous evaluation of an institutionally-based communication skills program for post-graduate oncology trainees. *Patient education and counseling: Patient Educ Couns*; 2018. p. 1924-33.
461452. Kissane DW, Bylund CL, Banerjee SC, et al. Communication skills training for oncology professionals. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2012. p. 1242-7.
462453. Bylund CL, Brown RF, Bialer PA, Levin TT, Lubrano Di Ciccone B, Kissane DW. Developing and implementing an advanced communication training program in oncology at a comprehensive cancer center. *Journal of cancer education : the official journal of the American Association for Cancer Education: J Cancer Educ*; 2011. p. 604-11.
463454. Bylund CL, Brown R, Gueguen JA, Diamond C, Bianculli J, Kissane DW. The implementation and assessment of a comprehensive communication skills training curriculum for oncologists. *Psycho-oncology* 2010; **19**(6): 583-93.
464455. Langewitz W, Denz M, Keller A, Kiss A, Rütimann S, Wössmer B. Spontaneous talking time at start of consultation in outpatient clinic: cohort study. *BMJ (Clinical research ed): BMJ*; 2002. p. 682-3.
465456. Decise D, Gheran MP, Kimhi E, et al. Putting words into practice. *Breast* 2020; **49**: 171-3.
466457. Fallowfield L, Boyle FM, Travado L, et al. Gaps in Care and Support for Patients With Advanced Breast Cancer: A Report From the Advanced Breast Cancer Global Alliance. *JCO Glob Oncol* 2021; **7**: 976-84.
467458. Weeks JC, Catalano PJ, Cronin A, et al. Patients' Expectations about Effects of Chemotherapy for Advanced Cancer. *New England Journal of Medicine: New England Journal of Medicine (NEJM/MMS)*; 2012. p. 1616-25.
468459. Weeks JC, Cook EF, O'Day SJ, et al. Relationship Between Cancer Patients' Predictions of Prognosis and Their Treatment Preferences. *JAMA: American Medical Association*; 1998. p. 1709-14.
469460. Smith-Uffen MES, Johnson SB, Martin AJ, et al. Estimating survival in advanced cancer: a comparison of estimates made by oncologists and patients. *Supportive Care in Cancer: Springer*; 2020. p. 3399-407.
470461. Chen CH, Kuo SC, Tang ST. Current status of accurate prognostic awareness in advanced/terminally ill cancer patients: Systematic review and meta-regression analysis. *Palliative medicine: Palliat Med*; 2017. p. 406-18.
471462. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA: JAMA*; 2008. p. 1665-73.
472463. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2012. p. 4387-95.
473464. Kaplowitz SA, Campo S, Chiu WT. Cancer patients' desires for communication of prognosis information. *Health communication: Health Commun*; 2002. p. 221-41.
474465. Back AL, Arnold RM. Discussing prognosis: "How much do you want to know?" Talking to patients who are prepared for explicit information. *Journal of Clinical Oncology: J Clin Oncol*; 2006. p. 4209-13.

475466. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. *British journal of cancer: Br J Cancer*; 2001. p. 48-51.
476467. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Annals of internal medicine: Ann Intern Med*; 2001.
477468. Baile WF, Lenzi R, Parker PA, Buckman R, Cohen L. Oncologists' attitudes toward and practices in giving bad news: an exploratory study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2002. p. 2189-96.
478469. Fenton JJ, Duberstein PR, Kravitz RL, et al. Impact of Prognostic Discussions on the Patient-Physician Relationship: Prospective Cohort Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2018. p. 225-30.
479470. Vasista A, Stockler MR, Martin A, Lawrence NJ, Kiely BE. Communicating prognostic information: what do oncologists think patients with incurable cancer should be told? *Internal medicine journal: Intern Med J*; 2020. p. 1492-9.
480471. Fallowfield LJ, Jenkins VA, Beveridge HA. Truth may hurt but deceit hurts more: communication in palliative care. *Palliative medicine: Palliat Med*; 2002. p. 297-303.
481472. Barnett MM. Does it hurt to know the worst?--psychological morbidity, information preferences and understanding of prognosis in patients with advanced cancer. *Psycho-oncology: Psychooncology*; 2006. p. 44-55.
482473. Enzinger AC, Zhang B, Schrag D, Prigerson HG. Outcomes of Prognostic Disclosure: Associations With Prognostic Understanding, Distress, and Relationship With Physician Among Patients With Advanced Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2015. p. 3809-16.
483474. Hagerty RG, Butow PN, Ellis PM, et al. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2005. p. 1278-88.
484475. Gattellari M, Voigt KJ, Butow PN, Tattersall MHN. When the treatment goal is not cure: are cancer patients equipped to make informed decisions? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2002. p. 503-13.
485476. Nahm SH, Stockler MR, Martin AJ, et al. Using three scenarios to explain life expectancy in advanced cancer: attitudes of patients, family members, and other healthcare professionals. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer: Support Care Cancer*; 2022. p. 7763-72.
486477. Kiely BE, McCaughan G, Christodoulou S, et al. Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer: Support Care Cancer*; 2013. p. 369-76.
487478. Kiely BE, Martin AJ, Tattersall MHN, et al. The median informs the message: Accuracy of individualized scenarios for survival time based on oncologists' estimates. *Journal of Clinical Oncology: American Society of Clinical Oncology*; 2013. p. 3565-71.
488479. Stockler MR, Tattersall MHN, Boyer MJ, Clarke SJ, Beale PJ, Simes RJ. Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer. *British Journal of Cancer: Nature Publishing Group*; 2006. p. 208.
489480. 3 SCENARIOS FOR SURVIVAL. 2019. <https://ctc.usyd.edu.au/3scenarios/> (accessed 30 August 2023).
490481. CancerSurvivalRates. 2022. <https://cancersurvivalrates.com/> (accessed 30 August 2023).
491482. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology: J Clin Oncol*; 2010. p. 1203-8.

- ~~492483.~~ WHO traditional medicine strategy: 2014-2023. 2013. <https://web.archive.org/web/20230430163013/https://www.who.int/publications/i/item/9789241506096> (accessed 30 April 2023).
- ~~493484.~~ Witt CM, Balneaves LG, Cardoso MJ, et al. A Comprehensive Definition for Integrative Oncology. *JNCI Monographs* 2017; **2017**(52).
- ~~494485.~~ Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How Many Cancer Patients Use Complementary and Alternative Medicine: A Systematic Review and Metaanalysis. *Integrative Cancer Therapies* 2012; **11**(3): 187-203.
- ~~495486.~~ Spence D, Brown K, Smith S, et al. Jamaican Cultural and Spiritual Guidance in Caring for Cancer Patients, Jamaica. *Global Perspectives in Cancer Care: Religion, Spirituality, and Cultural Diversity in Health and Healing*: Oxford University Press; 2022: 0.
- ~~496487.~~ Abrams D, Weil A. *Integrative Oncology*: Oxford University Press; 2014.
- ~~497488.~~ Lyman GH, Greenlee H, Bohlke K, et al. Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline. *Journal of Clinical Oncology* 2018; **36**(25): 2647-55.
- ~~489.~~ About Herbs, Botanicals & Other Products. 2023. <https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs> (accessed 1 May 2023).
- ~~498490.~~ Yonas MA, Jones N, Eng E, et al. The art and science of integrating Undoing Racism with CBPR: challenges of pursuing NIH funding to investigate cancer care and racial equity. *Journal of urban health : bulletin of the New York Academy of Medicine* 2006; **83**(6): 1004-12.
- ~~499494.~~ Baker SL, Black KZ, Dixon CE, et al. Expanding the Reach of an Evidence-Based, System-Level, Racial Equity Intervention: Translating ACCURE to the Maternal Healthcare and Education Systems. *Frontiers in public health*: Front Public Health; 2021.
- ~~500492.~~ Enard KR, Nicks SE, Campbell BA, McClure SM. In pursuit of equity: partnering to improve breast and prostate cancer outcomes among African Americans. *Cancer causes & control : CCC: Cancer Causes Control*; 2021. p. 473-82.
- ~~501493.~~ Rodriguez NM, Casanova F, Pages G, et al. Community-based participatory design of a community health worker breast cancer training intervention for South Florida Latinx farmworkers. *PloS one*: PLoS One; 2020.
- ~~502494.~~ Lynch KA, Bernal C, Romano DR, et al. Navigating a newly diagnosed cancer through clinician-facilitated discussions of health-related patient values: a qualitative analysis. *BMC palliative care* 2022; **21**(1).
- ~~503495.~~ Desai AV, Michael CL, Kuperman GJ, et al. A Novel Patient Values Tab for the Electronic Health Record: A User-Centered Design Approach. *Journal of medical Internet research: J Med Internet Res*; 2021.
- ~~504496.~~ Kamen CS, Reichelt M, Dadgostar P, et al. Sexual and gender minority cultural humility training for oncology settings: An example of iterative adaptation and implementation. *Frontiers in health services: Front Health Serv*; 2022.
- ~~497.~~ Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011; **12**(10): 933-80.
- ~~498.~~ Strasser Weippl K, Chavarri-Guerra Y, Villarreal-Garza C, et al. Progress and remaining challenges for cancer control in Latin America and the Caribbean. *Lancet Oncol* 2015; **16**(14): 1405-38.
- ~~499.~~ Ngwa W, Addai BW, Adewole I, et al. Cancer in sub-Saharan Africa: a Lancet Oncology Commission. *Lancet Oncol* 2022; **23**(6): e251-e312.
- ~~500.~~ Lawler M, Davies L, Oberst S, et al. European Groundshot addressing Europe's cancer research challenges: a Lancet Oncology Commission. *Lancet Oncol* 2023; **24**(1): e11-e56.
- ~~501.~~ Jaffee EM, Dang CV, Agus DB, et al. Future cancer research priorities in the USA: a Lancet Oncology Commission. *Lancet Oncol* 2017; **18**(11): e653-e706.

502. — Frenk J, Chen L, Bhutta ZA, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. *Lancet* 2010; **376**(9756): 1923–58.

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Dear Charlotte

Thanks for all your work on this excellent Commission. We are nearly there! I had this re-reviewed and also reviewed by a statistician and health economist. You can find the reviewer comments at the end of this email. Directly below are my comments and other editor's comments. I have been through these with you this morning via zoom and am happy to go through them again once you and your team have had time to reflect on them. We have agreed that I will discuss internally about a potential launch date of mid-April 2024 and get back to you. If we do agree on this date we will need to accept this 3 months in advance.

Editorial comments:

Jessamy:

This is an excellent and extensive piece of work. There are many moving parts and novel insights. At the moment it lacks a cohesive narrative or elevator pitch. For me, some of the most interesting parts of this work are on metastatic breast cancer, patient empowerment and the hidden burden of suffering. I think it would be good if a more cohesive message could be built around these important parts. We discussed a number of different routes that you could take today and we can discuss again after you have had time to consider and discuss. It's your choice, which one to take and what you want the focus to be of course, there will be many different approaches to this but we need to work on making the messaging more powerful. More specific points:

1. It is unclear how indicators were developed or how realistic these are. There should be some justification and rationale for them

A new paragraph has been added to the introduction.

2. It is unclear, which parts are new to the Commission and which parts are being referred to - this is mainly a problem in the panels

This has been addressed throughout the manuscript and made clearer.

3. The personalised prevention section needs further work. At the moment it is not contextualised within current practice. Figure 1 needs further work.

This has been amended and the figure legend for figure 1 has been expanded.

4. Should the section on personalised breast cancer treatment come closer to the section on equitable access to cancer medicines? There seem to be many similarities/uniting messages and it feels strange to come back to this later

The writing committee have discussed this at length and conclude that although there are some similarities there are also different important messages in terms of global inequities. Therefore, we feel that the cancer medicines section is best placed in this section. If the themes are moved, then MBC comes later in the report and we do not think that is appropriate for such an important section.

5. The technology section needs further work. I like figure 3 but the text around it does not really match the figure. There is then another section on technologies for early breast cancer diagnosis and it feels strange having these separated with metastatic breast cancer in between. Some thought needed around this.

This section has been revised so that that text fits better with the figure. The writing committee has discussed this point and feel that digital health is best suited to the personalisation section whereas the innovative technologies are more aligned with the global inequities section. Both sections have been extensively revised to prevent repetition.

6. The learning from past failures in breast cancer management is good but also comes out of the blue and as there is a focus on early diagnosis, should it be closer to or connected to the prevention section?

This has been re-worded slightly, but it is essential that it is placed in this section as early diagnosis is a key component of closing the global inequity gap in late diagnosis. Early diagnosis is distinct from prevention, so it is not best placed in the prevention section.

7. Please reference the women, cancer and power Commission in the patient empowerment section.

This has been added.

8. Please remove panel 27 on ongoing work on Lancet Commission and health systems Commission

This has been removed.

9. Think more could be made of CASCARA study?

The text from the over-long panel has been added to the text and more respondents' quotes have been added to a now shorter panel.

10. The executive summary needs revising. I think better to have as a cohesive set of prose rather than broken down into numbers. This should incorporate some of the overall messaging and 'elevator type pitch/summary'.

This has been completely re-written. The elevator type pitch summary is in panel 1.

11. The conclusion needs further work. Could be more forward looking, what the Commission might want or call for next? Or some other focus that is satisfying and interesting.

A future directions section and a new conclusion section have been added.

12. Liked the 6 key messages but could be more specific and not sure the focus is right

These have been revised as per the elevator pitch.

13. Need to bring recommendations together at the end in one place – not necessarily all of them but the important ones that links to narrative.

Key targets have been added to a final panel.

Other editorial comments:

Some of the panels are actually panels, so I make the totals: 7 figures, 7 tables (panels 5, 10, 16, 23, 28, 32, and 35), and 28 panels.

The figures and the tables are all good to stay. Many of the panels are short bullet points of text, which are also good as they will break up the flow of the report. Some of the panels though are very long – eg, panels 26, 27, and those describing case studies/reports. Long panels do not work as well – especially when they go over more than one column. So my suggestion would be to shorten those long ones, or keep them in their entirety but move them to the appendix.

Long panels have been shortened.

This is a really strong Commission with lots of interesting parts as you say. It needs a separate recommendations section/table towards the end, doesn't really need the conclusion as written right now, for the conclusion it would be good to include a forward looking part, ie what would the Commission commit to do next/monitor...etc.. I am also missing an overall elevator pitch/narrative. In various parts they hint at something, such as "breast cancer as an index condition to improve women's health and close inequity gap" (that might be too close to the Cancer in Women Commission's headline), or "breast cancer's relative success story in HICs needs to focus now on those left behind (metastatic breast cancer, those in LMICS diagnosed late and no access to treatment ('closing the equity gap), or an overall "roadmap to improve breast cancer care globally"

See previous response.

This is a thorough and well-thought through Commission. If I were to be nit-picking, it could benefit from a little more on access to medicines in LMICs, how to tackle the workforce deficit, and the need for UHC and more state-sector intervention on controlling private practices in LMICs. Plus, each section has an action plan, but a summary of those plans in a single small panel the Conclusion might be helpful, too. But, otherwise, very good.

See previous response.

I really like the framing of this Commission. The challenge though is how to focus on reducing inequities globally that could drive new breast cancer cases and deaths down if precision medicine which includes expensive medications and surgeries (like they suggest for weight loss) is out of reach for many women and in LIC/LMICs? Could they perhaps be more direct about this? Is it possible to take some of the lessons from the TLO Cancer commission report? There is a lot of great stuff to work with here but it feels mainly directed at HICs. They could strengthen and provide a realistic protocol for incorporating their very nice risk reduction counseling strategy into LIC/LMIC NCD guidelines in countries. Thanks for this commission on such an important topic!

The prevention section has been revised to take these comments into account. The TLO cancer Commission report is excellent. However, we feel that the recommendations for prevention are aimed more at health education, whereas we highlight prevention through policy change in addition to behavioural change.

Goal of the commission: this still needs to be more precisely and consistently framed. For example, authors point out different objectives:

Executive Summary : "... this Commission report with a single purpose: to increase prevention and improve outcomes for every individual affected by breast cancer today and in the future."

Section on a new narrative for change: "The Commission seeks to emphasise how its recommendations may go beyond the specific setting of breast cancer to transform culture in ways that lead to the more equitable empowerment of all individuals in making decisions related to their own health and beyond."

Goals have been simplified and unified – see new executive summary and revised introduction.

Key messages (Panel 1): These still sound quite vague . For example:

1. "Action now could prevent **many** of the 3 million per year..." – Do we know how many?

No, we don't know exactly. This would depend on what actions are taken. This sentence has been modified for clarity.

We also include the following statements:

Up to one quarter of breast cancers in HICs could be prevented by modifying risk factors.

Women who followed the American Cancer Society guidelines on weight control, physical activity, alcohol intake and diet⁶⁵ had 22-31% lower risk of breast cancer compared to women who were less adherent.

Inexpensive medications (tamoxifen, raloxifene or aromatase inhibitors) taken daily for 3 to 5 years reduce the relative risk of breast cancer by 30%-60%.

2. "Innovation through **breast cancer science**..." - What is breast cancer science?

This has been changed to breast cancer research.

3. "With adequate resources and a shift **in attitudes**..." - Which attitudes?

This has been changed for clarity:

With adequate resources and a shift in the current negative attitudes toward the disease, it may be possible to cure some of these patients, treat most, alleviate the suffering of all and forget no-one.

4. "Poorer women everywhere are **often** diagnosed with advanced stage disease..." - How often, do we know?

We acknowledge that this sentence was ambiguous and has been changed:

Women with low incomes and those from minoritised populations in all countries, often have their breast cancer diagnosed at late-stage with a high-risk of dying from their cancer.

5. "Costs of breast cancer and associated suffering are **immense**" What does immense means

We do not measure these costs routinely for all patients. Our pilot work suggests that there is considerable unmet need. The sentence has been modified:

We have identified that the hidden costs of breast cancer and associated suffering are considerable, varied, with far-reaching impact.

6. **Key Actions:** I couldn't find a panel or section with the summary of the key actions. Every section ends with a panel setting out measurable indicators for change. I think the panels could be improved by including the specific action that will lead to change. At the moment the actions seem to be muddled in the text and its not clear how are they linked to the key messages.

A summary panel is now placed after the conclusion.

7. **Executive Summary:** I think instead of having a summary of each section of the report, the Exec Summary should build around the key overarching message (s) of the Commission including the recommended actions. These actions could be unpacked with a paragraph of summary text for each.

We have re-written the executive summary to align with the summaries. Other reviewers have found these summaries helpful in previous reviews, so these have been edited and remain.

Section 6. : Communication and empowerment – The narrative of this section is very much similar to the narrative from the Women, Power and Cancer Commission.

This is not surprising as the section is around gender and the greatest risk factor for breast cancer is being a woman. This section was written without prior knowledge of the Women, Power, and Cancer Commission, but nevertheless we have cited this publication.

For instance they say “ *Our vision is that empowering patients with breast cancer to be engaged in decisions about their care in all healthcare settings is a step towards wider female empowerment, addressing the lack of bodily, social, and financial autonomy for women in some societies worldwide.* ” . This is one of the messages of the Women, Power and Cancer Commission. Reference

Response as above. This is also an important message for this Commission and needs to remain.

Panel 27: Linking to the Lancet Commission on Cancer and Health Systems

Would like removed.

This has been removed.

Commissioner's members: In the table in appendix they include the names of editors as members of the commission. Jessamy says please remove.

These have been removed.

Commented [CC1]: Ingrid - please check

Reviewers' comments:

Reviewer #1:

Thank you for the opportunity to read the revised report.

Revisions are adequate. However, the report is still long, with excessive narrative - there is more value (to readers) in being concise and reporting summary messages or key points instead of large amounts of text as per current version of report. The style of writing changes from section to section, although this has improved compared to the initial manuscript.

See previous responses.

Remove overlap between several sections relating to technology and digitization, technology innovation etc. For example:

Digital health interventions, telemedicine and other digital approaches are discussed under 'Digital health innovations for breast cancer care and research' - but the shift to virtual multidisciplinary tumour boards using existing teleconferencing is also discussed as a main example of one category of leap-frogging tech under 'Smart leap frogging technologies for early breast cancer diagnosis and treatment'.

See previous response.

I recommend that the entire section on leap-frogging technology be removed from this report. It is generic, thin on quality evidence, does not highlight a specific strategy to improve breast cancer care or outcomes, the text of that section discusses specific examples of technologies that are actually incremental tech and not leap-frogging tech. Looking specifically at panel 19, summarising key issues of leap-frog tech, there is nothing about breast cancer, this is a generic health system and technology narrative. There is a fair amount of content on digital and innovative technology elsewhere in report as well.

See previous response. We feel strongly that this section remains and has been extensively edited.

Avoid unnecessary critique of the Canadian screening RCT given a history of non-consensus on this matter - suggest either don't use knowledge from that trial at all, or if you do then focus on the message of the current paper (ie control arm findings suggest that breast awareness and clinical evaluation can help earlier detection) and remove the blurb about it being outlier (delete: 'whilst controversy continues about the Canadian trials, which were outliers in not showing a survival benefit in the mammographically screening arm...')

This is in supplementary material and has been amended.

Concluding section needs to be shorter: focus on key issues/directions, and (respectfully) suggest less pontifications at this point of the report (some already articulated in the earlier part of report).

See previous response. A short new conclusion has been added.

Reviewer #8: THELANCET-D-23-02788R1 The Lancet Breast Cancer Commission Report

Statistical review

General comments

Overall, this is a very good document - very clear, with a strong narrative and call for action.

The statistical issues were minor - there is extensive summary of evidence, which necessarily doesn't go into substantial methodological detail (e.g., about the various techniques of systematic review and/or meta-analysis - full details would be available for those interested in the referenced papers); there were some surveys included (one of which at least that was included seemed to have been commissioned by this group for the purposes of this report - it wasn't clear if it has been published and peer reviewed); and the use of tables and figures throughout the report was clear and informative. The call for better quality data (both completeness and accuracy) was particularly important from a methodological perspective.

See previous response – this has been addressed.

So, I am happy to recommend Accept after minor Revision from the statistical / methodological perspective!

Specific queries / comments

1. Page 1 'Policy makers must reject commercial marketing for products that increase breast cancer risk'. This is an important point e.g.; we have seen for lung cancer the problem with the tobacco industry and supine governments not willing to forego tax revenue - but I didn't get a good sense of what these products were in relation to breast cancer?

a. Useful if space permits to be more specific e.g., nutrition (including baby milk powder), smoking/drinking, etc?

b. Page 7 mentions 'vested interest groups that profit from exposing populations to breast cancer risk factors' but again is non-specific.

The text has been edited for clarity.

c. Page 9 in fairness does state 'The top targets are alcohol consumption, obesity, physical inactivity, and inadequate breastfeeding' - but more insight would be good e.g., it isn't clear what commercial entity is specifically interested in promoting physical inactivity;

This has been clarified. We have added a sentence regarding urban planning policies that permit development without footpaths or without adequate public transport which reduce walking.

d. And the breastfeeding / milk powder issue is more complex than e.g., alcohol (including for example the baby welfare when breastfeeding is not working or the mother is too sick)? Page 14 then 'Moreover reductions in the sale of alcohol and baby formula would also indicate progress' seemed too simplistic, perhaps?

We have the statement:

Changing health behaviour to reduce the risk of breast cancer may be more challenging for women struggling with other health and social problems.

2. Page 1 - useful to explain what it meant (broadly) by 'digital health'?

This has now been clarified in panel 8.

3. Page 1 - likewise, not sure that 'decentralise trial participation' is well understood?

This has been re-phrased.

4. Page 2 - the call for 'stage-shifting' and earlier diagnosis was well made, but it wasn't clear where the threshold of 60% (of invasive cancers at stage I-II) came from; and the appeal to integrate this in existing mammographic screening programmes (if that is what was meant) might risk widening inequalities (in general) and exacerbating the problem of over-treatment?

This is the work of the WHO Global Breast Cancer Initiative and is explained in the text and referenced. For the reviewer, this is also explained below:

THRESHOLD: The 60% threshold was identified by WHO through a systematic review of 141 countries and published in 2021 (Duggan, et al., Lancet Oncology, 2021). Among the 35 countries in this systematic review with available breast cancer TNM staging data, all 20 that achieved sustained mean reductions in age-standardised mortality rate of 2% or more per year for at least 3 consecutive years since 1990 had at least 60% of patients with invasive breast cancer presenting as stage I or II disease. Conversely, no country that has failed to achieve the 60% threshold has successfully reduced breast cancer mortality at the population level. On this basis, WHO advises Ministries of Health that the 60% threshold is necessary for countries to achieve and is a target for their early detection programs regardless of what stage-shifting strategy is used. WHO notes that while the 60% threshold may be necessary based on the experience of successful countries, it may not be sufficient as mortality reduction also requires that effective and timely treatment also be provided.

SCREENING METHOD: While mammographic screening is a well-established method for achieving the 60% threshold, recent data from a randomized trial in Mumbai, India (Mitra et al., BMJ 372:n256, 2021), shows that screening with clinical breast examination (CBE) performed every three years can also achieve this threshold. This is not an indictment of mammographic screening but rather is an indication that it is not the only method by which adequate stage shifting can occur. Of note, the Mumbai trial showed a mortality benefit to women 50 and above, supporting the concept that adequate early detection in the absence of mammographic screening can be achieved in previously unscreened populations.

INEQUITIES OF EARLY DETECTION PROGRAMS: You have raised the question of whether inequalities might result from this recommendation. If clinical downstaging can be achieved in the absence of mammographic screening, then we are identifying a method by which adequate early detection can be achieved without the establishment of a mammographic screening program. Certainly, a country might go on to establish mammographic screening in future iterations, but it is not a requirement for beginning early detection programs.

OVERTREATMENT: You also raised the question of whether overtreatment might result from these efforts. A strength of clinical detection methods is that approximately 98% of palpable masses that prove to be breast cancer are invasive probably measuring at least 1cm (T1c) (hence the requirement for the threshold) and does not relate to DCIS, which with rare exception is identified through mammographic screening. Once cancers are invasive measuring 1cm, the negative impact of overtreatment is markedly curtailed, in contrast to mammographic screening where 20 – 25% of

new cancers can be non-invasive disease. The overtreatment discussion is most applicable to DCIS and has limited relevance to T1-T2 invasive cancers.

5. Page 4: It was good to see an explicit acknowledgement that ~1% of breast cancer occurs in men.

6. Page 4: the section on maternal orphans was thought provoking - but it wasn't clear how the statistic 'between 14 and 30 children will die as result' (for every 100 maternal deaths) - over what time period, say?

This is a relative mortality contribution based on a simulation model developed by the IARC team. The prediction is that for every 100 women who die of breast and cervical cancers, 14-30 children in Africa will die as a direct result of their mothers death. No time frame is applied.

7. Page 5 - I didn't understand what 'positive beacon' meant.

This has been removed.

8. Page 8 - Panel 3 - sometimes the authors given an 'n' and a '%' e.g., 98,000 ... 4%; other times just the % e.g., 8-13% in some HIC - if possible, useful to be consistent and always give both?

Data is reported as published and this varies.

9. Page 9 - the theme around inadequate data collection is important - we need that baseline to show what is and is not working, and how rapidly. Perhaps this could be emphasised more prominently in the conclusions / recommendations?

Agreed. This has been emphasised in the report.

10. Page 13 'This is a much larger group than women at very high risk' - this would be useful to quantify if possible?

This is included in the text:

First, identifying the 20-30%14,15 of women at substantially higher than average risk of breast cancer using existing tools.

11. Page 14 - the qualifier 'Thought must be given to downstream workforce issues ...' - seemed a real understatement - there probably isn't a huge lack of willingness and/or recognition of the importance of the problem - but creating space and resource to do something about this alongside so many other important initiatives is a major problem, surely? An important reason that this could fail?

The text has been modified:

Currently there is very little prescribing of preventive medications; workforce education is a major barrier Clinician capability and knowledge has been identified as a major barrier to the discussion of, and prescribing of, risk-reducing medications.^{148,149} This will need to be addressed, and resources,

prioritised for successful widespread implementation of preventive medications that can bridge the current large evidence-implementation gap.

12. Page 19 'For example, regulation of clinical trials should ensure that these are risk-adapted and fit for purpose, else breast cancer trials will not be feasible or affordable aside from those motivated and conducted by pharmaceutical companies' - struggled to understand this - how is a route to better more relevant trials through changed regulation? Its an important objective but as written it doesn't seem to land?

This has been revised for clarity.

13. Page 19 - perhaps it could be made clearer that what is needed are better models to predict both benefit, and harm; and then better methodology for integrating the possible benefit and harms from a population and then an individual level?

This has been revised for clarity.

14. Page 19 - I didn't really understand the 'prognostic biomarkers (common)' and 'predictive biomarkers (uncommon)' - what do the 'common' and 'uncommon' mean in this context?

Common and uncommon have been removed in the panel and the text has been edited.

15. Page 22 - it would have been useful to have a sentence or two on what 'valued based healthcare' (and Page 48 'valued-based pricing') is - or a reference or two?

A definition has been added and referenced.

16. Page 22 - ditto - I am not sure most readers will understand what Open Science is ('the outcomes of research freely available ...') so good to have an explanation and/or a reference to this new paradigm.

17. Page 25 - not obvious what is meant by 'data inoperability' in this specific context?

18. Page 25 + elsewhere - the integration of PROMs into the electronic health records (and the overall focus on Quality of Life rather than say technical success outcomes) is hugely important and perhaps could be given more emphasis, as this needs investment (and raised awareness)?

19. Page 26 'It is important to ensure that datasets used to train AI-algorithms are representative of the real-world breast cancer patient population' - important not to be alarmist here but this is a significant challenge for AI models, that faithfully represent the current observed behaviours - diagnosis/treatment pathways - riddled with inequalities and lack of access etc? This is an important limitation that must not end with inequalities widening as a result?

The section on digital health has been re-written to address these comments.

20. Page 31 - not sure why 'without first acquiring employer permission' is bolded?

Bold has been removed.

21. Page 32 - following the comment on the importance of better data, the section on 'standard essential datasets' seemed to brief. Could more detail be included - for example, possibly a clinical area where a core essential dataset has been agreed and implemented, to act as an exemplar to be copied, say?

We have been asked to reduce the word count so do not feel there is scope to increase the discussion on this. However, we do stress the importance of data collection in the executive summary and throughout the report. In particular, we mention that cancer registries should collect data on relapse for all cancers not just breast cancer.

22. Page 36 - for the Lancet Breast Cancer Commission Health Care Practitioner survey - 382 responses from how many invites (or was it web-based)? Has this survey been peer reviewed and independently published? Similar comment for Page 55 - the CASCARA patient survey? How many invites (what was non-response rate) and is it published / peer reviewed?

This has been clarified in the text.

23. Figure 4 is striking - what happened in 1985-1990 to reverse the trend?

A sentence has been added to explain this.

24. Figure 5A on the other hand - I struggled to get the message from 5A. What are MG and CBE - please spell out (MG presumably is Millennium Goals?)

MG=mammogram; CBE=clinical breast examination. These have been added to the figures.

25. Page 48 '... or when 'real world data' fails to demonstrate benefits' - understood the general issue here that findings from highly selective randomised designs don't carry over into diverse unselected populations - but using RWE for this purpose is itself replete with many challenges. Might be useful to give a reference or two to the issue of integrating RCT and RWE?

These have been added.

26. Page 49 - would be useful to define 'advocacy' in this context?

This definition has been added.

27. Page 52 - the concept of 'Serious Health Related Suffering' was good to be introduced to - but 'To accurately count the number of people and their days with SHS (SHS days per year) mortality data needs to be differentiated from prevalence data' - not sure what was meant here?

The passage was changed from "To accurately count the number of people and their days with SHS (SHS days per year), mortality data needs to be differentiated from prevalence data. " to "SHS can affect patients throughout the breast cancer trajectory and hence the measure is relevant not only for imminently dying patients (year of death measured by mortality), but also at earlier stages

(before year of death). Hence, to accurately count the number of people and their days with SHS (SHS days per year), both mortality and prevalence data are required. "

28. Page 61 - I found this 'FACT ...' style a bit challenging in respect of saying 'some traditional, complementary, and integrative therapies can be beneficial' - with a reference (number 434) to a meta-analysis(?) when elsewhere in this report (page 69 ref 486 and panel 34) \ it is acknowledged that such interventions can be ineffective and actually harmful? I think this needs to be clearer?

This has been re-written for clarity.

Reviewer #9: I joined the peer review process after the first round of review, and the revised manuscript is well-organized, clearly written, and thought-provoking. I annotated my versions with notes about potential research projects. I respect The Commission's decision to address the questions, "What is distinctive about breast cancer and what can we learn from it?" amidst the contemporaneous work of the five other groups that they report are addressing breast cancer: Lancet Commission on Cancer and Health Systems, Lancet Commission on Access to Palliative Care and Pain Relief, WHO Global Breast Cancer Initiative, and ABC Alliance.

My three main recommendations are below, followed by other comments.

Panel 22, pages 48 and 49. Is reference 1 for the WHO Breast Cancer 2021 Fact sheet correct? While the website reports, "The great majority of drugs used for breast cancer are already on the WHO Essential Medicines List (EML)," I didn't find the information reported in this panel. Information on the ESMO and ASCO tools is well-received. Given the trends in higher prices for new drugs however, the recommendation "transparent strategic discussion involving all interested players is needed" detracts from the urgency of this issue. It should either be strengthened or removed.

The sentence was modified, and 2 additional references were added.

Page 53, section on Serious health-related suffering (SHS). The term SHS seems to conflate two concepts: morbidity and stigma. Many of the symptoms that the group of 14 experts reported (e.g. "pain or fatigue, and reproductive health challenges") are addressed in current measures of morbidity such as disability weights and health-related quality of life. My understanding is that people who conduct research on measures of morbidity are concerned about how well they capture pain, but funding for this research topic is unavailable. A recommendation from The Commission to fund research to improve how breast cancer symptoms are measured would be a more direct way to improve the measures of morbidity rather than/in addition to supporting a parallel system of measures such as SALYs (See Panel 25, page 54).

Current measures of morbidity often focus on physical, and to a lesser degree on psychological symptoms. One of the interesting new findings of the pilot study on SHS in breast cancer was that social stigma and existential distress can add considerably to the burden of suffering, but both have been neglected in evidence-building and hence in priority setting. SHS differs complements existing measures of morbidity, with detailed symptom assessment translated into a measure of the burden of suffering that allows for comparisons between different population groups and stages of the breast cancer trajectory (such as early and metastatic breast cancer). In addition, existing measures such as quality-adjusted life years or disability-adjusted life years have been criticised because they heavily depend on length of survival and are less suited for patients with short survival times. We agree with the call for more research funding on measures of morbidity that incorporate suffering and have strengthened our recommendation on population-based measures. We have limited the

focus to SHS because work on SALYs is still in the development stage.

Panel 27, page 58, paragraph 2, sentence beginning "Traditional economic evaluation..." is incorrect. The US Panel on Cost-Effectiveness in Health and Medicine has always recommended including the cost of caregiver time in estimates for the societal perspective, even if analysts omit them in practice. The updated recommendations also include foregone labor market earnings, cost of unpaid lost productivity due to illness, and cost of uncompensated household production. See Sanders et al. JAMA 2016 <https://jamanetwork.com/journals/jama/article-abstract/2552214> For Panel 27, page 58, paragraph 3. See comment 2 above on SHS.

Passage was changed to "Traditional economic evaluation techniques (i.e. cost-effectiveness and cost-utility analysis) focus narrowly on health gains to individual patients. The inclusion of lost labour market earnings, unpaid lost productivity due to illness and cost of uncompensated household production in economic evaluations has been recommended (ref. Sanders et al 2016) although too seldom implemented, even in efforts to reduce the risk of financial hardship and impoverishment and abandonment of care. Other benefits associated with alleviating suffering, as well as the impact on orphaned children, families, and communities, has been neglected. Understanding and measuring these limitations for the specific case of breast cancer provides a model to elucidate and estimate the broader impacts for individuals and families associated with many types of cancer diagnosis and is being further taken up by the Lancet Commission on Cancer And Health Systems.

Other comments.

Page 13, paragraph 2 beginning with "At subsequent timepoints..." It's unclear when the risk assessments would occur in health systems that don't offer annual check-up. If this question is addressed by the Lancet Commission on Cancer and Health Systems, please refer to that work here.

This is not stipulated as the assessments need to be adapted to local context, for example at the time of maternity care. This is beyond the remit of this commission to give this level of detail.

Page 31, paragraph 4, sentence beginning with "For HIC, the solution is complex..." Remove the phrase "the solution is complex," because it is unnecessary and the implication that solutions in other settings are not complex could be interpreted as derogatory.

This has been removed.

Page 44, Figure 5B. I can understand why the number of breast cancer cases would increase with population and increased life expectancy. This figure however, shows a large increase in the breast cancer cases per 100,000 women. Does the rate increase due to exposure to breast cancer risk factors such as obesity and alcohol use?

Thank you for your questions about the Kenya model that was produced for the Ministry of Health by WHO and colleagues as funded by the World Bank. The breast cancer portion of which has just been submitted for peer-review publication. The projected increase in number of breast cancer cases requiring treatment is a direct result from increased early detection efforts and is modelled after was seen in the U.S. in the 1980s (see Verdial, et al., J Surg Oncol, 115:517, 2017). There are no assumptions made in the Kenya model regarding changing "Westernised" breast cancer risk factors including obesity and alcohol usage, which as the reviewer indicates would further increase breast cancer cases over time.

Page 45, Figure 6. Please report the number of cases. I would like to calculate whether or not the cost of treatment per case is lower with early detection.

The average cost of breast cancer treatment per patient was addressed in the complete Kenya modelling analysis. We did not include this additional graph in the Lancet Commission for lack of space, but the topic is addressed in the peer-reviewed publication. The Kenya modelling projects that the current (status quo) cost is 118,999 Kenya Shillings (KS), which will decrease to 108,188 KS per case with early diagnosis efforts on the basis of stage shifting and without the introduction of population-based screening. Both screening by CBE and by mammography will further reduce the cost of treatment per case as the reviewer suspects.

Page 46, paragraph 4, two sentences beginning "However, these technologies may be helpful as training..." and "Moreover, the training sets..." The term "training" in the first sentence appears to refer to human capacity, and in the second sentence to input data machine learning. Use another term in one of the sentences, probably the first one.

This has been edited.

Page 53, paragraph 2 beginning "The expert group agreed that on average there were 175 days of reported SHS..." Please explain this "back-of-the envelope" calculation in the text. If a person lives one-half year on average during the last year of life, this means they experience SHS every day.

Last year of life does not refer to the calendar year of the patient's death, but to the last 12 months of life. The passage was changed to "The expert group agreed that half a year of SHS - about 175 days - is experienced by patients in the last 12 months of life."

Panel 26, page 56, The second quote beginning "I need to take time off..." seems most relevant to the theme on caring. The third quote beginning "My husband had to take unpaid leave..." seems most relevant to the theme on employment.

This has been changed.