Ethical Issues Surrounding Access to Care for BRCA Mutations



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Caroline Jane Huang

Merton College, University of Oxford

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Abstract

Ethical issues surrounding access to care for BRCA mutations

Caroline Huang
Merton College, University of Oxford
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Harmful BRCA (breast cancer susceptibility genes 1 and 2) mutations greatly increase women's risks of breast and/or ovarian cancer but are found in less than 1 per cent of the general population. Thus, care is targeted at women with strong family histories of breast and/or ovarian cancer. Genetic testing can determine if these high-risk women carry harmful mutations; if so, they may pursue care that facilitates cancer prevention, detection, and/or treatment.

In this thesis, I examine in which cases it is problematic that some British and American women do not access this potentially life-saving care. In recognition of the difficulty in measuring access, a view informed by preliminary interviews and a literature review, I use three complementary approaches to illustrate different aspects of access. First, a critical review surveys how British and American clinical guidelines, laws, policies, and legal rulings govern service availability. Second, a scoping study describes the US and UK literature on barriers and facilitators to access. Third, an empirical study involving focus groups with UK and US genetics professionals and support group members details how women provide and pursue care.

Using Beauchamp and Childress's 'four principles' framework, I analyse how these approaches inform four elements of access: availability of services, barriers to care, relevance and effectiveness of services, and equity of access. I distinguish between cases in which women do not want and/or need care and cases in which women are denied care they want and need, and I propose strategies to redress current inequities in access. I further suggest that offering Ashkenazi Jewish population screening alongside family history-based screening may be appropriate. I conclude that whilst most problematic cases are country-neutral, only US women are problematically constrained by insurance and legal loopholes, and only UK women are problematically constrained by regional variations in health authority funding.

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List of abbreviations and acronyms

ACA ..... Patient Protection and Affordable Care Act
ACGS ..... Association for Clinical Genetic Science
ACS ..... American Cancer Society
AJ ..... Ashkenazi Jewish
BOADICEA ..... Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA ..... Breast cancer susceptibility genes 1 and 2
BRCA1 ..... Breast cancer susceptibility gene 1
BRCA2 ..... Breast cancer susceptibility gene 2
BSE ..... Breast self-examination
CA-125 ..... Cancer antigen 125
CBE ..... Clinical breast examination
CDC ..... Centers for Disease Control and Prevention
CINAHL ..... Cumulative Index to Nursing and Allied Health Literature
CLIA ..... Clinical Laboratory Improvements Amendment
CMS ..... Centers for Medicare and Medicaid Services
CR UK ..... Cancer Research UK
DOL ..... United States Department of Labor
DTC ..... Direct-to-consumer
FDA ..... United States Food and Drug Administration
FDR ..... First-degree relative
FHAT ..... Ontario Family History Assessment Tool
FORCE ..... Facing Our Risk of Cancer Empowered
GP ..... General practitioner
GINA ..... Genetic Information Nondiscrimination Act
HBOC ..... Hereditary breast and ovarian cancer
HHS ..... United States Department of Health and Human Services
HGC ..... Human Genetics Commission
HIPAA ..... Health Insurance Portability and Accountability Act
HPSS ..... Department of Health, Social Services and Public Safety (Northern Ireland)
IVDD ..... In Vitro Diagnostic Medical Devices Directive
LDT ..... Laboratory-designed test
MHRA ..... Medicines and Healthcare Products Regulatory Agency
MRI ..... Magnetic resonance imaging

MSS ..... Manchester Scoring System
NCCN ..... National Comprehensive Cancer Network
NHGRI ..... National Human Genome Research Institute
NHS ..... National Health Service
NICE ..... National Institute for Health and Care Excellence
NCI ..... National Cancer Institute
PAT ..... Pedigree Assessment Test
PGS ..... Personal Genome Service
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RST ..... Referral Screening Tool
SDR ..... Second-degree relative
SIGN ..... Scottish Intercollegiate Guidelines Network
TDR ..... Third-degree relative
Treasury ..... United States Department of the Treasury
TVUS ..... Transvaginal ultrasound
UK NSC ..... United Kingdom National Screening Committee
UNESCO ..... United Nations Educational, Scientific and Cultural Organization
USPSTF ..... United States Preventive Services Task Force
VUS ..... Variant of uncertain significance

1 Chapter One: Introduction

Imagine the following scenario: Patient A has just been diagnosed with breast cancer at age 43, and she has a sister who was previously diagnosed with ovarian cancer at age 47. A different woman, Patient B, has no personal history of cancer, but her sister was just diagnosed with breast cancer at age 47. Patient A is eligible to access genetic services at no cost to her in the United Kingdom, but this is not the case in the United States. Conversely, Patient B is eligible to access genetic services at no cost to her in the United States, but this is not the case in the United Kingdom. Is it problematic that there is differential access to care for Patients A and B, simply depending on their country of residence?

In the above situation, Patients A and B are being assessed to see if they are at high risk for harmful BRCA (breast cancer susceptibility genes 1 and 2) mutations, which can be inherited from either parent and are linked to greater risks of breast and/or ovarian cancer. They are rare but significant: BRCA mutations occur in less than 1 per cent of the general population, but they account for roughly 5 to 10 per cent of all breast cancers and 15 per cent of all ovarian cancers (National Cancer Institute [NCI], 2015; Petrucelli, Daly, & Feldman, 2010). As a result, it is not responsible from an economic perspective, or useful from a clinical perspective, for every woman to be referred to genetic services. Instead, referrals are aimed at patients with an unusually strong family history of breast, ovarian, and other related cancers, such as pancreatic or prostate (National Institute for Health and Care Excellence [NICE], 2013, p. 5). Guideline-informed eligibility for referral to genetic services helps determines whether high-risk British and American women are able to receive care at no cost, but as the example above shows, the definition of 'high risk' is not always standard.

I first became interested in the question of who receives access to care for BRCA mutations through my service with Camp Kesem, an American non-profit organisation providing year-round support for children whose parents have cancer. One Camp Kesem parent had spent the last three years undergoing breast cancer treatment, and her older sister had been diagnosed with breast cancer as well. She told me that her doctor had said there was some kind of blood test she could take that would help her figure out if her two daughters might get cancer when they grew up. Tears dripping down her face, she sharply inhaled and then whispered that her insurance company did not cover the cost of testing.

Later, when I searched online for information about genetic testing for breast cancer, I was stunned to come across the following statement in an official NCI fact sheet: 'Currently, there are no standard criteria for recommending or referring someone for BRCA1 or BRCA2 mutation testing' (NCI, 2009, p. 3). The next item on the fact sheet read, 'The cost for BRCA1 and BRCA2 mutation testing usually ranges from several hundred to several thousand dollars. Insurance companies vary with regard to whether or not the cost of testing is covered' (NCI, 2009, p. 4).

That startling realisation occurred in spring 2009. Nearly eight years later, the NCI's current fact sheet contains detailed referral criteria for BRCA testing, and all private insurance companies are required by law to cover the cost of testing for some high-risk women. Yet against this backdrop of technological advancement and policy change, both Patient A and the Camp Kesem parent would be potentially disqualified from free testing in the United States because they are undergoing current cancer treatment. But even if they did qualify based on the guidelines, they might encounter other obstacles: a long drive to genetic services, the prospect of having to pay for childcare for four hours while attending an

appointment, the anxiety that another clinician might have to share bad news, the prospect of guilt that their children inherited their mutation, and so on.

These examples highlight the complexity of assessing access to care for BRCA mutations: Whilst guidelines largely inform whether women *can* access care for BRCA mutations at no cost, myriad other factors such as income, time, and location impact whether women actually *do* access care, a comment that is true in both the United States and United Kingdom. These two countries are particularly appropriate for comparison because they share Western culture and English language, and with the passage of the Patient Protection and Affordable Care Act of 2010 (ACA), the United States adopted certain policy positions regarding government-guaranteed care that are closer to those of the United Kingdom (Lieberman, 2012). Both countries also aim to balance respect for patient autonomy against the prudence of evidence-based care (Goldberg, 2009; Williamson, 2014; Woolf, Grol, Hutchinson, Eccles, & Grimshaw, 1999). Another reason to examine these particular countries has to do with their capacity to offer genetic services: The United States employs the most genetic counsellors in the world, whilst the United Kingdom employs the most genetic counsellors in Europe (Pain, 2016). In theory, there should be a sizeable population of American and British patients and clinicians who have pursued and provided care for BRCA mutations available to study, and the conclusions from this research should be relevant to many US and UK clinicians and future patients.

Whilst finding out who currently accesses care in these two countries is an important question in itself, a more nuanced issue is whether the women who want and need care for BRCA mutations have the opportunity to access it. Put another way, are there cases in which it may be problematic that UK and US women do not access care for BRCA mutations? (Note that this thesis does not aim to re-litigate the scientific question of which

women are at risk for BRCA mutations, but rather to focus on situations when women who are considered at risk for BRCA mutations do not access care.) The remainder of this introductory chapter lays out how this thesis seeks to answer this question.

Chapter Two begins with an explanation of what 'care for BRCA mutations' means in the clinical sense, followed by a discussion of what 'access to care' commonly means in the health services and bioethics literature. I pay particular attention to Levesque, Harris, and Russell (2013), which is a systematic review describing the dimensions of access to care that arise in the health services and bioethics literature. Next, I use several years' worth of preliminary research results to explain why I made certain methodological choices, including choosing Gulliford et al. (2002) as this dissertation's model of access and coupling a series of small reviews and studies with ethical analysis to explore problematic situations where women do not access care.

Chapter Three, which describes availability of services and barriers to care, is a critical review that examines how regulatory mechanisms currently affect access to care for BRCA mutations. I begin by explaining how specific clinical guidelines, laws, legal rulings, and policies were selected and analysed. Next, I introduce prominent American and British clinical guideline-making bodies, and then I compare and contrast their guidelines for BRCA risk assessment, BRCA carrier management, and population breast screening. Afterwards, I examine the American and British regulatory frameworks – i.e., each country's laws, legal rulings, and policies – individually and then together. Chapter Three's discussion section explores similarities and differences between the US and UK regulatory mechanisms and considers practical and ethical consequences of several laws, legal rulings, and policies.

Chapter Four – which informs the barriers to care, relevance and effectiveness of services to different patient groups, and equity of access – details a scoping study that examined factors, barriers, and facilitators that may affect current uptake of care for BRCA mutations in American and British populations. After briefly overviewing previous reviews on aspects of access to care for BRCA mutations, I detail the specific methodology used for the scoping study. The results section categorises and describes 46 factors that had statistically significant relationships with uptake of genetic counselling, genetic testing, or any type of screening, medication, or surgery. Barriers and facilitators that were qualitatively identified are separately categorised and described. The discussion section attempts to contextualise the scoping study results, including the importance of context in interpreting uptake figures and the potential applicability of American findings in Britain and British findings in America.

Informed by the findings of Chapters Three and Four, Chapter Five aims to provide empirical evidence germane to the availability of services, barriers to care, and relevance and effectiveness of services to different patient groups. I open with an accounting of the study methodology, i.e., the recruitment process for US and UK genetics professionals and support group members, participant group descriptions, and data collection and analysis approach for focus groups and interviews. Next, I segue into the results of a process mapping exercise in which participants were asked to draw their personal or professional experience of how patients access care for BRCA mutations. The rest of the section shares the results of open coding, covering the participants' perspectives on how regulatory mechanisms affect care; which factors, barriers, and facilitators may affect uptake of care; and what service improvements they wish to see implemented. The analysis section employs axial coding to look at the deeper patterns in the data, e.g., the influence that country (United States or United Kingdom) and role (clinician or support group member) had on

responses. Chapter Five's discussion section situates the axial coding analysis within the literature on access to genetic services. I then discuss the strengths and limitations of the empirical study and close with a summary of the chapter.

Through an ethical analysis of the previous chapters' findings, Chapter Six puts forward an account of situations in which it may be problematic that US and UK women do not access care for BRCA mutations. I begin with a short review of why access to care for BRCA mutations is an important and complex topic. Next, I briefly revisit the project methodology, and then I analyse the findings of Chapters Three through Five to consider potentially problematic barriers to care, the most ethical approach to BRCA services, and possible facilitators that may redress inequity of access. Finally, I summarise the country-based differences and similarities in access to care and consider strengths, weaknesses, and implications of this thesis.

2 Chapter Two: Definitions of terms and methodological choices

2.1 Introduction

This chapter explores literature relevant to access to care for BRCA mutations in the United States and United Kingdom. First, I explain what 'care for BRCA mutations' means by describing what BRCA mutations are, what clinical effects they have, and how they are identified and managed. Second, I explore possible definitions of and models for 'access to care' through an evaluation of influential health service delivery papers and reviews. Third, I explain how extensive preliminary research informed the choice of the model around which findings from this thesis are organised. Fourth, I describe the methodological choices (and in some cases, circumstantial adjustments) made to enable comprehensive study on access to care for BRCA mutations.

2.2 What is 'care for BRCA mutations'?

This section provides some background information on how BRCA genes function and how BRCA mutations may affect women's health. In particular, I introduce the types of care that are relevant for identifying and managing BRCA mutations: genetic counselling, genetic testing, and post-test care including screening, medication, and/or surgery.

2.2.1 Background on BRCA genes and harmful mutations

BRCA1 and BRCA2 are tumour suppressor genes found in every human genome. When functioning normally, the BRCA genes direct the production of proteins that regulate cell growth and division and repair damaged genetic material (Lister Hill National Center for

Biomedical Communications, 2016). However, a harmful BRCA1 or BRCA2 mutation may inactivate these tumour suppression functions, which may prevent the repair of damaged genetic material and ultimately cause cancer (American Cancer Society, 2014).

As noted in Chapter One, pathogenic BRCA mutations significantly increase a woman's risk of breast and ovarian cancer. One in eight women, or about 12 per cent of women, born in the United States or United Kingdom will develop breast cancer during their lives; risk factors ranging from family history of cancer to breast density may increase their chances of developing cancer above this population risk (Cancer Research UK [CR UK], 2015a; NCI, 2012b). In particular, having a harmful BRCA1 or BRCA2 mutation is a risk factor that increases a woman's lifetime risk of breast cancer to roughly 60 to 80 per cent (Wessex Clinical Genetics Service, 2016). In other words, a BRCA mutation carrier is usually at least five times more likely to develop breast cancer than a population-risk woman. The influence a BRCA mutation has on lifetime risk for ovarian cancer in American and British women is even starker. Compared to a population-risk woman with a lifetime risk of less than 2 per cent, a BRCA1 mutation carrier has a lifetime risk between 40 to 60 per cent and a BRCA2 mutation carrier has a lifetime risk between 10 to 30 per cent (CR UK, 2015b; NCI, 2016b). Thus, having a BRCA mutation makes a woman between 5 and 30 times more likely to develop ovarian cancer than a woman at population risk.

BRCA mutations are also associated with other conditions, including fallopian cancer, peritoneal cancer, pancreatic cancer, prostate cancer, male breast cancer, and Fanconi anaemia (NCI, 2015). There are also potential associations between BRCA1 mutations and uterine body cancer and cervical cancers, as well as between BRCA2 mutations and melanoma, bile duct cancer, gallbladder cancer, and stomach cancer (Petrucelli, Daly, & Feldman, 2013).

2.2.2 Identifying and managing BRCA mutations

Given that BRCA mutations have such important health implications, the next question is how clinicians identify people with potential BRCA mutations. Because harmful BRCA mutations only occur in somewhere between 1 in 400 and 1 in 800 – e.g., less than 1 per cent – of people (Petrucelli et al., 2010), it has been considered unjustifiable to test every single patient coming through a primary care office. However, germline BRCA mutations are passed down through an autosomal dominant mode of inheritance, i.e., only one parent has to pass down a BRCA mutation for a child to inherit it (Cancer Genetics & Prevention, 2013). This means clinicians can identify patients with unusually strong family histories of breast, ovarian, and related cancers – also known as hereditary breast and ovarian cancer syndrome (HBOC) – as candidates for referral to genetic services. In rare cases, a BRCA mutation develops spontaneously, though adoption, alternate paternity, and assisted reproductive technology are more likely reasons why a patient would be the only family member with a mutation (Petrucelli et al., 2013). Additionally, clinicians may consider ethnicity when making a referral; Ashkenazi Jewish (AJ) women, for instance, are known to have higher prevalence of pathogenic BRCA mutations than non-AJ women. Since Chapter Three contains a detailed analysis of three prominent American and British BRCA risk assessment guidelines, this section will not examine specific referral criteria.

If a patient has not already filled out a detailed personal and family history form before referral, she will typically need to fill one out before attending genetic counselling (Hanning et al., 2014; Young et al., 2006). Topics discussed during a genetic counselling session usually include the patient's risks of having a mutation and developing cancer, how genetic test results would be used personally and disclosed to family members, and the risks and benefits of pursuing genetic testing (Center for Surveillance, Epidemiology and Laboratory Services, 2014). If the patient wishes to pursue genetic testing, the genetic counsellor will

consider if she is the appropriate family member to be tested at that time. (In order to provide the most informative results, BRCA testing typically begins with family members affected by cancer first and then is extended to family members unaffected by cancer afterwards; the exception is if every affected family member is unable or unwilling to test [Breastcancer.org, 2016]. This topic is discussed more in Chapter Three.) If the patient is an appropriate testing candidate, then she will provide a blood or saliva sample for a laboratory to analyse.

The results of a BRCA test will fall into one of three categories: a positive result, a negative result, or a 'variant of uncertain significance' (VUS) result (Facing Our Risk of Cancer Empowered [FORCE], n.d.). A positive result means that a harmful mutation was found; a negative result means no harmful mutation was found; and a VUS result means a mutation was found, but whether it affects the patient's risk of cancer is uncertain. Given that positive and VUS results occur less than 1 per cent and 3 per cent of the time, respectively (Eggington et al., 2012; Petrucelli et al., 2010), the vast majority of test results will be negative. Furthermore, negative test results are divided into two different types: If the test was negative and the patient's relative has a known harmful mutation, then it is a 'true negative' and the woman is at population risk for breast and ovarian cancer (NCI, 2015). If the test was negative and there is no known familial mutation, then the result is an 'uninformative negative', meaning the woman may have a harmful BRCA mutation that is currently unidentified or a harmful non-BRCA mutation (NCI, 2015).

Whilst VUS and negative results are not actionable, a woman who tests positive for a harmful BRCA mutation is typically eligible for BRCA carrier management options. Depending on the individual patient's age, risk profile, and preferences for care, she may elect various screening, medication, and/or surgical options. Chapter Three compares the

BRCA carrier management guidelines for two prominent guideline-making bodies, so this section will not discuss these options in any more depth.

In sum, 'care for BRCA mutations' may include genetic counselling, genetic testing, and post-test care options including screening, medication, and/or surgery.

2.3 What does 'access to care' mean?

As mentioned in Chapter One, 'access to care' is a widely used but vaguely defined term that aims to describe whether and how patients are able to use healthcare services. In this section, I examine papers that define and/or operationalise access to care in order to generate (1) commonly agreed upon features of access to care in general and (2) potential models for use specifically in this thesis.

To begin, I will discuss the most thorough analysis of definitions and models of access to date: Levesque, Harris, and Russell (2013). Through a systematic review, Levesque et al. generated a comprehensive set of characteristics describing access and ultimately developed their own conceptual framework of access. The authors ran searches using the words 'access', 'accessibility', 'utilisation of health care services', 'availability', 'affordability', and 'acceptability' in two databases, Pubmed and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Additionally, they employed snowball searches of the reference sections of public health and health administration textbook chapters on access to care and rounded out their strategy with searches on Google and Google Scholar.

Overall, Levesque et al. drew on a total of 38 sources, which provided background information on access, definitions of access, and/or operational models of access. The authors ultimately defined access as an opportunity to obtain care and proposed a 10-

dimensional framework that considers the accessibility of services and the abilities of patients to use those services. The five dimensions falling under service accessibility are approachability, acceptability, availability and accommodation, affordability, and appropriateness. The five dimensions falling under patient ability are ability to perceive, ability to seek, ability to reach, ability to pay, and ability to engage. Whilst Levesque et al. produced a rigorous accounting of the different components of access, they did not suggest how to evaluate these myriad components. However, the authors did discuss what kinds of instruments might be appropriate:

> Methodological research should enable our field to develop the measurement instruments that will better capture the complexity of access. Adding to the complexity is the fact that various sources of information can inform the varied dimensions of access, but it can be difficult to merge together to draw a complete picture of access. Mixed method analyses of consumer surveys, quality of care data, epidemiological surveys of utilisation, as well as organisational surveys may be necessary. (Levesque et al., 2013, p. 8)

With this in mind, it may be helpful to examine a subset of the 38 papers informing Levesque et al.'s definition of access and conceptual framework. In particular, the 10 papers that proposed models of access with distinct components and were locatable as full-text English versions are in Table 2.1.

Table 2.1: Models of access informing Levesque et al. (2013)

Models	Definitions	Components of access
Donabedian (1973)	Accessibility comprising the concept of degree of adjustment between resources and populations	Temporal characteristics
		Spatial characteristics
		Socio-organisational characteristics
Aday & Andersen (1974)	Entry into the health care system	Predisposing factors
		Enabling factors
		Need for healthcare
Salkever (1976)	Quantitative measure of accessibility combining attributes of the resources and attributes of the population	Financial accessibility
		Physical accessibility
Penchansky & Thomas (1981)	General concept summarising a set of more specific dimensions describing fit between the patient and the healthcare system	Affordability
		Accessibility
		Accommodation
		Availability
		Acceptability
Dutton (1986)	The product of patient characteristics plus provider and system attributes	Financial
		Time
		Organisational factors
Margolis, Carey, Lannon, Earp, & Leininger (1995)	The timely use of personal health services to achieve the best possible outcomes	Financial
		Personal
		Structural
Waters (2000)	Quantitative egalitarian indicators that measure equity in terms of access to care	N/A
Gulliford et al. (2002)	Helping people command appropriate healthcare resources in order to preserve/improve their health	Availability
		Barriers to care
		Relevance/effectiveness of services across groups
		Equity of access
Shengelia, Murray & Adams (2003)	Combination of coverage (probability of receiving a necessary health intervention, conditional on need) and utilisation (quantity of services and procedures used)	Physical access
		Resource availability
		Cultural acceptability
		Financial affordability
		Quality of care
Peters et al. (2007)	Includes actual use of services; emphasis given to consider both users and services characteristics in evaluation of access	Quality
		Geographic accessibility
		Availability
		Financial accessibility
		Acceptability of services

Donabedian (1973) outlined different models for organising and evaluating healthcare delivery. The author suggested that access be represented by service utilisation rates and

informed by barriers to access; however, access should not be unlimited, e.g., services should only be available to patients who need them. Donabedian ultimately proposed that when organising healthcare services to promote access, three types of characteristics should be considered: temporal characteristics (when and how quickly services are available), spatial characteristics (location and physical size of services), and other socio-organisational characteristics (traits like race or class that may affect the quality and provision of services).

Aday and Andersen (1974) noted that there were two main concepts of access in the literature: one based on patient and healthcare system characteristics, and another based on quantitative outcomes. Their framework incorporated both concepts:

> A basic framework for the study of access, then, may be conceptualized as proceeding from health policy objectives through the characteristics of the health care system and the populations at risk (inputs) to the outcomes or outputs: actual utilization of health care services and consumer satisfaction with these services. (Aday & Andersen, 1974, pp. 211–212)

Furthermore, the authors emphasised the appropriateness of taking a needs-based approach, e.g., whether patients are able to receive medical services at the moment they are necessary.

Penchansky and Thomas described access as 'a concept representing the degree of "fit" between the clients and the system' (1981, p. 128). Their model involved five dimensions of access: availability, accessibility, accommodation, affordability, and acceptability. First, availability described whether services were adequately supplied. Second, accessibility described whether clients were located sufficiently close to services. Third, accommodation described whether clients found administrative systems user-friendly. Fourth, affordability described whether clients found care appropriately priced and within their means. Fifth, acceptability described whether clients and providers found each other's personal characteristics and behaviour to be compatible with their own. These dimensions were then examined using patient satisfaction – but not service utilisation – measures.

Margolis, Carey, Lannon, Earp, and Leininger (1995) used an Institute of Medicine definition of access, i.e., the timely use of healthcare to attain the best possible health outcomes (Millman, 1993), and posited that there are three types of barriers affecting services: financial, personal, and structural. The authors considered use of services in terms of visits and procedures; mediators of service usage in terms of appropriateness, treatment efficacy, quality of providers, and patient adherence; and outcomes in terms of health status and equity of services. This paper specifically discussed how to facilitate access to care for disadvantaged children from a US GP perspective.

Gulliford et al. (2002) proposed a four-dimensional model of access to care that built on papers including Donabedian (1973), Aday and Andersen (1974), and Penchansky and Thomas (1981). One key distinction the authors highlighted was between 'having access' and 'gaining access': the former referred to the potential to use a service, and the latter referred to the process of trying to use a service. The Gulliford model incorporated these concepts into its first two dimensions, with 'having access' converted to the availability of services and 'gaining access' converted to financial, organisational, and cultural or social barriers to care. The remaining two dimensions, relevance and effectiveness of services for different groups of patients and equity of access, addressed whether services helped achieve their intended outcomes.

Peters et al. (2008) examined systemic disparities in access in resource-poor countries, providing a framework centred on quality of care. The four secondary components included geographic accessibility, or short travel time to healthcare services; availability, or the ability to use care when it is needed; financial accessibility, including the direct and indirect costs; and acceptability of services, meaning the alignment of care within local contexts and values. This paper focussed on care for individuals in developing countries, including a brief review

of structural and organisational ways to redress inequities, and did not explicitly discuss how this model of access would translate to developed countries.

Salkever (1976), Dutton (1986), Waters (2000), and Shengelia, Murray, and Adams (2003) all approached access from mainly quantitative perspectives informed by qualitative components. Salkever thought accessibility was the combination of resource and population attributes, using regression analysis to estimate how barriers affect the likelihood of patients receiving physical examinations. Dutton considered access to be the intersection of patient, provider, and system attributes, particularly focussing on financial, time, and organisational factors; she evaluated these effects using regression analysis. Waters described access as utilisation of care by individuals in need, applying microeconomic techniques to create two numerical indicators for equality of access. Shengelia et al. examined the juncture of coverage and utilisation for necessary procedures, considering five kinds of barriers: physical access, resource availability, cultural acceptability, financial affordability, and quality of care. The authors suggested equations to measure and combine these components, with the stipulation that the equations (and ultimately, the model) require empirical testing.

A few other key papers consulted were Daniels (1982) and Mooney (1983), which did not put forward frameworks but provided helpful context. Daniels discussed how difficult it is to evaluate equity of access, both because access is an ambiguous term and because there are different theories of what access should seek to measure. He compared the merits of a utilisation-based approach, as articulated by Aday and Andersen; a patient satisfaction-orientated approach, as described by Sloan and Bentkover (1979); and a so-called market approach, which Daniels drew from research on health planning and economics such as that of Enthoven (1980). Ultimately, Daniels argued for an account based on fair equality of opportunity, which incorporates both the right for individuals to function normally (i.e., free

of disease or disorder) and some elements of the utilisation-based and patient satisfaction-orientated approaches. Mooney, meanwhile, sketched out seven plausible definitions of access in order to show how uncertain the term 'equity of access' could be. Mooney singled out two definitions as particularly important: equality of access for equal need and equality of utilisation for equal need. Ultimately, Mooney suggested that healthcare systems may be able to achieve equality of access through sufficient investment of resources into services, but equality of utilisation requires patient populations to also have equivalent desire for services; this distinction is important to this thesis.

To summarise the results of the 10 papers informing the Levesque model, as well as Daniels and Mooney's papers, access may be considered both quantitatively and qualitatively. Access may be measured through quantitative outcomes variables such as utilisation rates and patient satisfaction ratings, though these kinds of data require interpretation because we cannot tell why a person did or did not use a service. Additionally, access may be qualitatively informed by barriers and facilitators, e.g., characteristics of both patients and healthcare systems that hinder or help patients seeking care.

2.4 Which model of access to care should be used?

With these characteristics of access to care in mind, I drew on several years' worth of preliminary research in surveying the US and UK cancer genetics communities to inform my choice of a model of access to care. This preliminary work included attending various genetics-related conferences and meetings; reading various books, journal articles, and online sources about care for BRCA mutations; discussing observations and readings with Professors Michael Parker and Anneke Lucassen; and conducting semi-structured interviews with four genetics professionals (two American and two British).

Developing my overall thesis methodology was an iterative process, informed by the results of the activities described above (particularly for content development of the preliminary focus group guides) as well as readings on various qualitative research techniques (e.g., papers and books on interview and focus group techniques, case studies, documentary analysis, and systematic reviews) and a cursory look into quantitative analysis (which I ultimately decided not to use). I also attended the Department of Continuing Education's weeklong course on 'Qualitative Research Methods in Health Care', where I changed the empirical component from stakeholder interviews to primarily stakeholder focus groups with supplementary interviews if needed.

Additionally, a fellow course attendee described an exercise called 'process mapping', a technique that helps people intimately involved in a particular process to re-examine and (hopefully) improve that process. Given that the referral process – how patients reach medical specialties such as cancer genetics services – was a recurrent topic in the preliminary interviews, literature review, and readings of various government policies and professional guidelines, I subsequently adapted this technique to use in the opening exercise in focus groups. Process mapping enables visual comparison of different stakeholders' perceptions of and experiences with services, which I hoped to use to examine similarities and differences between cancer genetics communities. I tested the technique in an Ethox research presentation and in informal discussions/meetings with several clinicians, and it was a successful way of examining how people think a process currently works and how it should ideally work. (Section 5.2.3.2 discusses the adoption and use of process mapping in more depth.)

The culmination of the preliminary research phase involved the four preliminary interviews. These were conducted with (1) a National Health Service (NHS) trainee and clinical genetics

specialist who spent six weeks observing genetic counselling at Sloan-Kettering, an academic hospital in New York; (2) a clinical geneticist who trained in Bristol, worked in Oxford and London for 12 years, and gained US wet lab experience; (3) a senior genetic counsellor at Massachusetts General Hospital who specialised in cancer genetics for eight years; and (4) a research oncologist who trained in Ireland and came to Massachusetts General Hospital to pursue an academic medicine fellowship. Additional input on the topics selected and methodology came from informal conversations with attendees at the Genethics Club, a nationwide UK forum run by Professors Parker and Lucassen where clinical genetics professionals discuss ethical issues arising in their daily practice. (See Appendix 8.1 for the preliminary interview guide.)

Topics emerging as particularly interesting during the preliminary phase included (1) relationships within and between different cancer genetics communities; (2) ethical issues arising in shifting US and UK policy landscapes, e.g., resource allocation and insurance; (3) referrals to and from cancer genetics services; and (4) demographics of patients seen and unseen, including potential ethnic, racial, gender, and religious disparities in genetic services uptake. Returning to the working definition of access to care, these topics required a model that incorporated barriers and facilitators as well as service availability. Additionally, the models needed to accommodate both subjective and objective outcomes, e.g., measures of patient satisfaction and rates of utilisation of services.

Of the 10 frameworks informing the Levesque model that are described above, Aday and Andersen (1974), Margolis et al. (1995), Gulliford et al. (2002), Shengelia et al. (2003), and Peters et al. (2008) fit these characteristics. The Shengelia model was too quantitative for this thesis, however, given that it provided equations to measure access that could not be tested using the data I planned to collect. The Peters model was also ruled out because it

heavily drew on quality of care, which was another characteristic that this thesis was not designed to assess. That left the Aday and Anderson, Margolis, and Gulliford models to consider. Ultimately, the Gulliford model was selected because its third dimension – relevance and effectiveness of services for different groups of patients – provided a way to consider potential country-based differences between care in the United States and care in the United Kingdom.

As the Gulliford model plays a central role in understanding this thesis, the abstract summarising the model is reproduced in its entirety below:

> Access is a complex concept and at least four aspects require evaluation. If services are available and there is an adequate supply of services, then the opportunity to obtain health care exists, and a population may 'have access' to services. The extent to which a population 'gains access' also depends on financial, organisational and social or cultural barriers that limit the utilisation of services. Thus access measured in terms of utilisation is dependent on the affordability, physical accessibility and acceptability of services and not merely adequacy of supply. Services available must be relevant and effective if the population is to 'gain access to satisfactory health outcomes'. The availability of services, and barriers to access, have to be considered in the context of the differing perspectives, health needs and material and cultural settings of diverse groups in society. Equity of access may be measured in terms of the availability, utilisation or outcomes of services. Both horizontal and vertical dimensions of equity require consideration. (Gulliford et al., 2002, p. 186)

Put another way, the four dimensions of the Gulliford model are as follows: (1) Availability and adequacy of supply refer to whether services are offered in great enough supply to satisfy need. (2) Financial, organisational, and social or cultural barriers refer to patient, provider, and healthcare system characteristics that may impede patients' ability to use offered services. (3) Relevance and effectiveness of services refers to how well the offered services meet the expectations and needs of different groups in society. (4) Equity of access refers to objective criteria including utilisation, availability, and health outcomes, which can be assessed in two ways. Horizontal equity means equal access for equal needs, e.g., providing services equally to high-risk poorer people and high-risk wealthier people, whilst

vertical equity means unequal access for unequal needs, e.g., prioritising services for high-risk individuals over low-risk individuals.

Strengths of the Gulliford model include the diversity of barriers considered, the attention paid to how different societal groups may require differently tailored services, and the recognition that both horizontal and vertical equity matter in evaluations of access. First, the model's incorporation of both individual and systemic barriers means it reflects the various ways that service utilisation may be impacted, e.g., one woman may find services are incompatible with her cultural beliefs whilst another woman may find the wait times for services unacceptable. Second, the suggestion to consider how different groups experience services is important because not all barriers (or facilitators) affect all groups the same way; a Black or Hispanic woman may not find services as tailored to her environment as a White woman does, for instance. Third, the explicit reference to both vertical and horizontal equity reinforces the idea that risk of a health condition, not social or economic circumstances, should determine who has access to care.

Conversely, the main weakness of the Gulliford model is its lack of clear quantitative application. Unlike other models cited in this chapter, there are no equations supplied or even recommendations about choosing between regression analysis and a coefficient of inequality, for instance. For the purposes of this thesis, that omission is not a problem, as Chapters Three through Six employ qualitative methods. If this thesis were to be extended, though – e.g., if identified barriers were to be quantified through a survey – other resources would be required to determine the appropriate kind of quantitative analysis.

2.5 How should access to care for BRCA mutations be studied?

Here I should note that after finishing this preliminary research in summer 2012, my initial methodological plan was somewhat different. I intended to combine theoretical analysis of UK and US professional guidelines, policy documents, and legal rulings with empirical case study research on the four topics mentioned above. The case studies were going to draw on focus groups with cancer genetics stakeholders in four geographically distinct cancer genetics communities: Oxford and Southampton in the United Kingdom, and Cambridge/Boston and Baltimore/Washington DC in the United States. However, as I was working on the theoretical analysis and planning my case studies, I suffered an injury in May 2013 and sustained catastrophic neurological and vascular damage that has required nearly four years' worth of invasive medical treatment.

As a result, I needed to scale back my empirical work considerably to involve only focus groups with a small set of US and UK genetics professionals and support group members. This rendered the prospect of conducting case studies quite slim and forced me to reconceptualise my methodology whilst maintaining a balance of theoretical and empirical approaches and continuing to examine the four emergent findings from my preliminary research. Because healthcare in the United States and United Kingdom is largely governed by clinical guidelines, laws, legal rulings, and policies, the theoretical analysis has been preserved in Chapter Three as a critical review of these four types of regulatory mechanisms; this covered the 'shifting health policy landscape' topic in the proposed list of case studies, as well as the 'availability of services' dimension of the Gulliford model. Because of the extremely limited literature comparing access to care in the United States and United Kingdom, I recast Chapter Four as a scoping study of factors, barriers, and facilitators affecting access to care in one or both countries. This enabled analysis of the

intended case study on 'patients seen and unseen' and the factors affecting their use of services, and it clearly examined the 'barriers to care' dimension of the Gulliford model. The empirical component became a small-scale examination of how US and UK genetics professionals and support group members provide and pursue care in day-to-day practice in Chapter Five, which permitted examination of 'referrals to and from genetic services' and 'relationships within and between different genetics communities'. Because these participant groups are intimately familiar with how multiple women access services, they were also particularly helpful in considering relevance and effectiveness of services for different groups and proposing ideas to enhance equity of access to care. Finally, I envisioned Chapter Six as the chapter that would bring together the findings of Chapters Three through Five using ethical analysis, thus drawing on each small study to help answer the larger question of whether there are situations in which it is problematic that US and/or UK women do not access care. Table 2.2 shows that Chapters Three, Four, and Five each address two or more dimensions of the Gulliford model of access to care, followed by Chapter Six examining all four dimensions.

Table 2.2: Dimensions of access addressed in Chapters Three through Six

Dimension of access to care	**Chapter Three**	**Chapter Four**	**Chapter Five**	**Chapter Six**
Availability/supply of services	X		X	X
Barriers to care	X	X	X	X
Relevance/effectiveness of services across groups		X	X	X
Equity of access		X		X

2.6 Summary

This chapter has described two relevant terms that will be used throughout this thesis – access to care and care for BRCA mutations – as well as explained the motivation behind choosing the Gulliford model of access. I have also introduced the methodological adjustments I made to my project to continue researching the most interesting preliminary research results. In the next chapter, I continue the 'review' portion of this thesis with a thorough examination of regulatory mechanisms governing access to care.

3 Chapter Three: Regulatory mechanisms that may affect access to care

3.1 Introduction

This chapter serves as a comprehensive accounting of the first dimension of the Gulliford model, i.e., which services for BRCA mutations are currently available and in what supply, as well as a partial accounting of the second dimension, i.e., which barriers may limit use of these services. To accomplish these purposes, this chapter examines how regulatory mechanisms – clinical guidelines, laws, legal rulings, and policies – shape the patient pathway to accessing care for BRCA mutations in the United States and United Kingdom.

Section 3.2 describes how and why certain clinical guidelines, laws, legal rulings, and policies were selected for comparison. First, it explains why three key BRCA-specific guidelines – produced by the UK-based NICE, the US-based National Comprehensive Cancer Network (NCCN), and the United States Preventive Services Task Force (USPSTF) – were chosen. Second, it examines how tables comparing the NICE, NCCN, and USPSTF guidelines for BRCA risk assessment and BRCA carrier management were developed. Third, it gives an overview of how population breast screening is related to BRCA risk assessment and why the USPSTF, NCCN, and UK National Screening Committee (UK NSC) guidelines were chosen for comparison. Fourth, it explores the criteria for identifying major laws, legal rulings, and policies that create a regulatory framework for access to BRCA services in the United States and United Kingdom. Fifth, it briefly describes how the four tables outlining the US and UK regulatory mechanisms were developed.

Section 3.3 examines the development, content, and use of BRCA-related guidelines. Characteristics of the USPSTF, NCCN, and NICE and their guidelines are itemised in Table 3.1 and further explained in the supplementary text. Accompanying Tables 3.2 through 3.4, which contain criteria for referral to genetic services, are four key observations about these guidelines. NICE and NCCN recommendations for BRCA carriers are listed in Table 3.5, and important takeaways from these guidelines are also discussed. Finally, the USPSTF, NCCN, and UK NSC guidelines for population breast screening are described in Table 3.6 and discussed in relation to BRCA carrier management guidelines.

Section 3.4 explores the American and British regulatory frameworks governing the provision of genetic services. Tables 3.7 and 3.8 contain the main laws, legal rulings, and policies that affect access in the United States, and the corresponding text describes the general restrictions and protections established through these regulatory mechanisms. This process is then repeated for the British regulatory mechanisms, which are situated in Tables 3.9 and 3.10. The two regulatory frameworks are then compared and contrasted, with particular attention paid to how each country approaches genetic discrimination and genetic testing regulation.

Section 3.5 summarises and critiques the overall effect that clinical guidelines, laws, legal rulings, and policies have on American and British access to care for BRCA mutations. In particular, this section explores why there might be differences in which women are eligible for care through clinical guidelines and which laws, legal rulings, and policies might help or hinder women seeking care.

Finally, Section 3.6 reiterates the main observations from Sections 3.3 through 3.5 on clinical guidelines, laws, legal rulings, and policies. It also emphasises the relationship of this

chapter to the overall thesis, particularly with respect to which aspects of the first and second dimensions of the Gulliford model have been addressed.

3.2 Selection of regulatory mechanisms

As mentioned in the introduction, four types of regulatory mechanisms from the United States and United Kingdom were examined in this chapter: clinical guidelines, laws, legal rulings, and policies. These mechanisms help explain the Gulliford model's first dimension of access: whether services are available in adequate supply. Specific to BRCA mutations, clinical guidelines help determine which genetic services and post-test interventions are available and to which patients, whilst laws, legal rulings, and policies establish protections for and restrictions on how care is supplied. This section describes which regulatory mechanisms were selected for comparison and why, as well as how analyses were carried out.

3.2.1 Selection of BRCA risk assessment and carrier management guidelines

One British and two American BRCA-specific guidelines were compared in Section 3.3. NICE, a non-departmental public body sponsored by the UK Department of Health, produces evidence-based clinical guidance for care provided by the NHS in England and Wales (NICE, 2016); accordingly, the most recent NICE guideline on familial breast cancer was an obvious choice (NICE, 2013b). Because health is a devolved issue, the Northern Ireland Assembly and Scottish Parliament are responsible for Health and Social Care in Northern Ireland and the NHS in Scotland, respectively (Ham, Heenan, Longley, & Steel, 2013; NICE, 2016b). This means that NICE guidance only applies in Northern Ireland or Scotland if the respective devolved administration approves it. In practice, the Department of Health, Social Services and Public Safety (HPSS) in Northern Ireland has a process for

endorsing, implementing, and monitoring specific NICE guidelines (McBride, 2013), whilst the Scottish Intercollegiate Guidelines Network (SIGN) develops Scotland-specific guidelines for NHS Scotland to implement but maintains a collaboration agreement with NICE (SIGN, 2012, 2017). Specific to familial breast cancer guidance, HPSS endorsed the current NICE guideline with two small policy caveats about informed consent and off-label use of chemoprevention drugs in Northern Ireland (HPSS, 2014). Because SIGN does not have its own familial breast cancer guideline, a SIGN working group evaluated the NICE guidance and concluded that NHS Scotland should prioritise implementation of updated NICE recommendations for genetic testing, breast screening, and chemoprevention (Healthcare Improvement Scotland, 2014). As a result, no additional British guidelines were evaluated.

Whilst there is no perfect American analogue to NICE, the USPSTF is a reasonable equivalent. The USPSTF is an independent but government-funded clinical group that uses systematic reviews to inform national recommendations for preventive care and establish minimum standards for both public and private insurance coverage (Agency for Healthcare Research and Quality [AHRQ], 2012); hence, the most recent USPSTF guideline for BRCA-related cancer was selected. The USPSTF guideline does not apply to women who are symptomatic of or presently being treated for cancer, nor does it consider management options (USPSTF, 2013), so a second American guideline was needed. Thus, a complementary guideline from NCCN – a non-profit alliance of 27 renowned American cancer centres that focusses on clinical care, research, and education – addressing BRCA risk assessment and management options for US women of all cancer statuses was selected (NCCN, 2016b, n.d.).

3.2.2 Analysis of BRCA risk assessment and carrier management guidelines

Analysis of the NICE, USPSTF, and NCCN guidelines for BRCA risk assessment was conducted through the construction of Tables 3.2 through 3.4. Every combination of patient characteristics that resulted in an adult woman being referred according to at least one guideline was evaluated. For NICE, this included referrals made to both secondary care and genetic services, given that secondary care does not always exist in practice and referrals are often made directly from primary care to genetic services. For the USPSTF, this included referrals indicated by any guideline-approved risk assessment tool. For NCCN, this included referrals made specifically because of BRCA risk assessment but not general cancer genetic risk assessment. Five types of cancers – breast, ovarian, pancreatic, prostate, and colorectal – were mentioned in at least one guideline. Criteria involving these cancers were then organised into one table involving personal history of cancer (Table 3.2) and two tables involving known familial mutations and family history of cancer (Tables 3.3 and 3.4). Breast cancer-related criteria were further stratified using age of diagnosis, and in the case of family history, sex of the affected relative.

For BRCA carrier management, all recommendations made by NICE and NCCN for post-test interventions were organised in Table 3.5. The main categories of post-test interventions were screening, which was further sub-divided into breast screening and ovarian screening; medication; and surgery. Each intervention was listed under its corresponding category and accompanied by age and frequency/timing specifications.

3.2.3 Selection and analysis of population breast screening guidelines

Age-based population breast screening guidelines from the United Kingdom and United States were also examined in the 'Clinical guidelines' section. Population breast screening guidelines are relevant to BRCA guidelines for two reasons: BRCA-related breast cancer is associated with younger age of diagnosis, and some women only learn of their risk for a BRCA mutation after being diagnosed with breast cancer (NCI, 2015). Since the BRCA-specific guidelines came from NICE, the USPSTF, and NCCN, the three groups were the first port of call when selecting population breast screening guidelines.

NICE does not issue population breast screening guidelines, but the guideline currently in operation in England, developed by the independent but government-funded UK NSC, was a natural replacement (UK NSC, 2012). [Wales, Northern Ireland, and Scotland all run their own population breast screening programmes, but since each country offers the same services at the same frequency as the UK NSC recommends (National Services Division, 2015; Public Health Agency, n.d.; Public Health Wales, n.d.), no additional UK population breast screening guidelines required analysis.] The USPSTF produced a population breast screening guideline that established baseline requirements for insurance coverage, but US legislation requires insurers to follow the less restrictive 2002 version rather than the more restrictive 2009 or 2016 revisions (Herszenhorn, 2009). Ultimately, it made sense to consider the current NCCN guideline for population breast screening as well, given that one of the main reasons for that unusual US Senate requirement was criticism from specialist organisations like NCCN (Oncology, 2009). Analysis was conducted through the construction of Table 3.6, which lists the ages for which different types of screening are recommended, if at all, by each guideline.

3.2.4 Selection of laws, legal rulings, and policies

In terms of which laws, legal rulings, and policies were analysed, three basic criteria guided selection. Each mechanism had to (1) relate to access to genetic services, (2) impact regulations in the United States and/or United Kingdom, and (3) exist in written form. Identification and selection of regulatory mechanisms involved looking for and reading through both primary and secondary sources related to genetic laws, legal rulings, and policies to determine if a particular mechanism satisfied the three criteria above. Primary sources – e.g., the laws, legal rulings, and policies themselves – were found via searching US and UK legislative databases and court dockets, in addition to websites for governmental divisions like the US National Human Genome Research Institute (NHGRI) and UK Department of Health. Secondary sources – e.g., academic articles, position papers, and blog posts interpreting laws, legal rulings, and policies – were chiefly found via searching Pubmed, Google, and Google Scholar; reviewing citations in genetic policy articles such as Soini (2012) and Borry et al. (2012); and studying materials from non-profit advocacy organisations such as Genetic Alliance UK and the US-based Genetic Alliance. Examining legal blogs such as the Genomics Law Report (www.genomicslawreport.com) and IPKat (ipkitten.blogspot.com) also helped contextualise several international laws and legal rulings that shape American and British national law.

3.2.5 Analysis of laws, legal rulings, and policies

The methods described in Section 3.2.4 yielded a total of 23 British regulatory mechanisms (17 laws, three legal rulings, and three policies) and 15 American regulatory mechanisms (11 laws, one legal ruling, and three policies). Analysis involved organising these mechanisms into four tables: Tables 3.7 and 3.8 list important US regulatory mechanisms in chronological order from 1914 through 2013, whilst Tables 3.9 and 3.10 catalogue important UK regulatory mechanisms in chronological order from 1953 through 2013. Each

table summarises key information about selected regulatory mechanisms, including type (e.g., law), year, shorthand title, source (e.g., UK Parliament), major effects, and any other relevant notes. [Three notes concern devolution, meaning that a few regulatory mechanisms did not entirely apply throughout the entire United Kingdom because those issues were not reserved to the UK Parliament (Scottish Parliament, 2017). Specifically, the Scottish Parliament passed its own version of two UK Parliament laws and has its own enforcement procedure for life sciences regulation; these differences are noted in Tables 3.9 and 3.10 and also described in the accompanying text.] Selected mechanisms address genetic discrimination in employment and insurance, privacy of genetic information, quality and availability of genetic testing, and patentability of genes. These topics were first discussed in relation to each country's own regulatory framework, and the American and British regulatory frameworks were subsequently compared to each other.

3.3 Clinical guidelines

Sections 3.2.1 and 3.2.3 introduced several key groups responsible for developing guidelines for BRCA risk assessment, BRCA carrier management, and population breast screening, as well as the methods by which their guidelines were analysed. Section 3.3.1 considers why guidelines exist in general and how the organisational structures of the USPSTF, NCCN, and NICE impact BRCA-specific guidelines. Section 3.3.2 discusses four key observations about how BRCA risk assessment guidelines are written and used in practice. Section 3.3.3 focusses on the level of evidence underlying NCCN and NICE recommendations for breast and ovarian screening, medications, and surgery. Section 3.3.4 highlights the relationship between population breast screening and BRCA risk assessment, as well as the amount of mammography recommended by NCCN, the USPSTF, and the UK NSC. Finally, Section 3.3.5 concludes with summarised observations about the three major guideline-making bodies and the three sets of BRCA-related guidelines.

3.3.1 Purpose of guidelines and structure of guideline-making bodies

Broadly speaking, clinical guidelines exist to provide the right patients (e.g., the individuals most likely to benefit from care and/or at highest risk for a condition) with the right kinds of care (e.g., care proven to be clinically effective for the condition in question). Supporters say that when executed properly, clinical guidelines can increase clinical effectiveness, resource efficiency, care uniformity, and patient and clinician knowledge (Timmermans & Mauck, 2005). But who and what qualify as the right patients and the right kinds of care, as well as who should make those determinations, are not always easy questions to answer. Clinicians and patients may question the composition of guideline development groups, the kinds of evidence considered in guidelines, and the flexibility with which clinicians can interpret guidelines (Woolf et al., 1999). These and other characteristics of NICE, NCCN, and the USPSTF and their BRCA-specific guidelines are addressed in Table 3.1 and the accompanying text.

Table 3.1: Characteristics of BRCA guideline-making groups and guidelines

	NCCN	USPSTF	NICE
Membership	Generalist Specialist Patient advocate	Generalist	Generalist Specialist Patient advocate
Funding source	Internal (NCCN Cancer Institutions)	US Government	UK Government
National implications	None	Sets baseline insurance standards through 'A' and 'B' recommendations	Non-binding recommendations for NHS bodies to implement
Flexibility	Clinician discretion	Clinicians required to offer 'A' and 'B' recommendations; 'C' recommendations are at clinician's discretion	Clinician discretion
Intended users	Clinicians Insurers Patients and families	Primary care providers Insurers	National Health Service Local authorities Local/national organisations
Population of interest for BRCA guidelines	Adult men and women who may be at high risk for BRCA-related cancer; all cancer statuses included	Asymptomatic adult women who may be at high risk for BRCA-related cancer but are not presently in active treatment	Adult men and women who may be at high risk for BRCA-related cancer; all cancer statuses included
Guidelines cover BRCA risk assessment/testing	Yes	Yes	Yes
Guidelines cover BRCA carrier management	Yes	No	Yes

3.3.1.1 Membership of guideline-making groups

As the 'Membership' row of Table 3.1 shows, NICE and NCCN guideline-making groups incorporate relevant specialists, generalists, and patient advocates, whereas USPSTF membership consists solely of generalists. The Guideline Development Group that created the NICE BRCA guideline included specialists in breast care, genetics, oncology, radiology, and surgery; generalists in primary care and public health; patient and carer members; and voluntary health organisation members (NICE, 2013b, pp. 50–53). Similarly, the NCCN BRCA guideline panel comprised specialists in medical oncology, cancer/medical genetics, haematology/haematology oncology, gynaecology/gynaecologic oncology, and breast surgical oncology; generalists in internal medicine and public health/preventive medicine; and patient advocates (NCCN, 2016b, p. 2). In contrast, the USPSTF uses the same 16-person group of primary care and public health clinicians to develop all guidelines, and these clinicians are appointed to four-year terms (USPSTF, 2016a).

The composition of each guideline-making group is reflected in each BRCA guideline's intended users, population of interest, and included topics. In general, USPSTF guidelines are intended for insurers and primary care providers, and as the USPSTF's remit is preventive care and not disease management, guidelines do not extend to symptomatic individuals or include treatment recommendations (USPSTF, 2016a). Thus, the USPSTF BRCA guideline covers risk assessment but not carrier management, and its population of interest is women who may be at risk for BRCA-related cancer but are currently asymptomatic and not in treatment (US Departments of Labor [DOL], Health and Human Services [HHS], and the Treasury [Treasury], 2015). In contrast, NICE and NCCN guidelines are designed for much broader use: The target audience of NICE guidelines is the NHS, health authorities, and private and voluntary organisations, whilst the target audience

of NCCN guidelines is anyone involved in cancer care, including clinicians, insurers, and patients and their families (NCCN, 2016a; NICE, 2016a). Specific to BRCA guidelines, NICE and NCCN's populations of interest are women and men of all cancer statuses who may be at risk for HBOC, and both groups make recommendations for risk assessment and carrier management (NCCN, 2016b; NICE, 2013b).

3.3.1.2 Funding sources and national implications of guidelines

As stated in Section 3.2.1, NICE and the USPSTF were chosen for analysis because they are both government-funded bodies producing nationally influential guidelines. This connection between funding sources and national implications of guidelines likely fuels one of the misperceptions noted by Woolf et al. (1999), e.g., cost effectiveness may appear to wield undue influence over guidelines.

There are a few reasons why this assertion is off-base. First, both the USPSTF and NCCN explicitly state that their guidelines do not incorporate or evaluate costs of interventions, and indeed, the evidence their guidelines cite is entirely clinical, rather than clinical and economic (NCCN, 2016a; USPSTF, 2016d). Second, cost effectiveness can actually be a by-product of clinical effectiveness in the sense that guidelines target the patients most likely to have certain conditions and promote evidence-based interventions for those patients. For example, all three BRCA guidelines strongly recommend testing affected relatives before unaffected relatives unless all affected relatives are unavailable, e.g., deceased or unwilling to test (NCCN, 2016b; NICE, 2013b; USPSTF, 2013). The reason to test affected relatives first is twofold. If an affected relative tests positive for a mutation, all other relatives can be tested for that single mutation alone (Breastcancer.org, 2016). If no mutation is found in affected relatives, unaffected relatives do not need to be tested right then. (The family might have a currently unidentified harmful BRCA mutation or a harmful non-BRCA genetic

mutation, though, so future genetic testing might be warranted [NCI, 2015].) In this case, each guideline helps control costs by providing necessary testing and avoiding unnecessary testing where possible. Third, NICE has a policy of not vetoing an intervention on costs alone; it considers the clinical benefit alongside the cost impact of an intervention and additionally accounts for social value judgments such as justice (NICE, 2014). For example, NICE uses economic modelling to determine the risk threshold for BRCA testing, which is a way of targeting the patients most likely to have BRCA mutations without allocating disproportionate resources to BRCA testing.

Now that the idea of relying too much on cost effectiveness has been dispelled, the national implications for each guideline can be discussed. The USPSTF probably holds the greatest influence of the three guideline-making bodies, with NICE a close second and NCCN a distant third. First, the USPSTF's power is derived from the ACA, which requires private American insurers to cover preventive services receiving grade 'A' or 'B' recommendations but not 'C', 'D', or 'I' recommendations. To receive an 'A' or 'B' grade, the USPSTF must find 'there is high certainty that the services have a substantial or moderate net benefit' for specific patient populations (The Henry J. Kaiser Family Foundation, 2015). ('C', 'D', and 'I' grades mean that a service has a small benefit, no benefit or harms that outweigh the benefits, or an incalculable benefit due to insufficient evidence, respectively [USPSTF, 2016c].) In its BRCA guideline, the USPSTF issued a 'B' grade that requires insurers to cover risk assessment, counselling, and testing of women whose family histories suggest increased risk for BRCA mutations (USPSTF, 2013). Second, NICE guidelines are non-binding recommendations that the local NHS authorities are left to implement. According to the NHS Commissioning Board, NICE guidelines can be overridden for compelling reasons such as 'availability of resources and competing priorities' (NHS Commissioning Board, 2013, p. 5), with cost considered systemically. Third, NCCN guidelines are funded

internally by the 27 NCCN Cancer Institutions and have no mandatory effect on insurance or defined role in health authority commissioning. There are, however, US insurers like BlueCross BlueShield and Humana that voluntarily follow NCCN guidelines because they are produced by a respected, independent organisation (NCCN, 2010).

An important caveat to the theoretical influence that guidelines have is whether and how they are implemented in daily practice. For instance, Francke, Smit, de Veer and Mistiaen (2008) conducted a systematic meta-review of the factors affecting implementation of new clinical guidelines, noting that more complex guidelines appear less likely to be used by clinicians. Grol (2001) also points out that '[a] program to implement a guideline should be well designed, well prepared, and preferably pilot tested before use' in order to improve its likelihood of affecting clinical practice (p. II-46). Although evaluating whether NICE, the USPSTF, and NCCN have successfully implemented their BRCA-related guidelines is beyond the scope of this chapter, it is worth noting how each organisation approaches dissemination and implementation in general. NICE has made a concerted effort to assess the effect of its guidance on daily practice, culminating in the publication of its first biannual uptake and impact report in September 2016 (NICE, 2016c). The USPSTF invites federal agencies, professional groups, and quality improvement organisations to provide feedback on its guidance and help circulate its guidance to clinicians; additionally, the group freely disseminates recommendations online and in medical journals (USPSTF, 2014). NCCN makes guidelines freely available to anyone registering for an NCCN.org online account, and it produces a lay version of all clinical guidelines for patients (NCCN, 2017a, 2017b).

3.3.1.3 Flexibility built into guidelines

As shown in the 'Flexibility' row of Table 3.1, all three guideline-making bodies build flexibility into their guidelines in various ways. Before any clinical guideline, each group prefaces its recommendations with a statement about how clinicians must exercise discretion in order to accommodate patients' needs and choices. For example, the NCCN disclaimer states: 'Any clinician seeking to apply or consult the NCCN guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment' (NCCN, 2016b). Within the BRCA guidelines, both NCCN and NICE also include phrases like 'Discuss option of [intervention]' and '[U]se clinical judgment when deciding whether to offer [intervention]' (NCCN, 2016b; NICE, 2013b, p. 7). Because of the ACA requirement that clinicians must offer 'A' and 'B' recommendations, the USPSTF does not afford primary care practitioners any flexibility in whether they offer certain preventive services. However, clinicians have the latitude to offer 'C' recommendations to patients in accordance with patient preferences and their clinical judgment, as well as some freedom in how they implement 'A' and 'B' interventions (USPSTF, 2016c).

3.3.2 Guidelines for BRCA risk assessment, counselling, and testing

Now that some general features of the NICE, NCCN, and USPSTF guideline-making bodies have been introduced, their guidelines for BRCA risk assessment, counselling, and testing can be explored. The guidelines described throughout this section are the NCCN 'Genetic/familial high-risk assessment: Breast and ovarian' guideline from March 2016; the USPSTF 'BRCA-related cancer: Risk assessment, genetic counseling, and genetic testing' guideline from December 2013; and the NICE 'Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related

risks in people with a family history of breast cancer' guideline from June 2013 (NCCN, 2016b; NICE, 2013b; USPSTF, 2013).

An important caveat is that eligibility for a genetics referral does not necessarily translate to eligibility for genetic testing. The DOL, HHS, and the Treasury jointly issued a clarification that the USPSTF 'recommendation includes both genetic counseling and BRCA testing, if appropriate, for a woman as determined by her provider' (DOL, HHS, and the Treasury, 2015). Under the USPSTF guideline, a patient assessed as high risk is therefore eligible to be referred for counselling and testing. Similarly, the NCCN stipulates that if a woman meets any BRCA-specific referral criterion, she is entitled to 'further personalized risk assessment, genetic counseling, and often genetic testing and management' (NCCN, 2016b, p. BRCA-1). In contrast, the NICE guideline recommends testing to a subset of patients referred for genetic counselling, as only women with a combined BRCA1/2 mutation carrier probability of 10 per cent or more are eligible for testing. (That said, Section 3.3.2.4 emphasises how this threshold is a flexible recommendation, not a rigid requirement.)

Tables 3.2 through 3.4 compare the three organisations' referral criteria for personal and family history of BRCA-related cancer and known familial mutations. In the tables, 'Yes' means a woman should be offered a referral under the specified circumstances; 'No' means a guideline excludes personal and/or family history of a particular cancer from its referral criteria; and 'Not directly' means a guideline includes personal and/or family history of a particular cancer in its referral criteria, but not in a significant way. If a relative is listed without an explicit designation of cancer, she or he has the condition indicated in the corresponding leftmost column (or in the case of Table 3.3, all relatives with unspecified conditions have breast cancer). Additionally, several terms for familial relationships are used in the tables and in the explanatory text that follows. First-degree relatives (FDRs) include

parents, siblings, and children; second-degree relatives (SDRs) include grandparents, grandchildren, aunts and uncles, nieces and nephews, and half-siblings; and third-degree relatives (TDRs) include first cousins and great-aunts and great-uncles (NCCN, 2016b). A close relative is any FDR, SDR, or TDR.

Following the tables themselves, four key observations about the referral criteria in Tables 3.2 through 3.4 are discussed. These observations include (1) the use of two different risk assessment methods; (2) the role of age of diagnosis in driving referrals; (3) the way colorectal, pancreatic, and prostate cancers impact referrals; and (4) the difference between referral criteria in theory and in practice.

Table 3.2: Referral criteria for personal history of breast, ovarian, and pancreatic cancers

	Age patient diagnosed	NCCN	USPSTF	NICE
Breast cancer	≤ 45 y	Yes	[See criteria for '≤ 50 y']	Not directly
	≤ 50 y	Yes, w/ any of the below: - Additional BC primary - CR w/ BC, PANC, or PROC (GS ≥ 7) - Limited/unknown family history	Yes, w/ either of the below: - CR w/ BC (≤ 50 y) - Ashkenazi Jewish ancestry	Not directly
	≤ 60 y	Yes, w/ triple negative BC	[See criteria for 'Any age']	Not directly
	Any age	Yes, w/ any of the below: - CR w/ BC (≤ 50 y), male BC, or OVCAR - Two CRs w/ BC - Two CRs w/ PANC and/or PROC (GS ≥ 7) - Ethnicity linked to higher mutation frequency	Yes, w/ any of the below: - Personal history of OC - CR w/ OC, male BC, or BC and Ashkenazi Jewish ancestry - Two CRs w/ BC - BRCA1 or BRCA2 MSS ≥ 10 - Combined BRCA1/2 MSS ≥ 15	Yes, if ≥ 10% chance of mutation
Ovarian cancer	Any age	Yes, if OVCAR	Yes, w/ any of the below: - Personal history of BC - CR w/ OC, male BC, or BC (≤ 50 y) - Two CRs w/ BC - Ashkenazi Jewish ancestry - BRCA1 or BRCA2 MSS ≥ 10 - Combined BRCA1/2 MSS ≥ 15	Yes, if ≥ 10% chance of mutation
Pancreatic cancer	Any age	Yes, w/ any of the below: - CR w/ BC (≤ 50 y) or OVCAR - Two CRs w/ BC, PANC, and/or PROC (GS ≥ 7) - Ashkenazi Jewish ancestry	Not directly	Not directly

Key: BC = breast cancer; unless listed as 'male BC', BC patients are female. OC = ovarian cancer. OVCAR = ovarian carcinoma. PANC = pancreatic cancer. PROC = prostate cancer. Y = years. CR = close relative (first-, second-, or third-degree relative). GS = Gleason score. MSS = Manchester Scoring System.

Table 3.3: Referral criteria for family history of breast cancer

Age relative diagnosed	NCCN	USPSTF	NICE
< 40 y	[See criterion for '≤ 45 y']	[See criterion for '< 50 y']	FDR
≤ 45 y	FDR/SDR	[See criterion for '< 50 y']	[See criteria for '< 50 y']
< 50 y	FDR/SDR (can be 50 y) w/ any of the below: - Additional BC primary - CR w/ BC, PANC, or PROC (GS ≥ 7) - Limited/unknown family history	CR (can be 50 y if Ashkenazi Jewish)	Yes, if either of the below: - FDR w/ bilateral BC (first diagnosis < 50 y) - FDR/SDR and CR w/ OC (OK if FDR has both cancers)
≤ 60 y	FDR/SDR w/ triple negative BC	[See criteria for 'Any age (female)']	Yes, if either of the below: - SDR and SDR w/ bilateral BC (AAD < 60 y) - Two SDRs (AAD < 60 y) and CR w/ OC
Any age (female)	FDR/SDR w/ any of the below: - CR w/ BC ≤ 50 y or OVCAR - Two CRs w/ BC - Two CRs w/ PANC and/or PROC (GS ≥ 7) - Ethnicity linked w/ high mutation frequency TDR and two CRs w/ BC (at least one ≤ 50 y) and/or OVCAR	Yes, w/ any of the below: - FDR - CR w/ bilateral BC - CR w/ BC and OC - CR and CR w/ BC, OC, or CRC	Yes, w/ any of the below: - FDR and FDR/SDR - FDR/SDR and FDR/SDR w/ OC (one must be FDR) - Three FDRs/SDRs - FDR and three CRs - ≥ 10% chance of gene mutation - ≥ 8% risk of BC in next 10 years - ≥ 30% lifetime risk of BC
Any age (male)	Yes, w/ either of the below: - Male FDR/SDR - Male CR and FDR/SDR w/ BC	Male CR	Yes, w/ any of the below: - Male FDR - Male CR and FDR/SDR w/ BC (< 50 y) - Male CR and two FDR/SDRs w/ BC (AAD of FDR/SDRs < 60 y)

Key: BC = breast cancer; unless specified as male, BC patients are female. CRC = colorectal cancer. OC = ovarian cancer. OVCAR = ovarian carcinoma. PANC = pancreatic cancer. PROC = prostate cancer. Y = years. FDR = first-degree relative. SDR = second-degree relative. TDR = third-degree relative. CR = close relative (FDR, SDR, or TDR). GS = Gleason score. AAD = average age of diagnosis.

Table 3.4: Referral criteria for known familial mutations and family history of colorectal, ovarian, pancreatic, and prostate cancers

	Age relative diagnosed	NCCN	USPSTF	NICE
Known mutation	Any age	CR	CR	CR
Colorectal cancer	Any age	No	CR and CR w/ BC or CRC	No
Ovarian cancer	Any age	Yes, w/ any of the below: - FDR/SDR w/ OVCAR - CR w/ OVCAR and FDR/SDR w/ BC - TDR w/ OVCAR and two CRs w/ BC (at least one ≤ 50 y) and/or OVCAR	Yes, w/ any of the below: - FDR - CR w/ OC and BC - CR w/ OC and CR w/ BC or OC - CR and Ashkenazi Jewish ancestry	Yes, w/ any of the below: - FDR/SDR and FDR/SDR w/ BC (one must be FDR) - CR and FDR/SDR w/ BC < 50 y (OK if FDR has both cancers) - CR and two FDR/SDRs w/ BC (AAD of BC < 60 y) - Two CRs - ≥ 10% chance of gene mutation - ≥ 8% risk of BC in next 10 years - ≥ 30% lifetime risk of BC
Pancreatic cancer	Any age	FDR/SDR w/ any of the below: - CR w/ BC (≤ 50 y) or OVCAR - Two CRs w/ BC, PANC, and/or PROC (GS ≥ 7) - Ashkenazi Jewish ancestry	Not directly	Not directly
Prostate cancer	Any age	FDR/SDR (GS ≥ 7) w/ either of the below: - CR w/ BC (≤ 50 y) or OVCAR - Two CRs w/ BC, PANC, and/or PROC (GS ≥ 7)	Not directly	Not directly

Key: BC = breast cancer (female). CRC = colorectal cancer. OC = ovarian cancer. OVCAR = ovarian carcinoma. PANC = pancreatic cancer. PROC = prostate cancer. Y = years. FDR = first-degree relative. SDR = second-degree relative. TDR = third-degree relative. CR = close relative (first-, second-, or third-degree relative). GS = Gleason score. AAD = average age of diagnosis.

3.3.2.1 Use of two risk assessment methods

The first observation relates to the two risk assessment methods – concrete criteria and calculated probabilities – that appear in the three guidelines. Concrete criteria are specific personal and family history patterns that should result in referrals if met, e.g., NCCN recommends referring any woman with a personal history of ovarian carcinoma (NCCN, 2016b). Calculated probabilities are risks of BRCA mutations and breast cancer determined using validated tools, e.g., NICE recommends referring any woman whose risk of a BRCA mutation meets or exceeds 10 per cent (NICE, 2013b). The NCCN guideline only uses concrete criteria, whereas the USPSTF and NICE guidelines use both concrete criteria and calculated probabilities.

By design, NCCN's concrete criteria for personal history of cancer and family history of cancer are similar throughout Tables 3.2 through 3.4. This is because the guideline explicitly says '[f]irst- or second-degree blood relatives meeting any of the above [personal history] criteria' should be referred (NCCN, 2016b, p. BRCA-1). For example, both a woman diagnosed with breast cancer at age 44 and a woman whose FDR or SDR was diagnosed at age 44 should be referred. There are also some referral criteria limited to family history of cancer alone, e.g., a woman with three TDRs who have ovarian carcinomas.

In contrast, the USPSTF allows clinicians to use any of five approved tools to guide their referral decisions. Two tools, the FHS-7 and the Referral Screening Tool (RST), are checklists requiring one and two positive responses, respectively, for referral (Ashton-Prolla et al., 2009; Bellcross, Lemke, Pape, Tess, & Meisner, 2009). The other tools – the Ontario Family History Assessment Tool (FHAT), the Manchester Scoring System (MSS), and the Pedigree Assessment Tool (PAT) – are points-based tools that indicate referral if a patient's

score meets a certain threshold (Evans et al., 2004; Gilpin, Carson, & Hunter, 2000; Hoskins, Zwaagstra, & Ranz, 2006). Thus, the USPSTF guidelines include both concrete criteria from the FHS-7 and RST and calculated probabilities through the FHAT, MSS, and PAT. Because the FHS-7 and RST indicate referral for a broader range of patients than the FHAT, MSS, and PAT, though, nearly all referral criteria included in Tables 3.2 through 3.4 are derived from the FHS-7 and RST alone.

The format of the NICE guideline echoes the mix of concrete criteria and calculated probabilities in the USPSTF guideline. NICE provides a large set of concrete family histories for which referral is indicated, in addition to calculated probability thresholds for breast cancer and BRCA1/2 mutations. This combination of methods is unsurprising because the NICE guideline separates referral from primary care to secondary care (e.g., a breast clinic) and referral from secondary care to a genetic service. The former uses easily applied concrete criteria, such as 'one first-degree female relative diagnosed with breast cancer at younger than age 40 years'; the latter uses calculated probabilities such as '30% or greater lifetime risk of developing breast cancer', along with a more complex set of concrete criteria (NICE, 2013b, pp. 19–23). Notably, NICE does not specify which calculated probability tools should be used, though it does cite the MSS and BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), a statistical model that estimates risk based on personal and family history of BRCA-related cancers (Antoniou, Pharoah, Smith, & Easton, 2004), as acceptable options.

Despite their contrasting formats, concrete criteria and calculated probabilities often lead to the same result for very high-risk women. A woman with breast cancer diagnosed before age 50 and a close relative diagnosed with ovarian carcinoma at any age satisfies the MSS threshold of 15 points and therefore merits referral per both the NICE and USPSTF

guidelines. This history also warrants referral according to the NCCN's concrete criteria. Similarly, a woman whose two FDRs have ovarian cancer is eligible for referral across all three guidelines, regardless of whether concrete criteria or calculated probabilities are used. For lower-risk women, however, concrete criteria may provide a lower threshold to referral than calculated probabilities. For example, a woman with two relatives diagnosed with breast cancer after age 50 is eligible for referral under the FHS-7 and RST, but no USPSTF-approved calculated probability tool recommends referral.

3.3.2.2 Impact of age of diagnosis on referrals

The second observation, alluded to in the paragraph above, is how age of diagnosis is incorporated into both risk assessment methods in Tables 3.2 through 3.4. Age of diagnosis matters because on average, women develop BRCA-related breast and ovarian cancers at younger ages than sporadic cancers (NCI, 2015). The 'two-hit' hypothesis, originally proposed by Alfred Knudson to explain the development of the hereditary cancer retinoblastoma, explains this discrepancy in age of onset (Knudson, 1971). Knudson hypothesised that before cancer develops, two mutations – or two 'hits' – have to occur to inactivate both tumour suppressor genes. BRCA mutation carriers are born with one mutation and therefore require only one spontaneous mutation before cancer develops, whereas non-mutation carriers require two spontaneous mutations (Brandt, Bermejo, Sundquist, & Hemminki, 2008). Theoretically, then, it takes less time for a single hit to occur in a BRCA carrier than for two hits to occur in a non-BRCA carrier, leading to BRCA carriers developing cancers at earlier ages than non-BRCA carriers.

As Tables 3.2 and 3.4 demonstrate, age of diagnosis does not factor into concrete referral criteria for ovarian, colorectal, pancreatic, prostate, or male breast cancer. Conversely, Tables 3.2 and 3.3 show that age of diagnosis directly factors into concrete criteria for

certain referrals involving breast cancer. For instance, all three guidelines incorporate age into their referral criteria for women who have a single female relative diagnosed with a single breast cancer. The USPSTF recommends referral if a close relative is diagnosed before age 50; NCCN recommends referral if an FDR or SDR is diagnosed by age 45; and NICE recommends referral if an FDR is diagnosed before age 40. If these guidelines are read strictly, then age of diagnosis may mean the difference between being eligible and ineligible for referral in cases where women have few relatives with BRCA-related cancer. For example, a woman whose FDR is diagnosed with breast cancer at age 39 is eligible for referral under all three guidelines, but if her FDR is diagnosed at age 49 instead, she is only eligible under the USPSTF guideline. The 'Any age (female)' boxes in Tables 3.2 and 3.3 also indicate that when combined personal and family history is significant enough, age of diagnosis does not factor into concrete criteria involving breast cancer. Thus, a woman with three FDRs who have been diagnosed with breast cancer should be referred according to all three guidelines.

Though the content of calculated probability models cannot be visualised in Tables 3.2 through 3.4, models including the MSS and BOADICEA incorporate age of diagnosis for female and male breast cancer, ovarian cancer, pancreatic, and prostate cancer (Antoniou et al., 2004; Evans et al., 2004). In a points-based model like the MSS, early-onset cancers score more points to reflect their association with greater mutation probabilities. For example, a 45-year-old breast cancer patient whose mother had ovarian cancer at age 60 scores 16 points, but that score decreases to 14 points if the breast cancer is diagnosed at age 55 instead. Since the referral threshold is 15 points, the woman is technically eligible for referral in the former case and ineligible for referral in the latter case. Likewise, if a woman is first diagnosed with breast cancer at age 35 and then has another breast cancer primary diagnosed at age 39, she is eligible for referral with a score of 16. But if those cancers

occurred at 41 and 45 instead, she would no longer be eligible for referral with a score of 12. In a statistical model like BOADICEA that simply returns a numerical estimate of mutation likelihood, it is difficult to see exactly how influential age is. For the first example, BOADICEA yields the same results as the MSS: Referral is indicated for the 45-year-old patient but not the 55-year-old patient. For the second example, though, BOADICEA recommends referral for both sets of ages, thus contradicting the MSS recommendation for the older set of ages.

Ultimately, age of diagnosis has variable impact within and between the two risk assessment methods, even those included in the same guideline. Returning to the case of a woman whose female FDR was diagnosed with breast cancer at age 39 helpfully makes this point. Whilst the woman is eligible for referral according to all three guidelines' concrete criteria, no USPSTF-approved or NICE-recommended calculated probability tool supports her referral. This discrepancy underscores the importance of which risk assessment tool a clinician selects; Section 3.3.2.4 further examines this point.

3.3.2.3 Influence of colorectal, pancreatic, and prostate cancers on referrals

The third observation is why and how colorectal, pancreatic, and prostate cancers influence each of the three guidelines. Why these cancers appear in one or more guidelines is straightforward: There is evidence, albeit of varying strength, that BRCA mutations increase susceptibility to each of these cancers. How these cancers factor into guidelines is more complicated, but in general, they contribute to referral only if accompanied by personal or family history of breast and/or ovarian cancer.

All three guidelines include prostate and pancreatic cancers, which is unsurprising given that BRCA mutations have repeatedly been linked to increased risks of both cancers. For prostate cancer, a lifetime risk of about 12.5 per cent in a non-carrier increases to up to 30 per cent in a BRCA1 carrier and up to 39 per cent in a BRCA2 carrier (Breast Cancer Linkage Consortium, 1999; CR UK, 2015d; NCI, 2016d; Petrucelli et al., 2013; Risch et al., 2001). For pancreatic cancer, a lifetime risk of about 1.5 per cent in a non-carrier increases to up to 3 per cent in a BRCA1 carrier and up to 7 per cent in a BRCA2 carrier (Breast Cancer Linkage Consortium, 1999; CR UK, 2015e; Hahn et al., 2003; NCI, 2016c; Petrucelli et al., 2013; Stadler et al., 2012). As for the content of the guidelines, two findings are notable: (1) The MSS reflects that BRCA2 mutations influence prostate and pancreatic cancer risks more than BRCA1 mutations; and (2) unlike breast and ovarian cancer, pancreatic and prostate cancer do not drive referrals. The first finding is simply that the MSS, which calculates BRCA1 and BRCA2 sub-scores, only assigns BRCA2 points for prostate and early-onset pancreatic cancer diagnoses (Evans et al., 2004). The second finding is that regardless of which risk assessment method is used, prostate and pancreatic cancer diagnoses are not weighted heavily enough to result in a referral without numerous familial diagnoses or accompanying breast or ovarian cancer diagnoses. The FHAT and MSS only award 1 or 2 points for a diagnosis of prostate or pancreatic cancer, which falls far short of the points the respective tools require for referral (10 for the FHAT, 10 for the BRCA2 MSS sub-score, and 15 for the combined BRCA1/2 MSS score). Similarly, NCCN requires a woman whose FDR or SDR was diagnosed with pancreatic or prostate cancer to have additional risk factors, e.g., a high Gleason score accompanying a prostate cancer diagnosis and another relative affected by early-onset breast cancer. (Gleason score is a numerical measure ranging from 2 to 10 that indicates how likely prostate cancer is to spread [NCI, n.d.].)

In contrast to each guideline including prostate and pancreatic cancer, only the USPSTF guideline includes colorectal cancer. That fewer guidelines include colorectal cancer makes sense, as the evidence is mixed on whether a BRCA mutation increases the lifetime risk of 5 per cent found in non-carriers (CR UK, 2015c; NCI, 2016a). Although several studies report an increased risk of colorectal cancer in BRCA1 or BRCA2 carriers (Brose et al., 2002; Phelan et al., 2014; Risch et al., 2001; D. Thompson, Easton, & Breast Cancer Linkage Consortium, 2002), others suggest that neither mutation affects colorectal cancer risk (Chen-Shtoyerman et al., 2001; Mersch et al., 2015). Consequently, it is instructive to consider why two USPSTF-approved tools, the FHAT and FHS-7, incorporated family history of colorectal cancer into their referral criteria at all. Gilpin et al. (2000) included family history of colorectal cancer in the FHAT because Ford, Easton, Bishop, Narod, and Goldgar (1994) reported a fourfold increase in colorectal cancer risk for BRCA1 carriers. Notably, the FHAT creators found that the single point awarded for a colorectal cancer diagnosis did not affect any individual's referral eligibility. The FHS-7 authors included a question about familial breast and/or colorectal cancer because their previous study '[suggested] a higher than [expected] prevalence of such association in cancer genetics clinics of Porto Alegre' (Ashton-Prolla et al., 2009, p. 285). Whilst the authors reported moderate agreement between this item and a clinical geneticist's risk assessment, they did not report whether this agreement was attributable to multiple breast cancers, multiple colorectal cancers, or both breast and colorectal cancers. Thus, the utility of including colorectal cancer in either the FHAT or the FHS-7 is unclear.

As this sub-section has shown, the inclusion of non-breast and ovarian cancers into the BRCA risk assessment guidelines is unlikely to affect referral eligibility in many cases. In a handful of cases, though, including these phenotypes may make it harder for non-genetics professionals to identify patients at uniformly high risk. For instance, a woman who has four

relatives with colorectal cancer is technically eligible for BRCA risk assessment under the USPSTF-approved FHS-7, even though her family history is more indicative of conditions like Lynch syndrome or familial adenomatous polyposis. This reality underscores the need for guidelines to be interpreted using clinical judgment, which is discussed more in the next sub-section.

3.3.2.4 Referral criteria in theory and in practice

The fourth observation relates to how the three risk assessment guidelines compare to each other in theory and in practice. 'In theory' refers to what a guideline says in writing, and 'in practice' refers to how a guideline might be interpreted by experienced clinicians. This is the difference between following guidelines verbatim and understanding that guidelines are meant to guide care, not restrict it (Lugtenberg, Zegers-van Schaick, Westert, & Burgers, 2009; Woolf et al., 1999). For BRCA risk assessment, there are three main situations to consider: cases where clinicians make referrals and offer testing that guidelines support, cases where clinicians make referrals and offer testing that guidelines do not support, and cases where clinicians decline to make referrals and offer testing that guidelines support.

When the guidelines recommend referrals and testing in theory and experienced clinicians agree in practice, women who are clearly at high risk for BRCA mutations are likely involved. For example, Table 3.4 shows that all three guidelines recommend referring a woman to a genetic service if there is a known BRCA mutation in her family. No GP would knowingly deny that patient a referral, and no genetics professional would deny her the opportunity to undergo counselling or testing. Likewise, Table 3.4 confirms that a patient who has two FDRs diagnosed with ovarian carcinomas is clearly eligible for referral according to all three guidelines. Presented with this family history, an experienced GP would likely refer the patient without needing to consult any risk assessment guideline, and a

genetics professional would offer counselling and work with the patient to try to have an appropriate relative tested.

When skilled clinicians make referrals and offer testing that the guidelines do not support, their patients are likely on the cusp of being designated high-risk. For instance, Table 3.3 shows that the NCCN and USPSTF guidelines support referral and testing for a woman whose sister was diagnosed with breast cancer at age 41 and died before undergoing testing. Although the NICE guideline does not explicitly support referral in this situation because the woman's sister is over 39, the woman may still be referred if her GP believes she is at sufficiently high risk. Likewise, the patient may not meet NICE's 10 per cent risk threshold for testing, but her clinical geneticist may offer testing nonetheless because this threshold is not rigid. Table 3.1 contains another reason for clinicians to overrule a guideline: If the USPSTF guideline is followed exactly, some high-risk women will be denied counselling and testing. Whereas the NICE and NCCN guidelines include high-risk women who are symptomatic of or in treatment for BRCA-related cancer, the USPSTF guideline omits these women entirely (USPSTF, 2013). Since US clinicians are able to offer care beyond the scope of the USPSTF guideline, cancer patients at high risk for BRCA mutations may be referred and tested anyway. (The caveat is that women outside the scope of a USPSTF guideline may be liable for the costs of their care, though many insurers cover the costs of counselling and testing for cancer patients.)

In the rare cases where clinicians decline to offer referrals and testing that a guideline supports, the guideline in question may be inappropriately broad. Section 3.3.2.3, for instance, discussed women who are eligible for BRCA services even though they have no personal or family history of breast or ovarian cancer. The most incongruous case was a woman whose strong family history of colorectal cancer made her eligible for BRCA

services under the USPSTF guideline. In conversation with this patient, an experienced GP is likely to explain why a referral for hereditary colorectal cancer counselling is more appropriate than a referral for BRCA counselling. Similarly, if there is a more appropriate genetic test to order, a clinical geneticist will not order gratuitous BRCA testing just to comply with a guideline.

Ultimately, the three guidelines appear to be more similar in practice than their referral criteria would suggest in theory. Moreover, differences between the three guidelines that hold up in theory and in practice most likely involve the lowest-risk cases that result in referral. For example, Table 3.3 shows that only the USPSTF guideline recommends referral for a woman who has a TDR with (1) male breast cancer or (2) female breast cancer diagnosed at age 49. Although clinicians following the NICE or NCCN guidelines are able to refer patients with those histories, they may not consider those histories compelling enough to overrule the guidelines.

3.3.3 Guidelines for BRCA carrier management

Whilst the risk assessment guidelines help clinicians identify women at risk for BRCA mutations, the carrier management guidelines help clinicians care for women who carry harmful BRCA mutations. Of the three selected guideline-making groups, only the NICE and NCCN guidelines contain carrier management recommendations. As first discussed in Section 3.3.1, the USPSTF considers disease management beyond its purview and therefore does not prescribe care for women identified as BRCA carriers. The USPSTF guideline does, however, include a three-paragraph summary on 'Interventions for women who are BRCA carriers' that notes the effectiveness of mastectomy and oophorectomy. Additionally, there is a paragraph in the 'Research needs and gaps' section that states the need for research on 'effectiveness of intensive cancer screening and risk-reducing medications and

the effects of age at intervention on improving long-term outcomes' (USPSTF, 2013, p. 276).

In Table 3.5, NCCN and NICE's BRCA carrier management guidelines for breast and ovarian screening, surgery, and medication have been compared side by side. Three key observations about the management guidelines involve (1) generally similar recommendations for breast screening modalities, albeit with different age specifications; (2) lack of support for ovarian screening modalities; and (3) fairly limited recommendations for surgical and medication interventions, with emphasis on individual patient choice.

Table 3.5: BRCA carrier management guidelines

		NCCN		NICE	
Modality		**Age (y)**	**Specifications**	**Age (y)**	**Specifications**
Breast screening	**Breast awareness**	≥ 18	Year-round	≥ 18	Year-round
	Breast ultrasound	N/A	Not mentioned	--	If MRI unsuitable or results difficult to interpret
	Clinical breast exam	≥ 25	Every 6-12 months	N/A	Not mentioned
	Magnetic resonance imaging (MRI)	25-75	Annually	30-49	Annually
		> 75	On an individual basis	50-69	Only if dense breast pattern
	Mammography	25-29	Annually, if no MRI	30-39	On an individual basis (annually if elected)
		30-75	Annually	40-69	Annually
		> 75	On an individual basis	≥ 70	Triennially by request (population breast screening)
Ovarian screening	**Cancer antigen 125 test**	≥ 30-35	At clinician's discretion	N/A	Not mentioned
	Transvaginal ultrasound	≥ 30-35	At clinician's discretion	N/A	Not mentioned
Surgery	**Oophorectomy**	35-40	After family completed	--	On an individual basis, after family completed
	Mastectomy	--	On an individual basis	--	On an individual basis
Medication	**Chemoprevention**	--	On an individual basis	--	5 years of tamoxifen (or raloxifene sometimes)
	Oral contraceptive pills	--	On an individual basis	--	On an individual basis

3.3.3.1 Breast screening recommendations

Table 3.5 shows that NICE and NCCN recommend magnetic resonance imaging (MRI) and mammography to all BRCA carriers, though NCCN advocates screening a wider age range of BRCA carriers than NICE. Under the NICE guideline, unaffected carriers are routinely offered annual MRIs from ages 30 to 49 and annual mammograms from ages 40 to 69 (NICE, 2013b). Affected carriers are offered annual mammography for five years post-treatment, followed by screening based on their risk of breast cancer. Under the NCCN guideline, affected and unaffected carriers are routinely offered an annual MRI or mammogram from ages 25 to 29, followed by annual MRIs and mammograms from ages 30 to 75 (NCCN, 2016b). In addition to what is offered through routine screening, NICE also recommends extending annual MRIs for patients with dense breast tissue, and both NICE and NCCN contain provisions allowing patients to elect additional screening.

The guidelines for the other three types of screening – breast awareness, breast ultrasound, and clinical breast examinations (CBE) – are more straightforward. Both NICE and NCCN recommend that all BRCA carriers over the age of 18 practise year-round breast awareness, e.g., becoming familiar with how their breasts normally look and feel so that they can detect any potentially harmful changes (NHS Cancer Screening Programmes, 2016). Found only in the NICE guideline, breast ultrasound is a backup option if a BRCA carrier cannot have an MRI (e.g., if she is claustrophobic) or receives screening results that require further interpretation (NICE, 2013b). Found only in the NCCN guideline, CBE is a clinician-performed physical examination that is recommended annually or semi-annually for women beginning at 25.

Unsurprisingly, there is more clinical evidence underlying the modalities that are routinely recommended by both guidelines and less clinical evidence underlying the modalities that are recommended only by one guideline. The combination of mammography and MRI has regularly been reported as being more effective in reducing late-stage cancer diagnoses and reducing mortality than either method alone (Lowry et al., 2012; Warner et al., 2008, 2011). Whilst a literature review found no connection between breast awareness and reduced mortality, it also suggested that breast awareness contributes to reduced psychological morbidity by empowering women to take active roles in their health (McCready, Littlewood, & Jenkinson, 2005). Conversely, there is little evidence supporting the effectiveness of either breast ultrasound or CBE. Breast ultrasound is not considered an adequate replacement for MRI or mammography because it generates the most false negatives of the three modalities (Weinstein et al., 2009). Lee et al. (2010) also reported that screening with MRI, mammography, and ultrasound is no more effective than screening with MRI and mammography alone. Hence, it makes sense that NICE includes ultrasound only as a secondary option. As for CBE, there has never been a clinical trial establishing whether CBE is more beneficial than no screening at all (Thistlethwaite & Stewart, 2007). The NCCN acknowledges this reality but includes CBE anyway as a potential aid in the detection of interval cancers, i.e., cancers detected in between regularly scheduled mammograms or MRIs (NCCN, 2010).

3.3.3.2 Ovarian screening recommendations

Table 3.5 contains entries for two ovarian screening modalities, transvaginal ultrasound (TVUS) and cancer antigen 125 (CA-125) testing, but neither NICE nor NCCN recommends the routine use of either modality. NICE does not include ovarian screening at all; it is barely even mentioned in the lengthy evidence review accompanying the main guideline (NICE). NCCN, meanwhile, notes that whilst ovarian screening has not been

proven effective, clinicians may wish to consider TVUS and/or CA-125 testing for patients over the age of 30 who choose not to have oophorectomies (NCCN, 2016b, p. BRCA-A2).

Given that neither guideline recommends ovarian screening, it makes sense that there is no convincing evidence to support the effectiveness of either TVUS or CA-125 testing. A systematic review of annual combined TVUS and CA-125 testing reported high false positive rates and high false negative rates, along with a high proportion of ovarian cancers diagnosed at late stages (Fawunmi, Gojon, & Valachis, 2013). Another study found that TVUS and CA-125 testing did not identify ovarian cancers early enough to reduce mortality (Evans, Gaarenstroom, et al., 2009). Why, then, did NCCN allow clinicians to consider TVUS and/or CA-125 testing at all? The NCCN guideline does not provide an explicit answer, but the Memorial Sloan Kettering Cancer Center provides one possible rationale: allowing informed, high-risk women to contribute to research on the effectiveness of ovarian screening by participating in clinical trials (Memorial Sloan Kettering Cancer Center, n.d.).

3.3.3.3 Surgery and medication recommendations

Each surgery and medication listed in Table 3.5 is accompanied by a specification of 'On an individual basis' for at least one guideline; this is patient-orientated language and contrasts with the specification of 'At clinician's discretion' found in the NCCN ovarian screening entries. One reason for the emphasis on informed patient choice is that surgeries and medications involve significantly greater risks than screening. For example, oral contraceptives may reduce the risk of ovarian cancer, but they also may increase the risks of breast cancer, myocardial infarction, and ischemic stroke; thus, neither NICE nor NCCN recommends the routine prescription of oral contraceptives for cancer risk reduction purposes (NCCN, 2016b; NICE, 2013b; Roach et al., 2015). Likewise, mastectomy

drastically reduces cancer risk but involves major physiological and psychological consequences that do not occur with mammography or MRI (H.-P. Huang, Chen, Liang, & Miaskowski, 2014; Polivy, 1977). Oophorectomy differs from mastectomy, however, in that screening is not an acceptable alternative to surgery. The lack of effective screening explains why NCCN would routinely recommend risk-reducing salpingo-oophorectomy, i.e., removal of the ovaries and fallopian tubes, to women ages 35 to 40 who have completed their families (NCCN, 2016b). At the same time, the seriousness of the potential harms of surgery justifies why NICE would suggest patients consider risk-reducing oophorectomy on an individual basis rather than as routine care (NICE, 2013b).

Relatedly, evidence may point towards an intervention being effective, but not strongly enough to result in universally positive recommendations from guideline-making groups once side effects have been factored in. Such is the case for chemoprevention – i.e., medications like tamoxifen and raloxifene taken to reduce the risk of cancer – which is routinely recommended by NICE but not NCCN. In the discussion section of its guideline, NCCN notes that 'only limited data are available on the specific use of these agents in patients with BRCA1/2 mutations' (NCCN, 2016b, p. MS-32). Coupled with the fact that the side effects of chemoprevention agents include blood clots and stroke (NCI, 2012a), NCCN's lack of confidence in the evidence explains why it suggests chemoprevention be considered on an individual basis. On the other hand, NICE decided that the benefits of reducing cancer risk generally outweighed the harms, given that it recommends offering tamoxifen (or in some cases, raloxifene) to BRCA carriers for five years. It further addressed the side effects of the drugs by restricting the subgroups to whom chemoprevention is recommended, e.g., women who have never had breast cancer and are not at risk for thromboembolic disease or endometrial cancer (NICE, 2013b). However, tamoxifen and

raloxifene still must be prescribed off-label or accessed through research, as neither drug is approved for chemoprevention in the United Kingdom (Chustecka, 2013).

3.3.4 Guidelines for population breast screening

This sub-section examines three sets of population breast screening guidelines: the NCCN 'Breast cancer screening and diagnosis' guideline from July 2015, the USPSTF 'Breast cancer: screening' guideline from January 2016, and the UK NSC 'NHS Breast Screening Programme' guideline from October 2012 (NCCN, 2015; Public Health England, 2015a; USPSTF, 2016b). These guidelines are charted side by side in Table 3.6 below and described over the next few pages. Two observations in particular are discussed: (1) the similarities and differences between the three guidelines, and (2) the relationship between population breast screening and BRCA risk assessment.

Table 3.6: Population breast screening guidelines

<table>
<tr><th></th><th colspan="2">NCCN</th><th colspan="2">USPSTF</th><th colspan="2">UK NSC</th></tr>
<tr><th></th><th>Age (y)</th><th>Details</th><th>Age (y)</th><th>Details</th><th>Age (y)</th><th>Details</th></tr>
<tr><td>Breast awareness</td><td>≥ 25</td><td>Year-round</td><td>N/A</td><td>No letter grade</td><td>--</td><td>Year-round</td></tr>
<tr><td rowspan="2">Clinical breast exam</td><td>25-39</td><td>Every 1-3 years</td><td rowspan="2">N/A</td><td rowspan="2">No letter grade</td><td rowspan="2">N/A</td><td rowspan="2">Not mentioned</td></tr>
<tr><td>≥ 40</td><td>Annually</td></tr>
<tr><td rowspan="4">Mammography</td><td rowspan="4">≥ 40</td><td rowspan="4">Annually</td><td rowspan="2">40-49</td><td rowspan="2">Biennially
Individual choice</td><td>(47-49)</td><td rowspan="3">Triennially; age extension study in some areas</td></tr>
<tr><td>50-70</td></tr>
<tr><td rowspan="2">50-74</td><td rowspan="2">Biennially</td><td>(71-73)</td></tr>
<tr><td>≥ 71</td><td>Triennially
By request</td></tr>
</table>

3.3.4.1 Comparison of population breast screening guidelines

As shown in Table 3.6, NCCN supports more screening than the USPSTF, which in turn supports more screening than the UK NSC. This is true for breast awareness and CBE – neither the UK NSC nor the USPSTF formally mention either, but NCCN suggests that both start at age 25 – as well as mammography. One way to compare mammography recommendations is to examine the maximum number of routine mammograms a woman would receive from ages 40 to 74 under each guideline. Under the NCCN guideline, she would receive 35 (annual after the age of 40); under the USPSTF guideline, she would receive 13 (biennial from 50 to 74); and under the UK NSC guideline, she would be invited to receive 7 (triennial from 50 to 70).

The USPSTF and UK NSC guidelines both contain provisions allowing women to undergo additional screening if they so desire. Under the USPSTF guideline, women may choose to begin biennial mammograms at age 40. Insurers are not obligated to cover this elective screening, though, because the USPSTF only gave a 'C' grade to mammograms for women ages 40 to 49 (USPSTF, 2016b). (Insurers are required to pay for mammograms for women ages 50 to 74, as the USPSTF assigned a 'B' grade for those.) Under the UK NSC guideline, women may opt to continue triennial screening from age 71. The NHS is also phasing in an age extension across England that broadens screening to women ages 47 to 73, although the trial that aims to assess the mortality benefit of extended screening has not been completed (McCartney, 2014; Public Health England, 2014).

3.3.4.2 Relationship between population breast screening and BRCA risk assessment

Because BRCA-related breast cancer is associated with a younger age of diagnosis, women at high risk for BRCA mutations are eligible for earlier and more frequent screening than

women at population risk. (Tables 3.5 and 3.6 illustrate this difference quite clearly.) However, not all high-risk women know they are at high risk, particularly if they are unaware of or have no family history of BRCA-related cancer. In response, American advocacy group FORCE, an organisation serving individuals and families affected by HBOC, has called for all women to start annual screenings at 40 (2015). FORCE argues that unidentified BRCA carriers may receive later-stage breast cancer diagnoses and face delays in seeking BRCA testing if screening does not begin at 40, which in turn may affect any relatives who are unidentified BRCA carriers.

Current evidence does not support the view that earlier mammography would more quickly and accurately detect breast cancers, however. In a study based on 2003 data, which were collected when American women typically began mammograms at age 40, Roth et al. (2011) reported that detection through mammography only outstripped self-detection of breast cancer once women reached their 50s. This finding is likely attributable to two facts: Mammography is less sensitive to dense breast tissue than fatty breast tissue, and younger women generally have denser breasts than older women (Checka, Chun, Schnabel, Lee, & Toth, 2012; Mandelson et al., 2000).

Moreover, altering the parameters of a population screening programme only for the benefit of a small number of BRCA carriers conflicts with how such programmes are created. The UK NSC, for instance, requires screening programmes to reduce morbidity or mortality, provide more benefit than harm, and be cost effective; it also suggests that 'evidence related to wider benefits of screening, for example those related to family members, should be taken into account where available' (Public Health England, 2015b). By this standard, BRCA-positive breast cancer patients and their families should already have been accounted for in the evidentiary review underlying the population breast screening programme. Thus,

the UK NSC would be ignoring its screening efficacy standards if it overrode its existing harm-benefit calculation in order to further benefit a small number of BRCA-positive women and their families.

3.3.5 Summary of observations about BRCA-related clinical guidelines

Section 3.3.1 began with an introduction to three major UK and US guideline-making groups – NICE, NCCN, and the USPSTF – and their BRCA guidelines. NICE and the USPSTF are both government-funded, independently run groups that have national influence: NICE provides non-binding advice to the NHS, and the USPSTF establishes legally recognised insurance standards. In contrast, NCCN is an internally funded specialist organisation that has no explicit national leverage but is relied upon for its oncology expertise. Whilst all three organisations use cost effectiveness information indirectly by aiming services at the patients most likely to benefit, only NICE evaluates cost effectiveness directly. Additionally, NICE and NCCN incorporate specialist, generalist, and patient advocate perspectives on their BRCA guideline panels, but the USPSTF BRCA guideline panel is solely comprised of generalists.

Next, four key observations about the NICE, NCCN, and USPSTF BRCA risk assessment guidelines were examined. All three guidelines contain concrete personal and family history criteria that should result in referrals; in addition, the NICE and USPSTF guidelines include calculated probability tools that determine whether risks of BRCA mutations and breast cancer are high enough to warrant referral. Section 3.3.2 also delved into the similarities and differences in how each guideline and risk assessment method incorporates age of diagnosis and non-breast or ovarian cancers into referral criteria. In general, concrete criteria only factor in age of diagnosis for breast cancer, whilst calculated probability models consider age

of diagnosis for all BRCA-related cancers. Pancreatic and prostate cancers, which are strongly associated with BRCA2 mutations, are included in all three guidelines but do not significantly influence referrals; colorectal cancer, which has a considerably weaker link to BRCA mutations, only appears in the USPSTF guideline and is of questionable utility. Finally, this sub-section closed with a discussion of how referral and testing criteria compare in theory and in practice, noting that experienced clinicians are expected to interpret guidelines using their clinical expertise rather than following guidelines rigidly.

Section 3.3.3 reflected on current BRCA carrier management recommendations from the NCCN and NICE guidelines. (The USPSTF guideline does not address carrier management because it is not considered preventive care.) The two themes of this sub-section were the level of evidence underlying each recommendation and the distinction between supporting an intervention, highlighting clinician discretion, and emphasising patient choice; an example of each type of recommendation is provided here. First, both NCCN and NICE support the routine use of MRI, mammography, and breast awareness; evidence backs a combined MRI and mammography programme as reducing mortality and breast awareness as reducing psychological, if not physiological, morbidity. Second, NCCN highlights clinician discretion in the prescription of TVUS and CA-125 testing, which are not evidence-backed and should ideally occur in clinical trials if offered. Third, NICE emphasises patient choice for oophorectomy, which the evidence says reduces the risk of ovarian cancer but involves serious potential harms.

Lastly, Section 3.3.4 reviewed three population breast screening guidelines from NCCN, the USPSTF, and the UK NSC. For routine mammograms, the NCCN guideline prescribes the most screening, followed by the USPSTF guideline and then the UK NSC guideline. The advocacy group FORCE has supported lowering the age at which routine population breast

screening begins to benefit unidentified BRCA carriers, even though breast cancer in young women is mainly found because of self-detected breast abnormalities.

3.4 Laws, legal rulings, and policies

This section examines the US and UK regulatory frameworks governing access to genetic services through an in-depth look at laws, legal rulings, and policies. The 'Selection of laws, legal rulings, and policies' sub-section explained why these mechanisms were chosen, and the 'Analysis of laws, legal rulings, and policies' sub-section explained how these mechanisms were analysed. The sub-section on the American regulatory framework looks at the 15 US regulatory mechanisms listed in Tables 3.7 and 3.8, and the sub-section on the British regulatory framework examines the 23 UK regulatory mechanisms catalogued in Tables 3.9 and 3.10. Within each country's sub-section, discussion topics include genetic discrimination and privacy, as well as the quality and availability of genetic testing. This section concludes with a comparison of American and British regulatory frameworks.

3.4.1 American regulatory framework

The 15 American regulatory mechanisms detailed in Tables 3.7 and 3.8 and explained over the next few pages include 11 laws, three policies, and one legal ruling. The majority of mechanisms fall under the 'Genetic discrimination and privacy' category, which covers provisions for health insurance, employment, and data protection. The remaining mechanisms are in the 'Quality and availability of genetic testing' category, which explores the regulation of genetic testing and the legality of gene patenting.

Table 3.7: Regulatory protections and restrictions, United States, 1914 – 1995

Type	Year	Title	Source	Effects	Notes
Law	1914	Federal Trade Commission Act	US Congress	Prohibited false and misleading health-related advertising	
Law	1921	Snyder Act	US Congress	Established federal healthcare (Indian Health Service) for all American Indians and Native Alaskans	Limited by lack of funding
Law	1959	Federal Employees Health Benefits Act	US Congress	Provided health insurance to all federal employees	
Law	1976	Medical Devices Amendments	US Congress	Regulated safety and effectiveness of medical devices such as genetic test kits	
Law	1988	Clinical Laboratory Improvement Amendments	US Congress	Regulated clinical laboratories conducting laboratory testing to ensure testing quality	
Law	1990	Americans with Disabilities Act	US Congress	Prohibited discrimination on basis of disability in employment and other areas	Did not mention genetic information
Policy	1990	Veterans Health Administration policy	US Department of Veterans Affairs	Covered genetic conditions manifesting after service enrolment	
Policy	1995	Interpretation of Americans with Disabilities Act 1990	Equal Employment Opportunities Commission	Suggested discrimination on basis of genetic information would be prohibited	Not legally binding

Table 3.8: Regulatory protections and restrictions, United States, 1996 – present

Type	Year	Title	Source	Effects	Notes
Law	1996	Health Insurance Portability and Accountability Act	US Congress	Protected privacy and security of health information, including limiting group insurers' access to genetic information	Did not apply to most individual insurers Permitted some forms of genetic discrimination
Law	1997	Universal Declaration on the Human Genome and Human Rights	UN Educational, Scientific and Cultural Organization	Established basic standards for human genetic research and health applications	Considered influential 'soft law' (not legally binding)
Law	2000	Executive Order 13145	US President	Prohibited federal employers from discriminating on basis of genetic information	
Law	2008	Genetic Information Nondiscrimination Act	US Congress	Prohibited health insurers and employers from discriminating on basis of genetic information	Excluded life, disability, and long-term care insurance Not applicable to certain populations
Policy	2008	US Military policy	US Department of Defense	Covered genetic conditions manifesting after service enrolment, if individual has served six months	Derived from National Defense Authorization Act of 2008 and associated Directive-Type Memorandum
Law	2010	Patient Protection and Affordable Care Act	US Congress	Prohibited health insurers from discriminating on basis of pre-existing, including genetic, conditions	Excluded life, disability, and long-term care insurance
Legal ruling	2013	Association for Molecular Pathology v. Myriad Genetics, Inc.	US Supreme Court	Ruled naturally occurring gene sequences non-patentable, but non-naturally occurring gene sequences patentable	Did not discuss data sharing

3.4.1.1 Genetic discrimination and privacy

Of the 11 mechanisms involving genetic discrimination and privacy, the Health Insurance Portability and Accountability Act (HIPAA), the Genetic Information Nondiscrimination Act (GINA), and the ACA confer the broadest protections. Five mechanisms address the gaps in HIPAA, GINA, and the ACA, whilst another three mechanisms were essentially superseded by HIPAA, GINA, and the ACA.

The 1996 passage of HIPAA resulted in national protections for the privacy and security of individuals' health information (Office for Civil Rights, 2003). Specific to genetic information, HIPAA provides certain group (i.e., employer-based) insurance protections for patients; for instance, individuals with genetic conditions cannot be excluded from group insurance. The law falls short in several important ways, though. HIPAA allows higher group premiums on the basis of genetic information, permits insurers to require testing and collect and disclose genetic information, and applies only to individual insurers if insured individuals change jobs (NHGRI, 2012). Furthermore, it does not address life, disability, or long-term care insurance underwriting.

Signed into law in 2008, GINA prohibits employers and health insurers from practising genetic discrimination and remedies most of the loopholes in HIPAA. Employers and insurers cannot request genetic information or require genetic testing, base employment decisions on genetic information, or use genetic information to determine eligibility for or cost of coverage (NHGRI, 2016a; US Congress, 2008a). However, GINA does not apply to life, disability, or long-term care insurance, nor does it extend protections to individuals who are symptomatic or employed in a workplace with fewer than 15 employees (National Coalition for Health Professional Education in Genetics, 2010; NHGRI, 2016a).

Additionally, GINA does not cover certain populations because the laws it amends – the Employee Retirement Income Security Act, the Public Health Service Act, and the Internal Revenue Code – do not include them (DOL, 2010).

Introduced earlier in this chapter, the ACA was designed to expand public and private health insurance coverage whilst controlling costs and improving care (The Henry J. Kaiser Family Foundation, 2013). Individuals symptomatic of genetic conditions benefit from the ACA provision banning insurers from discriminating based on pre-existing conditions (Assistant Secretary for Public Affairs, 2015). Thus, a BRCA-positive woman who develops breast cancer will not have to pay for more expensive health insurance.

Five laws and policies address the populations to which GINA does not apply, i.e., federal employees and individuals who receive care through the Indian Health Service, the Veterans Health Administration, or the US Military's TRICARE programme (NHGRI, 2016a). Federal employees receive GINA-like protections through the Federal Employee Health Benefits Act of 1959 and Executive Order 13145 of 2000; these laws ensure insurance is free of underwriting and workplaces are free of genetic discrimination, respectively (President of the United States, 2000; US Office of Personnel Management, n.d.). The Snyder Act of 1921 established the Indian Health Service, which provides federal healthcare to all American Indians and Native Alaskans regardless of health status; however, limited funding may restrict access to care for genetic conditions (NHGRI, 2016a; US Congress, 1921). The Veterans Health Administration and the US Military authored internal policies derived from law in 1990 and 2008, respectively, which cover genetic conditions manifesting after service enrolment (NHGRI, 2016a; US Under Secretary of Defense, 2008; Veterans Administration General Counsel, 1990). The military further stipulates that service members must serve six months before entering medical retirement (Baruch & Hudson, 2008; US

Congress, 2008b). Thus, a BRCA-positive woman diagnosed with breast cancer would be eligible for coverage if she enlisted seven months prior, but not if she enlisted five months prior.

Key aspects of the final three US mechanisms related to genetic discrimination are captured in HIPAA and GINA. The Universal Declaration on the Human Genome and Human Rights 1997 set out 'soft law' (i.e., non-binding) guidelines for enshrining human dignity and rights in genetic services and research in United Nations member countries (Andorno, 2007; United Nations Educational, Social and Cultural Organization [UNESCO], 1997). Several Declaration provisions, including the right to be free from genetic discrimination, overlap with HIPAA and GINA provisions. The Americans with Disabilities Act of 1990 outlawed discrimination against individuals with disabilities in the workplace, but the law did not discuss genetic information (NHGRI, 2016a; US Congress, 1990). However, a non-binding 1995 US Equal Employment Opportunity Commission interpretation suggested that genetic information-based discrimination might violate the Americans with Disabilities Act (NHGRI, 2016a; Rothstein, 2008; US States Equal Employment Opportunity Commission, 2005). With the passage of GINA, though, this interpretation of the Americans with Disabilities Act became moot.

3.4.1.2 Quality and availability of genetic testing

Of the four American mechanisms related to the quality and availability of genetic testing, three are laws and one is a legal ruling. Each law permitted a federal agency to regulate an aspect of genetic testing, whilst the legal ruling involved gene patenting.

The most influential of the three laws is the Clinical Laboratory Improvement Amendments (CLIA) of 1988, which gave the Centers for Medicare and Medicaid Services (CMS) the

jurisdiction to regulate clinical laboratories conducting genetic testing (NHGRI, 2016b; US Food and Drug Administration [FDA], 2014). CMS establishes expertise requirements for laboratory personnel, requires clinical testing to be analytically valid (i.e., accurate and reliable), and inspects and enforces laboratories' compliance with CLIA requirements (NHGRI, n.d.).

Through the Medical Devices Amendments of 1976, the FDA has the power to regulate the safety and effectiveness of medical devices, including commercial genetic tests (US Congress, 1976). Test kits sold to multiple laboratories are always regulated (NHGRI, 2016b), whereas enforcement is selective and risk-dependent for laboratory-designed tests (LDTs), which are 'designed, manufactured, and used within a single laboratory' (FDA, 2015). One example of selective enforcement occurred in 2013, when the FDA sent direct-to-consumer (DTC) genetic testing company 23andMe a warning letter to stop marketing its LDT (Gutierrez, 2013).

The third law related to genetic testing is the Federal Trade Commission Act of 1914, which allowed the Federal Trade Commission to regulate advertising of DTC genetic testing (NHGRI, 2012; US Congress, 1914). Companies are prohibited from advertising false or misleading health-related information, e.g., a DTC testing company that only tests for three common AJ BRCA mutations cannot claim it provides comprehensive BRCA testing (Federal Trade Commission, 2014).

In *Association for Molecular Pathology v. Myriad Genetics, Inc.* (Supreme Court of the United States, 2013), the US Supreme Court ruled that naturally occurring genes cannot be patented, but synthetically developed genes can be patented (Denniston, 2013). This 9-0 decision allows universities, hospitals, and laboratories to conduct BRCA research and

testing without fear of a lawsuit from Myriad Genetics, Inc. (American Civil Liberties Union, 2013).

3.4.2 British regulatory framework

The 23 British regulatory mechanisms detailed in Tables 3.9 and 3.10 include 17 laws, three legal rulings, and three policies. Twelve mechanisms fall under the 'Genetic discrimination and privacy' category, which covers provisions for data protection, employment, human rights, and life insurance. The other 11 mechanisms are in the 'Quality and availability of genetic testing' category, which discusses regulation of genetic testing and the legality of gene patenting.

Table 3.9: Regulatory protections and restrictions, United Kingdom, 1953 – 2000

Type	Year	Title	Source	Effects	Notes
Law	1950	European Convention on Human Rights	Council of Europe	Established human rights and fundamental freedoms	Enforced by European Court of Human Rights
Policy	1962	Advertising Standards Authority	Advertising Association	Monitored advertising and regulated misleading and harmful content	Independent regulator
Law	1988	Control of Misleading Advertisements Regulations	UK Parliament	Allowed Office of Fair Trading to levy sanctions for misleading advertisements	Office of Fair Trading dissolved in 2014
Law	1995	Disability Discrimination Act	UK Parliament	Banned employers from discrimination against individuals with disabilities	Disabilities had to be symptomatic
Law	1995	Data Protection Directive 95/46/EC	European Parliament and Council	Set basic standards for handling and accessing sensitive data	
Law	1997	Universal Declaration on the Human Genome and Human Rights	UN Educational, Scientific and Cultural Organization	Established basic standards for human genetic research and health applications	Considered 'soft law' (not legally binding)
Law	1998	Legal Protection of Biotechnological Inventions Directive 98/44/EC	European Parliament and Council	Allowed patenting of gene sequences isolated through technical processes	Violations difficult to enforce
Law	1998	Data Protection Act	UK Parliament	Set data handling responsibilities and gave individuals right to access data	Implemented Directive 95/46/EC
Law	1998	In Vitro Diagnostic Medical Devices Directive 98/79/EC	European Parliament and Council	Required consumer-orientated medical devices to be safe and accurate	
Law	1998	Human Rights Act	UK Parliament	Codified European Convention on Human Rights into UK law	Scotland passed own Act in 2006
Law	2000	Employment Equality Directive 2000/78/EC	European Parliament and Council	Banned employers from discriminating on grounds including disability	
Law	2000	Patents Regulations	UK Parliament	Allowed patenting of gene sequences isolated through technical processes	Implemented Directive 98/44/EC

Table 3.10: Regulatory protections and restrictions, United Kingdom, 2001 – present

Type	Year	Title	Source	Effects	Notes
Policy	2001	Concordat and Moratorium on Genetics and Insurance	Association of British Insurers and UK Government	Banned critical illness, life, and income protection insurers from practising genetic discrimination	Voluntary agreement currently signed through 2019
Legal ruling	2001	Kingdom of the Netherlands v European Parliament and Council of the European Union	Court of Justice of the European Union	Ruled patents on gene sequences do not violate human dignity	Upheld Directive 98/44/EC
Law	2003	Disability Discrimination Act 1995 (Amendment) Regulations	UK Parliament	Prohibited employers from 'direct discrimination'	Implemented Directive 2000/78/EC
Law	2004	Human Tissue Act	UK Parliament	Regulated removal, storage, use, and disposal of human tissue	Scotland passed own Act in 2006
Law	2007	Treaty of Lisbon	European Parliament and Council	Gave Charter of Fundamental Rights legal status	
Law	2009	The Accreditation Regulations	UK Parliament	Designated UK Accreditation Service as national accreditation body	
Law	2010	Equality Act	UK Parliament	Banned disability-based discrimination and health information requests in employment	Succeeded Disability Discrimination Act 1995
Legal ruling	2010	Monsanto Technology LLC v Cefetra BV and Others	Court of Justice of the European Union	Ruled patents on genes extend only to functions for which patents were granted	Interpreted Directive 98/44/EC
Legal ruling	2011	Human Genome Sciences Inc v Eli Lilly and Company	UK Supreme Court	Ruled that plausible application of isolated genes is sufficient for a patent	Interpreted Patent Regulations 2000
Policy	2013	Guidance on the In Vitro Diagnostic Medical Devices Directive 98/79/EC	Medicines and Healthcare Products Regulatory Agency	Explained UK regulations for in vitro diagnostic medical devices	Interpreted Directive 98/79/EC; enforced differently in Scotland
Law	2013	Enterprise and Regulatory Reform Act	UK Parliament	Created Competition and Markets Authority, which protects consumers	Replaced Office of Fair Trading and Competition Commission

3.4.2.1 Genetic discrimination and privacy

Of the 12 genetic discrimination and privacy mechanisms, 11 are laws and one is a policy. The UK Parliament enacted six laws; the European Parliament and Council passed three more; and UNESCO and the Council of Europe each legislated one apiece.

Four laws with applications to genetic conditions deal with discrimination in employment. The Disability Discrimination Act 1995 prohibited employers from discriminating against employees with disabilities, i.e., long-term conditions that substantially affected their daily lives (Parliament of the United Kingdom, 1995). However, the Human Genetics Advisory Committee pointed out that only symptomatic genetic conditions would be considered disabilities (Human Genetics Commission [HGC], 2011). The Employment Equality Directive 2000/78/EC outlawed EU employers from discriminating against employees on characteristics including disability, though it did not discuss genetic information (European Parliament and Council, 2000; HGC, 2011). The UK Parliament implemented the Directive through the Disability Discrimination Act 1995 (Amendment) Regulations; this amendment specified that an employer could not treat an employee with a disability 'less favourably' than another employee without cause (Parliament of the United Kingdom, 2003). One interpretation is that less favourable treatment because of a genetic predisposition would constitute discrimination (HGC, 2011). This interpretation became moot when the Disability Discrimination Act and its amendment regulations were replaced by the Equality Act 2010, which prevents employers from gratuitously asking health questions or discriminating based on disabilities, including if a disability is only perceived (Advisory, Conciliation and Arbitration Service, 2015; Parliament of the United Kingdom, 2010). Thus, it is illegal for employers to treat employees unfavourably because their genetic predispositions might lead to disability.

Four other mechanisms focus on anti-discrimination as a matter of human rights. The European Convention on Human Rights 1950 established a set of human rights and fundamental freedoms for European citizens, including provisions on the right to respect for private and family life and the right not to be discriminated against (Council of Europe, 1950). The Human Rights Act 1998 codified in UK law many of the rights granted in the Convention (Parliament of the United Kingdom, 1998b). Whilst neither law mentions genetic characteristics, genetic discrimination may be prohibited based on the Convention provisions mentioned above (HGC, 2011). [In Scotland, Convention rights are similarly enshrined in both the Scotland Act 1998 and the Scottish Commission for Human Rights Act 2006 (Scottish Government, 2014; Scottish Parliament, 2006b).] In contrast, the non-binding Universal Declaration on the Human Genome and Human Rights explicitly states that individuals should not be subject to genetic discrimination (UNESCO, 1997). The Treaty of Lisbon 2007, which gave the EU Charter of Fundamental Rights legal status, also bans discrimination on grounds of genetic features in EU member states (The European Network of Legal Experts in the Non-Discrimination Field, 2013).

The lone anti-discrimination policy is the Concordat and Moratorium on Genetics and Insurance, an agreement between the UK Government and the Association of British Insurers. First signed in 2005, the concordat contains three principles, the most important one being that insurers will not disfavour customers with genetic disorders without cause (HM Government and Association of British Insurers, 2011). First signed in 2001, the moratorium states that insurers will not ask customers to disclose results unless they have both undergone testing Huntington's disease and applied for life insurance exceeding £500,000 (BBC News, 2005). The voluntary agreement, which is currently signed through 2019, must be reviewed three years before the end date, though there is no evidence that the agreement will not be renewed in the future.

The three remaining laws involve genetic privacy. The Data Protection Directive 95/46/EC set basic standards for data privacy in EU member nations (European Commission, n.d.; European Parliament and Council, 1995). The UK Parliament implemented the Directive through the Data Protection Act 1998, which grants individuals the right to access their data and prescribes responsibilities for data controllers who handle sensitive data (Parliament of the United Kingdom, 1998a). The Human Tissue Act 2004 regulates the removal, storage, use, and disposal of human tissue, but in extreme cases, it also allows genetic testing to proceed without consent for a relative's benefit (Lucassen & Kaye, 2006; Parliament of the United Kingdom, 2004). [Whilst Scotland has the Human Tissue (Scotland) Act 2006 (Scottish Parliament, 2006a) to regulate the handling of tissue specifically from the deceased, the portion of the Human Tissue Act 2004 regulating DNA analysis applies UK-wide (Medical Research Council, 2016).]

3.4.2.2 Quality and availability of genetic testing

Of the 12 regulatory mechanisms related to the quality and availability of genetic testing, seven concern regulation of testing and five involve gene patenting. The genetic testing-orientated mechanisms comprise laws and policies for DTC advertising and testing evaluation, whilst the gene patenting mechanisms are a mix of laws and legal rulings.

Three mechanisms involve fair advertising. Established in 1953, the Advertising Standards Authority is an independent industry regulator that monitors and regulates misleading and harmful content for all UK products (Advertising Standards Authority, 2015). The Control of Misleading Advertisements Regulations 1988 gave the Office of Fair Trading the ability to levy sanctions for misleading advertisements, which it exercised only if Advertising Standards Authority intervention failed (Office of Fair Trading, 2013; Parliament of the United Kingdom, 1988). The Enterprise Regulatory Reform Act 2013 replaced the Office of

Fair Trading and the Competition Commission with the Competition and Markets Authority, which now holds the power to sanction companies for misleading advertisements (Parliament of the United Kingdom, 2013). As an example, if a DTC testing company like 23andMe claims it can predict if a woman will develop breast cancer, the Advertising Standards Authority may tell the company to amend or pull the advertisement. If the company does not comply, the Competition and Markets Authority has the ability to levy sanctions.

The Accreditation Regulations 2009, which designated the United Kingdom Accreditation Service as the national accreditation body, is a statute applicable to both DTC and clinical genetic testing (Parliament of the United Kingdom, 2009). Clinical and commercial laboratories may voluntarily seek accreditation to demonstrate that their testing is performed in compliance with internationally recognised standards (United Kingdom Accreditation Service, n.d.). Two other mechanisms relate to DTC genetic testing: the In Vitro Diagnostic Medical Devices Directive (IVDD) 98/79/EC and the Guidance on the IVDD 98/79/EC. The IVDD requires EU medical devices to be safe and accurate (European Parliament and Council, 1998b). However, the IVDD only mandates pre-market assessment for test kits sold directly to consumers for at-home use; LDTs created in health institutions and test kits sold to laboratories do not have to undergo pre-market assessment, though the latter should meet IVDD standards (Border, 2012). In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) has been responsible for enforcing the IVDD since it was fully implemented in 2003. [In Scotland, however, the MHRA only has investigatory powers; it would have to work with Scotland's Crown Office and Procurator Fiscal Service to enforce any violations it uncovered (C. O'Neill & Marshall, 2013).] To help companies comply with the IVDD, the MHRA published its 'Guidance on the IVDD' document, which outlined a risk-based device classification system (MHRA, 2013). The

IVDD is currently being revised, and changes may affect both DTC genetic testing and genetic testing in general (European Academies Science Advisory Council and Federation of European Academies of Medicine Working Group, 2012).

The remaining five mechanisms concern the legality of gene patenting. The Legal Protection of Biotechnological Inventions Directive 98/44/EC allows patenting of gene sequences if they are isolated through novel technical processes (European Parliament and Council, 1998a; Lamping, 2013). The Patents Regulations 2000, a statutory instrument, fully implemented the Directive in the United Kingdom, supporting the patentability of inventions related to gene sequences (Intellectual Property Office, 2016; Parliament of the United Kingdom, 2000). In *Kingdom of the Netherlands v European Parliament and Council of the European Union* (Court of Justice of the European Union, 2001), the Court of Justice upheld the Directive by ruling that gene patenting does not violate human dignity (Lamping, 2013). In *Monsanto Technology LLC v Cefetra BV and Others* (Court of Justice of the European Union, 2010), the Court of Justice interpreted the Directive to mean that patents only extend to the function for which they were granted (Phillips, 2010). In *Human Genome Sciences Inc v Eli Lilly and Company* (Supreme Court of the United Kingdom, 2011), the UK Supreme Court ruled that even a plausibly claimed use for a gene sequence satisfies the requirement that an invention be 'capable of industrial application' (Fisher, 2011).

3.4.3 Comparison of US and UK regulatory frameworks

Both the American and British regulatory frameworks contain laws, legal rulings, and policies that address genetic discrimination, genetic privacy, clinically based genetic testing, DTC genetic testing, and gene patenting. Given the entries in Tables 3.7 through 3.10 and the accompanying commentary, though, it is clear that there are some divergences in how

each country approaches regulation of access to genetic services. This sub-section highlights key similarities and differences between frameworks.

One systemic difference arises from the British framework containing relevant EU laws and legal rulings, which partially explains why the British framework includes 23 mechanisms and the American framework only includes 15 mechanisms. For example, the European Parliament and Council's Data Protection Directive was implemented in British law via the Data Protection Act. There is no North American version of the European Union, so the American framework is almost exclusively comprised of US laws, legal rulings, and policy. The one exception is UNESCO's Universal Declaration on the Human Genome and Human Rights, which applies to all UN countries – including the United Kingdom.

Both US and UK laws and policies prohibit genetic discrimination in employment and health insurance and protect genetic privacy, though there are some differences in scope. First, the United States has a law explicitly banning genetic discrimination in employment and health insurance, whereas the United Kingdom derives protections from anti-discrimination employment and human rights laws. Second, only the United Kingdom prevents life, disability, and long-term care insurers from practising genetic discrimination (an exception for Huntington's disease applies). Third, US legal protections do not extend to individuals whose workplaces have fewer than 15 employees. Fourth, both US and UK laws address how genetic information should be handled, but only the United Kingdom has a law specifically regulating the handling of human tissue.

There is less common ground between countries for clinical and DTC genetic testing regulation. Laboratory accreditation is required for all US genetic testing laboratories and overseen by a government agency, but UK laboratories seek accreditation voluntarily

through a government-appointed company. Both countries have national governmental agencies regulating harmful and misleading advertising content for products including DTC genetic testing, but an independent industry regulator is the primary actor in this process in the United Kingdom. Regarding medical device regulation, test kits sold to multiple laboratories are regulated in the United States but not assessed for compliance in the United Kingdom; US LDTs are subject to selective enforcement, but UK LDTs from health institutions are not regulated; and UK test kits sold to consumers for at-home use are regulated.

Finally, the United States and United Kingdom hold different positions regarding gene patenting. In the United States, naturally occurring genes are not patentable, but synthetic genes are patentable. In the United Kingdom, naturally occurring genes can be patented if they are isolated through innovative technical processes. Patents are only valid for the functions for which they were granted, and those functions must be plausible to implement.

3.5 Discussion

In this chapter, major American and British guidelines for BRCA risk assessment, carrier management, and population breast screening have been reviewed. The US and UK regulatory frameworks of laws, legal rulings, and policies that govern access to genetic services have also been assessed. This section takes a more holistic look at these regulatory mechanisms and makes observations in three key areas: (1) similarities and differences in the US and UK approaches to clinical guidelines versus laws, legal rulings, and policies; (2) consequences of BRCA gene patenting in each country; and (3) regulatory approaches to DTC genetic testing in each country. Strengths and limitations of the approach taken in this chapter are also explored.

3.5.1 US and UK approaches to different types of mechanisms

The 'Summary of observations about BRCA-related clinical guidelines' sub-section showed that compared to the chosen British guidelines, the chosen American guidelines generally recommend more care to women who may be at high risk for BRCA mutations or are known BRCA carriers. However, the 'Comparison of US and UK regulatory frameworks' sub-section showed that British laws, legal rulings, and policies generally offer more protections to individuals seeking to access genetic services than American laws, legal rulings, and policies. In the United Kingdom, this means that fewer high-risk women are eligible to access care, but those who do access care receive substantial protections for health insurance and employment. In the United States, more high-risk women may be eligible to access care more frequently, but there are gaps in protections for health insurance and employment for those who elect to test.

3.5.1.1 Reasons why more US women may be eligible for care than UK women

There are a few possible reasons for why more American women are generally eligible for BRCA risk assessment, testing, screening, medication, and surgery than British women. The clearest one is that although US and UK guideline-making groups aim to recommend evidence-based services, each group applied different evidentiary standards to the services in question. As discussed earlier in this chapter, part of this discrepancy may stem from the inclusion of cost-effectiveness data in NICE and UK NSC guidelines but not NCCN or USPSTF guidelines. For example, the USPSTF's recommendation of BRCA testing for a woman whose TDR was diagnosed with breast cancer at age 49 only affects private insurers' costs. If NICE lowered its risk threshold to match this recommendation, local health authorities would have to consider allocating limited NHS resources to cover the costs of testing lower-risk women. Likewise, the NCCN suggesting that clinicians offer CA-125

testing or TVUS at their discretion – without any convincing evidence to support the practice of ovarian screening – is only possible because the costs will be borne by insurers and/or patients, not a nationally funded healthcare system.

Another reason is that the number of organisations that produce and/or comment publicly on guidelines is much higher in the United States than in the United Kingdom. This discrepancy may manifest in a greater volume of organised feedback and concrete actions taken in response to the USPSTF guidelines than the UK NSC or NICE guidelines. For instance, when the USPSTF issued its 2009 population breast screening guideline, specialist groups like NCCN and FORCE immediately issued public statements criticising the USPSTF. These groups also joined with like-minded patient advocate organisations to lobby US Congress members to prevent the implementation of that guideline – an effort that was ultimately successful (Stop the Guidelines, 2015). Whilst there was fierce disagreement over the UK NSC population breast screening guideline, this disagreement primarily played out between individuals supporting and opposing screening in medical journal letters. Moreover, the rhetoric did not reach the level of UK Parliament members seeking to circumvent an independent panel's recommendations.

Relatedly, critics of the US breast screening guidelines typically argue that not enough emphasis is placed on early diagnosis, whereas critics of the UK breast screening guidelines generally suggest that not enough emphasis is placed on overdiagnosis and overtreatment. For instance, American specialist groups like NCCN and the American College of Radiology suggested that the 2009 USPSTF guideline would result in late-stage diagnoses and unnecessary deaths; unsurprisingly, their own guidelines continue to favour earlier and more frequent screening (Oncology, 2009). Conversely, well-known opponents of the 2012 UK NSC recommendations like Michael Baum argue that screening should not take place at all

because overdiagnosis and overtreatment cause more deaths than screening prevents (Baum, 2013). This difference in perspective is especially interesting because the USPSTF guideline already recommends roughly double the number of mammograms over a lifetime as the UK NSC guideline.

There is one notable exception to the idea that US women are typically eligible for more care than UK women, however. Under the CMS guideline, which applies to US women insured publicly through Medicare and Medicaid, eligibility for BRCA testing is contingent upon having a personal history of BRCA-related cancer (Friedman, n.d.). This requirement is a striking contrast to the USPSTF guideline, which originally barred any woman with a personal history of BRCA-related cancer from undergoing testing. The discrepancy between the CMS and USPSTF guidelines is the result of the Social Security Amendments of 1965 restricting Medicare and Medicaid from paying for preventive care unless the US Congress specifically grants an exception or an evidence-based National Coverage Determination process results in a service being covered nationwide (Jacques, 2008; Segovis, 2015). (CMS criteria for BRCA testing were not analysed in the 'Clinical guidelines' section because there has never been a National Coverage Determination for BRCA-related services, and the existing Local Coverage Determinations vary depending on insurance carrier and region [CMS, 2015a, 2015b].)

3.5.1.2 Reasons why UK women may receive more protections than US women

A straightforward reading of why UK women may be better protected against genetic discrimination than US women is that the US regulatory framework leaves open two loopholes that the UK regulatory framework does not. First, American protections against genetic discrimination do not extend to individuals in workplaces with fewer than 15

employees, whereas British employee protections are not affected by workplace size. Second, US life, disability, and long-term care insurers are allowed to practise genetic discrimination, whilst UK life and critical illness insurers are banned from practising genetic discrimination in nearly all cases. The latter loophole is particularly glaring because US women may rely on these kinds of insurance to supplement their usual health insurance if they face major healthcare costs, such as those associated with BRCA-related cancer; in contrast, UK women already receive free lifetime care through the NHS and therefore may not consider these kinds of insurance relevant.

A more holistic view is that even without a specific anti-genetic discrimination law, the United Kingdom has more effectively addressed genetic discrimination than the United States. To wit, Britain's laws banning nearly all discrimination in the workplace and enshrining human rights appear to shield all individuals from genetic discrimination in employment. Whilst several occupations are exempt from the Equality Act for non-genetic equality reasons, e.g., race- or sex-based requirements for actors, there are no exemptions from human rights laws. That said, the claim that the Human Rights Act prohibits genetic discrimination has not been tested in court, and the Treaty of Lisbon provision outlawing genetic discrimination would be difficult to enforce in practice (HGC, 2011). As for banning genetic discrimination in life and critical illness insurance, the UK House of Commons Science and Technology Committee in 2001 called for insurers to either enter into a moratorium voluntarily or face a legislation-imposed ban; the Association of British Insurers chose the former (BBC News, 2001). This call coincided with a 2001 HGC report recommending that insurers suspend genetics-based underwriting for three years and built on the work of the now-defunct Genetics and Insurance Committee, which evaluated insurers' requests for genetics-based underwriting (Morrison, 2001). Unsurprisingly, insurers initially wanted BRCA test results to inform underwriting, but the only Genetics and

Insurance Committee-approved exception was for life insurance applications above £500,000 for those who had been tested for Huntington's disease.

In comparison to this UK Government-driven effort, the US Government has not attempted to construct an agreement with industry or craft national-level legislation on life, disability, and long-term care insurance. Per Sharon Terry of Genetic Alliance, GINA's initial provisions for life, disability, and long-term care insurance had to be removed to make the bill politically viable (Farr, 2016). The only regulation for these types of insurance exists at the state level, and just 17 of 50 states have any prohibitions on the use of genetic information in underwriting (National Conference of State Legislatures, 2008). Notably, this lack of US regulatory protections has led to concerns from patients and patient advocates that individuals will decline genetic testing for manageable conditions, including BRCA mutations, for fear of insurance discrimination (Farr, 2016; Peikoff, 2014).

3.5.2 Consequences of BRCA gene patenting

The US-based company Myriad Genetics, Inc. filed numerous American and European patents on the BRCA1 and BRCA2 genes in the 1990s (Gold & Carbone, 2010). In June 2013, however, the US Supreme Court ruled that naturally occurring genes cannot be patented, whilst synthetically created genes can be patented. This ruling invalidated Myriad's American patents on the BRCA genes themselves, but it also preserved over 500 patents on BRCA tests that involved synthetic genes (Ahuja, 2013). Meanwhile, researchers mounted legal opposition to Myriad's European patents and successfully had numerous claims invalidated; other claims remain valid today because EU law allows the patenting of naturally occurring genes isolated through innovative processes (Matthijs, Huys, Van Overwalle, & Stoppa-Lyonnet, 2013). Overall, roughly 20 years of BRCA gene patents in

the United States and United Kingdom have had two main consequences: how much BRCA testing costs and how test results are shared within the research and clinical community.

In terms of testing costs, BRCA gene patents led to higher prices in the United States but not in the United Kingdom. In America, Myriad's commercial monopoly allowed it to charge exorbitant fees; these were typically quoted as being between USD 3,000 and USD 4,000 (Agus, 2013; Sulik, 2013). Once the *Myriad* ruling ended the monopoly in 2013, other companies began rolling out BRCA tests at lower costs. Today, the companies conducting BRCA testing range from traditional laboratories like Quest Diagnostics and Ambry Genetics, which offer BRCA testing for an estimated USD 1,000, to start-up laboratories like Color Genomics, which offers BRCA testing for USD 249 as part of a 30-gene hereditary cancer panel (Herper, 2015; Welch, 2015). In Britain, Myriad signed a licencing agreement in 2000 with Rosgen Ltd that, among other functions, gave the UK-based company the purview to 'decide whether and how to enforce Myriad's patents in the United Kingdom and Ireland' (Gold & Carbone, 2010, p. S43). Rosgen and the NHS then agreed that the NHS could continue testing without paying Rosgen any royalties; this policy remained in effect until Rosgen declared bankruptcy. In 2005, Myriad signed a new licencing agreement with UK-based Lab21, but Lab21 never entered into an agreement with the NHS. Nevertheless, the NHS has continued testing for over a decade without paying royalties or being sued by Lab21 for patent infringement (Reardon, 2011). (That said, it is possible – though unlikely – that the NHS will have to pay Lab21 at some point: 'A [2011 HGC report] claimed that the NHS and the Department of Health were ignorant of patent issues, were probably guilty of multiple infringements, and may soon face lawsuits and the prospect of paying backdated royalties' [Ahuja, 2013].)

In terms of how test results are shared, Myriad has slowed the classification of VUS results worldwide through its patents and 2005 decision to treat VUS results as trade secrets. (As explained in Chapter Two, VUS results are genetic variants that may or may not increase the risk of cancer.) Myriad argues its decision was necessary because 'the data is proprietary information gathered as a result of its BRCA Analysis tests, on which it retains the patent rights' (Connor, 2012). Although neither the 2013 US Supreme Court ruling nor any European or British regulatory measure requires companies like Myriad to share their data, patients who receive VUS results may be negatively affected when genetic databases are not publicly shared. The reasoning is simple: If companies openly share all test results, VUS results may be re-classified more quickly, thus allowing patients to act on pathogenic results or be reassured by benign results sooner. Lack of data sharing may also be particularly harmful for minority women, e.g., Blacks, Hispanics, and Asians (C. Huang, 2013), who are more likely to receive VUS results than White women (M. J. Hall et al., 2009; Oloparde, 2004; Saulsberry & Terry, 2013).

Moreover, company-specific variant databases introduce a dichotomy between cost of testing and comprehensiveness of testing. That is, Quest Diagnostics, Ambry Genetics, and Color Genomics – which all provide cheaper tests than Myriad – may not be able to classify certain variants that only Myriad has studied extensively. It is conceivable that some minority women, for instance, may feel they need to pay for more expensive Myriad-provided testing to try to lower their chances of receiving VUS results. Short of Myriad voluntarily changing its policy on data sharing or regulations being introduced that compel Myriad to share its database (Conley, Cook-Deegan, & Lázaro-Muñoz, 2014), current data sharing campaigns will likely remain the primary way researchers and clinicians seek to end this dichotomy. For instance, research groups formed the Evidence-based Network for the Interpretation of Germline Mutant Alleles – more commonly called ENIGMA – in 2009 as

an international research consortium focussed on speeding up the classification of VUS results (Spurdle et al., 2012). Participating researchers hail from countries including Australia, France, Germany, Italy, the Netherlands, Spain, Sweden, and the United States (ENIGMA Consortium, 2016). BRCA Share and the Sharing Clinical Reports Project, which encourage clinicians to deposit patients' test results into open-access databases, aim to collect information on BRCA variants from as far back as 2006 (Kolata, 2013; Miller, 2015). The American Civil Liberties Union has taken a different approach, leveraging HIPAA complaints to compel Myriad to release full BRCA reports to four previously tested individuals (Couzin-Frankel, 2016). Given that Myriad has stated it will provide full reports within 30 days to all patients who make such requests (Samuel, 2016), re-contacting patients and asking them to request their reports from Myriad would also be a viable strategy.

3.5.3 Regulatory approaches to DTC genetic testing

One way to examine the US and UK regulatory approaches to DTC genetic testing in depth is to use the example of 23andMe, a prominent US-based company that has marketed and sold its flagship Personal Genome Service (PGS) in each country. The first iteration of the PGS was a 'saliva test that estimates your predisposition for more than 90 traits and conditions' (Hamilton, 2008). 23andMe first reported results for three common AJ BRCA mutations as part of the PGS in February 2009, and it has never expanded its reports to include any other harmful variants (23andMe, 2016c; Angrist, 2009; Jensen, 2015).

In the United States, the PGS came to market in 2008 but did not receive an FDA 'warning letter' until November 2013. Broadly speaking, the FDA worried that 23andMe was providing health-related information that might not be analytically or clinically valid, which could lead to harmful consequences. The FDA letter also included a BRCA-specific example:

> For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist. (Gutierrez, 2013)

Separating the legitimate issue of whether 23andMe offered analytically and clinically valid testing in 2013, the FDA's specific fears about BRCA testing seemed overblown. First, 'morbidity-inducing actions' like mastectomy would only be possible with a clinician's consent, which would likely require both a follow-up genetic test for confirmation and a consultation about whether mastectomy is suitable for a particular patient. Second, 23andMe explicitly mentioned that it only tested for three BRCA mutations in its consent process and further underscored that detail in its results-reporting process.

Regardless of whether the company agreed with the FDA's logic, 23andMe stopped providing all health-related reports in order to comply with the letter. Customers purchasing the PGS were still able to find out ancestry-related information and download their raw data, though, which meant that they could continue to find health-related information through third-party software (Wojcicki, 2013). After producing the requested evidence to prove analytic and clinical validity, 23andMe finally received FDA approval to provide some health-related reports in October 2015, but BRCA mutation results were not on the list of approved reports (23andMe, 2016b; Ossola, 2015). Thus, American women were only able to receive DTC testing reports of their results for the three common AJ mutations between February 2009 and November 2013.

In the United Kingdom, at-home tests like the PGS are considered in vitro devices and require pre-market certification from the MHRA, which 23andMe received in December 2014 (Border, 2012). Pre-certification for the UK version of the PGS involved the MHRA

speaking with the FDA about its experiences with 23andMe, requiring 23andMe to participate in an enhanced surveillance programme for product safety and performance, and asking 23andMe what the burden of follow-up care for PGS results might be for the NHS (Anekwe, 2014; Howe, 2014). (Additional UK regulations would have applied if 23andMe's UK PGS was analysed in a UK laboratory, but as all 23andMe tests are analysed in a US laboratory, 23andMe only had to comply with US testing regulations.) Whilst the UK-specific PGS does not test for all of the traits and conditions that it did when the FDA issued its warning letter, it is more expansive than the current FDA-approved, US-specific PGS (Howe, 2014). Notably, the three common AJ mutations have been included in the MHRA-approved, UK-specific PGS since December 2014 (23andMe, 2016a).

Compared to the UK approach to DTC testing, the US approach to DTC testing appears to be more orientated to harm reduction than potential benefit. The exclusion of BRCA testing from the US PGS and the inclusion of BRCA testing in the UK PGS seem to underscore this thought. So too do the comments from the FDA about the possible consequences of women misunderstanding the implications of their results, especially juxtaposed against the MHRA stance that 23andMe could bring its product to market if it submitted to enhanced surveillance. Interestingly, the FDA is working to finalise a new framework for LDT regulation that would more closely approximate the MHRA approach to at-home tests (FDA, 2014b, 2015), so that may lead the US approach to shift away from harm reduction and more towards potential benefit.

3.5.4 Strengths and limitations

Strengths of this chapter include critical review of major US and UK BRCA-related guidelines; comprehensive examination of US and UK laws, legal rulings, and policies; and discussion of the practical implications of gene patenting and DTC genetic testing. First, this

chapter employed tables, in-depth analysis, and summaries of BRCA risk assessment, BRCA carrier management, and population breast screening guidelines. The tables made it possible to visualise different features of the guidelines, and the accompanying text described how those features affect which US and UK women are eligible for certain kinds of care in theory and in practice. Second, chronologically listing the laws, legal rulings, and policies that comprise each country's regulatory framework in tables; analysing each country's framework separately; and comparing the US and UK frameworks to each other was a cohesive approach to the complicated task of comparing international regulations. Third, whilst charts and analysis of regulatory mechanisms are useful, accurately describing which patients are eligible for care and what organisational structures may help or hinder care requires delving into the practical consequences of regulatory mechanisms. Rulings on the patentability of genes and regulations for DTC testing carry especially interesting implications for patient access and will be revisited later in this thesis.

Limitations of this chapter arise from the decision to include only nationally applicable regulatory mechanisms. First, no BRCA-related guidelines for Medicare and Medicaid could be included because only regional, not national, guidelines exist for BRCA risk assessment and carrier management. However, Medicare and Medicaid insure roughly one third of all insured Americans, so not being able to analyse Medicare and Medicaid guidelines alongside USPSTF and NCCN guidelines is a clear weakness (Kaiser Commission on Medicaid and the Uninsured, n.d.). Second, the lack of a USPSTF guideline for BRCA carrier management meant that only NCCN and NICE guidelines were compared, and the two guideline-making groups have asymmetric influence on care in their respective countries. Third, the omission of local laws precluded a comparison of whether any US states offer the same level of protections against genetic discrimination in life, disability, and long-term care insurance as Britain. Whilst such a comparison would have been lengthy to write about and difficult to

capture in the American regulatory framework tables, it would have been an interesting relationship to consider.

3.6 Summary

This chapter has examined which women may access care for BRCA mutations according to major US and UK clinical guidelines, as well as how American and British laws, legal rulings, and policies may affect the provision of such care. The NICE, NCCN, and USPSTF BRCA risk assessment guidelines each apply risk assessment methods, incorporate age of diagnosis, and account for non-breast and ovarian cancers in their own ways. No matter which guideline is used, however, experienced clinicians have the opportunity to refer roughly the same group of high-risk women to genetic services and offer these women counselling and testing. Greater variation is found in the US and UK guidelines for BRCA carrier management and population breast screening, though: Compared to the UK guidelines, the US guidelines generally recommend (1) BRCA carriers be offered a wider set of screening, medication, and surgical management options, and (2) women at population risk be offered earlier and more frequent breast screening. Whilst both US and UK regulatory mechanisms confer genetic anti-discrimination provisions for health insurance and employment, only the United Kingdom extends these protections to life, disability, and long-term care insurance and employees of companies of all sizes. This chapter has also discussed potential reasons for these differences in regulatory mechanisms, such as how cost-effectiveness information is accounted for in guidelines, as well as practical implications of DTC genetic testing and gene patenting, such as challenges in re-classifying VUS results.

Overall, this chapter has comprehensively described the first dimension of the Gulliford model of access to care (availability and supply of services) and partially illustrated the second dimension (organisational, financial, and social or cultural barriers to care). The next

chapter in this thesis builds on this chapter's foundation to thoroughly examine the literature on potential barriers and facilitators affecting access to care for BRCA mutations.

4 Chapter Four: Factors, barriers, and facilitators that may affect access to care

4.1 Introduction

This chapter complements Chapter Three's analysis of the availability of services for BRCA mutations and barriers posed by regulatory mechanisms by examining how, against this background, certain characteristics of patients, clinicians, and healthcare systems may affect uptake of care for BRCA mutations, which informs how women access care for BRCA mutations today. In addition to informing the second dimension of access more fully, this chapter also sheds light on the Gulliford model's third and fourth dimensions, i.e., the relevance and effectiveness of services for different groups of patients and equity of access.

Previous reviews have examined aspects of access to care for BRCA mutations, such as uptake rates of breast cancer genetic testing (Ropka, Wenzel, Phillips, Siadaty, & Philbrick, 2006) and utilisation of screening and surgical procedures after mutation disclosure (Wainberg & Husted, 2004). Several reviews have specifically focussed on how race and ethnicity impact access: Allford, Qureshi, Barwell, Lewis, and Kai (2014) analysed hindrances and helpers for ethnic minorities seeking cancer genetic services; Halbert, Kessler, and Mitchell (2005) assessed BRCA testing in African Americans; and Forman and Hall (2009) examined the influence of race and ethnicity on HBOC counselling and testing. To date, though, there has not been a comprehensive review summarising the factors, barriers, and facilitators affecting access to care for BRCA mutations in both the United States and United Kingdom. This chapter aims to address this gap.

A scoping study was selected as the appropriate method to achieve this goal, based on the rationale that Arksey and O'Malley (2005) laid out in their methodological framework and Levac, Colquhoun, and O'Brien (2010) extended in their commentary. In contrast to systematic reviews, Arksey and O'Malley contended that scoping studies can be both completed rapidly and 'designed to identify gaps in the evidence base where no research has been conducted' (p. 7). Furthermore, such studies can be carried out in conjunction with a 'consultation exercise' that allows key stakeholders to comment on scoping study findings (p. 9). Levac et al. (2010) considered the consultation exercise as a principal component rather than an ancillary one, suggesting that it contextualises study results and promotes knowledge transfer. Among other functions, the empirical work described in Chapter Five of this thesis serves as a consultation exercise on the findings from this chapter.

4.2 Methods

The study design drew on Arksey and O'Malley's five-stage framework: (1) identification of the research question, (2) identification of relevant studies, (3) selection of studies, (4) charting of the data, and (5) collation, summarisation, and dissemination of the results (2005, pp. 8–9). The methods for all five stages are described in this section, and the results of the fifth stage are reported in Section 4.3.

4.2.1 Identifying the research question

Identification of the research question resulted in the following query: 'What factors affect access to care for BRCA mutations?' This question was left intentionally broad to avoid biasing the results towards Chapter Three topics or the contents of previous reviews, but study parameters were defined carefully as the search strategy was refined. 'Care' was limited to genetic counselling, genetic testing, and post-test interventions involving screening, surgery, or medication. 'Access' was defined by the four-dimensional model described in

Gulliford et al. (2002), first introduced in Chapter Two. [Briefly, the dimensions are as follows: (1) available services in adequate supply for a certain population; (2) financial, organisational, and social or cultural barriers limiting service usage; (3) relevance and effectiveness of services for diverse patient groups; and (4) equity of access.]

A final parameter requiring definition was who qualified as being at high risk for a BRCA mutation, given that the intended study population was all high-risk American and British adults. Separate criteria for risk were applied to US and UK populations in accordance with the national guidelines governing BRCA services in each country. For American participants, personal history of cancer determined which guideline they had to meet: the USPSTF guideline applied to those without cancer, and the NCCN guideline applied to those with cancer (NCCN, 2016b; USPSTF, 2013). British participants simply had to meet NICE referral criteria, which are used in all four UK constituent countries (NICE, 2013b). (See Chapter Three for an in-depth comparison of NICE, NCCN, and USPSTF guidelines.)

4.2.2 Identifying relevant studies

To identify relevant studies, the search strategy combined terms pertaining to 'access', 'genetic services', and 'breast cancer gene mutations', as shown in Table 4.1. The strategy was developed through an iterative process that involved testing different phrasing, pluralisation, and American and British English spellings of terms.

Table 4.1: Terms combined in the search strategy

Access	Genetic services	Breast cancer gene mutations
Access	Genetic services	Breast cancer gene mutations
Barriers	Genetic counselling	Hereditary breast and ovarian cancer
Facilitators	Genetic testing	BRCA
Uptake		HBOC
Utilisation		Breast cancer gene
		Ovarian cancer gene
		Inherited breast cancer
		Inherited ovarian cancer
		Familial breast cancer
		Familial ovarian cancer

The search terms yielded a total of 150 unique combinations, each of which was run through six electronic databases: CINAHL via Ovid, Cochrane Trials, Embase via Ovid, Medline via PubMed, PsycINFO via Ovid, and the Web of Science's Core Collection via the Web of Knowledge. Results were limited to works published online or in print before August 2014; they were originally retrieved in October 2014 and re-checked in March 2015 to account for any database updates. Given the volume of items identified through these searches, alternative means of identifying studies (e.g., hand-searching of journals or citation indexing) were not pursued.

4.2.3 Selecting studies

As illustrated in Figure 4.1, the 900 database searches yielded a total of 8,664 records, which were condensed into 779 unique results after de-duplication. Initial screening of titles and abstracts led to the exclusion of 595 records, which met at least one of the following exclusionary criteria:

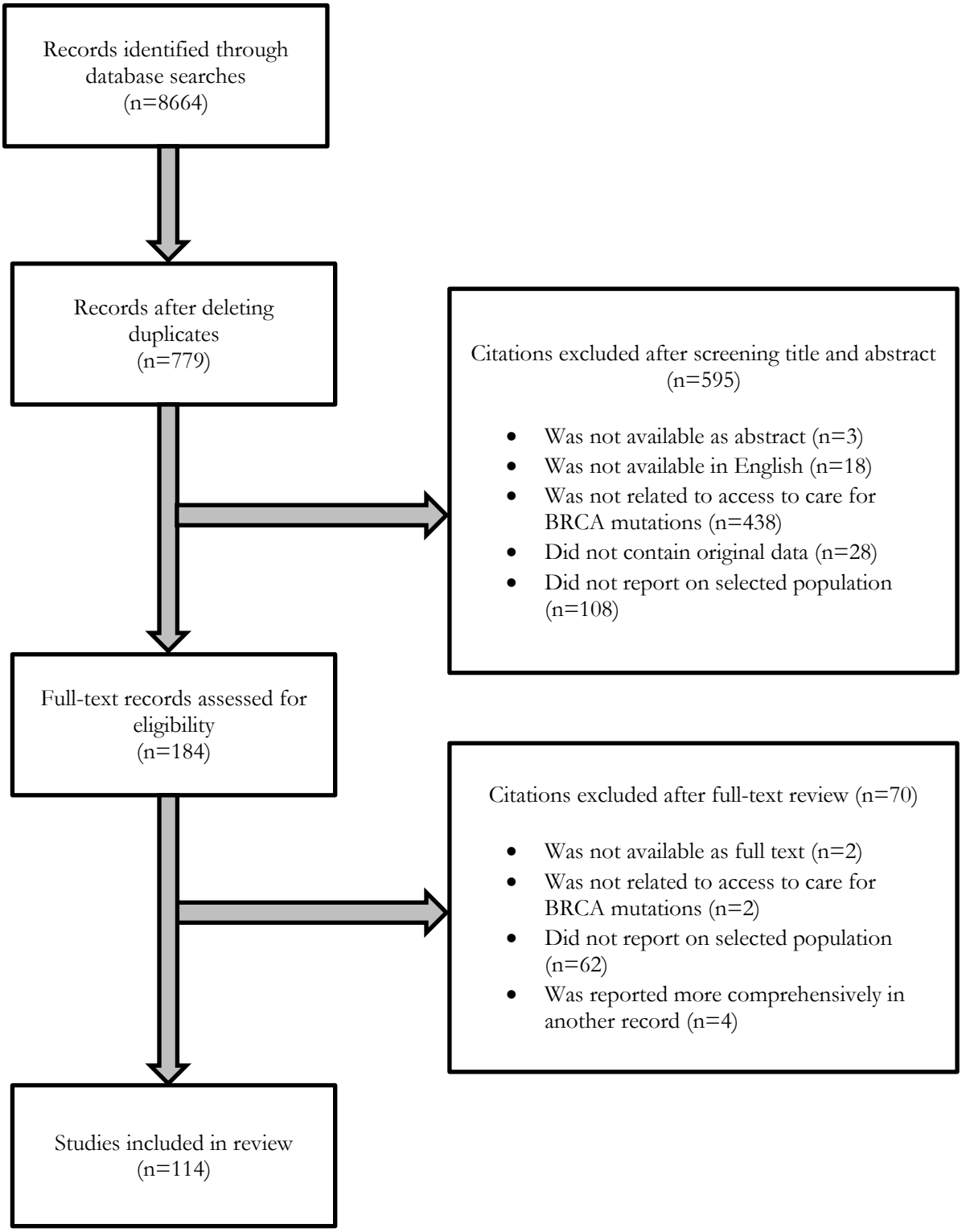
- Articles could not be retrieved through any link generated in the database results;

- Articles were not written in English;
- Articles were unrelated to access to care for BRCA mutations;
- Articles did not contain original, empirically collected data; or
- Articles did not involve high-risk American and/or British adult participants.

During initial screening, the 'access' parameter required refinement, as several studies could not be ruled in or out using the Gulliford definition alone. Studies had to either (1) include discussion of barriers or facilitators to pursuing genetic services or (2) examine outcomes such as genetic testing uptake. For example, a study examining how familial communication impacts genetic counselling attendance would be included, but a study only discussing how families communicate would be excluded. Studies involving pooled data (e.g., counselling uptake for multiple hereditary cancer syndromes) or population-based testing (e.g., testing all breast cancer patients) were also excluded, unless partial data relating to high-risk HBOC populations could be readily extracted. Finally, studies citing intentions, anticipated uptake, attitudes, perceived risk, knowledge, and psychosocial characteristics were excluded unless directly related to barriers, facilitators, or outcomes.

The remaining 184 articles were then reviewed against the same eligibility criteria at full text, leading to exclusion of 66 more studies. (For poster and oral presentations, 'full text' meant the abstracts were reviewed alongside any relevant supplemental visual aids, e.g., electronic copies of posters or graphs.) A final four studies were excluded because their findings were reported more comprehensively in another result, e.g., a presentation abstract was excluded because a journal article reported the same data. Thus, the 114 included studies contained original, empirically obtained data from high-risk American and British adult populations and were retrievable, written in English, and related to access to care for BRCA mutations.

Figure 4.1: Scoping study flow diagram



4.2.4 Charting of the data

The included studies were read at full text and examined through the data charting approach introduced by Arksey and O'Malley (2005) and clarified in Levac et al. (2010); this involved developing and using a standardised data extraction form. Informing the development of the data extraction form was a Cochrane Methods chapter on 'Extracting qualitative evidence' by Noyes and Lewin (2011), which included sample forms from Munro et al. (2007), Noyes and Popay (2007), and the National Collaborating Centre for Mental Health (2007). Additional sources consulted were the evidence-based Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009); a commentary on scoping review methodology and reporting by the Levac et al. authors and their colleagues (Colquhoun et al., 2014); a methodological manual on scoping reviews (The Joanna Briggs Institute, 2015); and a research note on framework analysis that discusses data charting practices in qualitative research (Srivastava & Thomson, 2009). Table 4.2 contains the components of the data extraction form used to evaluate the 114 included studies.

Table 4.2: Data extraction form components

General information	Study characteristics	Outcomes
Title	Study design	Key qualitative findings
Author(s)	Study location	Key quantitative findings
Database	Participants	
Journal	Type of medical service	
Year of publication	Data collection/analysis approach	
Web address	Additional comments	

The 'General information' section of the data extraction form covered basic details for each included item: title, author(s), database in which it was found, journal, year of publication,

and web address. The 'Study characteristics' section described what was done, where, to whom, and how. This originally included study design (e.g., retrospective medical record review), study location (e.g., Washington, DC or Edinburgh, Scotland), participants in the study (e.g., breast cancer patients under the age of 50 diagnosed between 2009 and 2012), and data collection/analysis approach (e.g., quantitative survey mailed to patients and analysed using descriptive statistics and regression analysis). After extracting several studies, however, it seemed as though type of medical service (e.g., academic cancer centre or regional genetics service) might also be relevant, so that criterion was added to the data extraction form. [This iterative approach to adjusting the extraction form is in line with those advocated in the methodological resources mentioned above, such as Arksey and O'Malley (2005) and The Joanna Briggs Institute (2015).] Any relevant additional comments were also recorded, e.g., if an included item was a conference presentation abstract or if only a subset of patients met the inclusion criteria.

The 'Outcomes' section captured important quantitative and qualitative findings. Quantitative factors/variables were the characteristics associated with uptake of a type of care at the $p \leq 0.05$ level. These variables were generated by studies using certain methodologies (e.g., retrospective reviews or cross-sectional studies) that allowed categorical responses to be transformed into numerical data (e.g., 'no insurance' could be converted to '0' and 'insurance' could be converted to '1'). Thus, a cross-sectional study could report a significant association between insurance and uptake of genetic testing, which means 'insurance' would be considered a quantitative factor. Other quantitative data described uptake and timing of interventions, though these were usually only reported as descriptive statistics. Qualitative data were specific to barriers and facilitators that patients perceived as hindering or helping their access to care, respectively, and were extracted from studies incorporating interviews, focus groups, and multiple-choice questionnaires.

4.2.5 Collating, summarising, and disseminating results

After completing data charting, the next task was to collate, summarise, and disseminate the findings, which meant conducting thematic analysis on the qualitative data and concurrently organising and analysing the quantitative data. Thematic analysis involved the six steps detailed in Braun and Clarke (2006): (1) familiarising oneself with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and renaming themes, and (6) producing the report.

First, the charted qualitative and quantitative data were read and re-read several times to create familiarity with the findings, and general impressions of the findings were jotted down next to the data charts. Second, generating initial codes for the qualitative data involved importing codes directly from the quantitative variables where possible, e.g., 'clinician recommendation' was a quantitative variable associated with genetic testing that also emerged in the qualitative data. Descriptive codes were assigned to the small number of qualitatively identified barriers and facilitators that did not completely align with quantitative variables, e.g., there was no corresponding quantitative variable for 'travel concerns' or 'distance to clinic', so those qualitative findings were coded as 'location'. In all, 14 quantitative variables had qualitative counterparts, and four emergent codes were assigned to the remaining qualitative data.

Third, searching for general themes involved sorting all of the coded qualitative and quantitative data into possible themes. This step was done manually by writing each code on a slip of paper and grouping related codes together, which resulted in four themes: demographic variables, clinical variables, awareness variables, and psychosocial variables. Fourth, reviewing themes required re-reading the coded data extracts and then the entirety of the charted data to ensure that the proposed themes accurately represented the data set as

a whole. Whilst no themes were changed, a few variables like 'family history of cancer' were re-classified from 'demographic' to 'clinical' at the recommendation of Professors Parker and Lucassen, who provided feedback during this stage.

Fifth, defining and renaming themes meant considering how the qualitative and quantitative data within a theme fit into that particular theme, and more broadly, with the other three themes. As Braun and Clarke (2006) recommended, single-sentence descriptions of each theme were developed to test how well the themes captured the data describing factors, barriers, and facilitators that may affect access to care for BRCA mutations: Demographic variables included population characteristics such as sex and health insurance status. Clinical variables related to personal and familial medical choices and histories of cancer, as well as clinician behaviours like recommending patients undergo genetic testing. Awareness variables involved knowledge, attitudes, and perceptions of breast cancer genetics, ranging from perceived cancer risk to medical mistrust. Psychosocial variables comprised factors related to personal and familial well-being, such as family hardiness and self-efficacy.

Sixth, reporting the data involved putting the analysed data into tables and describing the data in accompanying text. Quantitative findings and qualitative findings were organised and written up separately, with the four themes applied to the tables and narratives in both cases. Sections 4.3.1 through 4.3.3 discuss the quantitative factors significantly associated with uptake of counselling, testing, and post-test interventions, respectively, as well as descriptive statistical findings about the proportion, timing, and results of women electing interventions. Given that data charting resulted in far fewer qualitative data than quantitative data, the qualitative data were not separated by category of care; thus, all patient-identified barriers and facilitators are listed in one table and described in Section 4.3.4. Additionally, Section 4.3.5 details a brief secondary analysis that breaks down which variables came from

which country (or countries), i.e., factors appearing only in US studies, factors appearing only in UK studies, and factors appearing in both US and UK studies.

One noteworthy decision about the reporting of results was the choice to focus on breadth of results, not depth of results. To that end, factors were not explicitly ranked based on how frequently they appeared in the extracted data or whether there were contradictory findings in the extracted data, e.g., a positive association in one study and a negative association in another study. This decision is in line with the methodological literature on scoping studies, as the purpose of a scoping study is to map the breadth of available evidence without critically appraising the quality of the evidence (Arksey & O'Malley, 2005; Tricco et al., 2016). Ranking factors would be better suited to a much narrower systematic review, e.g., if the research question specifically examined whether income and insurance affect uptake of care, rather than a much broader scoping study that does not consider predetermined outcome measures. Thus, Sections 4.3.1 through 4.3.3 include tables that present all factors identified at least once as being significantly associated with uptake of a type of care, without mentioning how frequently each factor was studied and subsequently found to be significantly associated. Frequency can be indirectly considered in the accompanying text, though, which reports all significant associations as well as any contradictory findings. Similarly, Section 4.3.4 contains a table detailing patient-identified barriers and facilitators to care without any information on frequency of responses, though the accompanying text provides context on how many studies reported certain findings.

4.3 Results

As explained above, Sections 4.3.1 through 4.3.3 discuss the quantitative results, i.e., the 46 unique factors that were significantly associated with uptake of genetic counselling, genetic testing, and/or post-test interventions involving screening, surgery, and medication. Section

4.3.4 considers the qualitative results, i.e., the 18 barriers and facilitators identified by patients as hindering or helping care. Section 4.3.5 briefly describes the quantitative and qualitative results – i.e., the 46 factors and 18 barriers and facilitators – when broken down by country.

4.3.1 Genetic counselling

Counselling uptake was associated with the 10 factors listed in Table 4.3, with clinician referral the most-cited positive predictor of counselling and the only clinical variable. The remaining nine factors linked to uptake were split equally between the demographic, awareness, and psychosocial categories. Income was associated with counselling uptake but not non-uptake in a Pittsburgh study of breast cancer patients (O'Neill, Peters, Vogel, Feingold, & Rubinstein, 2006), whilst social deprivation and younger age were both associated with non-uptake in a pair of Scottish studies (Hanning et al., 2014; S. M. Holloway, Bernhard, Campbell, Cetnarskyj, & Lam, 2008). Negatively correlated concerns included greater anticipation of negative emotions, greater concern about stigmatisation, higher levels of family-related guilt and medical mistrust, and lack of knowledge about cancer genetics (Sheppard, Mays, LaVeist, & Tercyak, 2013; H. S. Thompson et al., 2002). The only positively correlated psychosocial factor was cancer-related distress (H. S. Thompson et al., 2002).

Table 4.3: Factors associated with uptake of genetic counselling

Demographic	Clinical
Age Income Social deprivation	Clinician referral
Awareness	**Psychosocial**
Concern about stigmatisation Knowledge about cancer genetics Medical mistrust	Anticipation of negative emotions Cancer-related distress Family-related guilt

One recurrent theme was that among women eligible for a referral, relatively few actually received a referral and attended counselling. The eight counselling-related studies with cancer patient populations, detailed in Table 4.4, illustrate this phenomenon (Anderson et al., 2012; Hayes et al., 2013; Henretta et al., 2011; Meyer et al., 2009; O'Neill et al., 2006; Pal, Cragun, et al., 2014; Powell, Littell, Hoodfar, Sinclair, & Pressman, 2013; Vadaparampil et al., 2009). First, the three studies examining referral rates all cited rates below 45 per cent. Second, among all women referred for counselling, the average percentage of women who attended counselling was just 39.2 per cent (499/1273 patients).

Though demographic variables (e.g., race and ethnicity) did not appear to correlate with either referral or counselling uptake, a clinician's knowledge and cancer expertise may affect both. Vadaparampil et al. (2009) found that 62 per cent of breast cancer patients attended counselling after receiving a surgeon's letter recommending it. Similarly, Halbert, Brewster, et al. (2005) found that referral from oncology practices, but not general practices, correlated strongly with counselling participation. Conversely, poor clinician-patient communication may hinder referrals: Bellcross et al. (2015) reported that just 20.2 per cent of eligible women received referrals, despite 89.5 per cent discussing family history with a clinician, and

Kinney et al. (2001) wrote that two thirds of a BRCA1 African American kindred wished to discuss HBOC risk factors with a healthcare provider. Additionally, recognition of populations that traditionally struggle to access healthcare services, such as ethnic and racial minorities, seemed low. One study found outright that high-risk African Americans were less likely to be referred than high-risk White or Hispanic women (Meyer et al., 2009), whilst a multi-site American study reported a less obvious interaction: Latina ethnicity was associated with lack of knowledge about counselling (Gammon et al., 2011).

Table 4.4: Referral of and genetic counselling (GC) uptake by cancer patients

Location	Population	Referral for GC	GC uptake
Florida	287 Black women with breast cancer, <50 years	All met criteria; 95/287 (33.1%) referred	51.6% (49/95)
Michigan	289 women with breast cancer (249 White, 24 Black, 16 other), <50 years	All met criteria; referrals not specified	42.2% (122/289)
Virginia	101 women with breast cancer, ≤45 years, 'race similar across all groups'	All met criteria; referrals not specified	26.7% (27/101)
California	340 women with breast cancer <40 years or ovarian cancer <60 years, race not specified	110/340 (32.4%) women met criteria; 47/110 (42.7%) referred - 40/67 breast, 7/33 ovarian	42.7% (47/110)
Texas	3765 women (3110 White, 155 African American, 360 Hispanic, 140 'other or unknown') with ovarian cancer, mean age 56	896/3765 (23.8%) women met criteria; 276/896 (30.8%) referred	33.3% (92/276)
New York	340 women with ovarian cancer, 21-89 years, race not specified	All met criteria and were referred	39.1% (133/340)
Florida	26 women with breast cancer, 31-70 years, 'homogenous' race	All met criteria and received surgeon's referral letter	62.0% (16/26)
Illinois	36 women (34 White, 2 'other') with breast cancer and ≥10% risk of BRCA mutation, 21-70 years	All met criteria and were referred	36.1% (13/36)

4.3.2 Genetic testing

Linked to testing uptake were 27 different factors, which are organised by theme in Table 4.5 and explained over the next few pages. Most identified factors were positively or negatively associated with testing uptake, but several factors – especially age – had contradictory associations with uptake. Three additional findings outside of the factors associated with testing are also discussed in this sub-section.

Table 4.5: Factors associated with uptake of genetic testing

Demographic	Clinical
Age	Clinician recommendation
Education	Family history of breast or ovarian cancer
Health insurance	Family information session attendance
Income	Family member tested
Parity	Genetic counselling
Race and ethnicity	Personal history of breast or ovarian cancer
Religiosity and spirituality	Post-counselling risk estimate
Sex	Proactive genetic services
Awareness	**Psychosocial**
Actual cancer or mutation risk	Cancer-related distress
Attitudes to testing	Decisional conflict
Concern about stigmatisation	Family hardiness
Knowledge about cancer genetics	Family-related guilt
Medical mistrust	Self-efficacy
Perceived cancer risk	

4.3.2.1 Demographic variables

Eight demographic factors were found to be significant. Higher income and more education were associated with greater uptake, as were being female and having health insurance

(Finlay et al., 2008; M. J. Hall et al., 2013; S. M. Holloway, Bernhard, Campbell, Cetnarskyj, et al., 2008; S. M. Holloway, Bernhard, Campbell, & Lam, 2008; Kieran, Loescher, & Lim, 2007; Lerman et al., 1996; Lynch et al., 2009; Olaya et al., 2009; Pal, Bonner, et al., 2014; Pal, Cragun, et al., 2014; N. Peters et al., 2005; Ruddy et al., 2010). Two positively associated modifiers of insurance were eligibility for free testing (S.-C. Lee, Bernhardt, & Helzlsouer, 2002) and point-of-service plans as compared to health maintenance organisation plans (Levy et al., 2011). Although six of the above studies reported that insurance correlated with uptake, Elrafei et al. (2014) and Olaya et al. (2009) found insurance was not a factor; the latter also found no relationship between income and testing, contrasting with three studies cited above.

Findings of both non-associations and significant associations also applied to parity, race and ethnicity, religiosity and spirituality, and age. Olaya et al. (2009) reported non-associations for all four factors, whilst Pal, Cragun, et al. (2014) only reported a non-association for parity. Otherwise, parity was associated with uptake in one study (S. M. Holloway, Bernhard, Campbell, & Lam, 2008), and greater spirituality correlated with non-uptake in another (Schwartz et al., 2000). In terms of race and ethnicity, AJ heritage was associated with greater uptake, whereas African American heritage (and in one joint study, Hispanic heritage) was associated with lower uptake (Fehniger, Lin, Beattie, Joseph, & Kaplan, 2013; Fowler, Neese, & Schwartzberg, 2005; S.-C. Lee et al., 2002; Levy et al., 2011; Susswein et al., 2008; Vig et al., 2013).

Eight studies reported a significant association between testing and age, suggesting a non-linear relationship potentially influenced by cancer status. In three studies of cancer patients diagnosed before age 50, younger age at diagnosis correlated with testing (Pal, Cragun, et al., 2014; N. Peters et al., 2005; Ruddy et al., 2010); a fourth study of cancer patients found that those under age 50 were more likely to test than those over age 50 (Vig et al., 2013).

Conversely, three studies of unaffected individuals found that older women were more likely to be tested than younger women. The two UK studies reported the median ages for test acceptors and decliners were in the 40s and 30s, respectively (Foster et al., 2004; S. M. Holloway, Bernhard, Campbell, & Lam, 2008), whilst the US study said the average ages for test acceptors and decliners were in the mid-50s and low 50s, respectively (Lynch et al., 2009). The eighth study involved an American BRCA1 kindred in which women ages 40 to 49 were more likely to test than women under 40 or over 50 (Kinney et al., 2006).

4.3.2.2 Clinical variables

All eight clinical variables were positively associated with testing. In terms of utilisation of services, attending a family information session on HBOC and attending genetic counselling correlated with testing uptake (Henretta et al., 2011; Lynch et al., 2009; Pal, Cragun, et al., 2014). In terms of clinician behaviour, recommending that patients pursue testing (a distinct act from referring the patient), providing a post-counselling risk estimate, and contacting family members of mutation carriers proactively were also linked to greater uptake (Evans, Binchy, Shenton, Hopwood, & Craufurd, 2009; Kieran et al., 2007; Schwartz et al., 2005). Additionally, Vadaparampil, McIntyre, and Quinn (2010) noted sub-ethnic differences in how at-risk Hispanic women wanted physicians to recommend testing and impart information.

The remaining three clinical variables related to medical histories and choices: having a family member tested, having a personal history of breast or ovarian cancer, and having a strong family history of breast or ovarian cancer, particularly on the maternal side (Bellcross et al., 2015; Finlay et al., 2008; Katapodi, Northouse, Milliron, Liu, & Merajver, 2013; Kieran et al., 2007; S.-C. Lee et al., 2002; Lerman et al., 1996; Lynch et al., 2009; N. Peters et al., 2005; Ruddy et al., 2010; Vig et al., 2013). Olaya et al. (2009) reported a positive association

and a non-association for personal history and family history of cancer, respectively. Finally, testing was more likely in cancer patients with more recent diagnoses than more remote diagnoses (Susswein et al., 2008).

4.3.2.3 Awareness variables

Both actual and perceived risk of having a harmful mutation or cancer generally correlated with testing uptake, as did knowledge of cancer genetics (Bellcross et al., 2015; Fowler et al., 2005; Katapodi et al., 2011; Kinney et al., 2001, 2006; N. Peters et al., 2005; Ruddy et al., 2010; H. S. Thompson et al., 2002). (Notably, whilst Katapodi et al. [2011] found that tested relatives had greater perceived breast cancer risk than untested relatives, the opposite relationship was true for perceived ovarian cancer risk.) Unsurprisingly, positive attitudes towards testing (e.g., thinking the benefits of testing outweigh its harms) were associated with greater uptake, whilst medical mistrust, stigmatisation concerns, and negative attitudes towards testing (e.g., fear of false-positive results) were associated with lower uptake (Armstrong et al., 2003; Katapodi et al., 2013; Lerman et al., 1996; N. Peters et al., 2005; Sheppard et al., 2013; H. S. Thompson et al., 2002).

4.3.2.4 Psychosocial variables

Four psychosocial factors were associated with greater uptake: greater self-efficacy, greater cancer-related distress, greater decisional conflict (including treatment indecision), and greater family hardiness (Katapodi et al., 2011, 2013; Schwartz et al., 2005; Sheppard et al., 2013). Lower levels of cancer-related distress – including lesser cancer worry and greater belief in cancer controllability – and higher levels of family-related guilt were associated with declining testing (Foster et al., 2004; Katapodi et al., 2011; H. S. Thompson et al., 2002).

4.3.2.5 Additional findings

Three additional testing-related topics emerged during data charting: the quantification of testing uptake, the role of VUS results, and the timing of testing. The most prominent was testing uptake, which ranged dramatically among the 53 studies in which it was discussed. For example, 1.41 per cent of high-risk, unaffected women underwent testing in one study based on US Census data (Levy, Garber, & Shields, 2009), whereas 80 per cent of individuals with a known BRCA1 mutation in the family pursued testing in another paper (Patenaude et al., 1996). Given the significant variation in terms of which high-risk populations were considered (e.g., women with unidentified familial mutations versus women with identified familial mutations) and when data were collected (e.g., studies conducted in the 1990s versus studies conducted in the 2010s), there was no attempt to estimate average testing uptake across studies. (See the 'Discussion' sub-section on 'Low uptake across categories of care' for more analysis of expected sources of this variation.)

VUS results were discussed in relation to additional testing, rates of results, race and ethnicity, and site differences. One study found that individuals receiving VUS or uninformative negative results 'will not consistently pursue additional or enhanced genetic testing', e.g., BRCA1 rearrangement panel testing as a follow-up to BRCA1/2 full gene sequencing (Shannon, Muzikansky, Chan-Smutko, Niendorf, & Ryan, 2006, p. 740). Although a 2013 study reported that the rate of VUS results decreased over time (Lynce, Stein, Demarco, Isaacs, & Smith, 2013), a 2014 study of Black women still found a considerable percentage (93/283 women, or 32.9 per cent) received VUS results (Pal, Bonner, et al., 2014). Hodes and Chen (2011) reported that though there was no difference in rates of BRCA mutations or variants between Asian, Black, and Caucasian women, the specific mutations and variants found among these groups differed. Similarly, a comparative study of three public American hospitals found no difference in VUS result occurrence

between sites despite differences in ethnic makeup of testers, funding structures, and referral systems at each hospital (Beattie et al., 2011).

Testing timing related to how long most patients waited to test and the relationship between testing and cancer surgery. Brooks et al. (2004) and Rosenberg et al. (2014) reported that uptake appeared to peak within a year of cancer diagnosis or familial disclosure of a mutation, but some patients tested years later. A third study confirmed those findings and additionally reported that men waited longer to test than women and testing occurred more quickly over time (M. J. Hall et al., 2013). Also, testing was more common after surgery than before surgery (Lynce et al., 2013; Stolier, Fuhrman, Mauterer, Bolton, & Superneau, 2004; Trosman, Weldon, Gradishar, & Schink, 2010), and younger age was associated with greater pre-surgery uptake in the Trosman et al. (2010) study. Two final studies reported little incorporation of testing results into surgical decisions, as many women did not receive their results before having surgery (Fleming et al., 2011; Schwartz et al., 2005).

4.3.3 Post-test interventions

A total of 28 factors were linked to at least one of nine post-test interventions: breast self-examination (BSE), clinical breast examination (CBE), mammography, MRI, CA-125 testing, TVUS, chemoprevention, mastectomy, and oophorectomy. To enable both theme-specific and intervention-specific analysis, these factors were organised into four tables: (1) factors associated with screening, organised by the four overarching study themes; (2) factors associated with screening, organised by modality; (3) factors associated with medication and surgery, organised by the four overarching study themes; and (4) factors associated with medication and surgery, organised by modality.

4.3.3.1 Screening variables, organised by theme

In Table 4.6, the 20 factors associated with screening are broken down by the four overarching themes. The most-referenced demographic factor was age, followed by income and marital status. Clinical variables dealt with genetic services, personal and family medical history, and clinician behaviour (e.g., clinicians offering CBE during routine practice), and personal and family medical history. Awareness variables comprised intentions to have oophorectomy and perceptions of ovarian cancer risk, screening utility, and time for screening. Psychosocial variables involved psychological distress and confidence in overcoming barriers.

Table 4.6: Factors associated with uptake of screening, by theme

Demographic	Clinical
Age Income Marital status	Clinician practice Clinician recommendation Clinician relationship Family history of breast or ovarian cancer Genetic counselling Genetic testing Genetics professional consultation Length of genetic counselling sessions Mutation status Personal history of breast or ovarian cancer
Awareness	Psychosocial
Intent to have oophorectomy Perceived risk of ovarian cancer Perceived utility of screening Perceived time for screening	Anxiety Cancer-related distress Confidence in overcoming barriers

4.3.3.2 Screening variables, organised by modality

When broken down by screening modality, as in Table 4.7, several additional findings are apparent. First, mammography had the most factors associated with uptake (13); the other breast cancer screening modalities only had three or four factors apiece. Second, having a BRCA mutation correlated with all screening modalities except BSE (Botkin et al., 2003; Lerman et al., 2000; Lynch et al., 2006; Schwartz et al., 2003, 2012). Third, family histories of ovarian cancer and greater perceived risk of ovarian cancer were associated with uptake of ovarian, but not breast, cancer screening (Isaacs et al., 2002; Pal, Lee, et al., 2014; Schwartz et al., 2003; Tinley et al., 2004). Fourth, nine factors were common across at least two types of screening, and these items are all in bold in Table 4.7.

Table 4.7: Factors associated with uptake of screening, by modality

BSE	CBE	Mammography	MRI	CA-125	TVUS
		Age		Anxiety	
		Clinician recommendation			**Clinician recommendation**
Cancer-related distress	**Cancer-related distress**	Clinician relationship			
	Clinician practice	**Confidence in overcoming barriers**			**Confidence in overcoming barriers**
		Family history of breast cancer		**Family history of ovarian cancer**	**Family history of ovarian cancer**
Genetic counselling	**Genetic counselling**	**Genetic counselling**	Genetics professional consultation	**Genetic counselling**	
Genetic testing		**Genetic testing**			
		Income			Intent to have oophorectomy
		Marital status	Length of genetic counselling sessions		
	Mutation status	**Mutation status**	**Mutation status**	**Mutation status**	**Mutation status**
Personal history of breast/ovarian cancer		**Personal history of breast cancer**			
		Perceived time for screening		**Perceived risk of ovarian cancer**	**Perceived risk of ovarian cancer**
		Perceived utility of screening			

Delving deeper into breast cancer screening, two studies found that BSE and CBE uptake correlated with cancer-related distress (Foster et al., 2002; Tinley et al., 2004), but a third reported no such association (Isaacs et al., 2002). Additional factors that were significantly related to BSE were genetic counselling (Watson et al., 2005), genetic testing (Botkin et al., 2003), and a personal history of breast or ovarian cancer (Tinley et al., 2004). Adherence to CBE was associated with seeing a physician who offered CBE to patients twice yearly (Tinley et al., 2004), as well as genetic counselling (Watson et al., 2005). MRI uptake positively correlated with two aspects of genetic counselling: genetics professionals conducting counselling and longer sessions (Pal, Lee, et al., 2014).

Of the 13 factors associated with mammography uptake, seven were clinical variables: clinician recommendation, clinician relationship, genetic counselling, genetic testing, family history of breast cancer, personal history of breast cancer, and mutation status. Patients who received annual screening recommendations, formed more satisfactory relationships with clinicians, attended counselling, and underwent testing were more likely to have mammograms than patients who received no screening recommendations, formed less satisfactory relationships with clinicians, declined counselling, and decided against testing, respectively (Botkin et al., 2003; Tinley et al., 2004; Watson et al., 2005). Likewise, having a previous diagnosis of breast cancer and being closely related to more breast cancer patients correlated with higher rates of mammography (Isaacs et al., 2002; Tinley et al., 2004). Mutation status was associated with mammography uptake, but Lerman et al. (2000) attributed that finding to non-carriers' decreased adherence to screening rather than carriers' increased adherence to screening.

The remaining six variables associated with mammography were a mixture of awareness, psychosocial, and demographic factors. Tinley et al. (2004) found that uptake correlated

positively with greater perceived time for and usefulness of screening, as well as confidence in overcoming barriers. Married and higher-income women were more likely to have mammograms than single and lower-income women, respectively (Isaacs et al., 2002; Tinley et al., 2004). Age had the most nuanced relationship to mammography of any variable. Botkin et al. (2003) reported that among mutation carriers, younger age was associated with greater uptake; however, Lerman et al. (2000) found that women ages 40 and over were more likely to have mammograms than women ages 25 to 39, regardless of mutation status. In a third study reporting significant findings, the highest compliance rates were among women ages 40 to 49, followed by women ages 50 to 64, women ages 65 and over, and women ages 30 to 39 (Isaacs et al., 2002).

A final demographic factor, religiosity and spirituality, failed to reach main effect significance but produced a significant interaction with heightened risk cues – such as mutation status or breast cancer diagnosis – that affected mammography behaviour. Dunn reported, '[A]mong participants with a heightened risk cue … greater [religiosity and spirituality] was associated with decreased odds of adherence to screening guidelines, while conversely, among women without these heightened risk cues, greater [religiosity and spirituality] was associated with increased odds of guideline adherence' (2014, pp. viii–ix).

Turning to the ovarian cancer screening interventions, the positive associations of both CA-125 testing and TVUS with mutation status, family history of ovarian cancer, and perceived risk of ovarian cancer were previously mentioned. CA-125 testing uptake correlated with attending genetic counselling sessions and harbouring more anxiety (Henretta et al., 2011; Schwartz et al., 2003), whilst TVUS uptake was associated with greater confidence in overcoming barriers, intent to have oophorectomy, and clinician-recommended TVUS (Tinley et al., 2004). Two modifiers to TVUS uptake related to mutation status: Lynch et al.

(2006) reported a non-significant decrease in TVUS adherence for non-carriers, and Tinley et al. (2004) noted that more educated carriers were more likely to have TVUS than less educated carriers.

4.3.3.3 Medication and surgery variables, organised by theme

In Table 4.8, the 12 factors associated with chemoprevention, mastectomy, and oophorectomy are broken down by the four main themes. Seven of the 12 factors were clinical; three were interventions themselves (e.g., oral contraceptives), and the other four related to personal and family medical histories (e.g., personal history of breast cancer). The three demographic variables were age, parity, and race and ethnicity, whilst the two awareness variables were actual and perceived risk of cancer. There were no psychosocial variables.

Table 4.8: Factors associated with uptake of medication and surgery, by theme

Demographic	Clinical
Age Parity Race and ethnicity	BRCA mutation type Family history of breast or ovarian cancer Mastectomy Mutation status Oophorectomy Oral contraceptive use Personal history of breast cancer
Awareness	Psychosocial
Actual cancer risk Perceived risk of ovarian cancer	

4.3.3.4 Medication and surgery variables, organised by modality

When broken down explicitly by chemoprevention, mastectomy, and oophorectomy, as in Table 4.9, a few findings stood out. First, mutation status was associated with all three interventions, as well as the only variable associated with chemoprevention (Lynch et al., 2006; Schwartz et al., 2012). Second, five demographic and clinical factors were associated with both risk-reducing surgeries, and mastectomy and oophorectomy were also associated with each other. These six factors are all in bold in Table 4.9 below.

Table 4.9: Factors associated with uptake of medication and surgery, by modality

Chemoprevention	Mastectomy	Oophorectomy
Mutation status	**Mutation status**	**Mutation status**
	Age	**Age**
	Family history of breast or ovarian cancer	**Family history of breast or ovarian cancer**
	Parity	**Parity**
	Personal history of breast or ovarian cancer	**Personal history of breast or ovarian cancer**
	Oophorectomy	**Mastectomy**
	Actual risk of breast cancer	BRCA mutation type
		Oral contraceptive use
		Perceived risk of ovarian cancer
		Race and ethnicity

The two demographic variables associated with both surgeries were parity and age. Two studies reported that women with children were more likely to have oophorectomies than women without children (Bradbury et al., 2008; Friebel et al., 2007), and one reported the

same trend for both oophorectomy and mastectomy (Singh et al., 2013). Similar to genetic testing, age had a complicated, non-linear relationship to surgery uptake. Evans, Lalloo, et al. (2009) found that women ages 35 to 45 elected both surgeries more frequently than women under 35 or over 45, whilst Beattie et al. (2011) concluded that women below age 60 were more likely to have mastectomies and oophorectomies than women 60 and over. Specific to mastectomy, two studies refuted any association between surgery and age (Singh, Li, & Gordon, 2009; Singh et al., 2013). Specific to oophorectomy, three studies found that women age 40 or older were more likely to undergo surgery than women below age 40 (Bradbury et al., 2008; Friebel et al., 2007; Schwartz et al., 2012). Sidon et al. (2012) examined a different set of ages, reporting that women ages 40 to 59 were more likely to pursue oophorectomy than women age 60 or older.

Three clinical variables were associated with both surgeries, including the aforementioned mutation status. Beattie et al. (2011) linked a personal history of breast cancer to greater uptake of both surgeries. Schwartz et al. (2012), however, reported an interesting interaction: compared to a more remote diagnosis of breast or ovarian cancer, a diagnosis in the past decade was associated with increased mastectomy uptake but decreased oophorectomy uptake. The association of family history of cancer and both surgeries was also well studied. Three studies – Ricker et al. (2014), Singh et al. (2009), and Singh et al. (2013) – reported significant relationships between family history of breast cancer and mastectomy. (However, Pal, Lee, et al. (2014) and Fleming et al. (2011) reported no significant findings between family history and mastectomy, and Singh et al. [2009] found a relationship between familial deaths from breast cancer and mastectomy but not the number of familial cancers and mastectomy.) Four studies found associations between family history of cancer and oophorectomy: Schwartz et al. (2003), Bradbury et al. (2008), Ricker et al. (2014), and Singh et al. (2013).

In terms of the relationship between surgeries, two studies found oophorectomy uptake and mastectomy uptake were positively correlated (Beattie, Crawford, Lin, Vittinghoff, & Ziegler, 2009; Singh et al., 2009). Conversely, Schwartz et al. (2012) reported that mastectomy uptake was greater in women who had not undergone oophorectomy.

Of the remaining five factors, one related to mastectomy (actual risk of breast cancer) and four related to oophorectomy (perceived risk of ovarian cancer, oral contraceptive use, race and ethnicity, and BRCA mutation type). Greater risk of breast cancer and greater perceived risk of ovarian cancer were associated with mastectomy and oophorectomy uptake, respectively (Evans, Lalloo, et al., 2009; Schwartz et al., 2003), whereas oral contraceptive use was negatively associated with oophorectomy uptake (Garcia et al., 2014). In terms of race and ethnicity, Bradbury et al. (2008) reported that White women were significantly more likely to have oophorectomies than non-White (Black and Hispanic) women; Wexelman et al. (2014) reported a non-significant finding of the same trend. Finally, three studies found BRCA1 carriers were more likely to have oophorectomies than BRCA2 carriers (Evans, Lalloo, et al., 2009; Sidon et al., 2012), though a fourth study found no difference between BRCA1 and BRCA2 carriers in terms of oophorectomy uptake (Friebel et al., 2007).

4.3.3.5 Additional findings

Two additional topics emerged during data charting: the quantification and timing of post-test interventions. As with testing, average uptake was not quantified for any of the nine interventions, given the considerable variation in terms of which populations were considered and when data were collected. In terms of comparative uptake, though, there were a few findings to highlight. First, in the only multi-centre, international paper included in this scoping study, Friebel et al. (2007) examined oophorectomy and mastectomy uptake

in 14 US clinics and 2 UK clinics. Two findings were significant: (1) among all women, more patients had oophorectomies than mastectomies (55 per cent and 21 per cent, respectively), and (2) British women were more likely to have mastectomies than American women (31 per cent and 20 per cent, respectively). Additional large-scale studies that together spanned more than a decade of practice – such as Singh et al. (2013), Schwartz et al. (2012), Garcia et al. (2014), Beattie et al. (2009), Botkin et al. (2003), and Bancroft et al. (2010) – supported the finding of more women electing oophorectomy than mastectomy. (No comparisons were made about how absolute rates of oophorectomy and mastectomy have changed in either country over time.) Second, given the high-risk population investigated, overall uptake of screening, medication, and surgery was lower than might have been expected. Adherence to mammography appeared to outpace adherence to the other five screening modalities, and breast cancer screening generally seemed to take place more frequently than ovarian cancer screening (Lerman et al., 2000; Morgan, Sylvester, Lucas, & Miesfeldt, 2009; Tinley et al., 2004).

In terms of intervention timing, nearly all of the data from included studies pertained to prophylactic surgeries, and the relatively few non-surgical findings (e.g., on screening adherence) were discussed earlier. Uptake of oophorectomy and mastectomy occurred most frequently in the first two years after disclosure, particularly for unaffected BRCA carriers, though each study found a mean wait time for surgery of at least four months (Beattie et al., 2009; Evans, Lalloo, et al., 2009; Friebel et al., 2007; Garcia et al., 2014; Singh et al., 2009; Wexelman et al., 2014). However, there was noticeable variation in surgery timing, as Bradbury et al. (2008) noted that many women waited at least one year, if not more, to pursue surgery; Schwartz et al. (2012) found that mutation carriers having one or both prophylactic surgeries did so at a mean of 5.3 years post-test; and Bancroft et al. (2010) reported that some women pursued surgery more than eight years after disclosure. Bradbury

et al. (2008) found longer times to oophorectomy were associated with no children and younger age; Evans, Lalloo, et al. (2009) also reported the latter relationship. In Schwartz et al. (2005), receiving results more slowly than expected and having low anxiety levels correlated with breast cancer patients undergoing surgery before receiving their results. Finally, Wexelman et al. (2014) reported that White women waited over two months longer to have mastectomies than minority women, though oophorectomy timing was no different.

4.3.4 Barriers and facilitators

The 18 barriers and facilitators discussed here were all identified by adults at high risk for HBOC, or revealed in their subsequent usage of genetic services, as helping or hindering access to care. In Table 4.10, these barriers and facilitators are organised by the same four categories used in the counselling, testing, and post-test intervention sections.

Table 4.10: Barriers and facilitators potentially impacting access to genetic services

Demographic	Clinical
Health insurance Income Location Race, ethnicity, and culture	Administrative practicalities Clinician recommendation Communication Completion of family history forms Systemic interventions
Awareness	Psychosocial
Concern about stigmatisation Knowledge about cancer genetics Perceived mutation risk Perceived time for screening	Anticipation of negative emotional responses Anxiety Competing life concerns Decisional conflict Familial benefit

4.3.4.1 Demographic variables

Location was the only new demographic variable to emerge, as health insurance, income, and race, ethnicity, and culture had statistically significant associations with types of care. Women identified insurability concerns and limited coverage as barriers to pursuing care (Anderson et al., 2012; Mouchawar, Rahm, & Carroll, 2007; Rosenberg et al., 2014); conversely, they cited having comprehensive health insurance coverage as a facilitator (Sheppard et al., 2014). Likewise, income-related issues were both barriers and facilitators: four studies reported high testing costs impeded access (Kinney et al., 2001; Rosenberg et al., 2014; Sheppard et al., 2014; Vadaparampil et al., 2011), whilst one study found reduced testing costs improved access (Lacour et al., 2008). Location was only referenced as a barrier, as Foster et al. (2004) and Patenaude et al. (1996) both reported that women considered travel concerns when deciding to pursue genetic services. Finally, racial, ethnic, and cultural characteristics both helped and hindered access. In terms of facilitators, Sussner et al. (2011) found positive relationships between measures of ethnic identity and positive attitudes towards genetic testing, and Sheppard et al. (2014) reported that some women sought genetic testing because of its potential to benefit the African American community. In terms of barriers, Sussner et al. (2011) reported positive relationships between (a) ethnic search and negative attitudes towards genetic testing and (b) racial identity and concerns about confidentiality, and Sussner et al. (2009) also found a correlation between being born outside the United States and anticipating negative emotional responses.

4.3.4.2 Clinical variables

Administrative practicalities – which encompassed the non-medical components of pursuing genetic services – surfaced for the first time here. Barriers under this umbrella included difficulties navigating the administrative process and finding available testing (Kinney et al., 2001; Mouchawar et al., 2007); conversely, patients suggested that screening reminders and

increased post-test guidance would facilitate adherence to guidelines (Morgan, Sylvester, Lucas, & Miesfeldt, 2010). Another clinical barrier was trouble completing family history forms, which patients often are recommended, if not required, to fill out before genetic counselling (Mouchawar et al., 2007). Poor clinician-patient communication (e.g., medical interpretation issues) and strong clinician-patient communication (e.g., productive discussion about family history) hindered and helped care, respectively (Joseph & Guerra, 2015; Kinney et al., 2001; J. A. Ray, Loescher, & Brewer, 2005). Finally, receiving a clinician recommendation for testing was a facilitator (Morgan et al., 2009; Vadaparampil et al., 2011), but receiving a recommendation against testing – or no recommendation at all – was a barrier (Anderson et al., 2012; Benkendorf et al., 1997).

Clinicians also attempted to use systemic interventions to improve the identification and subsequent referrals of high-risk women and patient experiences with counselling. Seven American articles described pilot programmes consisting of a family history screening tool being incorporated into other breast care services, e.g., during mammography appointments. Patients identified as high risk were subsequently contacted by a clinician well-versed in genetics or provided with information for genetic services (Acheson, Lynn, & Wiesner, 2009; Traxler et al., 2014; Cohen & McIlvried, 2013; Hendrix et al., 2014; Joseph et al., 2012; Mays et al., 2012; Ray et al., 2014). Most studies were not sufficiently large to assess whether referral rates and counselling uptake increased significantly, but each study reported serving more high-risk patients with the intervention than without the intervention. An eighth intervention involved a clinic assistant calling patients who had been referred to further explain counselling and schedule appointments; this significantly shortened time from referrals to counselling appointments (Rahm, Sukhanova, Ellis, & Mouchawar, 2007). Another three studies evaluated telephone counselling and disclosure, which was generally viewed as a facilitator that could expedite the counselling and testing process and lessen the

costs of testing (Baumanis, Evans, Callanan, & Susswein, 2009; Patrick-Miller, Cummings, Fetzer, Schmidheiser, & Bradbury, 2009; Schwartz et al., 2014). In an assessment of group and individual education and counselling, patients found both methods equally satisfactory, but group education saved clinics 30 minutes of time per patient (Calzone et al., 2005). Finally, training a nurse practitioner to provide counselling and testing within a surgical breast service decreased wait times for counselling appointments (E. Smith, Lane, Butler, & Hsiang, 2009).

4.3.4.3 Awareness variables

All four awareness variables cited by patients were also associated with uptake of genetic services. In focus groups and interviews, some high-risk women demonstrated poor understanding of genetic counselling and testing that hindered their ability to pursue genetic services (Joseph & Guerra, 2015; Kinney et al., 2001; Sheppard et al., 2014), whilst other women cited knowledge about genetic risk as facilitating their cancer treatment decisions (Rosenberg et al., 2014). Sheppard et al. (2014) described another barrier, women's concerns about stigma and job discrimination, which a few participants echoed in Mouchawar et al. (2007). Two final barriers were low perceived risk of HBOC by either patients or physicians (Rosenberg et al., 2014), as well as perceived lack of time available for pursuing genetic services (Foster et al., 2004).

4.3.4.4 Psychosocial variables

Three of the five psychosocial variables were previously discussed: anticipation of negative emotional responses, anxiety, and decisional conflict. In multiple studies, high-risk women cited baseline anxiety and anticipation of negative emotional responses to test results as barriers to pursuing genetic services (Foster et al., 2004; Mouchawar et al., 2007; Patenaude et al., 1996; Sheppard et al., 2014), and Vadaparampil et al. (2011) reported women fearing

potential testing-induced pain. Ray et al. (2005) reported on decisional conflict barriers: 'Reasons for indecision about risk-reduction surgery included genetic testing results, concerns about surgery, timing in life, and early menopause' (p. 473). Facilitators related to decisional conflict, however, involved the desire to reduce risk and the ability to use test results to influence cancer treatments (Lacour et al., 2008; Morgan et al., 2010). One new psychosocial barrier was competing life concerns, e.g., testing was not a top priority (Rosenberg et al., 2014), whereas the single new facilitator was testing for familial benefit (Anderson et al., 2012; Joseph & Guerra, 2015; Lacour et al., 2008; Patenaude et al., 1996; Sheppard et al., 2014; Vadaparampil et al., 2011).

4.3.5 Variables organised by country

Of the 114 included studies, 100 involved only American participants, 13 involved only British participants, and one involved both American and British participants. Of the 46 identified factors, 35 were found only in US studies, three were found only in UK studies, and eight were found in both US and UK studies. The three variables found only in British studies were BRCA mutation type (i.e., BRCA1 mutation vs. BRCA2 mutation), proactive genetic services, and social deprivation (Evans, Binchy, et al., 2009; Hanning et al., 2014; S. M. Holloway, Bernhard, Campbell, Cetnarskyj, et al., 2008; Sidon et al., 2012). Four of the eight factors found in both American and British papers were demographic: age, income, parity, and sex. The remaining four factors were split between clinical, awareness, and psychosocial variables: actual risk of mutation or cancer, cancer-related distress, genetic counselling, and knowledge about cancer genetics.

The only UK study discussing barriers was Foster et al. (2004), which referenced location (i.e., travel difficulties), perceived lack of time for testing, and anxiety about test results as potential impediments to testing.

4.4 Discussion

Four findings from this scoping study of factors, barriers, and facilitators affecting access to care in the United States and United Kingdom are particularly striking: (1) the low rate at which high-risk British and American women utilised different kinds of care for BRCA mutations, (2) the number and breadth of variables affecting uptake of genetic services by these high-risk adults, (3) the relationship between factors associated with access to care and cited barriers and facilitators to care, and (4) the similarities and differences between UK and US variables, barriers, and facilitators. Several points related to decisions about study parameters, alternative routes to genetic services, and systemic interventions are also reviewed here.

4.4.1 Low uptake across categories of care

Across counselling, testing, and post-test interventions, women do not appear to utilise all of the genetic services that are available to them. Table 4.4, the chart showing referral rates and counselling uptake for cancer patients, showcased one such example. Young breast cancer patients should theoretically be the easiest population for US clinicians to evaluate appropriately, as the combination of their diagnosis and age should trigger an immediate offer of referral. Yet in the three studies without universal referrals, the highest referral rate was below 45 per cent. This low referral rate was then compounded by low uptake of referrals: among the cancer patients who received referrals, the average rate of counselling uptake was below 40 per cent.

These low referral and counselling rates require additional context, however. It is unclear whether the offer of referral was appropriately withheld because of then-current clinical guidelines, inappropriately withheld despite then-current clinical guidelines, or appropriately

offered by a clinician and declined by a patient. Likewise, it is unknown why these American women declined the offer of counselling: patients could have been occupied with cancer treatments, deterred by the cost of visiting additional specialists, limited by lack of patient and provider education, or empowered to turn down counselling. Evidence that clinicians inappropriately withheld referrals or patients declined counselling for reasons beyond their own informed personal choices would suggest barriers to care, but low rates may simply reflect the evolution of clinical practice and/or patients exercising their right to decline care. Thus, absolute uptake rates alone cannot determine whether women have appropriate access to care, whether for counselling, testing, or any post-test intervention; what they can do is highlight cases in which the relationship between clinical practice and clinical guidelines should be explored.

The rest of this sub-section examines ways in which the accepted date range, which ran from each database's inception through August 2014, might have influenced uptake rates. First, the inclusion of studies from the early days of BRCA testing may have depressed impressions of uptake. In line with the finding that testing rates increased dramatically between 2004 and 2007 in a national sample of young American breast cancer patients (Levy et al., 2011), uptake in studies from the late 1990s was likely lower than uptake in studies from the 2000s and early 2010s. Studies employing prospective cohort or retrospective review design also typically reported data gathered a few years prior, e.g., the Levy et al. (2011) study analysed data from 2004 through 2007. Had the studies been limited to only those in the mid-2000s and later, the uptake figures might have been higher and thus more representative of current genetic service utilisation. (That said, more recent studies did not universally report greater uptake than less recent studies; for example, Pal, Bonner, et al. [2014] reported a baseline 33 per cent testing rate for a population of 283 young Black women with breast cancer, using data recorded from 2009 to 2012.) Earlier results were

ultimately included to facilitate examination of factors that may have influenced access to genetic services in the past, as those findings may contribute to a fuller understanding of factors potentially influencing access in certain populations at present. (Analysis of the temporal variable this decision created can be found in the 'Choices affecting the parameters of the study' sub-section.)

Second, two external events that took place in 2013 have impacted BRCA testing uptake since then. In May 2013, actress and humanitarian Angelina Jolie published a *New York Times* op-ed explaining that she carried a BRCA1 mutation and had undergone a preventive mastectomy to reduce her risk of breast cancer (Jolie, 2013). In June 2013, the US Supreme Court issued its gene patenting decision and thus ended Myriad's monopoly on BRCA testing (Supreme Court of the United States, 2013), as discussed in depth in Chapter Three. Researchers have attributed increased post-2013 testing uptake to both the 'Angelina Jolie effect' – i.e., the global public awareness Jolie's piece generated – and increased US testing affordability in the wake of the US Supreme Court decision (Desai & Jena, 2016; Evans et al., 2014; Rosenberg et al., 2016). In other words, these studies suggest that women reacted to Jolie's story by requesting referrals or self-referring to genetic services; additionally, they report more privately insured US women being covered for testing. Restricting results to works published before August 2014, whilst necessary because of the project timeline, therefore meant that only the earliest analyses of uptake published after these two events could be captured in this scoping study. If results published through 2016 were included, the overall trend of testing uptake increasing over time would be expected to continue, if not increase much more sharply, and additional insights into the kind of women seeking testing within the past few years would be possible.

Third, the comprehensiveness of genetic testing increased over time, which likely increased the rate of post-test interventions. This predicted relationship hinges on two facts: more women received VUS or uninformative negative results in the early years of testing compared to recent years (Lynce et al., 2013; Shannon et al., 2006), and risk management choices cannot be informed by VUS or uninformative negative results. When the pool of results broadened as more patients underwent testing, there was more evidence available to reclassify VUS and uninformative negative results as deleterious or benign (Eggington et al., 2012); thus, more results could lead to post-test interventions in later years than in earlier years. In patient groups that have historically underutilised testing – e.g., women from ethnic minority groups – and therefore had particularly high rates of VUS results during the infancy of BRCA testing, this relationship is likely even stronger. (VUS result classification guidelines have changed over time to help separate results that truly have uncertain significance from 'those for which there is significant, but not irrefutable, evidence against or for pathogenicity' [Plon et al., 2008, p. 1284]. Such updated classification schemes and clinical reporting requirements, as detailed in the British Society for Genetic Medicine's 'Practice guidelines for the evaluation of pathogenicity and the reporting of sequence variants in clinical molecular genetics' [Wallis et al., 2013], could also lead to lower reported VUS rates.) In this study, mutation status was positively associated with eight of nine post-test interventions, but the act of testing itself was only positively associated with BSE and mammography; that is, those who received positive results pursued more care than those who received negative or uninformative results. This result supports the idea that post-test intervention uptake may have increased had only studies from later years been used.

Fourth, the complicated relationship between when women pursue services – both in terms of their age and how much time has elapsed since learning of their high risk – might impact the accuracy of reported uptake. Compared to studies of younger carriers, for instance,

studies of older carriers would be expected to find higher rates of post-test interventions like oophorectomies, particularly if the older participants were past childbearing age. Cross-sectional reports only looking at genetic testing at the time of cancer diagnosis – whilst crucial in determining how many women have access to genetic testing as a preventive service – may not adequately capture how many women avail themselves of genetic testing as a form of post-diagnosis care, as well as how many women take additional measures if a harmful mutation is found. Likewise, logistical reasons may preclude studies from following women through the potentially lengthy process of counselling, testing, and multiple post-test interventions, thereby underestimating actual utilisation by virtue of selecting a shorter time period. Given the number of studies consistently finding low uptake of all services, though, it seems unlikely that such potential underestimation drastically affected uptake figures.

4.4.2 Breadth of factors affecting uptake of genetic services

The previous sub-section explored why estimating uptake of genetic services is difficult; through examination of the sheer number and breadth of factors associated with uptake of genetic services, this sub-section underscores the complicated nature of access to genetic services. Overall, there were 46 unique factors significantly associated with counselling, testing, or at least one post-test intervention at the $p \leq 0.05$ level. Broken down by theme, there were 10 demographic variables, 19 clinical variables, 9 awareness variables, and 8 psychosocial variables. Broken down by category of care, there were 10 factors associated with counselling, 27 associated with testing, and 27 associated with post-test interventions. Only three variables – age, income, and cancer-related distress – were associated with counselling, testing, and at least one post-test intervention, and all three factors were significant in both American and British studies. Whilst income and cancer-related distress had straightforward positive associations with uptake of each kind of care, age was more

elusive. Broadly speaking, the peak age for pursuing genetic services appeared to be somewhere between 35 and 50, with some variation depending on personal and family histories of cancer.

Several broad patterns emerged when looking at the variables within each theme. Demographic variables, by definition, were population characteristics and thus could not be altered directly through genetic services. Clinical variables also included several fixed characteristics (e.g., BRCA mutation type), but the majority of factors related to clinician behaviour (how clinicians communicated with patients and how genetic services were organised) and patient behaviour (how patients elected to pursue care). Awareness variables were divided between knowledge (e.g., understanding cancer genetics), attitude (e.g., stigmatisation concerns), and perception (e.g., perceived cancer risk) factors. For psychosocial variables, the desire to find concrete answers about cancer risk and treatment and the ability to cope with difficult medical news appeared to influence uptake.

Given that there were so many variables cited as helping and/or hindering access, one question is how to use these results to improve access. Factors that cannot be altered directly through clinical intervention included all demographic and psychosocial variables (e.g., race and ethnicity, income, and self-efficacy) and some clinical and awareness variables (e.g., family history of cancer and medical mistrust). Addressing these factors might require the implementation of targeted education efforts designed to mitigate fixed patient characteristics and engrained patient beliefs and attitudes. For example, minority patients might be offered tailored genetic counselling that addresses aspects of medical mistrust and family-related guilt, and genetics professionals might intensify outreach efforts to patients with strong family histories of cancer who are being seen by general practitioners (GPs) or oncologists.

Factors that can be altered directly through clinical intervention, including the majority of clinical variables and the remaining awareness variables, present more obvious opportunities for clinicians to improve access. For example, arguably the most important clinical variable for American women was a clinician's referral, which functioned as a gateway for patients to access counselling and other services. (Since British women are only able to access genetic services through clinician referral – i.e., a patient cannot refer herself directly to genetic services, as in America – referral could not be a variable in Britain.) Clinicians may be able to alter their individual behaviours to encourage uptake of services (e.g., GPs and oncologists learning the personal and familial histories associated with HBOC and making appropriate referrals). Similarly, clinicians may be able to directly address knowledge-related awareness variables through patient education. However, optimal uptake requires that clinicians be supported at the systemic level as well (e.g., with the resources to invite at-risk relatives to genetic services proactively).

4.4.3 Overlap between barriers, facilitators, and factors associated with uptake

In general, the statistically significant associations between variables and uptake aligned with the barriers and facilitators described by at-risk women as affecting access, which suggests that research has largely captured women's concerns about access to care. Seven cited barriers and facilitators were statistically unexamined in the included papers, however: three barriers (location, competing life concerns, and completion of family history forms), two facilitators (familial benefit and systemic interventions), and two joint barriers and facilitators (administrative practicalities and communication).

Location was perhaps the most surprising omission from the factor list, given the number of pilot studies examining telephone disclosure as a means of promoting access to

geographically isolated women. Its absence might reflect some combination of the travel accessibility of the study locations themselves, which were generally in well-populated American and British cities; the intrinsic challenge of capturing reasons for declining services when primarily studying women who accepted services; and the practicality of collecting data points that have little bearing on individual patients' clinical care. That said, knowing how far women will travel for genetic services, and how that distance is impacted by factors such as socioeconomic status, could be useful for clinicians wishing to serve more at-risk women in their regions.

The omission of the remaining six barriers and facilitators from the list of factors makes sense because of the inherent difficulty in quantifying them in medical record review. Systemic interventions were logical facilitators, given that clinicians designed the interventions specifically to improve access to genetic services. The nature of how the interventions were examined – usually through descriptive reports or in small-scale pilots, precluding most statistical analysis – also explains why these interventions surfaced as facilitators but not factors. The emergence of competing life concerns, which amounted to prioritisation of family and work responsibilities over medical care, is not surprising given the findings about variances in testing and surgery timing. Familial benefit was a natural facilitator, given the shared nature of genetic information, and may relate to psychosocial variables such as family-related guilt and family hardiness. Contextualised by the importance of clinician behaviour to uptake of genetic services, the inclusion of administrative practicalities that made navigating services easier or harder was also a predictable outcome. Lack of completion of family history forms was more likely to appear as a barrier than a factor because family history forms almost always have to be filled out in order to attend counselling, unless the familial mutation is already known. Finally, the idea of clinician-

patient communication affecting uptake was reasonable, given that strong clinician-patient relationships were associated with uptake.

4.4.4 Similarities and differences between UK and US findings

The 'Variables organised by country' section identified a discrepancy in the number of barriers, facilitators, and factors associated with uptake of care in America and Britain. These findings require examination in light of what kinds of research took place and where, as well as how the UK and US healthcare systems are structured, in order to make sense of what these findings might suggest about access in each country.

Where research took place can be examined by breaking down the nationalities of women studied and the places in which those women resided. In terms of nationalities, there were more than seven times as many included studies on American populations only (100) as studies on British populations only (13). In terms of cities of residence, studies in each country were generally carried out in major academic hospitals situated in relatively large cities. Among the 100 US-only studies, a combined 35 took place in Boston, Houston, New York City, Philadelphia, and Washington, DC; researchers from the Washington, DC-based Georgetown University alone accounted for 17 studies. Despite the small sample size, the 13 UK-only studies were also somewhat clustered, e.g., five studies were carried out in Manchester and four more were based in Scottish cities. Thus, studies involving American women and women from more urban, research-orientated areas more heavily influenced findings than studies involving British women and women from more rural, non-research-orientated areas.

What kind of research took place – relative to within- and between-country differences and similarities – can partly be examined through the number of and research objectives for

comparative studies. Only five included studies directly compared genetic service uptake within and/or between countries. The sole international report assessed US and UK uptake of mastectomy and oophorectomy (Friebel et al., 2007). Of the two American studies comparing multiple sites, one study examined testing uptake in both a public hospital and a tertiary cancer centre (Fehniger et al., 2013), whilst the second studied BRCA-positive and VUS result rates between three hospitals with different referral sources and public funding levels (Beattie et al., 2011). Of the two British studies comparing multiple sites, one study compared mastectomy uptake for young affected BRCA carriers at both a dedicated breast cancer prevention facility and a general regional genetics clinic (Evans et al., 2005), and the second simply reported counselling and testing uptake percentages for hospitals in two cities (Brooks et al., 2004). Given the dearth of research permitting direct comparison within or between countries, the results in this study are best treated as descriptive rather than inferential, i.e., these results should not be generalised to the entire population of high-risk American and British women but instead taken as hypotheses about how access to care works in America and Britain.

Overall, there were more than 11 times as many US-only variables (35) as UK-only variables (3) identified in this study. Incorporating the eight variables common to both countries narrows the discrepancy – 43 US variables to 11 UK variables – but still leaves an appreciable ratio of nearly four US variables per one UK variable. Beyond the obvious reason that there was more US-focussed research than UK-focussed research, what might account for the division of variables in each country? One way of unpacking the results is to consider variables in five groupings: 'Variables found in America and Britain', 'Variables found in Britain only that could apply in America', 'Variables found in Britain only that could not apply in America', 'Variables found in America only that could apply in Britain', and 'Variables found in America only that could not apply to Britain'.

Beginning with the 'Variables found in America and Britain' grouping, four factors are demographic: age, income, parity, and sex. These make sense given age-specific recommendations provided in both countries' national guidelines, the NCCN recommendation that oophorectomy be considered once childbearing is complete, and previous findings of sex- and income-based differences in attitudes toward and utilisation of various kinds of cancer screening (NCCN, 2016b; NICE, 2013b; Organisation for Economic Co-operation and Development, 2013; Ritvo et al., 2013). The lone clinical variable, genetic counselling, seems plausible because NCCN and NICE guidelines both dictate that counselling should precede testing and inform HBOC syndrome management (NCCN, 2016b; NICE, 2013b). The three remaining variables – knowledge about cancer genetics, actual risk of having a BRCA mutation or cancer, and cancer-related distress – fit in the global context of health literacy and service usage. Being health-literate means that patients can read, understand, and make decisions using health information (Kickbusch, 2001); a patient pursuing genetic services based on her risk profile, knowledge of cancer genetics, and desire to address cancer-related distress seems a good example of health literacy leading to action. Overall, the variables in this grouping appear to be logically related to BRCA service usage and applicable to both US and UK populations.

Next are the three UK-only variables: BRCA mutation type, proactive genetic services, and social deprivation. Upon review, there is no compelling reason why these factors could not be found in America. Differences in the risk-reduction choices of BRCA1 and BRCA2 carriers are more likely attributable to different risk profiles associated with the mutations, as shown in Mavaddat et al. (2013), than between-country differences. Contacting patients directly, rather than waiting for patients to initiate contact, was an approach also used in several American pilot studies. Social deprivation is not as commonly measured in America as in Britain, but there is a well-documented history of US healthcare disparities resulting

from employment, social class, and income differences suggesting that deprivation could apply in America. Thus, there were three variables fitting into the 'Variables found in Britain only that could apply in America' category and no variables in the 'Variables found in Britain only that could not apply in America' category.

Turning to the US-only variables, there are some factors that clearly fall under the 'Variables found in America that could not apply to Britain' grouping. Most obviously, having insurance and receiving a clinician referral could not variably impact British women because all British women have national health insurance and can only access genetic services through clinician referral. Furthermore, the differences in UK and US guidelines about what kinds of care are considered evidence-based – described in depth in Chapter Three – likely contributed to the discrepancy in cited variables. The NICE guidelines do not support CBE, BSE, CA-125 testing, or TVUS because of poor evidence (NICE, 2013b). In contrast, the NCCN guidelines recommend CBE, as well as BSE as it relates to breast awareness; and whilst NCCN does not support CA-125 testing or TVUS, both kinds of ovarian screening are left to the clinician's discretion (NCCN, 2016b). (As discussed in Chapter Three, the USPSTF guidelines do not recommend for or against any interventions for BRCA carriers [USPSTF, 2013].) Hence, the US factors appearing only in association with one of these four screening modalities – clinician practice (CBE), anxiety (CA-125 testing), and intent to have oophorectomy (TVUS) – do not translate to current UK care. In sum, there were five US variables that could not be UK variables because of country-based differences between guidelines and healthcare systems.

The final 30 variables thus fall into the fifth grouping, 'Variables found in America that could apply in Britain'. The four remaining demographic variables were education, marital status, race and ethnicity, and religiosity and spirituality – characteristics that can be

recorded for women in both countries and have previously been evaluated for their impact on various health conditions (Centers for Disease Control and Prevention [CDC], 2014). The clinical variables ranged from HBOC-related care recommended in each country (e.g., genetic testing) to universally applicable attributes of counselling sessions (e.g., session length), clinician behaviour (e.g., clinician recommendation), and fixed patient characteristics (e.g., personal history of cancer). Five of the six awareness variables, including perceived cancer risk and stigmatisation concerns, did not seem at all country-specific. The sixth variable, medical mistrust, has predominantly been studied in American minority populations; given that it surfaces in studies of First Nations women in Canada and Aboriginal adults in Australia (Brener et al., 2015; Maar et al., 2013), however, there is no indication that medical mistrust could not apply to minority women in Britain. Finally, the six psychosocial factors (e.g., confidence in overcoming barriers and decisional conflict) were all characteristics dependent on individual patients' psychologies, not their nationalities.

Of the patient-identified barriers and facilitators, only the seven distinct from factors associated with care will be discussed here. In terms of UK-only factors, the single new barrier to emerge was location (in the context of where a patient would have to travel for care, not the region in which she lived). In terms of US-only factors, the two barriers were competing life concerns and difficulty completing family history forms; the two facilitators were familial benefit and systemic interventions; and the two joint barriers and facilitators were administrative practicalities and communication. There are no compelling reasons why any of these seven factors would not apply in both countries.

Overall, this sub-section illustrates that whilst most variables associated with care were found in the United States only (35/46), nearly all variables associated with care could

potentially be found in either country (41/46), as could the barriers and facilitators that do not overlap with factors associated with uptake of care (7/7). Thus, the bulk of the findings in this chapter could, but not necessarily would, apply to British and American populations alike. The US-only variables that could definitively not be found in Britain were ruled out on the basis of differences in national care guidelines and healthcare system structures.

4.4.5 Choices affecting the parameters of the study

Several decisions that shaped the parameters of the scoping study also merit more examination. The first set of issues dealt with participant eligibility, including which study populations qualified as high risk. The UK criteria were straightforward because of the existence and applicability of NICE guidelines for familial breast cancer to all UK constituent countries. The US criteria reflected influential guidelines to which primary care and genetics professionals might refer and to which insurance companies typically defer when determining eligibility for care. Patients with no history of cancer were included if they met any of the five USPSTF-approved referral tools; these patients would typically be referred by GPs, who were the target audience of USPSTF guidelines. Patients with a history of cancer qualified for inclusion if they met NCCN guidelines; these patients would typically be referred by oncologists, who were the target audience of NCCN guidelines. Another question was whether male participants should be eligible, given that this thesis concerns women's access to care. So that studies involving both men and women would not be summarily excluded, male participants were eligible if they were at high risk for HBOC; 11 studies involving both high-risk men and women were ultimately included. A third aspect of participant eligibility concerned studies that did not explicitly mention whether referrals were appropriate. Unless the authors specifically mentioned inappropriate referrals, these studies were included.

The second set of issues was how to address variation in when studies were published, as discussed briefly in reference to testing uptake. Guidelines – including which patients are considered high risk and what constitutes good clinical practice – have evolved over time. For example, the mutation probability that the NICE guidelines require for testing decreased in 2013. Given the difficulty in applying different guidelines to studies from different years, all potential populations were assessed to see if they would be considered high risk using guidelines current as of March 2016. Which women seek care for BRCA mutations also may have changed over time, e.g., BRCA counsellees appear to be more racially and ethnically diverse now that testing has expanded beyond the three common AJ mutations. Similarly, certain types of post-test interventions are no longer recommended for the populations in which they were previously studied, such as BSE and CBE in the United Kingdom (McIntosh et al., 2004). However, the heterogeneous nature of high-risk BRCA counsellees suggests that older findings that may not apply universally today may still apply to subsets of counsellees. Older findings with predominantly AJ participants might still apply to AJ patients today, just as factors previously associated with BSE and CBE in British women may now apply to American women, who are still instructed to have regular CBE and participate in BSE as it relates to breast awareness. Thus, relationships between factors and uptake of care should not be dismissed just because time has passed, but they should not be accepted uncritically either.

A third set of issues involved the decision to include any factor significantly associated with care at the $p \leq 0.05$ level in at least one study. Setting a low threshold for how frequently a factor had to be found in the literature and for what kind of study qualified as acceptable evidence allowed for a wide range of factors to be considered, albeit with the potential to distort how widely and consistently reported certain factors were. Some of the findings were very specific (e.g., seeing a clinician who offers CBE twice yearly), which made their

replicability difficult to assess. Moreover, except in the case of a few randomised controlled trials designed to test systemic interventions, included studies were generally observational. Thus, results only showed correlation and not causation, i.e., there was a relationship between the factor and uptake of care in the particular study population at that particular time, but the factor did not necessarily determine uptake of care or generalise to all high-risk populations in all years.

In sum, the parameters chosen for this scoping study underscore the importance of recognising what this study can and cannot do. This study outlines a wide variety of factors that have potentially influenced access to care in high-risk US and UK adult populations at some point since the inception of BRCA testing. Equally importantly, this study neither attempts to claim that all factors identified are relevant to all high-risk populations today, nor that factors identified here explicitly increase or decrease uptake of care.

4.4.6 Alternative routes to BRCA services

Two alternative routes to genetic services, DTC genetic testing and research study-provided counselling and testing, were minimally addressed in the 114 included studies. Just one study examined DTC testing: U. Francke et al. (2013) reported that 25 BRCA carriers described their experiences of receiving results directly from 23andMe as neutral to positive. As noted in Chapter Three, though, 23andMe only tested and reported results for three common AJ mutations, and 23andMe is no longer allowed to issue such reports in the United States. Thus, a person testing negative through 23andMe might actually have a different harmful mutation, and if clinician-provided testing later revealed that mutation, her satisfaction with DTC testing might be quite different from those testing positive immediately. Although DTC testing theoretically provides a low-cost opportunity for patients to obtain genetic

testing without a referral, this study is not a particularly compelling case for how DTC testing can widen access.

Research as an avenue to genetic counselling and testing was investigated in five studies. Pal, Bonner, et al. (2014) examined BRCA mutation prevalence in young Black breast cancer patients by providing free counselling and testing through a research programme; Lerman et al. (1996) studied participant reactions to counselling and testing provided in a research setting; Kinney et al. (2006) probed test acceptance in an African American BRCA1 kindred as part of a research study; DeMarco, Loffredo, Sampilo, and Tercyak (2006) looked into which cancer centre registry members were eligible and willing to participate in research that included testing; and Bancroft et al. (2010) surveyed attendees to gauge interest in research participation as part of a report on a British carrier clinic. In the United States, research-provided genetic services might widen access for lower income or uninsured patients if research funds cover the costs of counselling and testing. In the United Kingdom, substituting research access for clinical access would not affect high-risk patients financially; depending on recruitment methods, though, research-provided genetic services might widen access for patients who have not been able to obtain a referral through traditional clinical care. That said, research participation was neither a factor associated with any category of care nor a facilitator.

4.4.7 Systemic interventions

The systemic interventions found in included papers were mainly pilot programmes aiming to identify and refer high-risk women to genetic counselling and incorporate the offer of genetic counselling into comprehensive breast care services. They also shed light on what clinicians view as potential barriers, e.g., the demographics of women who might lack access and which points of service might hinder access. Several studies were specifically aimed at

low-income, uninsured, and minority women; others aimed to decrease the time between referral, counselling, testing, and disclosure of results. Unsurprisingly, these interventions essentially corroborated the two approaches clinicians might take to improve access that were discussed in the 'Breadth of factors affecting uptake of genetic services' sub-section.

4.5 Summary

This chapter has examined the factors, barriers, and facilitators potentially influencing access to care for BRCA mutations in the United States and United Kingdom through a rigorously designed scoping study. Forty-six unique variables fell into four main categories (demographic, clinical, awareness, and psychosocial) and were analysed both by type of care (genetic counselling, genetic testing, and nine post-test interventions involving screening, medication, or surgery) and country (America and/or Britain). Only three variables – age, income, and cancer-related distress – were significantly associated with counselling, testing, and one or more post-test interventions. Barriers and facilitators identified by patients at high risk for HBOC largely mirrored the identified variables. Moreover, nearly all barriers, facilitators, and factors could potentially affect high-risk patients in either country; the few exceptions stemmed from differences in healthcare systems and national care guidelines.

Overall, this chapter has significantly contributed to an understanding of the Gulliford model's second and third dimensions, i.e., organisational, financial, and social or cultural barriers to care and relevance and effectiveness of services for different patient groups. The scoping study has accomplished this by naming factors that were statistically associated with care utilisation, as well as barriers and facilitators identified by high-risk patients, for a variety of US and UK patient populations. To a lesser extent, this chapter has also provided insight into the fourth dimension of access, equity of access as measured by service utilisation and outcomes, through its interpretation of counselling and testing rates.

5 Chapter Five: Clinician and support group member views on access to care

5.1 Introduction

Whilst both Chapter Three and Chapter Four contributed to an understanding of how access to care might work, neither explicitly explored current day-to-day clinical practice from the dual perspectives of the clinicians and patients who provide and pursue care for BRCA mutations, respectively. Moreover, though both chapters were informed by the four-dimensional definition of access given by Gulliford et al. (2002), not all dimensions were comprehensively studied. Chapter Three examined the first dimension (which services exist and to whom they are available); both Chapters Three and Four provided insight into the second dimension (financial, organisational, and cultural or social barriers limiting service usage); and Chapter Four partially described the third (relevance and effectiveness of services for different groups of patients) and fourth dimensions (equity of access).

This chapter serves as a small-scale, pragmatic empirical examination of how American and British genetics professionals and support group members currently view access to care for BRCA mutations along the first three dimensions of access, especially the third. Through focus groups and interviews, participants helped contextualise the impact of regulations and findings in the literature against their own experiences and further developed the view that access to care for BRCA mutations extends far beyond a guideline determining patient eligibility and a patient undergoing testing.

5.2 Methods

This study took place in the Greater London and South East England regions in the United Kingdom and the Mid-Atlantic region in the United States. The University of Oxford Central University Research Ethics Committee reviewed and approved this project under reference MSD-IDREC-C1-2014-021 in February 2014. In order to capture the experiences of American and British clinicians and patients who provided and pursued care for BRCA mutations, focus groups (and when necessary, interviews) with genetics professionals and support group members were conducted. This qualitative approach, informed by principles of grounded theory (Green & Thorogood, 2013; Starks & Brown Trinidad, 2007; Strauss & Corbin, 1998; Teherani, Martimianakis, Stenfors-Hayes, Wadhwa, & Varpio, 2015), enabled in-depth examination of ethical issues related to access to care that arise in day-to-day practice in the United States and the United Kingdom. In particular, it facilitated the exploration of regulatory mechanisms and factors influencing access to care beyond those captured in Chapters Three and Four, as well as the contextualisation of identified mechanisms and factors within broader participant experiences and observations. (This approach was not, however, intended to form the basis of a full comparative study of UK and US genetic services, genetics professionals and support group members, or both.) Quantitative approaches, such as surveys of factors identified in Chapters Three and Four, were also considered but ultimately disregarded because the goal was not to measure how frequently particular factors affected daily practice, but to understand the larger phenomenon of how care for BRCA mutations is provided and pursued in daily practice.

5.2.1 Recruitment

Obtaining appropriate British and American 'clinician' and 'patient' perspectives required a multi-pronged recruitment strategy that was carried out from July through December 2015.

Sections 5.2.1.1 through 5.2.1.4 explain in detail how British genetics professionals, American genetics professionals, British support group members, and American support group members were respectively recruited. Before describing these specifics, though, it is important to explain which target populations were chosen to represent the 'clinician' and 'patient' perspectives.

The 'clinician' perspective was initially open to any healthcare professional who worked with women who may be offered care for HBOC; as the recruitment letter in Appendix 8.2 indicates, this wide net included primary care practitioners, oncologists, genetic counsellors, clinical geneticists, laboratory technicians, and so on. When the scoping study in Chapter Four was added and the design of this empirical study was refined, however, the target population was slimmed to genetics professionals – genetic counsellors and clinical geneticists – who were experts in providing care for women with or at high risk of BRCA mutations. As Section 5.2.3 explains in detail, the trade-off between fewer participants with greater expertise but less diverse viewpoints and more participants with less expertise but more diverse viewpoints was desirable because of the content and format of focus groups and interviews.

In terms of the 'patient' perspective, expertise was similarly prioritised over diversity by targeting particularly knowledgeable women with or at high risk for BRCA mutations who could speak to their own experiences, thoughts, research, and advocacy, as well as that of their peers. A natural source for these kinds of patients was through patient advocacy and support groups, which tend to attract a younger, more educated, more female, more cancer-aware, and more proactive set of patients than their non-support group counterparts (Grande, Myers, & Sutton, 2006; Im et al., 2007). Thus, the recruitment letter in Appendix 8.3 reflects the fact that potential participants were recruited through their membership in a

support group, rather than through their status as patients who sought care for a potential or identified BRCA mutation.

5.2.1.1 British genetics professionals

In the United Kingdom, genetics professionals were recruited through colleague recommendations. Seven prospective participants from South East England were identified through Professor Michael Parker, who had informally mentioned this project at a genetic service meeting to gauge interest. When Professor Parker connected these clinicians to me via e-mail, the clinicians provided the details of four additional colleagues who were also willing to be contacted about the project. I then followed up with these 11 clinicians – seven genetic counsellors and four clinical geneticists – by sending the clinician recruitment letter and participant information sheet via e-mail in July 2015. (As mentioned above, a copy of the letter is in Appendix 8.2; a copy of the participant information sheet is in Appendix 8.4.) All were asked to express interest directly to me via e-mail. Ultimately, three genetic counsellors and one clinical geneticist agreed to participate, whilst the other seven genetics professionals either declined to participate or simply did not respond.

5.2.1.2 American genetics professionals

In the United States, genetics professionals were recruited using publicly available clinician listings. Initial e-mails containing the clinician recruitment letter and participant information sheet were sent to three sets of genetics professionals within the Mid-Atlantic region in July and August 2015; their services self-identified as seeing patients at risk for BRCA mutations and published research related to access to care. These professionals included a genetic counsellor from a Delaware hospital, two clinical geneticists and one genetic counsellor from a Maryland hospital, and three clinical geneticists from a Washington DC hospital. All

were asked to express interest to me via e-mail. Although all three e-mails received responses, subsequent follow-ups did not result in any research participants.

A different approach was taken in October 2015. The National Society of Genetic Counselors maintains an online search function that can be used to find genetic counsellors at http://www.nsgc.org/page/find-a-gc-search. Restricting results to genetic counsellors who welcomed student contact, saw patients, and specialised in cancer genetics yielded a list of 53 genetic counsellors located in Delaware, Maryland, Pennsylvania, or Washington DC. After looking up each counsellor's affiliations and biography, this list was whittled down to 20 counsellors who provided BRCA-related counselling at one of eight different academic hospitals. An e-mail containing the clinician recruitment letter and participant information sheet was sent to the largest group of counsellors – four in total – affiliated with one hospital, and the counsellors were asked to express interest to me via e-mail. Several counsellors wrote back to confirm that their service would be happy to participate in a focus group; this led to six counsellors, including all four I had e-mailed, and one clinical geneticist participating in the project.

5.2.1.3 British support group members

Recruitment for British support group members was done in collaboration with non-profit organisation FORCE, which, as noted earlier in this thesis, stands for Facing Our Risk of Cancer Empowered and advocates for families with or at risk for HBOC. This collaboration arose out of the FORCE 2014 Annual Conference in Philadelphia, Pennsylvania, where I spoke to several paid staff members and a member of the organisation's UK (Essex) chapter. In July 2015, I followed up with the Essex peer coordinator via e-mail and, using the support group member recruitment letter and participant information sheet (located in Appendices 8.3 and 8.5, respectively), enquired about the possibility of holding a focus

group after a scheduled August 2015 FORCE meeting. The peer coordinator shared the information with the members who had confirmed attendance for the August meeting, and these members were asked to express interest in participating to both of us via e-mail. Of the seven women approached to participate, six – including the peer coordinator – ultimately participated, whilst the seventh declined.

5.2.1.4 American support group members

Recruitment for American support group members was also done in collaboration with FORCE, though the process was considerably more arduous with the Mid-Atlantic chapters than it was with the Essex chapter. I completed FORCE's US research request form in August 2015. After receiving approval from the organisation's director, I began sustained e-mail and phone contact with a different paid staff member of the organisation. This culminated in the study being verbally mentioned at September 2015 local meetings and written up in the October 2015 Philadelphia, Maryland, and Washington DC e-newsletters; members were asked to express interest directly to me via e-mail. Unlike the peer coordinator of the Essex chapter, however, the peer coordinators of the Philadelphia, Maryland, and Washington DC chapters were hesitant to pair planned support group meetings with focus groups. Because FORCE members are typically scattered across states and only come together for scheduled events, this logistical issue made it nearly impossible to set up focus groups. Although the in-person announcements and e-newsletters reached about 60 people, my collaboration with FORCE yielded only three participants.

Given the low yield of FORCE participants, I reached out to Camp Kesem, the US-based organisation referenced in Chapter One that provides year-round support for children whose parents have cancer, in December 2015. After discussing the project with the organisation's operations team, I received approval to recruit eligible members of the

Baltimore- and Philadelphia-based chapters. An e-mail containing the support group member recruitment letter and participant information sheet was sent to about 60 families the same month, and members were asked to express interest directly to me via e-mail. Because Camp Kesem serves families affected by all cancers, it was unclear how many members would be considered at high risk for BRCA mutations; nevertheless, collaboration with Camp Kesem yielded four eligible participants.

5.2.2 Participants

Twenty-four women participated in either a focus group or an interview, with at least four women representing each sub-group. (Whilst there was a gender requirement for support group members, there was no such requirement for genetics professionals. It was unsurprising that all genetics professional participants were women, though, because more genetics professionals are women than men; additionally, several male genetics professionals declined to participate.) As discussed earlier in Section 5.2, this study was designed to inform and contextualise how the regulatory mechanisms and findings in the literature factored into daily practice, so the resulting sample was both purposively selected for expertise in providing and pursuing care for BRCA mutations and intentionally small in size. Had this study been a stand-alone empirical examination of ethical issues related to accessing care for BRCA mutations in daily practice, I likely would have continued recruiting for each sub-group beyond at least four participants. In other words, I would have sought to increase the sample size by conducting multiple focus groups or more interviews within each sub-group. That said, Mason (2010) cites researchers such as Jette, Grover, and Keck (2003) as choosing a smaller sample size explicitly because of the participants' expertise in the topic. Additionally, as Section 5.2.3 explains, concurrent data collection and analysis revealed that data themes no longer required adjustment by the time the final few

interviews were coded and analysed. The decision to use a relatively small sample of expert participants is further discussed in Section 5.5.2, 'Strengths and limitations'.

Table 5.1 contains a summary of participating US and UK genetics professionals, including the dates of recruitment and data collection and the technique used for data collection. As indicated in Section 5.2.1, clinician groups were heavily skewed towards genetic counsellors, as just one clinical geneticist from each country participated. All American genetics professionals presently worked in the same teaching hospital-affiliated service in Pennsylvania, although all had experience working for other clinics and/or genetics companies. The British genetics professionals worked in a single teaching hospital-affiliated service in South East England; as above, all clinicians had experience providing care in another clinical setting.

Table 5.2 contains a similar summary for participating US and UK support group members. All support group members previously accessed BRCA testing, and in most cases, genetic counselling and some form of surveillance and/or surgery as well. British support group members hailed from a few cities in South East England, whilst American support group members were all based in a 250-kilometer stretch between Washington, DC and Philadelphia. Every British support group member was BRCA-positive and would be considered appropriate for referral to genetic services under current NICE guidelines. The American support group members, however, had more diverse testing results: two were BRCA-positive, one had a likely pathogenic mutation and was treated by her clinicians as BRCA-positive, and four were BRCA-negative (one true, two uninformative or VUS, and one true or uninformative). (See Chapter Two for an explanation of what different test results mean.) Interestingly, each US woman would be considered appropriate for referral to genetic services under current NCCN guidelines, but only five of the seven women would

be appropriate under USPSTF guidelines. (The other two women underwent genetic testing whilst symptomatic of or in active treatment for breast cancer, which contradicts the USPSTF requirement that genetic services be offered only to women who are asymptomatic of HBOC. This requirement is discussed in Chapter Three.)

Table 5.1: Summary of genetics professional participants

UK genetics professionals (n = 4)					US genetics professionals (n = 7)				
Description	**ID**	**Initial recruitment month**	**Data collection month**	**Data collection technique**	**Description**	**ID**	**Initial recruitment month**	**Data collection month**	**Data collection technique**
Genetic counsellor	UKCA1	Jul 2015	Aug 2015	Focus group (UKCA1-2)	Genetic counsellor	USCA1	Oct 2015	Nov 2015	Focus group (USCA1-6)
Genetic counsellor	UKCA2	Jul 2015	Aug 2015	Focus group (UKCA1-2)	Genetic counsellor	USCA2	Oct 2015	Nov 2015	Focus group (USCA1-6)
Genetic counsellor	UKCA3	Jul 2015	Nov 2015	Interview	Genetic counsellor	USCA3	Oct 2015	Nov 2015	Focus group (USCA1-6)
Consultant clinical geneticist	UKCA4	Jul 2015	Jan 2016	Interview (Skype)	Genetic counsellor trainee	USCA4	Oct 2015	Nov 2015	Focus group (USCA1-6)
					Genetic counsellor	USCA5	Oct 2015	Nov 2015	Focus group (USCA1-6)
					Genetic counsellor	USCA6	Oct 2015	Nov 2015	Focus group (USCA1-6)
					Consultant clinical geneticist/oncologist	USCA7	Oct 2015	Dec 2015	Interview

Table 5.2: Summary of support group member participants

UK support group members (n = 6)					US support group members (n = 7)				
Description	**ID**	**Initial recruitment month**	**Data collection month**	**Data collection technique**	**Description**	**ID**	**Initial recruitment month**	**Data collection month**	**Data collection technique**
FORCE member BRCA+, breast cancer	UKPT1	Jul 2015	Aug 2015	Focus group (UKPT1-6)	FORCE member BRCA+, no cancer	USPT1	Sept 2015	Dec 2015	Interview
FORCE member BRCA+, no cancer	UKPT2	Jul 2015	Aug 2015	Focus group (UKPT1-6)	Camp Kesem member BRCA- (UNINF[1]/ VUS[2]), breast cancer	USPT2	Dec 2015	Jan 2016	Interview
FORCE member BRCA+, no cancer	UKPT3	Jul 2015	Aug 2015	Focus group (UKPT1-6)	FORCE member BRCA+, no cancer	USPT3	Sept 2015	Jan 2016	Focus group (USPT3-4)
FORCE member BRCA+, breast cancer	UKPT4	Jul 2015	Aug 2015	Focus group (UKPT1-6)	FORCE member BRCA- (true), no cancer	USPT4	Sept 2015	Jan 2016	Focus group (USPT3-4)
FORCE member BRCA+, ovarian cancer	UKPT5	Jul 2015	Aug 2015	Focus group (UKPT1-6)	Camp Kesem member BRCA- (UNINF/VUS), breast cancer	USPT5	Dec 2015	Jan 2016	Interview
FORCE member BRCA+, no cancer	UKPT6	Jul 2015	Aug 2015	Focus group (UKPT1-6)	Camp Kesem member BRCA- (true/UNINF), colorectal cancer	USPT6	Dec 2015	Jan 2016	Interview
					Camp Kesem member BRCA+ (pathogenic?), breast cancer	USPT7	Dec 2015	Jan 2016	Interview

[1]UNINF = uninformative negative result. [2]VUS = variant of unknown significance.

5.2.3 Data collection and analysis

Decisions and processes related to data collection and analysis fall into four buckets: the use of both focus groups and interviews, the incorporation of a process mapping exercise, the details on data collection sessions, and the analysis of collected data.

5.2.3.1 Use of focus groups and interviews

The decision to use both focus groups and interviews was informed by qualitative research resources as well as practical constraints. In general, focus groups and interviews are both considered compatible data collection techniques with grounded theory-based research (Foley & Timonen, 2015; Soklaridis, 2009; Willig, 2013). Focus groups allow the interactions between participants to be captured, and as Leung and Savithiri (2009) note, 'Through facilitated discussion, participants build on each other's ideas through "piggybacking"' (p. 218). With focus groups comes the risk of more outspoken participants dominating the conversation, however, and the size of the groups has to be carefully managed in order to yield productive conversations (P. Gill, Stewart, Treasure, & Chadwick, 2008). In contrast, interviews facilitate the gathering of more in-depth information, and the privacy afforded each participant may encourage greater engagement with sensitive or unexpected topics (P. Gill et al., 2008). Interviews only permit researcher-participant interaction, though, so the quality of the data depends on the researcher-participant dynamic and the participant's ability to answer questions without the benefit of peer responses (R. Edwards & Holland, 2013).

Of the two data collection techniques, focus groups were ultimately prioritised for several reasons. First, genetics professionals and support group members were used to speaking openly about sensitive or unexpected topics in their clinical encounters and support group

meetings, respectively. Second, because some support group members might not be especially familiar with all intended discussion topics (e.g., regulatory mechanisms), focus groups seemed more likely to elicit informed conversation than interviews. Third, the plan to use a paper-and-pencil task to prompt participants to think about how patients access care was a natural fit for an interactive session in which participants could compare how well their drawings aligned. Fourth, given the unusual situation of being a researcher who found travel physically difficult, the prospect of conducting several focus groups was preferable to conducting numerous interviews. Despite the rationale for preferring focus groups, however, interviews were offered as a secondary option if prospective participants' schedules or locations did not permit them to attend focus groups. Here, the thought was that data collected through interviews were better than data not collected at all.

5.2.3.2 Incorporation of a process mapping exercise

Obtaining high-quality data in qualitative research partially depends on participants feeling comfortable enough to discuss sensitive topics (P. Gill et al., 2008; Pitney & Parker, 2009). One tactic to help participants open up is through 'icebreaker' activities, which range from structured introductions to group exercises (Asbury, 1995; Colucci, 2007; 'How to conduct focus groups', 1992). Additionally, written group exercises can capture a second kind of data to be analysed alongside transcripts and help potentially dissenting or shy voices to share their accounts without being silenced (Bloor, Frankland, Thomas, & Robson, 2001; Kitzinger, 1995; Krueger, 1997). Given that this project aimed to gather in-depth perspectives on access to care from experts on providing and pursuing care for BRCA mutations, the integration of a group exercise allowing participants to sketch out their experiences was appealing.

Colucci (2007) drew on myriad sources such as Bloor et al. (2001) and Krueger (1997) in outlining 13 types of potential exercises: free listings, rating scales, ranking tasks, pile sorting, forced-choice questions, label generation, picture sorting, magic tools and fantasies, storytelling, news bulletins, role-playing, projective techniques, and multitasking exercises. The type best suited to eliciting personal experiences with providing or pursuing care was storytelling, i.e., asking participants to share a narrative around the topic of interest. In written form, this kind of exercise may manifest as full essays, drawings, diagrams, bulleted lists, etc. Colucci also points out that whichever exercise is chosen, the degree to which it is integrated determines its usefulness:

> '[E]xercises are meant to be the input for further discussion, and they accomplish their role best if the moderator goes further than the fulfillment of the task and invites participants to describe their answers more in depth, provide more detail, apply them to a real situation, and express agreement or disagreement with other participants' answers.' (p. 1430).

As my goal was to quickly collect written representations of patient and provider journeys in a way that would stimulate discussion about access to care, I chose a method called 'process mapping'. This technique is used in business and healthcare to improve a service or patient pathway by examining how a service is used in practice, not in theory (Anthony et al., 2005; Layton, Moss, & Morgan, 1998; NHS Institute for Innovation and Improvement, 2008; Trebble, Hansi, Hydes, Smith, & Baker, 2010). Participants map their own experience of how a service works, and these maps are then examined together to identify how that pathway should be changed, if at all. Process mapping was also attractive because it is not prescriptive in how participants outline their journeys; paragraphs and bulleted lists are just as acceptable as diagrams and maps. [Other quality improvement techniques that incorporate aspects of storytelling, such as Six Sigma or stakeholder analysis, were considered but ultimately dismissed because they require specific training and more of participants' time (Benedetto, 2003; Schmeer, 1999).] As mentioned in Chapter Two, I piloted a process mapping task during my preliminary research; satisfied with how it

worked, I ultimately opened each of my focus groups and interviews with a process mapping exercise.

5.2.3.3 Details on data collection sessions

Twelve focus groups and interviews were conducted between August 2015 and January 2016. Whether participants took part in a focus group or interview depended on their scheduling availability and geographic location. The UK support group members participated in a single focus group convened after a FORCE meeting, whilst the US support group members were interviewed individually, except for sisters USPT3 and USPT4, who were interviewed together. The US genetic counsellors participated in one focus group; their clinical geneticist colleague required a separate interview. The UK genetic counsellors required a two-person focus group plus an individual interview, and the UK clinical geneticist was interviewed alone via Skype. Each support group conversation took place in a support group member's home, though a neutral location (e.g., a library) was always offered. US clinicians were interviewed in their offices, and the in-person UK clinician interviews took place in the researcher's workplace. Conversations were audio recorded and lasted between 45 and 85 minutes.

Each focus group or interview began with participants reviewing information sheets, asking any questions they had about the project, and providing written consent if they were satisfied. Next, participants completed a short process mapping task, which required clinicians to draw the path they thought patients followed to receive care for BRCA mutations and support group members to draw their own paths to receiving care. (Appendix 8.2 contains a blank copy of the process mapping handout that participants completed.) Next, participants annotated their sketches with barriers and facilitators, i.e., what they thought made it harder or easier to receive care. All were instructed to make their

maps as detailed or as broad as they liked, and they were encouraged to draw whatever kinds of care they thought related to BRCA mutations (e.g., they were not told to omit breast cancer treatment).

Participants were then asked to describe their process maps, as well as their thoughts on how women access care for BRCA mutations in general. The semi-structured focus group guide included six categories of questions based on the four dimensions of access described in Gulliford et al. (2002) and the topics covered in Chapters Three and Four: how patients accessed care, what made access harder or easier, what the 'typical patient' accessing care was like, how access to care was regulated, what necessary care was absent and what unnecessary care was present, and how patients could access care outside of genetic services. Given responses from early conversations, a seventh question – what service improvements participants wished to see – was added. (Appendix 8.3 contains all focus group guide questions.)

5.2.3.4 Analysis of collected data

Data analysis was concurrent with data collection and guided by Strauss and Corbin (1998) and Thomas (2006), who described the constant comparison technique and a general inductive approach to qualitative data analysis, respectively. Constant comparison involves iteratively comparing new data with previous data in order to confirm, disconfirm, or refine theories about the data (Foley & Timonen, 2015; Strauss & Corbin, 1998). Thomas's general inductive approach is broader in scope and not wedded to a particular theory, but it offers a simple way to organise findings related to research objectives. Additionally, both constant comparison and a general inductive approach involve exploring themes found in early data analysis in subsequent data collection sessions.

Each focus group or interview yielded three kinds of data: participants' process maps, the conversation itself, and my guide notes. Analysis of process maps meant examining similarities and differences between maps – e.g., which kinds of healthcare professionals were involved and how women reached genetic services – in accordance with the strategy in Trebble et al. (2010). Audio recordings of the focus group and interview conversations were transcribed verbatim and anonymised through use of the pseudonyms in Tables 5.1 and 5.2 and removal of identifying information. Analysis of transcripts involved both open coding, the process of reducing collected data into a small set of themes, and axial coding, the process of interconnecting the categorised data (Strauss & Corbin, 1998; Vickers & Offredy, n.d.). Guide notes were reviewed alongside transcripts during open and axial coding, as they contained my overall impressions of conversations and topics to consider following up on in future data collection sessions. All coding was done by hand in consultation with project supervisors and managed in Microsoft Office (Excel and Word). Emergent results of open and axial coding were used to inform later interviews and focus groups.

Open coding was used to determine the themes describing each of the six major question categories posed to participants. This process was straightforward for five questions, e.g., the only five avenues to genetic testing outside of genetic services identified by participants were DTC testing, mainstreaming, research studies, telegenetics, and population screening. For the 'barriers and facilitators' question, participants' related statements were combined where appropriate. For example, 'insufficient insurance' included both women who were uninsured and women whose insurance did not cover BRCA testing, and 'insufficient family history' included unknown family history as well as known family history without many HBOC diagnoses.

Axial coding was used to determine the interconnected themes cutting across questions and within and between participant group responses. For example, one major theme explored similarities and differences based on sub-groups, i.e., American vs. British and support group members vs. genetics professionals. As with open coding, most axial coding decisions were fairly straightforward. One of the more difficult decisions was choosing how many response categories across which barriers and facilitators had to appear to say they appeared consistently. Four or above, or at least two-thirds of the six response categories, seemed to separate factors that truly arose consistently from factors that arose only in obviously related response categories, e.g., questions about barriers and facilitators and the typical patient.

As discussed in Sections 5.2.2 and 5.5.2, cessation of data collection and sample size were not purely dependent on when themes stopped emerging. However, by the time systematic open and axial coding incorporated data from the last interview, it did not appear as though new themes were emerging. Analyses of the focus groups and interviews are reported in Sections 5.3 and 5.4. More specifically, the process mapping analysis is reported in Section 5.3.1; the results of open coding are reported in Sections 5.3.2 through 5.3.7; and deeper analysis using axial coding is reported in Sections 5.4.1 through 5.4.4.

5.3 Results of process mapping analysis and open coding

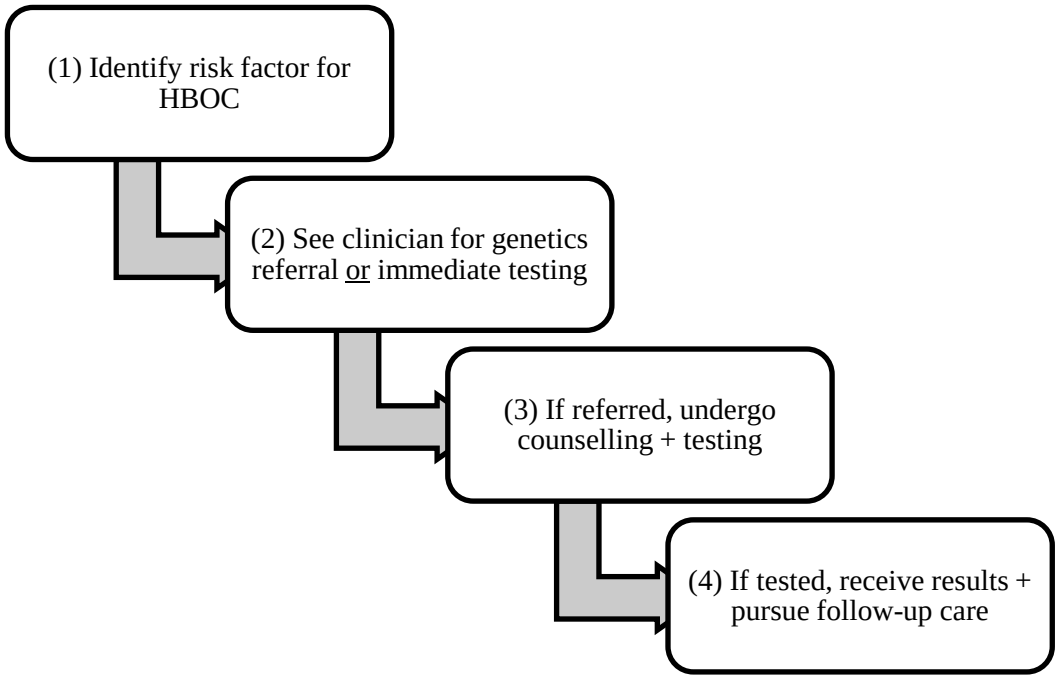
Nearly all participants' process maps contained the same four steps, though participants identified nearly 50 items that could hinder and/or help patient pathways. Participants also described the characteristics of the 'typical patient' accessing care; guidelines, laws, legal rulings, and policies governing care; kinds of care that needed to be eliminated or provided more frequently; five ways to obtain genetic testing other than through a genetics professional; and how problems with genetic services should be addressed. In this section,

themes from each category are highlighted, including similarities and differences between participant groups where appropriate.

5.3.1 Process mapping

Support group members drew the concrete steps they personally took to access care, and genetics professionals drew how they thought their patients accessed care. (See Appendices 8.9.1 through 8.9.8 for a sampling of process maps across different participant groups.) Nearly all support group members sketched their paths linearly, whereas many clinicians produced parallel tracks based on factors such as clinician referral and cancer status. Whilst support group members documented their paths meticulously (e.g., 'had post-surgery bone scan'), clinicians plotted patient paths more broadly (e.g., 'patient implements follow-up care plan'). For all their stylistic differences, however, Figure 5.1 contains the four steps that clinicians and support group members typically drew in their process maps:

Figure 5.1: Process mapping compilation



5.3.1.1 Step one: identify a risk factor for HBOC

The first step typically involved a patient or a clinician identifying a known familial BRCA mutation or a personal or family history of breast or ovarian cancer. In general, participants suggested a patient was more likely to notice a family history of cancer, whereas a clinician was more likely to notice a personal cancer diagnosis requiring referral. Below is a sampling of descriptions that participants gave about identifying a risk for HBOC:

> UKCA1: A recognition [that] either they get breast cancer themselves or a family member is diagnosed with breast cancer and that leads them to the GP.
>
> UKPT6: [My path] was linear for me personally and as well for my sister, who was the one that was diagnosed with BRCA. It would have been linear for her because we knew then that my auntie had had ovarian cancer and things.
>
> USCA3: Either self-identified referral, so seeking out services on their own, or referral by provider, due to mutation status but also personal and their family history.

Support group members generated three exceptions to this step: USPT1 had no personal or family history of cancer, so her risk factor was actually her positive DTC genetic testing result. UKPT2 volunteered for a research project, so neither she nor her clinician identified a risk factor. Despite being a breast cancer patient with AJ ancestry, UKPT4's risk factors were not picked up by her clinicians; instead, she had a 'down day' at the hospital, and by chance a clinician sent to check on her suggested BRCA testing.

5.3.1.2 Step two: see a clinician for genetics referral or immediate testing

The second step depended on the patient's cancer status. A patient without cancer would typically see a GP, who would then refer her to genetic services; a patient with cancer would typically see an oncologist, who would then either refer her to genetic services or carry out testing immediately. Participants also thought surgeons, gynaecologists, breast screening team members, nurses, social workers, and researchers might provide referrals or occasionally conduct testing themselves. Below is a sampling of responses about seeing a clinician for a referral or receiving immediate testing:

> UKPT3: Because [UKPT5] had paved the way, mine was textbook straight boom, boom, boom, so I went round to the GP and said, 'Can I be tested for BRCA?' I actually saw a local [GP], it wasn't my own GP, and she wrote a letter to [hospital #1]. I'd taken with me a letter showing [UKPT5]'s BRCA code and I think she may have enclosed that.
>
> USCA2: [I]n some cases those physicians are making a referral to genetics and a genetic counsellor, but in some other cases those physicians are doing the testing themselves.
>
> USPT5: So [the second GP] was a lot more amicable in her expressions, in her conversations. She understood and she said, 'Yes, if you want to have testing prior to surgery, we can do that'. So she referred me to … a division within the company that specifies only in genetic testing.

In a few cases, support group members had to request a second opinion (USPT5, as implied in her quote above) or lobby the GP for a referral (UKPT5) if their doctors did not agree to refer initially. Finally, a patient whose private insurance did not require clinician referral might refer herself for genetic testing, as UPST1 did upon finding out her DTC result. This situation primarily applied in the United States but could also apply to a lesser extent in the United Kingdom, e.g., UKPT3 and UKPT5 had private health insurance and genetic counsellor UKCA1 accepted private patients.

5.3.1.3 Step three: if referred, undergo counselling and testing

After referral, counselling and testing were relatively straightforward – provided the patient reached the clinic. Below is a sampling of responses about patients undergoing counselling and/or testing:

> UKCA4: [T]hey would come and meet a genetics professional and obtain information directly relevant to them. And then they would consider their options for testing and the implications of testing and decide if they want to have a test.
>
> USCA6: So in my mind people are tested, and understanding that not everybody goes through a genetic counsellor, but I have this very nice process where someone actually got referred to cancer genetics [laughter] and then we ordered the appropriate test.
>
> USPT4: And then it seemed almost like we forgot about it because it was such a long process till we finally got the call for the appointment to go down and have our blood drawn. And it wasn't a very long counselling session that I remember, the first one. She told us what would be happening: they'd take the blood and very generalisation type things.

A few American participants noted financial pressures impacting a patient's ability to attend genetic services. USPT1's insurer initially did not consider a DTC result an acceptable reason to approve confirmatory testing, and USPT6 had to delay testing until she found monetary assistance. British genetic counsellors explained that only high-risk referrals result in clinic appointments, albeit with a roughly 18-week wait. Average-risk patients receive letters suggesting they follow population-risk screening guidelines instead.

5.3.1.4 Step four: if tested, receive results and pursue follow-up care

Test results determined a woman's follow-up care options. A positive test typically led to an in-person appointment to discuss screening, medication, and/or surgeries; necessary referrals; support mechanisms; research studies; and familial communication. A negative test usually meant a patient would receive a letter or phone call advising her to follow population-risk screening guidelines. In some cases, clinicians might offer BRCA-negative patients the chance to participate in research; re-contact genetic services in the future; and/or undergo additional testing for other hereditary cancer syndromes (e.g., Li-Fraumeni or Cowden), depending on the patient's risk profile. Below is a sampling of responses about patients receiving results and, if they tested positive, pursuing follow-up care:

> UKCA2: When we do get the results we include screening advice with that and we offer them research studies if that's appropriate. Then if we have found something, we often offer them an appointment for them to discuss the implications and who else in the family might be affected and how to go about talking to them about that. If we don't find anything then sometimes there's some other testing we can do. If there is nothing else we can do, we often say, 'Things are changing very quickly at the moment. Please ask your GP to re-refer you in five years' time; we can review everything and see if there's anything else that we can be doing'.
>
> UKPT2: Once I had my [positive result], it was very much from a pragmatic point of view: 'Right, what surgery would you like? Do you want to have your ovaries removed? Do you want to have your boobs removed?' There was nothing about the emotional thing.
>
> USPT2: And then it was negative. So we move forward because if I had the mutation because I was having a baby, I was prepared to have the preventative measures done at that time. And then when it came back negative, I was like, 'Okay'.

Four variations on this path emerged. First, American genetic counsellors USCA1 and USCA3 further distinguished between whether a BRCA-positive patient is managed in a high-risk centre or required to coordinate her care between multiple medical centres; the latter would add an extra layer of complexity for the patient. Second, British support group member UKPT4 highlighted the role of age in determining available follow-up care, noting that she had to fight for a mastectomy because she was over the age of 60. Third, American support group member USPT5, who was unsure if she had an uninformative negative or VUS result, could not pursue additional testing for Li-Fraumeni syndrome because her insurance would not cover it. Fourth, US support group member USPT7, who had a likely pathogenic mutation, proceeded as though she had tested positive for a BRCA mutation and had a complete hysterectomy to prevent ovarian cancer.

5.3.2 Barriers and facilitators

After completing the process mapping exercise, participants were invited to draw and discuss the barriers and facilitators that could or did influence patient pathways; 31 barriers and 37 facilitators were identified overall. Both systemic and patient-orientated items arose, ranging from (dis)advantages of how genetic services are organised to patient characteristics like anxiety.

5.3.2.1 Items identified as both barriers and facilitators

Table 5.3 contains the 21 items that were mentioned as both barriers and facilitators, e.g., not receiving a clinician referral was a barrier and receiving a clinician referral was a facilitator. Key items that both helped and hindered care – i.e., those mentioned by all four sub-groups or described as particularly important by participants – are examined here.

Table 5.3: Items identified as both barriers and facilitators

Barriers	Facilitators
Anxiety (3, 4)*	Anxiety (2, 3, 4)
Insufficient clinical resources (3, 4)	Clinical resources (3)
Insufficient family history (1)*	Known/strong family history (1)*
Insufficient income (3, 4)	Income (3)
Insufficient insurance (3, 4)	Comprehensive insurance (3)
Incompatible clinician recommendation (4)	Clinician recommendation (3, 4)
Lack of clinician knowledge (1)*	Clinician knowledge (1)
Lack of education (1)	Education (1)
Lack of familial support (3, 4)	Familial support (3, 4)
Lack of internet access (1)	Internet access (1)
Lack of multidisciplinary care (4)	Multidisciplinary care (4)
Lack of patient knowledge (1, 4)*	Patient knowledge (1, 4)
Lack of patient navigation (3, 4)	Patient navigation (4)
Lack of support groups (4)	Support groups (4)
No clinician referral (2)	Clinician referral (2)
No family member tested (3)	Family member tested (1, 3)*
No personal history of cancer (1)	Personal history of cancer (1)
Perceived lack of time (3)	Perceived time (4)
Poor clinician-patient relationship (2, 3, 4)	Strong clinician-patient relationship (3, 4)
Race (Black) (2)	Race/ethnicity (Black/Ashkenazi Jewish) (3)
Unhelpful location (3, 4)*	Helpful location (3, 4)

*Cited by members of all participant groups. Numbers in parentheses indicate which step(s) from the 'Process mapping' section above correspond to an item: (1) identify risk factor for HBOC; (2) see clinician for genetics referral or immediate testing; (3) if referred, undergo counselling and testing; and (4) if tested, receive results and pursue follow-up care.

Participants in all four groups said lack of patient knowledge, lack of clinician knowledge, insufficient family history, unhelpful location, and anxiety impeded access to care. Lack of patient knowledge included misconceptions (e.g., a patient has to have bilateral mastectomy if she tests positive) and misunderstandings of test results or follow-up care options. For example, genetic counsellor USCA6 explained how a woman may not understand what her test results actually meant:

> USCA6: Misinformation, patient was told they weren't a candidate for testing 10 years ago and that's just blanket in their mind, so they're never going to seek it out until maybe their daughter says, 'Hey Mom, did you want to have this test now?' 'I didn't need it'. But that might have been 15 years ago when we couldn't identify these things.

Lack of clinician knowledge typically involved a GP or oncologist missing a family or personal history of cancer that warranted referral. British support group member and ovarian cancer patient UKPT5 expressed frustration that her oncologist still fails to refer patients to genetic services:

> UKPT5: It's appalling. I've been back to where I was first diagnosed, and I took all of my FORCE stuff, all the information, and said, 'I'm happy to talk to anybody'. And still [a patient I] sat next to having chemotherapy had ovarian cancer, she said, 'Oh yeah, my brother's got prostate cancer, my uncle had prostate cancer, and my aunt had breast cancer'. I said, 'Have they referred you for genetic testing?' 'No, what's that?' And it's like, how many people in your family have to die of cancer before they offer testing?

Insufficient family history meant a patient did not meet eligibility criteria for testing; this was either because (1) family history was weak or limited or (2) family history was not properly communicated or recorded. Unhelpful location encompassed issues such as distance from genetic services, inability to obtain pathology reports from other countries, and regional variations in care (e.g., challenges in finding high-quality oncologists or surgeons nearby). Anxiety manifested as a barrier in patients who dreaded seeing a clinician and/or testing positive so much that they avoided testing altogether.

Two facilitators noted by participants of all groups were family history of breast and/or ovarian cancer and a family member who had undergone testing. A strong family history was the most commonly cited risk factor for HBOC, and having a family member who already had testing usually indicated there was a known familial mutation. Both items typically led to self-referral or clinician referral, the absence and/or presence of which was discussed by members of all four groups. The earlier quote from UK support group member UKPT3 on page 183 highlights this dynamic, as does the following quote:

> USPT4: Our aunt was diagnosed in her 50s with ovarian cancer … She received her genetic counselling and tested positive for the gene. Then her daughter was diagnosed with breast cancer. She was 29. That same aunt then was diagnosed with breast cancer also and then had the recommendation from the genetic counsellors to have her siblings tested … My father tested positive, and then he came to all of us. So it was [USPT3] and I and we have two brothers, and then we individually decided if we wanted to participate [with the same genetic service].

Another theme cutting across participant groups was the impact of support and guidance on care. Falling under this category was the presence or absence of support groups, familial support, patient navigation, strong clinician-patient relationships, and clinician recommendations compatible with patient preferences. As an example of the last point, American genetic counsellor USCA6 described the importance of a clinician recommending a patient follow through with a referral:

> USCA6: I think too, though, motivation by the patient is also almost piggybacked onto the physician. So, 'Here, go see this girl'. Okay, I'll throw it into my bag and I'll never see it again. 'You really need to see them. This is going to help me manage you better'. So the physician sell, we used to call it. If you sell it, they'll buy it.

Support groups were especially popular: among 13 US and UK support group members, eight said not having support groups hampered access and 11 said having support groups improved access. Participants described support groups as a source of both emotional strength and information. For example, UKPT2 sought a support group after finding her clinicians only focussed on medical choices:

> UKPT2: I wasn't offered anything. Once I had my diagnosis, it was very much from a pragmatic point of view: 'Right, what surgery would you like? Do you want to have your ovaries removed? Do you want to have your boobs removed?' There was nothing about the emotional thing.

Her support group attendance ultimately affected her clinical choices, as it was UKPT5 who shared a pamphlet on what lifetime risk of cancer really meant. Empowered by this information, UKPT2 rejected the risk-reducing mastectomy she had been dreading.

Figuring prominently in American interviews and focus groups were insurance and income. In terms of barriers, nearly all US participants discussed how being uninsured or poorly insured can negatively impact ability to afford both direct (e.g., medical bills) and indirect expenses (e.g., unpaid time off from work). Genetic counsellor USCA1 described one such situation with a 29-year-old woman whose family history suggested HBOC:

> USCA1: [S]he came in saying, 'I really want to know this information'. Tested positive for a mutation. We talked about screenings and the situation, considering a certain standard of care likely covered by her insurance. So she has a breast MRI, which then required a biopsy, and all these other things happened. So she gets a bill for [USD] 1,000 and I get an upset email, 'You told me these services were going to be covered'. And my response is, 'They were covered, but your responsibility for those services was [USD] 1,000. It's not that it wasn't covered. MRIs cost a lot more than [USD] 1,000, but in order for you to do this, this is what it's going to cost'. And so she basically said, 'Well, I can't afford to do the MRI anymore'.

In terms of facilitators, US participants cited comprehensive insurance that covered genetic services and follow-up care; programmes offering low- or no-cost testing; and ability to pay deductibles. (Clinical geneticist USCA7 thought discounted testing programmes made cost more of a perceived barrier than an actual one.) Two British clinicians also weighed in on these issues: UKCA3 described private insurance policies that did not cover testing in average-risk patients and patients struggling to pay the hidden costs of testing (e.g., parking fees), and UKCA4 thought the UK insurance moratorium made patients more likely to test.

Clinicians from both countries highlighted resources, or the lack thereof, for genetic services. British counsellors pointed to an 18-week wait time and an increasing volume of patients as impeding access, as well as variations in MRI availability depending on where patients lived. Counsellor UKCA3 articulated the frustration that patients might feel when encountering long waits for their genetic service appointments:

> UKCA3: The one big thing that bugs me is the wait lists … because I appreciate someone might feel like a ticking time bomb. You get the odd person who says, 'Actually, I was glad for the wait list, it gave me time to have a think through and I'm a slow thinker, great', but I would imagine that they are not most people. I'd imagine

> if it was me, if I've finally got the courage, then I might want to see someone within a month, maybe, just being fair to the NHS.

American counsellors focussed on their inability to bill as service providers, a systemic quirk leading hospitals to underpay counsellors and ultimately contributing to a scarcity of counsellors. Counsellor USCA2 explained this phenomenon as follows:

> USCA2: The hospital will argue we don't bring in any money, and yet at the same time when you want the hospital to start contracting with insurers to actually get reimbursement, you're then also told that because you don't bring in a lot of money, it's not really worth their effort to work with the reimbursing entities. Coming back to not being recognised by Medicare and Medicaid, we're stuck in that area. It's hard to convince a hospital system to hire more genetic counsellors because we don't bring in money, and yet also at the same time, we don't get a lot of reimbursement for our services.

In terms of facilitators, US and UK clinicians emphasised the importance of an adequately funded, staffed, and trained service, along with electronic scheduling tools, family history forms, and health records. Web-based genetic counselling was also considered beneficial, though clinical geneticist USCA7 noted it would become financially unsustainable unless incorporated into a traditional hospital billing model.

Discussed by three American support group members, race and ethnicity comprised the final item of note that both helped and hindered care. USPT6 thought African American and AJ women were more likely to test because those women have higher rates of breast cancer than other women. However, Black breast cancer patients USPT2 and USPT5 believed their skin colour negatively influenced the way oncologists approached their care. Because fewer eligible Black women undergo testing than eligible White women, USPT5 felt that her surgical oncologist subconsciously assumed she would not want testing and therefore did not offer it:

> USPT5: I think people are genuinely unintentionally biased, genuinely speaking. The elephant in the room is I'm young, I'm Black, right? … I'm from a subset of a group that most people don't come in with a background in pharmacology with a doctorate. Most young Black people don't come in with that background and they're certainly not coming in questioning the physician … [H]e's really interacting with

people based on his experience and so he is not going to ask, he's not going to recommend [genetic services]. Not in a negative way though. Yeah, not in a negative way. Some people are negative and blatant about it, but I don't think that he was being negative.

5.3.2.2 Items identified as either a barrier or a facilitator

Table 5.4 contains the items that were mentioned as either a barrier or a facilitator, but not both. Overall, there were 26 items, of which 10 were barriers and 16 were facilitators. In general, these items were discussed less than items identified as both barriers and facilitators, and they focussed on patient choices and aspects of clinical care.

Table 5.4: Items identified as either barriers or facilitators

Barriers	Facilitators
Competing life concerns (3, 4)	Communication with family members (4)
Decisional conflict (4)	Confidence in overcoming barriers (2)
Lack of discussion about HBOC (1)	Electronic health record alert (1)
Lack of interest in testing (3)	Familial benefit (3)*
Lack of primary care access (2)	Genetic service letter for family members (4)
Language barriers (3)	High perceived risk of cancer (3)
Medical mistrust (3)	Older age (4)
No genetics consultation (4)	Positive test result (4)
No post-surgery psychological counselling (4)	Preference for female breast surgeons (4)
Rigid application of surgical guidelines (4)	Proactive approach to care by patient (2, 3, 4)*
	Public awareness of BRCA (1)*
	Research team recommendation (1)
	Resource centre attendance (4)
	Test ordered by oncologist (2)
	Testing for therapeutic benefit (3)
	Younger age (3)

*Cited by members of all participant groups. Numbers in parentheses indicate which step(s) from the 'Process mapping' section above correspond to an item: (1) identify risk factor for HBOC; (2) see clinician for genetics referral or immediate testing; (3) if referred, undergo counselling and testing; and (4) if tested, receive results and pursue follow-up care.

Participants from all four groups brought up three facilitators listed in the above table: a proactive approach to care for BRCA mutations, an increased public awareness of BRCA mutations, and familial benefit. The first facilitator applied to obtaining a referral, attending counselling and testing, and pursuing post-test care. Support group member UKPT5 gave an emblematic response:

> UKPT5: When I asked about genetic testing, when they finally agreed to let me see a genetic counsellor, the first thing she said was, 'Well, we can't test you until we've tested your mother'. I said, 'Well, I've got cancer. It's likely to be me'. 'But we can't assume that. We have to test your mother first'. And I had to push at the end for us both to be tested at the same time because they wanted to test my mother, wait eight weeks from the results from that test, then test me, and then wait another eight weeks for the result of that test. And I said, 'Well, what's the point? Might as well both', and in the end they finally acquiesced and let us have our results together, but it was push, push, push to do it.

The participants attributed the second facilitator to the 'Angelina Jolie effect', i.e., public awareness resulting from Jolie's op-eds on her decisions to undergo testing and pursue risk-reducing surgeries. Support group member USPT6 explained this phenomenon as follows:

> USPT6: I think for example, when you think of the celebrity that went really public, Angelina Jolie, not to say it was a game changer, but it really shifted gear even here in the suburban area. You're having coffee talking about your children, now you're talking about a celebrity and what that meant for her and wanting to identify and what she learned of in terms of mutation and making decisions.

Ten participants discussed the third facilitator, with USPT2 capturing many support group members' thoughts about testing to benefit their children:

> USPT2: Anything for my children. So that was my driving force, my kids … I'm the first one [in my family to have breast cancer], I have daughters, I have sons, they may have daughters, they [may] have [it] themselves – men get breast cancer.

Other items of note were competing life concerns, older and younger age, confidence in overcoming barriers, and testing positive. Competing life concerns that impeded care included fertility decisions (e.g., USPT7 wanting to continue fertility treatments instead of having a hysterectomy) and cancer treatments (e.g., a patient waiting to test until she was in remission). In terms of age facilitating care, American counsellor USCA2 thought younger

women would be more open to pursuing testing, but USCA5 felt older women would more likely follow through with oophorectomy and mastectomy. Confidence in overcoming barriers surfaced in relation to problems receiving a genetics referral, e.g., USPT5 trusted her ability to appeal her surgical oncologist's decision to deny her referral. Finally, testing positive was a seemingly counterintuitive facilitator, but USPT1 credited it with providing a definitive path forward.

5.3.3 Describing the 'typical patient'

Participants were asked to contemplate and comment on what they thought the 'typical patient' accessing care for a potential BRCA mutation would be like. Characteristics identified by participants largely aligned with facilitators mentioned above in the 'Barriers and facilitators' section. British support group members only gave two responses to this question: AJ ethnicity and 'lucky people', e.g., patients whose risk for HBOC was identified by chance:

> UKPT4: Lucky people like myself because I had no idea about any of this, didn't know anything about Ashkenazi Jews with their genes and stuff, and one day I was having a very down day at the hospital and I was very tearful and I think they passed me over to somebody called [name]… She looked at me and said, 'Are you Jewish?' And I said, 'Yes', and she said, 'We can test for your gene. Would you like us to test for you?'

More expansive were responses from the UK clinicians, US clinicians, and US support group members, whose shared vision of the typical patient was a well-educated, middle-class-or-above woman with a family and/or personal history of breast or ovarian cancer. The following quotes describe this amalgamated view:

> USCA5: Well-educated and plugged-in people.
>
> USCA6: I think overall higher socio-economic status.
>
> UKCA3: Would say we see a lot of large, White British families that I'd say are reasonably well educated, although not all families. More and more less well-educated families are coming in for it.
>
> USPT6: I'd say first and foremost someone with a family history of breast cancer, whatever that story may be, the history.

Another prominent theme among these three groups' responses was the influence of race, ethnicity, and culture on the typical patient. Several UK clinicians thought the racial and ethnic composition of their patients has diversified in recent years, though the typical patient is still relatively White and English-speaking. A few US clinicians focussed on why minorities might not attend genetic services and what might help them attend services, as illustrated in the following quotes:

> USCA1: Yeah, with a large Hispanic population, both of Caribbean and Mexican descent, a lot of it is, it's the will of God … God will decide, so a lot of, 'Why do I need to know, to test? If God wants me to have cancer, then I have cancer and there's nothing I can do to avoid that'.
>
> USCA7: At a centre like ours, we try to make every best effort to identify any good candidate for genetic testing, and we have electronic practice alerts on new ovarian cancer patients that tells them 'this woman should get genetic testing' so it won't matter how old they are or their race or their ethnicity because it's going to pop up and say, 'You should always consider it in this specific situation'.

American support group members also held strong views on race and ethnicity: USPT1 felt Jewish women were more likely to test because they do not perceive BRCA-related stigma, whereas USPT2 thought African Americans' longstanding fear of being used for research made them less likely to test. Breast cancer survivor USPT7 took a different tack, suggesting there might be too much emphasis on reaching women of certain races and ethnicities:

> USPT7: I find that they made such a predetermination of who of these people were going to be tested and get BRCA1/BRCA2, so it was a lot of Black people and then there were a lot of people who were Jewish … And it kind of felt like, okay, well, if you weren't one of them, then you probably don't get [tested] because you're probably not going to have [a mutation]. Because that's what they kept saying: 'The studies show that…' And I just feel like they were mostly women and either they're Jewish or they're Black. And you think that if you don't fit that category it doesn't happen, but that's not true. No.

Health insurance, age, and personal motivation were three other topics discussed by multiple participant groups. Regarding insurance, two US counsellors said the typical patient would have insurance or access to a discounted testing programme; and one UK counsellor thought a patient seeking a non-NHS route to care (e.g., a faster appointment or testing prior to in vitro fertilisation) would have private insurance. Regarding age, British counsellor

UKCA3 thought her usual patient was middle-aged, whereas four American support group members suggested the typical patient would be relatively young. Regarding personal motivation, both US clinicians and support group members believed the typical patient was proactive in seeking healthcare, and one genetic counsellor said men sometimes test for their daughters' benefit.

Finally, American support group members thought the typical patient had more knowledge of cancer genetics, time to pursue care, anxiety about cancer, and existing or past health issues compared to a patient who did not present to genetic services. Also mentioned were having a family member tested and receiving a clinician recommendation.

5.3.4 Regulation and governance of access to genetic services

Participants were asked to name any regulatory items – clinical guidelines, laws, legal rulings, and policies – that they thought related to care for BRCA mutations, as well as how those items currently influence and ideally would influence access to care. Participants across all groups agreed that clinical guidelines were beneficial if used as recommendations rather than restrictions, but conversation about the impact of existing laws, legal rulings, and policies yielded less common ground. American participants also named more of each type of regulatory item than British participants.

5.3.4.1 Clinical guidelines

Table 5.5 shows that clinicians named more guidelines than support group members. Whilst US clinicians identified more guidelines than UK clinicians, the opposite was true of support group members: the UK women named one guideline and the US women named none.

Table 5.5: Clinical guidelines identified by participants

UK clinicians	**US clinicians**
Departmental guidelines Institute of Cancer Research National Institute for Health and Care Excellence Royal College of Obstetricians and Gynaecologists	American Society of Clinical Oncologists Centers for Medicare and Medicaid Services National Comprehensive Cancer Network National Society of Genetic Counselors Society of Gynecologic Oncology United States Preventive Services Task Force
UK support group members	**US support group members**
National Institute for Health and Care Excellence	None identified

Participants from the British groups identified NICE as the main guideline-making body for BRCA-related care. Asked why departmental guidelines exist, UKCA1 explained NICE guidelines can be 'woolly and fuzzy':

> UKCA1: They're not so different in practice; they're just a little woolly and fuzzy and unclear sometimes … Yeah, the NICE guidelines say that you should use a tool to evaluate the risk that this is a BRCA gene and [they say], 'For example, this tool or this one', but they don't ever say to screening departments across the UK, 'We would prefer that all of you use this particular tool'. That's what the individual department manager or the lead clinician does, is decide what tool is going to be used.

UKCA3 expressed surprise at another department's potentially inappropriate use of Institute of Cancer Research guidelines in lieu of the NICE ones, and she said some surgeons may impede care by following Royal College of Obstetricians and Gynaecologists age specifications for mastectomy and oophorectomy too rigidly.

American support group members did not identify any specific guidelines, though several thought family history (and sometimes ethnicity) determined eligibility. In contrast, US clinicians named six guideline-making bodies: CMS, NCCN, the USPSTF, the American Society of Clinical Oncologists, the National Society of Genetic Counselors, and the Society of Gynecologic Oncology. Two sets of guidelines (CMS and USPSTF) were developed by

non-specialist bodies, and the other four sets of guidelines were produced by genetics and/or oncology specialist groups. Clinicians agreed that NCCN produced the most commonly used guidelines, whereas the CMS and USPSTF guidelines were primarily used for insurance purposes.

All four groups touched on the relationship between guidelines and costs of care. Two British support group members discussed how BRCA testing and prophylactic surgeries cost less than chemotherapy. The three UK genetic counsellors thought that despite national guidelines, there were still some local variations in MRI availability, which UKCA3 described as follows:

> UKCA3: There still is a little bit of a postcode lottery [i.e., differences in care depending on where a patient lives] in terms of implementing the NICE guidelines across our region. I am aware that some trusts don't have the money for MRIs or they've only just got it recently, and people have had to lobby their [Members of Parliament] to get that funding into their local NHS service … That's unfair.

A few American clinicians focussed on how guidelines are often subordinate to insurance coverage, with clinical geneticist USCA7 explaining that coverage for testing varies greatly across insurance companies:

> USCA7: The [USPSTF] and the NCCN have guidelines for who are considered good candidates for genetic testing. But in reality in the United States, it's mostly dictated by whether your insurance will pay for your test or not, and that is actually highly variable across insurance companies, meaning it's not like everyone follows the NCCN guidelines exactly for testing.

In contrast, support group member USPT3 attributed the lack of coverage for post-test care, including post-mastectomy and post-reconstruction follow-up appointments, to a lack of guidelines for post-test care.

As for how guidelines should be used, respondents from all groups thought clinicians needed both genetics knowledge and clinical judgment. As described in the 'Barriers and facilitators' section, lack of knowledge precluded some GPs and oncologists from referring

appropriately. However, participants argued that simply knowing the guidelines is not enough; clinicians also need to understand when to follow them. As one British counsellor explained, guidelines should not be a 'tick box exercise':

> UKCA3: Yeah, if you treat them as guidelines and you always use your clinical hat, I think they're fine. I don't think they are to be treated like a tick box exercise … But definitely it's a guideline and you still have to think and use your brain and think about the patient in front of you and their family history that is unique to them and not treat the guidelines as an excuse to say 'Computer says no'.

Participants suggested several situations where clinical judgment might override guidelines. For risk identification, a relatively young breast cancer patient who was adopted may require referral. For post-test care, a woman whose mother died from ovarian cancer at age 30 may need an oophorectomy at age 27. More commonly, clinical judgment actually reinforces guidelines, which explains why genetic counsellor USCA3 has used guidelines to 'talk [low-risk patients] out of testing'.

5.3.4.2 Laws, legal rulings, and policies

Table 5.6 juxtaposes a wide range of American laws, legal rulings, and policies and a smaller set of British ones.

Table 5.6: Laws, legal rulings, and policies identified by participants

UK clinicians	**US clinicians**
Disability Discrimination Act Equality Act Insurance moratorium	Association for Molecular Pathology v. Myriad Genetics, Inc. Genetic Information Nondiscrimination Act Health Insurance Portability and Accountability Act Health insurer requirements Inability for genetic counsellors to be reimbursed Military coverage No protections for life, disability, and long-term care insurance Patient Protection and Affordable Care Act
UK support group members	**US support group members**
Insurance moratorium	Law preventing insurers from raising baseline age for mammograms Association for Molecular Pathology v. Myriad Genetics, Inc. Breast Cancer Education and Awareness Requires Learning Young Act No protections for life, disability, and long-term care insurance Patient Protection and Affordable Care Act Requirement that reconstruction be covered if mastectomy covered

British participants named only three distinct regulatory items, with members of both groups mentioning the UK insurance moratorium on the use of genetic information. UKPT2 added a related recommendation on when BRCA carriers should consider disclosing their results:

> UKPT2: So if you wanted a pension, you would do better to volunteer that information because you'd probably get an enhanced annuity because they welcome the message you're not likely to live as long.

Genetic counsellor UKCA3 also suggested the Equality Act 2010 and the Disability Discrimination Act 1995 might impact BRCA carriers, but she did not elaborate how.

American participants named 11 unique laws, legal rulings, and policies. Support group members and clinicians both cited the ACA (sometimes colloquially as 'Obamacare'), the Myriad ruling, and the lack of protections preventing life, disability, and long-term care insurers from using genetic data. Participants gave the ACA mixed reviews, as the following quotes show:

> USPT1: [I]t's good that health insurance now cannot discriminate because of Obamacare. You still have to be given medical coverage, I believe even with a genetic mutation.
>
> USPT3: I don't know enough about it to be able to give you a 'yes it's a good thing' or 'no it's not', but I know [FORCE gets] a lot of things like, 'Now my MRI isn't covered for my surveillance and my doctor's trying to code it the right way and it keeps getting denied. Do you know what the code is?'
>
> USPT4: Just that when there's a new president, what else are they going to do? What new policies are they going to put in place? How long is Obamacare really going to be here? I don't know. At the moment all I know is it's made it very difficult for me to get health insurance.

Similarly, support group member USPT3 pointed out the trade-off that the Myriad ruling introduced between the cost of testing and the quality of interpreted results:

> USPT3: [I]t's good and bad because now that [Myriad is not] the only [company] that can deliver the test, it certainly has brought the cost down … But I can say that whenever one of the variants would come back and they were now able to classify it, they would then run through all the people they had in their database. So now that's the controversy: are these new labs going to have enough patience to be able to reclassify any of those variants to inform them that they now carry a different type of a mutation?

Relatedly, US genetic counsellors stressed that both patients and insurers now have financial incentives to choose cheaper, newer laboratories rather than the most comprehensive ones. Thus, the worst-case scenario would be a woman receiving a negative result from a newer company when she actually has a harmful mutation that Myriad would have identified.

The other laws discussed by support group members involved mammography and breast reconstruction. USPT7 alluded to the updated population-risk USPSTF mammography guidelines; the related law was the ACA amendment preventing insurers from actually

implementing the revised guidelines, as discussed in Chapter Three. USPT3 noted that FORCE supported the EARLY Act, which authorises the CDC to develop breast cancer education initiatives for young women. Finally, USPT1 said insurers are required to cover reconstruction if they cover mastectomy, a law formally known as the Women's Health and Cancer Rights Act of 1998.

The genetics professionals additionally cited two laws, one set of legal provisions, and two policies. Clinical geneticist USCA7 discussed the pros and cons of GINA, as well as its applicability to daily practice:

> UKCA7: Well, GINA at least makes it illegal to discriminate on the basis of genetic information for health insurance and jobs, but there are loopholes within that as well based on how many employees you have at your site and it doesn't apply to federal employees, so the military and things like that it doesn't apply to. In actuality we've never needed to invoke GINA, so I don't know that that's a problem. In the early days people were really worried about discrimination. I think that's a little bit less of an issue now.

Genetic counsellor USCA3 cited HIPAA without additional comment. USCA3 and USCA7 mentioned that the military has internal provisions derived from law. Several clinicians also discussed insurer requirements (e.g., mandating that genetic counsellors sign off on all tests) and counsellors' inability to bill as service providers (mentioned in the 'Barriers and facilitators' sub-section).

5.3.5 Genetic testing outside of genetic services

The next question for respondents was whether they knew any avenues by which women could access genetic testing, other than through genetic services. Participants identified five such avenues: DTC genetic testing, mainstreaming, research studies, telegenetics, and population screening.

5.3.5.1 Direct-to-consumer genetic testing

Several US and UK participants cited harms of DTC testing, e.g., a patient discovering she was a BRCA carrier without ever consenting to testing:

> USCA7: [T]he father, a dad who was divorced from his wife, sent a 23andMe [kit for] himself and his son who was underage, and his son had a BRCA1 mutation … So he then called his ex-wife and basically told her she needed to get checked out because she was an obligate carrier.

Genetic counsellor USCA5 said a negative DTC test actually concerned her more than a positive DTC test. Whilst a woman testing positive will usually seek medical management, a woman testing negative may be falsely reassured and never find out she has a mutation for which the DTC company did not test. Additional participant concerns included clinicians not being involved with interpretation of results and follow-up care, patients misunderstanding how results affect family members, and scant scientific evidence available to explain what a positive BRCA test means for a woman with no family history of cancer.

More positively, several US participants pointed out that DTC testing could widen access for patients who live in rural areas, patients who dislike seeing doctors, and patients who never knew they were at risk for HBOC. The only participant to have used DTC testing described herself as 'lucky' to have had access to a commercial test:

> USPT1: Most people that I know of went about it a pretty standardised way, just because they either knew that they had a history or knew that they had a mutation, or they were diagnosed with cancer at a surprisingly young age and found out they had a mutation that way. There are a lot of women who found out because of a cancer diagnosis. I'm just really lucky that wasn't me because it very well could have been because I never would have guessed.

Other benefits related to costs of care: USPT1 pointed out positive DTC results do not affect American life insurance policies, USCA7 said responsible DTC companies provide another low-cost avenue through which clinicians can order certain tests, and USPT6 viewed DTC testing as an option for low-income AJ women to obtain testing if they cannot

afford clinician-directed testing. A few participants also believed that DTC testing might be appropriate in the future once more information about genetic variants is available.

5.3.5.2 Mainstreaming

Primarily American and British clinicians discussed mainstreaming, e.g., clinicians providing genetic testing outside of genetic services (as in the second 'Process mapping' step). Participants identified oncology as the specialty best equipped for mainstreaming, particularly since cancer patients may need expedited testing to inform chemotherapy and surgical choices. Clinical geneticist UKCA4 also noted that more cancer patients will require testing as the threshold for testing decreases:

> UKCA4: In another five years, I'm sure [the threshold] will have gone down to 5 per cent, which will probably be a lot better [than 10 per cent]. At the moment we're in this transition of moving towards the oncologist requesting it, so as soon as it's significantly cheaper than it is now and quicker, it will be something that's very routinely done.

However, clinicians cautioned against mainstreaming too quickly, as oncologists do not always know when patients meet criteria for BRCA testing. A few clinicians also gave examples of GPs and gynaecologists testing inappropriately. For instance, gynaecologists may order BREVAGen breast cancer risk profile tests, which cannot detect BRCA mutations and may produce suspect results:

> USCA7: We've seen more and more lately gynaecologists sending the BREVAGen test, which is a little disturbing because the risk estimates on there, it's like, let's just multiply a bunch of stuff together and get a number. I'm not really sure that that's how we should be doing it. So we've had some really high numbers, like someone had a lifetime risk of 77% on her BREVAGen panel with one first-degree relative who had breast cancer at 80, so it just didn't feel right, you know?

Finally, support group member USPT3 pointed out that mainstream patients may not receive genetic counselling.

5.3.5.3 Research studies, telegenetics, and population screening

The remaining three avenues to access – research studies, telegenetics, and population screening – were each discussed only briefly by participants. Research studies influenced four support group members' paths: UKPT2 and sisters USPT3 and USPT4 received counselling and testing through UK- and US-based projects, respectively. Researchers from another British study recommended that UKPT6's sister undergo BRCA testing:

> UKPT6: When [my sister] was diagnosed with BRCA, it was the research team that alerted her to a possibility of BRCA because she was doing an epidemiological study. She was having to fill in questionnaires and sending them back, and it was then they wrote to her because obviously she had to say, 'My auntie had ovarian cancer. My cousin had breast cancer'. And they wrote to her saying, 'You should probably get tested and go and see your GP'.

American counsellors USCA1 and USCA2 spoke of their experiences collaborating on a telegenetics pilot programme and working for a telegenetics company, respectively; both provided web-based counselling for clinics with no on-site genetic counsellors. Counsellor USCA3 discussed the possibility of an AJ population screening programme, e.g., offering genetic testing to all AJ women, which might involve online education modules and test results sent to GPs. Geneticist USCA7, however, said implementation would be tough because patients might consider questions about ethnicity offensive or discriminatory. Genetic counsellor UKCA2 also raised the issue of testing women without family histories of BRCA-related cancer:

> UKCA2: [T]he other thing that I worry about a bit as well is that if someone has a BRCA test without a family history of cancer and something is found … We don't know whether they are at a very high risk of developing breast and ovarian cancer, which is what they're going to assume, or whether actually there are other modifier genes in the family that are protecting them against that and that's why no other family history's being seen.

5.3.6 Absence of necessary care and presence of unnecessary care

Having discussed the role of regulation in determining access to care, participants were then asked whether they thought patients ever fail to receive care they do need or receive care they do not need. Their responses fell into four categories: necessary care that patients do not receive, patients who do not receive necessary care, unnecessary care that patients receive, and patients who receive unnecessary care. Overall, support group members spoke more about the absence of necessary care, and clinicians spoke more about the presence of unnecessary care.

5.3.6.1 Necessary care that patients do not receive

Participants said patients do not always receive necessary screening, surgery, and post-surgery therapies. Both British groups cited regional variation in breast MRI availability, and several support group members had trouble obtaining prophylactic surgeries, bone density scans, post-mastectomy massages, physiotherapy, and surgical follow-up appointments. A few UK participants also worried that greater public awareness would create an impossible demand for genetic services:

> UKPT5: I don't know how it is going to cope with the added amount of people getting BRCA testing … [The NHS is] just literally splitting at the seams to take on new patients, but it's just going to get more and more as more people get diagnosed.

As for the American participants, support group members cited a lack of psychotherapy and limitations on care imposed by state law and insurance requirements.

5.3.6.2 Patients who do not receive necessary care

Characteristics of patients who do not receive necessary care generally aligned with barriers identified in the 'Barriers and facilitators' section. Participants suggested that patients missing out on care might lack education, income, knowledge, access to primary care, or

personal motivation; have an incomplete or unrequested family history; live in a rural location; identify as a racial or ethnic minority; or speak a language besides English. One support group member provided an interesting take on how culture impacts views on necessary care:

> USPT1: [M]y mother is actually Puerto Rican, and I think that in Hispanic and African American communities, there is an impression … that this is a White person thing … I know that some of my aunts feel that way on my mom's side of the family … 'Why are you voluntarily going into menopause early because you might get ovarian cancer? It'll either happen or it won't'.

5.3.6.3 Unnecessary care that patients receive

Respondents identified genetic testing, screening, and surgery as types of unnecessary care that some patients receive. Regarding testing, American counsellors thought the 'Angelina effect' has increased the volume of inappropriate BRCA testing. However, one genetic counsellor from each country suggested that testing an average-risk woman may actually be appropriate if she is privately insured and extremely anxious about being a carrier. Taking a broader approach, an American clinical geneticist explained how the US healthcare system encourages unnecessary testing:

> USCA7: [The UK] healthcare system is concerned about families, not individuals. So if you have a family it would make sense … to test the affected mother before you test the six daughters in a family that meets criteria. But in the United States, those seven people are insured by seven different insurance companies, so they can't mandate or even really suggest that you have to test mom first. So each individual patient's coverage for her genetic testing is irrelevant to their insurance plan, which means that – and we have seen this happen – all six unaffected daughters might be tested before the affected mother is tested. And when you think of that from a cost perspective, that makes no sense.

Regarding screening, clinicians described too-frequent mammography and ineffective ovarian cancer screening as unnecessary. Regarding surgery, participants from all four groups flagged unwarranted prophylactic mastectomies in women who are not confirmed BRCA carriers, as the following quote illustrates:

> USCA2: [W]e do hear stories from time to time of people getting inappropriate care, services they don't need, be it a woman with history of breast cancer whose family

> history is not particularly striking, BRCA negative, and decides to have a contralateral mastectomy for preventative purposes.

UKPT5 also described her 21-year-old BRCA-positive daughter's experience with a surgeon who openly worried that a mastectomy was unnecessary at her age; ultimately, he agreed to perform the surgery anyway.

5.3.6.4 Patients who receive unnecessary care

American participants said the 'worried well' (i.e., healthy people pursuing care to confirm they are healthy) received unnecessary testing and screening. Support member USPT1 explained this mind-set as follows:

> USPT1: I think there might be people who worry and get testing that they don't necessarily need. My sister is one of those people who would test for anything. There could be a disease that has only ever hit Eskimos and she would want to test for it if she heard about it because she wants to test for everything

According to several US counsellors, other candidates for inappropriate care include patients who are average risk, patients who mistakenly believe they are high risk, and patients who have low premium insurance or insurance with no referral requirements. No UK participant responses fit into this category.

5.3.7 Service improvements

Lastly, participants were asked how they would ideally improve care for BRCA mutations. Their suggestions largely aimed to remedy barriers identified in the 'Barriers and facilitators' section. Roughly three quarters of all participants advocated for genetics education that would increase patient and clinician knowledge. For example, UKCA2 referenced another clinician trying to demystify genetic services for students, and by extension, their parents:

> UKCA2: I know my colleague did a talk in a school just about what our service is and how it can be accessed, just with a view of bringing the next generation just knowing that those are options.

Likewise, UK and US genetics professionals mentioned talking to GPs, oncologists, surgeons, and medical students about BRCA referral criteria, and support group members UKPT2 and UKPT5 discussed giving talks to medical students about the emotional aspects of coping with BRCA mutations.

Another set of proposed changes sought to standardise the costs of care. For example, USPT1 described the wide variation in out-of-pocket costs that currently exists for American patients:

> USPT1: Uniform standards on what insurance companies have to cover for genetic stuff. Right now, it's a huge range. The women in the Facebook group I'm in range from not having to pay a penny out of pocket to basically no coverage for prophylactic surgeries, so I would have it be uniform.

Likewise, members of both British groups called for standardised, adequately funded care across all regions in response to the perception that there was a postcode lottery governing access to MRIs. Counsellors UKCA1 and UKCA2 also thought internationally standardised guidelines would help clinicians caring for immigrant and emigrant women.

A final set of improvements attempted to strengthen the infrastructure of existing genetic services. The UK clinicians wanted to reduce the 18-week wait time from referral to genetic service appointment; their ideas included more staff members, larger premises, and appropriate mainstreaming. UKCA1 and UKCA2 summed up this sentiment as follows:

> UKCA2: I think a lot of the things I would change are not the pathway but assisting the pathway so things like, well, yes, the triage team do collect information before we see a patient in clinic, but actually we've got so many referrals and not enough staff to get all of that information so things don't always work. Or they have to wait a long time to get their appointments, so it's not that I would change how it works. I would just change -
>
> UKCA1: Put some staff behind it.
>
> UKCA2: Change things so that it works in an efficient way.

The US clinicians focussed on making genetic counselling a more desirable profession – e.g., enabling counsellors to bill for services and paying counsellors on par with their education and expertise – so that more people would enter the field and help clinics meet increased demand for genetic services. USCA7 also proposed optimising online family history forms and appointment scheduling. Participants from US and UK support groups recommended that all patients have ongoing access to clinician-led support groups. UKPT5 also wanted genetic services to give all BRCA-positive patients informational letters for their family members, and USPT7 requested more psychotherapy and patient navigation.

5.4 Analysis using axial coding

Drawing on data gathered in focus groups and interviews, this chapter has thus far presented results on how UK and US genetics professionals and support group members perceive access to care for BRCA mutations in seven response categories. This section presents themes revealed during axial coding in four key areas: group-based similarities and differences, barriers and facilitators emerging in multiple response categories, clinical guidelines in daily practice, and potential harms arising from broader access to care.

5.4.1 Group-based similarities and differences

Similarities among the four participant sub-groups primarily emerged in Sections 5.3.1 ('Process mapping') and 5.3.2 ('Barriers and facilitators'). This suggests that the basic steps needed to access care for BRCA mutations may be shared and experienced similarly by different patients, and there may be numerous reasons why a patient does or does not access care. For example, the process maps below from USPT5 and UKPT2 show that both support group members identified a risk for a BRCA mutation, received a referral to genetic services, obtained counselling and testing, and received the results.

Figure 5.2: Process map from support group member USPT5

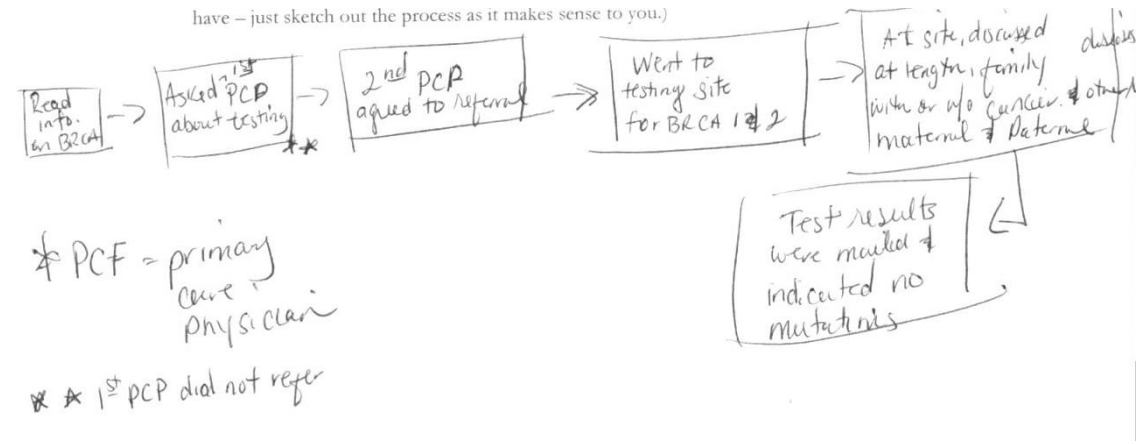
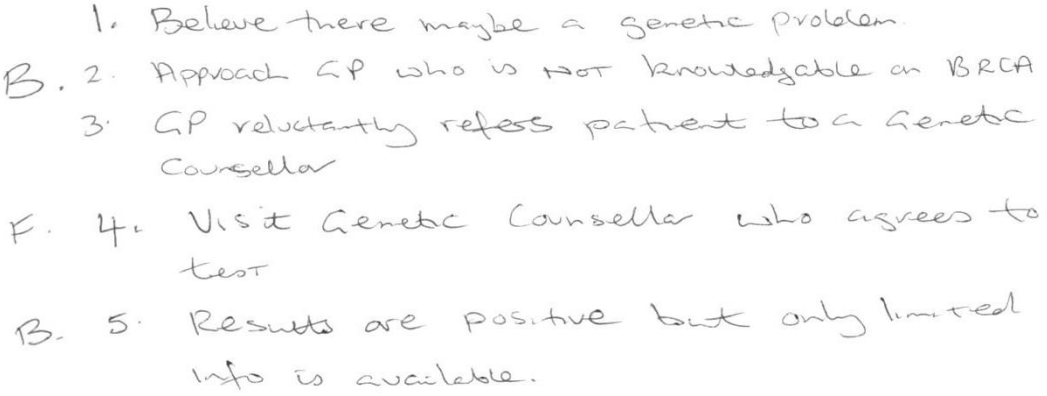


Figure 5.3: Process map from support group member UKPT2



In each case, the woman struggled to receive a referral, though USPT5's solution of requesting a second opinion differed from UKPT2's solution of persuading her unknowledgeable GP to provide the referral. The results also differed, with USPT5 testing negative (though discussion clarified that she was not sure which kind of negative she had) and UKPT2 testing positive but receiving limited information about follow-up care.

The fact that participants combined to cite 67 items hindering and/or helping care supports this interpretation. Choices made during participant recruitment also likely contributed to the similarities in process maps. The counterparts to the genetic professionals and support group members would have been non-genetics professionals who offer care for BRCA

mutations and women who declined genetic services, respectively. Neither of those populations was ultimately invited because they would not be able to provide insight into the remaining response categories. That said, seeking out more diverse participants for future process mapping research would help provide a fuller perspective on how patients access genetic services.

Differences between US and UK participant responses stemmed from differences in how US and UK health services are organised, financed, and regulated. As discussed in Chapter Three, American patient access is assessed individually, whereas British patient access is approached systemically. Encapsulating these divergent philosophies was the example USCA7 gave of unnecessary care that US patients receive that UK patients would not (full quote on page 206): testing six unaffected, individually insured daughters before their affected mother would never happen under the publicly funded NHS, which would test the mother first. Unsurprisingly, insurance and income were more important to US respondents, whilst UK respondents focussed on the perceived postcode lottery and wait lists for genetic services. Along the same lines, a participant's perspective on self-referrals seemed dependent on her nationality. For example, American counsellor USCA3 explained that some private insurers permit self-referral and effectively allow patients to bypass the second step of the patient pathway:

> USCA3: And I do generally think that people who have really low premium insurance who don't need a [clinician] referral do seek services and do actually appropriately so but not always appropriately so.

In contrast, British counsellor UKCA2 pointed out that British genetic services cannot accept self-referrals because of how NICE envisions the patient pathway:

> UKCA2: And we have to say, 'You need to go through your GP'. Occasionally we'll see someone, maybe someone who has been referred will bring their sister or something, and we'll give them advice and maybe test them and ask them to go back and get a referral from their GP because that's the way it's funded.

Perhaps the most obvious case of nationality influencing responses, though, came when participants described the regulatory framework for their country of residence. British participants mentioned fewer regulatory mechanisms than American participants, but they seemed to think there were adequate protections for women accessing care. Conversely, American participants discussed a larger but imperfect set of mechanisms, and they expressed qualms about the short- and long-term financial implications of accessing care. For example, the differential UK and US perspectives on life insurance are espoused in the quotes below from a UK genetic counsellor and a US support group member:

> UKCA1: Yeah, [anti-discrimination protections are] pretty good at the moment for people in this country. There's an agreement that they won't be asked for the results of pre-symptomatic genetic tests. There is one slight clause of that, but it doesn't involve BRCA genes.
>
> USPT3: [Other support group members] were very for [life insurance], and we do tell women who are considering prophylactic surgery to make sure that - or not, I'm sorry, not surgery, testing - if you want disability or life insurance, that you take care of that first.

Differences between genetics professionals and support group members surfaced in discussions about service improvements, (un)necessary care, and regulation and governance. Where clinicians sought to increase their patient volume and expedite care (albeit in ways reflecting their countries' health systems), support group members concentrated on improving patients' experiences with post-test care. Compared to clinicians, support group members offered more examples of necessary care being denied and fewer examples of unnecessary care being provided. Additionally, support group members spoke less about and identified fewer guidelines, laws, legal rulings, and policies than clinicians. All three findings reflect the orientation of the participants: clinicians know more about how care should be provided to patients, whilst support group members know more about how care is actually experienced by patients. Case in point, nearly all support group members thought care for BRCA mutations would improve with more clinician-organised support groups, as exemplified by the following quote from UKPT5:

> UKPT5: Well, that's how I got started with this because when I got diagnosed with BRCA, and literally it was like, 'Yes, you have the mutation'. And she had a photocopied sheet of paper with a little bit of information and she handed me that and I said, 'Well, where is my glossy booklet? Where's my support group?' [Laughter] 'Where is all the information? When is your next meeting about it? Where are all these other BRCA people?' 'No, we don't have anything like that'. And I remember saying to the genetic counsellor at the time that we really need something.

In contrast, no clinicians brought up support groups when answering the same question.

5.4.2 Barriers and facilitators emerging across multiple response categories

Four items – patient knowledge, clinician knowledge, race and ethnicity, and age – surfaced in participant comments across at least four response categories. Given the overall set of participant responses, the repetition of each item makes sense. Identification of a risk factor was the main entry point for access to care, so the degree to which participants from all groups emphasised both the presence and absence of patient and clinician knowledge was unsurprising. The quotes below illustrate the impact of clinician and patient knowledge on two British support group members' opportunities to access BRCA-related services:

> UKPT6: My GP was very good. They've always been very good. If you go to them, they listen to you and they take it on board and action it really. But it was her that suggested the Dexa [bone density] scan and it was her that sent the referral for the BRCA, for the genetics clinic, so they are very good. I think that's the thing: if you've got a good GP, they really are worth their weight in gold.

> UKPT5: Yeah, see, we got offered [testing] once you've been for the genetic counsellor, but you have to know to ask to be referred to a genetic counsellor, so if you don't know, and your oncologist or your doctor or your GP doesn't tell you, then you don't know about [testing]…

Likewise, it seemed plausible that race and ethnicity would surface frequently because of how ethnicity may contribute to risk for BRCA mutations and how minority patients utilise genetic services at lower rates than non-minority patients. For instance, the American clinical geneticist referenced how racial disparities emerge in her own research on factors affecting genetic testing:

> USCA7: We did a study … looking at individuals under age 50 in the state of Pennsylvania and Florida from the state registry, looking at Black women and White women. Basically Black women were less likely to be recommended for genetic testing, and we know that patients don't always do what their providers tell them to do, but the physician recommendation does help in decision making.

Support group member USPT7's comment about clinicians focussing too much on Black and AJ patients on page 194 also highlighted the difficulty in simultaneously targeting services towards the women most likely to have BRCA mutations, addressing racial disparities in genetic services, and providing necessary care to all high-risk women.

Finally, age was a natural discussion item because participants repeatedly conversed about when patients pursue testing, screening, and surgery, as well as how clinicians may use age to determine if preventive care is appropriate. As an example, one American support group member pointed to age of cancer diagnosis as a factor leading to women pursuing BRCA counselling and testing:

> USPT1: Most people that I know of went about it a pretty standardised way, just because they either knew that they had a [family] history or knew that they had a mutation, or they were diagnosed with cancer at a surprisingly young age and found out they had a mutation that way. There are a lot of women who found out because of a cancer diagnosis.

5.4.3 Clinical guidelines in daily practice

Participants from all four sub-groups generally agreed that guidelines should establish baseline recommendations, but clinicians should decide when and how to make exceptions. Even with this shared view, what constitutes appropriate application of guidelines in practice is unlikely to garner universal agreement. For example, British clinicians and support group members both mentioned regional variations in breast screening availability.

The genetic counsellors thought that some women who were denied MRIs fell in the proper age range – 30 to 49 in general, or 30 to 69 if breast tissue is dense (NICE, 2013b) – and

were therefore victims of a postcode lottery, as suggested in UKCA3's quote on page 197. However, some participants, especially support group members, may have conflated age-based variation manifesting in certain areas with region-based variation. That is, an over-50 woman who lives in one region and has average-density breast tissue may be denied an MRI; her over-50 friend who lives in a second region and has high-density breast tissue may be granted an MRI. The women are from different regions and are differentially accessing care, but the age guidelines themselves are appropriately driving the variation. That explanation may not sway the first woman, though, who may feel she should receive the same care as her friend regardless of breast tissue density.

More broadly, clinicians from both countries only discussed expanding eligibility for guideline-approved types of care, e.g., lowering the age at which certain BRCA carriers can receive prophylactic surgery and decreasing the risk threshold for adopted or highly anxious women seeking testing. In contrast, what support group members considered necessary types of care did not always align with guideline-approved types of care. For instance, British women thought necessary care included both post-oophorectomy bone scans, which some clinicians deem necessary to detect post-menopausal bone loss, and post-mastectomy massages, which the NHS had approved for some breast cancer patients to aid their post-surgery recovery. The following exchange between three British support group members captures the divergent ways that care that is not enshrined in NICE guidelines is offered:

> UKPT1: [W]hen I went to [Hospital #2] for the second time and saw the oncologist, actually he said, 'We're going to send you for a bone density scan', and actually I've got osteopenia, but nobody had ever said anything about that beforehand, that having the menopause at 43 …
> UKPT5: But it's only before you're 50, isn't it, [that] they'll do it, because I didn't get offered it.
> UKPT1: Didn't you.
> UKPT3: I pushed for it.
> UKPT1: No, I was offered it. I was told I had -

> UKPT3: No, I went round to my GP and pushed for it because I'd been to the FORCE conference, and it was something that they'd mentioned there. So I just went round to my GP and no hesitation, just put me up for one.

These disparate views spark questions about what kinds of care merit a clinician exception, why kinds of care meriting exceptions are not in the guidelines already, and whether the answer depends on who is responsible for funding that care. In this specific case, bone scans seem a more likely candidate for an exception than massage, given that osteoporosis can lead to serious bone fractures. Indeed, as indicated in the quote above, UKPT3 said her GP managed to get her a bone scan after she requested one.

A smaller observation involves the number of guidelines mentioned by each participant group. American clinicians named more guidelines than British clinicians, which was expected because there simply are more US guidelines than UK guidelines (see Chapter Three). The opposite relationship was true of the support group members, though: no American women identified a particular guideline by name, whereas several British women immediately cited NICE guidance. (In fact, several UK support group members even discussed how NICE calculated that it is more cost-effective for women to have genetic testing and preventive surgeries than prolonged cancer treatments.) On the American side, it may be that support group members find guidelines less salient than costs of care, given that all spoke about insurance and/or income at some point; this further reinforces USCA7's point about guidelines being subordinate to insurance in Section 5.3.4.1.

5.4.4 Potential harms arising from broader access to care

Participants indicated that access to care has broadened in several ways, including additional pathways to genetic testing, more companies able to provide testing, and greater uptake of post-test interventions. Whilst respondents generally viewed broader access as an

improvement, they also gave examples of how expanding access to testing and post-test interventions may create unexpected harms. For instance, genetic counsellor USCA6 described the downside to providing free testing to low-income minority women:

> USCA6: [W]e were giving free testing to any minority woman. So you test them, they come back positive, and then they are [out of luck] because they have no insurance … So you need an MRI? You can't get one. You need surgery? You can't get it. So here they are, probably done a disservice now. We think this is so wonderful, but then this woman has absolutely no insurance.

Other challenges included how to handle the increasing volume of patients seeking genetic services (e.g., mainstreaming without misinterpreting results), how to choose the right testing company (e.g., balancing affordability and comprehensiveness of results), and how to facilitate responsible access to genetic data (e.g., anticipating the long-term financial implications of DTC testing). Geneticist USCA7 also pointed out a US-specific concern about the impact of population testing on low-risk women's ability to obtain life insurance:

> USCA7: As we move into testing lower and lower risk patients and particularly if we move into population screening, I think that these [life insurance] issues will arise again because it's one thing if you're getting tested because you have a strong family history, so you have a reason to be doing it, it's another thing if you're identified and you don't have a family history.

These challenges are not a reason to summarily stop broadening access to care, however. In the case USCA6 described, withholding free testing from low-income minority women will do nothing to eliminate the racial and socioeconomic disparities in who receives testing – the very gaps the charitable programme was designed to address. In the case USCA7 described, understanding and communicating the potential consequences of testing – financial and otherwise – would have to be factored into any population screening programme. Thus, these ethical issues are a sign that both the positive and negative implications of expanding access deserve attention, as opposed to assuming that broader access is automatically better access.

5.5 Discussion

This section situates the findings from Chapter Five, specifically those from Section 5.4, within the broader literature on access to genetic services, both for BRCA/HBOC and other conditions. First, the group-based similarities and differences identified in Section 5.4.1 are discussed in relation to how clinicians and patients think about the same topics in other contexts. Second, the four barriers and facilitators emerging across at least four response categories that were discussed in Section 5.4.2 are contextualised against the broader literature on factors affecting access to genetic services. Third, the role of clinical guidelines in daily practice, as explained in Section 5.4.3, is considered in different contexts and from the perspective of guideline adherence. Fourth, the potential harms arising from broader access to care, as debated in Section 5.4.4, are considered in terms of how specialists have incorporated genetic testing for non-BRCA conditions.

5.5.1 Group-based similarities and differences

The fact that all four participant sub-groups drew generally similar process maps is in line with both the clinical guidelines for care for BRCA mutations and the wider literature on access to genetic services. As Chapter Three showed, the clinical guidelines describing how US and UK women are supposed to access care for BRCA mutations are generally similar, so it is not a surprise that most drawings of how patients access care for BRCA mutations were similar (NCCN, 2016b; NICE, 2013b; USPSTF, 2013). More broadly, the patients who are able to receive services for any genetic condition tend to follow proscribed patient pathways, e.g., being referred to a genetic service that provides counselling and, if desired, testing (Genetic Alliance & The New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, 2009; NHS Choices, 2016).

Country-based differences in participant responses arose from differences in US and UK healthcare organisation, financing, and regulation, as noted in Section 5.4.1. Both academic and lay articles have long pointed out these divergences: Roe and Liberman (2007), for example, thoroughly compared the United Kingdom's single-payer system with supplemental private insurance and the United States' combination of employer-based insurance, individual markets, and government-provided care. In an article for *The New Yorker*, Gawande (2009) discussed the different roles that the government plays in healthcare in America and England, respectively, noting that US patients lack the safety net for costs that UK patients are afforded and therefore find insufficient insurance and high out-of-pocket costs severely limiting. In a large retrospective cohort analysis, Forrest, Majeed, Weiner, Carroll, and Bindman (2002) found that compared to UK patients, US patients received significantly more specialty referrals, i.e., roughly 33 per cent versus 14 per cent. The authors specifically cited self-referral in the United States and long wait times in the United Kingdom, two factors that emerged in this chapter, as likely drivers of the disparity in referral rates. Similarly, postcode lotteries were a popular topic in British newspapers and medical journals, likely because of the NHS' own 'Atlas of Variation' that provides data on disparities in health resources across England (Ellis & Robert Fry, 2010; Ramesh, 2011; Torjesen, 2014). Finally, as Chapter Three explained in detail, the financial implications of genetic discrimination are more pressing for US patients than UK patients (Klitzman, Appelbaum, & Chung, 2014).

Role-based differences in responses are also reflected in the broader medical literature. It is a common desire of genetics professionals to increase service capacity so that they can see more patients and decrease wait lists (S. A. Cohen et al., 2012; Slade, Riddell, Turnbull, Hanson, & Rahman, 2015). Likewise, patients often wish to improve their satisfaction with services, which may relate to which kinds of post-test care and support they are offered and

how frequently (S. Holloway et al., 2004). In particular, support groups are a typical request of, as well as a recommendation for, patients coping with genetic conditions (Genetic and Rare Diseases Information Center, 2016; J. G. Hall, 2013; Weiss, 1992).

5.5.2 Barriers and facilitators emerging across multiple response categories

The four factors emerging across at least four response categories – patient knowledge, clinician knowledge, race and ethnicity, and age – all surface regularly in the literature as potential barriers and facilitators to access to genetic services. Patient knowledge is frequently cited as a determinant of referral to genetic services (Beene-Harris, Wang, & Bach, 2007; Delikurt, Williamson, Anastasiadou, & Skirton, 2015; Harris, 2001). Clinician knowledge matters for all aspects of care for BRCA mutations, but especially for referrals, and it is represented accordingly in the literature (Al-Habsi, Lim, Chu, & Hewison, 2008; Beene-Harris et al., 2007; Cornel & van El, 2017; Harris, 2001; Koil, Everett, Hoechstetter, Ricer, & Huelsman, 2003; Suther & Goodson, 2003; White, Bonham, Jenkins, Stevens, & McBride, 2008). Race and ethnicity appears in two ways throughout the literature, as a modifier of risk and in terms of disparities in utilisation of genetic services by minorities (Allford et al., 2014; Forman & Hall, 2009; Hann et al., 2017; Harris, 2001; Metcalfe et al., 2013; Suther & Kiros, 2009). Finally, age is referenced in the literature in terms of when patients pursue genetic services and what care is appropriate (Cragun et al., 2015; Emery, Watson, Rose, & Andermann, 1999; Kattentidt-Mouravieva, den Heijer, van Kessel, & Wagner, 2014).

5.5.3 Clinical guidelines in daily practice

In keeping with the participants' views in this study, the literature generally supports a theoretical combination of adherence to guidelines and clinician discretion (Guttmacher,

Porteous, & McInerney, 2007; Kyne et al., 2011). In practice, however, adherence to guidelines is less than ideal for suspected hereditary conditions, resulting in high-risk patients being referred too infrequently and low-risk patients being referred too frequently (d Marang-van, van Maarle, & Stouthard, 2002; Febbraro et al., 2015; White et al., 2008).

Whilst participants in this study spoke about expanding eligibility for guideline-approved types of care by raising or lowering age, a more popular angle appears to be emphasising targeted testing for very high-risk groups, e.g., AJ patients (Manchanda et al., 2017). (Section 6.4.1.2 discusses these kinds of studies in much more detail.) Similarly, although patients seem to consider more and different kinds of care necessary than what is contained in national guidance (S. Holloway et al., 2004), not many studies appear to be asking patients for their input on how to expand guidance. The closest analogue would be bodies such as NICE and NCCN including patient advocates in their guideline-making groups (NCCN, 2016a; NICE, 2016b).

5.5.4 Potential harms arising from broader access to care

Finally, the literature reflects the tension identified in this study about the trade-off between broadening access to care and potentially lowering the quality of care. For example, Rahman (2014) discussed the model of having oncologists offer genetic testing to cancer patients, as in the Mainstreaming Cancer Genetics programme; the benefit of expanding access is noted, as is the potential harm of incorrectly ordering tests. Research on post-trial access to care provides insight into how post-test care might be considered for low-resource populations, e.g., Doval, Shirali, and Sinha (2015) discuss providing medications based on genetic testing results, but their argument could be extended to services such as mammograms or MRIs for BRCA-positive women. Likewise, the financial implications of a woman without a strong family history testing positive for a genetic mutation – or the opposite, a woman with a

strong family history testing negative for a genetic mutation – are discussed in papers such as Klitzman et al. (2014) and Armstrong et al. (2003).

5.6 Strengths and limitations

The greatest strength of this empirical study was the incorporation of the process mapping technique, which provided a visual representation of access and prompted participants to discuss their experiences of providing and accessing care in an organised fashion. Another strong point was the variety of questions asked, which covered all four dimensions of the Gulliford model and addressed topics examined in Chapters Three and Four.

Participant recruitment choices introduced both strengths and limitations. Including genetics professionals and support group members enabled expert clinician and patient perspectives to be captured, whilst accounting for practical constraints on time and ability to travel. The size and composition of these groups may affect the generalisability of results in different ways, however. As noted in Section 5.2, all four participant groups were small and somewhat homogenous, especially in terms of geographic location and race and ethnicity. This general limitation could be addressed by including more participants in each of the four groups, with a particular focus on outreach to participants from more diverse geographic and racial and ethnic backgrounds.

Specific to the clinician groups, the samples overrepresented genetic counsellors' perspectives and only drew from one US and one UK genetic service apiece. Although the samples reflect the reality that there are typically more genetic counsellors than clinical geneticists in genetic services (Doyle, 2009), achieving a better balance between genetic counsellors and clinical geneticists would be helpful given the different roles these clinicians play. Likewise, it would be beneficial to recruit clinician participants from multiple services

in each country to avoid drawing conclusions that may not apply to other services. Since each clinician referenced her experience practising in another healthcare setting during her focus group or interview, however, this concern was somewhat mitigated. As a last thought on the clinician groups, it would be interesting to include non-genetics professionals, such as oncologists and GPs, to see if/how their perspectives and process maps differ from the genetics professionals.

Specific to the support group member samples, the participants may only represent certain kinds of women at high risk for BRCA mutations. Whilst the support group members gave richly detailed responses on how they and their peers navigated, researched, and advocated for care for BRCA mutations, these responses may have been influenced by membership in the groups themselves. For instance, the FORCE website describes the survival benefits of oophorectomies (FORCE, 2016), whilst Camp Kesem is only available to children whose parents have had cancer (Kesem, n.d.). Thus, participant perspectives may be most characteristic of women who exhibit proactive health-seeking behaviours and/or have undergone cancer treatment. Along the same lines, the sample did not include women who (1) never discovered they were at high risk for a BRCA mutation, (2) declined a referral to genetic services, (3) received a referral but declined testing, or (4) tested positive but declined all post-test interventions. Including participants who have declined or been denied the opportunity to obtain care is inherently difficult in all kinds of health research, and they would not have had much to contribute in terms of the process mapping exercise, but it is nonetheless a limitation not to have their perspectives in this project.

Another methodological choice that carried both advantages and disadvantages in the data collection and analysis process was the employment of both focus groups and interviews. As noted in Section 5.2.3, individual interviews were the only way that the clinical geneticists

and most US support group members could participate, but without attending a focus group, individuals could not compare their own process maps, thoughts, and experiences to those of their peers. In some situations, the intimacy of individual interviews may have facilitated deeper discussion of particularly sensitive topics, such as African American and Hispanic support group members talking about the role of race and ethnicity in receiving referrals. In other cases, though, interviewees may have given more comprehensive – and perhaps completely different – answers had they heard from other viewpoints during a focus group. To partially mitigate this concern, interview subjects were invited to compare their responses to their peers' anonymised responses when appropriate. For instance, 'Several other participants' process maps included the process of receiving referrals to genetic services from their GPs, but yours does not. Could you tell me how you ended up in genetic services, and whether you think your situation is representative of other women's experiences?'

Lambert and Loiselle (2008) also point out that whilst combining interview and focus group data may enhance overall data richness, the validity of the findings may be threatened if the two techniques are mixed improperly. The authors note that less work has been done on blending multiple qualitative research techniques than on blending qualitative and quantitative techniques; ultimately, they suggest that a framework be developed to guide this kind of mixed methods qualitative research. Specific to the present study, though, a few steps were taken to try to avoid biasing the results towards the data collected in the interviews. First, the interviews were considered tools that could increase data completeness, rather than vehicles to simply confirm focus group themes. Second, given the relative number of viewpoints involved, data from focus groups were weighted more heavily than data from each individual interview. Were this study to be extended, it would be interesting

to conduct both focus groups and interviews with each of the four participant groups to see how the findings changed, if at all, and to make broader methodological observations.

5.7 Summary

This chapter has painted a complex picture of how access to care for BRCA mutations may function in current clinical practice. American and British genetics professionals and support group members agreed on the general pathway patients follow to receive care, as well as certain barriers and facilitators affecting that pathway. Other responses were country-, role-, and person-dependent on topics such as how clinical guidelines and insurance interacted, what differentiates unnecessary and necessary care, and how race and ethnicity impact care, respectively. Throughout the course of discussion, participants also raised interesting ethical issues, especially the unintended negative consequences of creating new avenues to care and widening eligibility for existing avenues to care. In relation to the overall thesis, this chapter has ensured that all four dimensions of the Gulliford model of access to care have been explored through the critical review, scoping study, and/or empirical project.

6 Chapter Six: Discussion and conclusion

6.1 Introduction

This thesis has sought to answer the question, 'In which situations might it be problematic that American and British women do not access care for BRCA mutations?' Because BRCA mutations are linked to high rates of breast and ovarian cancer, the answer to this question is important for US and UK clinicians, patients and their families, insurers, and policymakers alike. Each of these stakeholders has a vested interest in preventing as many cancers as possible and diagnosing the cancers that cannot be prevented as early as possible. Genetic counselling and testing for BRCA mutations play a key role in early diagnosis and cancer prevention by enabling high-risk women to learn whether they need to consider enhanced surveillance and preventive measures. Women who test negative or receive VUS results do not need to pursue additional BRCA-related care unless their variants are later reclassified as harmful. Women who test positive are in a position to inform their family members that they are also at risk for HBOC and to consider counselling and testing themselves. Moreover, BRCA carriers with access to screening, medication, and/or surgery are also able to monitor their cancer statuses and possibly reduce their risks of HBOC.

Conversely, women at high risk for BRCA mutations who are unable to access counselling and testing cannot find out whether they would benefit from enhanced surveillance and preventive measures. Not only does this actively impede unidentified BRCA carriers from trying to prevent BRCA-related cancers or being vigilant about screening, but their family members also cannot be warned about their own risks for HBOC. Furthermore, some women access BRCA counselling and testing and are identified as BRCA carriers, only to find they cannot access post-test care to monitor or prevent BRCA-related cancers. These

women may be psychologically burdened by knowing they are at risk for HBOC but lack the resources to pursue appropriate carrier management options.

Given the scenarios above, determining the situations in which it is problematic for American and British women to lack access to care for BRCA mutations is unsurprisingly complicated. Which US and UK women *can* access care for BRCA mutations largely depends on whether GPs or oncologists judge women to be at high enough risk to merit referral to genetic services, but which women *do* access care for BRCA mutations also depends on a multitude of other factors. The laws, legal rulings, and policies defining the limits of genetic privacy and anti-discrimination protections affect whether eligible women pursue care; so too do many characteristics of high-risk women themselves and the healthcare systems in their communities. Chapters Three through Five of this thesis examined these factors through a critical review of regulatory mechanisms, a scoping study of factors affecting access to care, and an empirical study of focus groups and interviews on access to care with genetics professionals and support group members. This chapter builds on those three chapters' findings to accomplish three goals: (1) exploring how barriers to care may impede service availability in potentially problematic ways, (2) considering the most ethical approach to BRCA services in terms of relevance and effectiveness, and (3) examining how to enhance equity of access by redressing barriers to care. It ends by summarising similarities and differences between US and UK access to care, pointing out problematic cases in each country.

The 'Review of thesis methodology' section briefly overviews the methodological choices made in this thesis. It opens with a brief reminder of why the Gulliford model was selected, and it reviews the overall methodology and the specific approaches used in Chapters Three through Five. The section closes with a discussion of what ethical analysis means in this

chapter, drawing on the classic 'four principles' approach articulated by Beauchamp and Childress (2001).

In the 'Availability of services and potential barriers to care' section, barriers to care mentioned in Chapters Three through Five are organised based on the types of care they might impede. For non-referrals, non-uptake of counselling and testing, and non-uptake of carrier management options, barriers are divided in Tables 6.1 through 6.4 based on whether they are likely problematic or unproblematic, based on their evaluation through Beauchamp and Childress's approach.

This section is followed by a section on 'Relevance, effectiveness, and equity of access to services', which first explores the most ethical approach to providing BRCA services in terms of clinical and cost-effectiveness data. It then considers how to measure equity of access, as well as how specific facilitators and service improvements drawn from Chapters Three through Five may redress inequity of access.

Finally, this chapter closes with a 'Summary of country-based similarities and differences in access to care'. This section collates the comparisons made between access to care in the United States and United Kingdom throughout the thesis, and it explains which problematic cases are country-neutral and which are country-specific.

6.2 Review of thesis methodology

Because this thesis aims to explore whether there are cases in which it may be problematic that women do not access care for BRCA mutations, examining regulatory mechanisms alone would not be sufficient to capture the myriad reasons that women do not access care. Given that there is no universally accepted model of access to care, 10 multi-dimensional

models included in a systematic review of access by Levesque et al. (2013) were considered as possibilities. (Levesque et al. itself was also considered, but as it provided an unwieldy 10-dimensional supply-and-demand framework based on accessibility of services and abilities of users that the authors acknowledged would be difficult to operationalise, the sources informing that paper were considered more viable options.) After considering how these models aligned with my preliminary findings – gathered through interviews with genetics professionals, observational work, and other work surveying the cancer genetics communities – and the intention to compare access in the United States and United Kingdom, I ultimately selected the Gulliford model based on its incorporation of service availability, barriers, and facilitators; its recognition that both subjective and objective outcomes matter; and its emphasis on considering how different groups experience services.

Overall, the methodology of this thesis sought to use both theoretical and empirical approaches to examine what access looks like on paper (e.g., in regulatory mechanisms and in the literature) and how access functions in day-to-day practice. Thus, Chapter Three involved a critical review of four types of regulatory mechanisms, i.e., clinical guidelines, laws, legal rulings, and policies, which enabled analysis of availability and supply of services and organisational barriers to care. Chapter Four reported on a scoping study of factors that may affect access to care, which facilitated analysis of barriers to care, relevance and effectiveness of services for different patient groups, and equity of access. Chapter Five detailed an empirical study consisting of focus groups and interviews with American genetics professionals, British genetics professionals, American support group members, and British support group members. This small-scale project supported analysis of availability of services, barriers to care, and relevance and effectiveness of services.

As mentioned above, the present chapter, Chapter Six, is intended to tie together the thesis by applying ethical analysis to the findings of Chapters Three through Five and considering their broader implications. First, by examining how the availability of services intersects with potential barriers to care, Section 6.3 explores the question of whether there are cases in which it may be problematic that UK and US women do not access care for BRCA mutations. Each potential barrier identified in Chapters Three through Five is considered through the lens of the 'four principles' approach articulated by Beauchamp and Childress (2001), i.e., whether the potential barrier conflicts with respect for autonomy, beneficence, non-maleficence, and/or justice. 'Likely problematic' factors are those that conflict with at least one principle and therefore inhibit the ability of women at high risk for BRCA mutations to freely choose whether to pursue care, whilst 'likely unproblematic' factors do not conflict with any principles. Second, by considering how to evaluate and improve relevance and effectiveness of services for different patient groups and equity of access in general, Section 6.4 examines the question of how care for BRCA mutations can be most ethically provided. Three delivery models are debated in terms of clinical and cost effectiveness: family history-based assessment, population screening, and a combination of family history-based assessment and population screening for certain high-risk groups. Strategies for redressing the 'likely problematic' barriers identified in Section 6.3 within the preferred delivery model are then discussed, drawing on facilitators identified in Chapters Three through Five and the broader literature on genetic services and access to care. Finally, Section 6.5 summarises and discusses the country-based similarities and differences revealed throughout Chapters Three through Five and in Sections 6.3 and 6.4, considering where women are more likely to face certain problematic barriers and particularly benefit from certain facilitators.

6.3 Availability of services and potential barriers to care

This section organises and reflects on findings about the availability of services and the possible barriers to care identified and described in Chapters Three through Five. Three kinds of cases are examined: (1) cases in which women are not referred to genetic services, (2) cases in which women do not undergo counselling and testing, and (3) cases in which BRCA carriers do not elect certain types of post-test care. In each set of cases, potential barriers are separated based on whether they are 'likely unproblematic' or 'likely problematic' using the four principles articulated in Beauchamp and Childress (2001). In simple terms, respect for autonomy means allowing competent patients to freely make their own informed decisions; beneficence involves clinicians acting to benefit their patients; non-maleficence involves clinicians acting to avoid causing their patients harm; and justice means distributing resources fairly and treating similar patients equitably. If a barrier violates one or more principles, then it is likely problematic; and if it does not violate any principles, then it is likely unproblematic. For example, not having a strong family history of cancer is likely unproblematic: without a clear risk factor for a BRCA mutation, a woman typically has no reason to pursue or expect care, and a clinician – and more broadly, a healthcare system – has no reason to provide unnecessary care. So, too, is lack of interest in testing unproblematic: respect for autonomy means recognising that a high-risk woman has the right to make a free and informed choice not to pursue testing. On the other hand, it is likely problematic from both respect for autonomy and justice standpoints if a high-risk woman does not have access to primary care: an unequal distribution of health resources could prevent her from having the chance to decide whether to pursue genetic services. In sum, Sections 6.3.1 through 6.3.3 aim to distinguish between problematic barriers that truly hinder high-risk women from pursuing the care they want and need and unproblematic

'barriers' that actually reflect women (1) not needing care because they are not at high risk or (2) freely making informed decisions to decline care even though they are at high risk.

6.3.1 Cases in which women are not offered referrals to genetic services

In the first set of cases, women do not receive referrals to genetic services. These cases can be further divided into two kinds: women who are ineligible according to guidelines and women who are eligible according to guidelines but still do not receive referrals. Table 6.1 lists whether each potential barrier conflicts with one or more of Beauchamp and Childress' four principles, and the accompanying text in Sections 6.3.1.1 and 6.3.1.2 explains the evaluation of each identified barrier.

Table 6.1: Ethical principles in conflict with potential barriers to referral

Potential barrier	Respect for autonomy	Beneficence	Non-maleficence	Justice	Likely problematic?
No personal history of cancer	No	No	No	No	No
No/insufficient family history of cancer	No	No	No	No	No
Black racial identity	Yes	Yes	Yes	Yes	Yes
CMS guideline omission	Yes	No	No	Yes	Yes
Insufficient insurance*	Yes	No	No	Yes	Yes
Lack of clinician knowledge	Yes	Yes	Yes	No	Yes
Lack of education	Yes	No	No	Yes	Yes
Lack of HBOC discussion	Yes	Yes	Yes	No	Yes
Lack of internet access	Yes	No	No	Yes	Yes
Lack of patient knowledge	Yes	No	No	Yes	Yes
Lack of primary care access	Yes	No	No	Yes	Yes
Poor clinician-patient relationship	Yes	Yes	Yes	No	Yes
Uncritical use of guidelines	Yes	Yes	Yes	Yes	Yes
USPSTF guideline omission*	Yes	No	No	Yes	Yes

*Relevant only to US women. CMS = Centers for Medicare and Medicaid Services. HBOC = hereditary breast and ovarian cancer. USPSTF = United States Preventive Services Task Force.

6.3.1.1 Ineligible according to major guidelines

As Chapters Three and Five discussed, not meeting referral criteria usually means women are at low risk for BRCA mutations because they lack a personal or family history of cancer. Their inability to attend genetic services is a function of risk assessment working properly, does not violate any of Beauchamp and Childress's principles, and is therefore not the result of problematic barriers. However, Chapters Three and Five also touched on several situations in which strictly following guidelines may result in some women being denied beneficial care. First, privately insured US women, to whom the USPSTF (but not the CMS) guideline applies, are ineligible for referral if they are symptomatic of or in active treatment for a BRCA-related cancer. Second, publicly insured US women, to whom the CMS (but not the USPSTF) guideline applies, are ineligible for referral unless they have been diagnosed with breast and/or ovarian cancer. Third, some US and UK women are ineligible per guidelines but have compelling reasons to be referred.

For privately insured American women, the USPSTF guideline clearly states that women in treatment for BRCA-related cancer are not guaranteed fully covered BRCA testing (USPSTF, 2013). As explained in Chapter Three, this restriction exists because the scope of USPSTF guidelines includes preventive services but not disease management, and undergoing rapid BRCA testing to inform surgical decisions is considered the latter. (Moreover, there is a case for not making pure breast cancer management decisions based on BRCA testing, as the choice to undergo a mastectomy or a lumpectomy does not affect long-term morbidity or mortality caused by the existing cancer [Kurian et al., 2014; Veronesi et al., 2002].) The USPSTF overlooked several non-disease management reasons that cancer patients at high risk for BRCA mutations may wish to pursue testing, however. First, BRCA-positive breast cancer patients may elect mastectomies to concurrently treat their

existing cancer and reduce their risk of developing new cancers (Evans et al., 2005; Rosenberg et al., 2014; K. L. Smith & Isaacs, 2011). Second, BRCA-positive cancer patients may use the information to begin planning future preventive services, e.g., breast cancer patients electing oophorectomies and ovarian cancer patients electing mastectomies. Third, BRCA-positive cancer patients may not be able to benefit their families by sharing their test results if they die before being tested. In sum, the USPSTF guideline prevents privately insured American cancer patients from pursuing BRCA testing that can inform their own risk reduction options, as well as their families' options, and therefore institutionalises violations of respect for autonomy and justice.

Conversely, publicly insured American women are only eligible for BRCA testing if they have a personal history of breast and/or ovarian cancer (Noridian Healthcare Solutions, LLC, 2016). This requirement is a result of a Social Security Act restriction on CMS paying for most kinds of preventive care (Jacques, 2008; Segovis, 2015). In general, this restriction helps contain the costs of government-funded care by avoiding the provision of unnecessary services; this is analogous to how the NICE, NCCN, and USPSTF guidelines control costs by recommending BRCA testing to only high-risk women. As discussed in Chapters Three and Five, it is also standard practice to test affected family members before unaffected family members whenever possible. However, the CMS restriction extends beyond that reasonable requirement to prevent any unaffected women with family histories of HBOC – even those with known familial mutations – from pursuing genetic testing. As a result, high-risk women cannot pursue risk reduction procedures to prevent their first incidence of cancer at all; testing can only be done in time to prevent additional cancers. Identified BRCA carriers are also encouraged to share their test results with their relatives so that their relatives have the option to pursue testing. The CMS restriction therefore directly prevents unidentified BRCA carriers and indirectly prevents their family members from pursuing any

desired testing or risk reduction options; as in the above situation, this restriction impedes respect for autonomy and justice.

Finally, for a subset of guideline-ineligible US and UK women, their lack of referral may be the result of clinicians failing to consider their patients' cases holistically. On the one hand, there are clinical and economic reasons for clinicians to follow guidelines and avoid referring too many low-risk women. Inappropriate referrals will increase wait times in genetic services at the expense of women who are clearly at high risk, as well as typically require the NHS (UK) or the patients and insurers (US) to pay for unnecessary services. On the other hand, guidelines are meant to be interpreted using the clinical judgment referenced in Chapters Three and Five, not followed uncritically. For instance, a publicly insured American patient who is at high risk for a BRCA mutation but has no personal history of cancer may request a referral. If the patient understands that she may be billed for the full costs of counselling and testing because she does not meet referral criteria, there seems little reason for her doctor not to respect her autonomy and promote justice by referring her. Similarly, a 42-year-old British breast cancer patient who is adopted and unable to confirm her family history of cancer does not explicitly meet NICE criteria. If she does not receive a referral from her oncologist, it may be because her oncologist did not weigh the limited information available when making her decision, thereby failing to promote beneficence and avoid non-maleficence. A third example comes from Chapter Five: If a low-risk, privately insured woman is consumed by anxiety over her unknown BRCA status, denying her the opportunity to attend genetic services may be poor clinical practice. Overall, these cases show violations of all four principles and underscore why clinicians should use guidelines to guide care, but not to the exclusion of patients' individual circumstances.

Of the three situations discussed above, all constitute problematic organisational barriers to care. The USPSTF and CMS restrictions clearly prevent some high-risk American women from receiving referrals. More broadly, uncritical acceptance of any clinical guideline may result in some American and British women being denied beneficial care and reinforce systemic inequalities.

6.3.1.2 Eligible according to major guidelines

As noted in Chapters Three through Five, referrals are an important entryway to care: British women can only access NHS-provided genetic services with referrals, and American women either need referrals or insurance policies permitting self-referrals. However, some eligible women may not receive referrals because of certain clinician behaviours or patient characteristics that interfere with high-risk women retaining autonomy over their care.

In terms of clinician behaviours, three barriers were identified that may affect whether a clinician gives a referral. Referrals are likely to be limited if a clinician does not initiate a discussion about HBOC (Chapter Five) or if a poor clinician-patient relationship precludes a patient from bringing up her family history (Chapters Four and Five). A clinician's lack of knowledge of cancer genetics may also translate to unfamiliarity with clinical guidelines, which would likely reduce referrals (Chapters Four and Five). In all three cases, these behaviours violate both the clinician's duty to be beneficent and non-maleficent and the patient's ability to make a freely informed choice about care.

In terms of patient characteristics, six barriers affect whether a patient is in a position to be offered a referral. Not having access to primary care (Chapters Three and Five), which may be associated with a lack of insurance in American women (Chapters Three through Five), typically precludes a patient from being referred to specialty services. A lack of knowledge

about cancer genetics may prevent a woman from bringing up her family history of cancer and enquiring about a referral (Chapters Four and Five). Relatedly, a lack of internet access (Chapter Five) and a lack of education (Chapters Four and Five) may limit a woman's ability to research and understand what BRCA mutations are and why they might matter. In all five cases, these characteristics reflect systemic inequality (justice violations) and diminished ability to pursue care (respect for autonomy violations). Lastly, two US support group members felt that being Black meant they were less likely to be offered referrals than other women (Chapter Five). Their statements suggest both systemic inequality and unequal treatment from individual clinicians that impact Black women's ability to elect care, representing violations of all four principles.

To summarise, each of these nine barriers is likely problematic, as each violates respect for autonomy and at least one other principle. Black racial identity is the only barrier in which all four principles are violated, however, which makes it particularly troubling.

6.3.2 Cases in which women do not undergo counselling and testing

In this second set of cases, eligible women who have been referred to genetic services do not undergo counselling and testing. Potential barriers to counselling and testing primarily arose in Chapters Four and Five, with a few possible barriers also coming from Chapter Three. Table 6.2 lists whether each potential barrier conflicts with one or more of Beauchamp and Childress' four principles. As in the previous section, the accompanying text in Sections 6.3.2.1 and 6.3.2.2 explains the evaluation of each identified barrier.

Table 6.2: Ethical principles in conflict with potential barriers to counselling and testing

Potential barrier	Respect for autonomy	Beneficence	Non-maleficence	Justice	Likely problematic?
Competing life concerns	No	No	No	No	No
High religiosity/spirituality	No	No	No	No	No
Lack of interest in testing	No	No	No	No	No
Low actual risk of mutation	No	No	No	No	No
Low cancer-related distress	No	No	No	No	No
Low decisional conflict	No	No	No	No	No
Low perceived mutation risk	No	No	No	No	No
Negative attitude to testing	No	No	No	No	No
No children	No	No	No	No	No
No family member tested	No	No	No	No	No
No personal history of cancer	No	No	No	No	No
No/insufficient family history of cancer	No	No	No	No	No
Young age	No	No	No	No	No
Anticipated negative reactions	Yes	No	No	No	Yes
Anxiety	Yes	No	No	No	Yes
Black racial identity	Yes	Yes	Yes	Yes	Yes
Concerns about stigma	Yes	No	No	Yes	Yes
Family-related guilt	Yes	No	No	No	Yes
Hispanic ethnicity	Yes	Yes	Yes	Yes	Yes
Insufficient income	Yes	No	No	Yes	Yes
Insufficient insurance*	Yes	No	No	Yes	Yes
*Relevant only to US women.					

Table 6.2: Ethical principles in conflict with potential barriers to genetic counselling and testing (continued)

Potential barrier	Respect for autonomy	Beneficence	Non-maleficence	Justice	Likely problematic?
Insufficient resources	Yes	No	No	Yes	Yes
Issues with family history forms	Yes	No	No	No	Yes
Lack of education	Yes	No	No	Yes	Yes
Lack of familial support	Yes	No	No	No	Yes
Lack of patient knowledge	Yes	Yes	Yes	No	Yes
Lack of patient navigation	Yes	Yes	Yes	No	Yes
Lack of time	Yes	No	No	Yes	Yes
Language barriers	Yes	Yes	Yes	Yes	Yes
Limited legal protections*	Yes	No	No	Yes	Yes
Low family hardiness	Yes	No	No	No	Yes
Low self-efficacy	Yes	No	No	No	Yes
Medical mistrust	Yes	Yes	Yes	Yes	Yes
No clinician recommendation	Yes	Yes	Yes	No	Yes
No clinician referral	Yes	Yes	Yes	Yes	Yes
Poor clinician-patient communication	Yes	Yes	Yes	No	Yes
Poor clinician-patient relationship	Yes	Yes	Yes	No	Yes
Social deprivation	Yes	No	No	Yes	Yes
Unhelpful location	Yes	No	No	Yes	Yes
*Relevant only to US women.					

6.3.2.1 Barriers to counselling and testing that are likely unproblematic

Of the 13 items that fit under this heading, several simply reflect decisions made because of a woman's actual risk of a BRCA mutation and/or cancer. First, a low-risk woman (Chapters Three and Five), who usually has no personal history of cancer and/or a weak family history of cancer (Chapter Four), usually does not need to undergo testing unless there are compelling individual circumstances. Second, a woman's low perceived risk of a BRCA mutation (Chapter Four) is not an issue if she is at low actual risk; if she is at high actual risk, though, it may be an infringement on respect for her autonomy and a breach of her clinician's responsibility to be beneficent and non-maleficent because she is not properly informed. Third, it is not problematic for a woman's relatives not to have been tested (Chapters Four and Five) if there was no reason to think they were at risk for BRCA mutations or if they chose not to be tested. If they were not offered testing and they were clearly at high risk, though, their relatives would have been inappropriately denied care.

Other traits correlated with not testing may simply indicate that testing is less relevant for some women than others; moreover, respecting autonomy means accepting that informed patients may decline or defer testing as they wish. For instance, lack of interest in testing (Chapter Five), negative attitudes to testing (Chapters Four and Five), and low levels of cancer-related distress (Chapter Four) may not be barriers so much as personal preferences about pursuing genetic information. Similarly, low decisional conflict (Chapter Four) may suggest a woman has already settled on her breast cancer treatment plan and therefore wishes to decline testing, and a highly spiritual/religious woman may refuse testing if it conflicts with her personal beliefs. Younger women unaffected by cancer and/or women without children (Chapter Four), as well as women with competing life concerns (Chapters

Four and Five), may also decide to delay testing until they are ready to act on the information; these generally qualify as life circumstances rather than barriers.

In sum, the characteristics described above are likely reflective of patients being at low risk or exercising their autonomy to defer or decline testing; thus, these cases are unlikely to be barriers at all, as long as the women are freely making informed choices.

6.3.2.2 Barriers to counselling and testing that are likely problematic

Many more systemic and patient-specific barriers – 26 in all – seem likely to impede a woman's ability to choose whether to attend counselling and undergo testing in a problematic way. Systemic organisational barriers include unhelpful clinician behaviours, insufficient legal protections, and inadequate resources for genetic services. Patient-specific personal and financial barriers include various psychosocial, awareness, and demographic characteristics.

Ten barriers involved violations of respect for autonomy, beneficence, and non-maleficence, meaning that individual clinicians' behaviour affected their patients' abilities to pursue counselling and testing. Most obviously, lack of clinician referral (Chapters Three through Five) violates all four of Beauchamp and Childress's principles: Women cannot elect care that is not offered, and there are systemic disparities in terms of which women receive referrals. Relatedly, five barriers from Chapters Four and Five – lack of patient knowledge, clinician recommendations, and patient navigation, as well as poor clinician-patient relationships and communication – may lead to women declining genetic services without understanding why genetic services may be important for them. Social and cultural factors – medical mistrust, Black racial identity, Hispanic ethnicity, and language barriers – round out this list. All four barriers represent systemic justice issues in addition to challenges to respect

for autonomy and with individual clinicians' duties to promote beneficence and practise non-maleficence by appropriately tailoring care to meet patient needs.

Another nine barriers breached both respect for autonomy and justice, i.e., the barriers affected patients' abilities to make informed choices and could lead to systemic disparities. Insufficient insurance (Chapters Three through Five) may render the cost of genetic services unaffordable for American women, whilst insufficient income (Chapters Four and Five) may put genetic services out of reach for both US and UK women, e.g., if the cost of missing work is too high. Insufficient resources (Chapters Three and Five) may constrain the ability of genetic services to serve prospective patients, e.g., increased patient volumes have increased UK wait times and CMS restrictions have led to a scarcity of US counsellors. Limited legal protections for American BRCA carriers do not permit them to buy life, disability, or long-term care insurance or work in a company with fewer than 15 employees without fear of discrimination (Chapters Three and Five). Likewise, concern about stigma, lack of education and time, social deprivation, and unhelpful location are societal factors constraining women's abilities to pursue care individually and systemically, e.g., worry that they might be blamed for their test results by uneducated people. All five factors arose in Chapters Four and Five except for social deprivation, which was only in Chapter Four.

The final seven barriers violate only respect for autonomy, as they affect individual women's abilities to elect care but are not hindered by individual clinician behaviour or particularly systemic issues. For instance, trouble filling out family history forms (Chapter Four), which is usually a prerequisite to attending a genetic service appointment, may discourage some women from attending genetic services. Also, women preoccupied by how their families or they themselves may handle test results may have clouded judgment about using genetic services. Specifically, patients who express family-related guilt, lack of familial support, low

family hardiness, anxiety, anticipation of negative emotions, or low self-efficacy (all in Chapters Four and Five) may decline testing without really thinking through its relevance.

Overall, the likely problematic barriers to genetic services include organisational reasons why women may struggle to attend counselling and undergo testing, as well as myriad social, cultural, and financial barriers that explain why women may decline genetic services for reasons beyond informed choice. The barriers involving violations of all four principles – lack of referrals, medical mistrust, Black racial identity, Hispanic ethnicity, and language barriers – are once again particularly troubling.

6.3.3 Cases in which women test positive, but do not elect post-test care

In the third and final set of cases, women who been identified as BRCA carriers do not elect certain forms of post-test care, i.e., screening, medication, and surgery. Potential barriers to post-test care primarily came up in Chapters Four and Five, with a single barrier emerging in Chapter Three. As in the counselling and testing sub-section, identified barriers are divided based on whether they seem more likely to affect post-test care decisions in problematic or unproblematic ways. Table 6.3 lists whether each potential barrier conflicts with one or more of Beauchamp and Childress' four principles. As in the previous two sections, the accompanying text in Sections 6.3.3.1 and 6.3.3.2 explains how barriers were evaluated.

Table 6.3: Ethical principles in conflict with potential barriers to post-test care

Potential barrier	Respect for autonomy	Beneficence	Non-maleficence	Justice	Likely problematic?
BRCA mutation type	No	No	No	No	No
Competing life concerns	No	No	No	No	No
Low actual risk of cancer	No	No	No	No	No
Low cancer-related distress	No	No	No	No	No
Low decisional conflict	No	No	No	No	No
Low perceived ovarian cancer risk*	No	No	No	No	No
Low perceived screening use	No	No	No	No	No
No children	No	No	No	No	No
No multidisciplinary care	No	No	No	No	No
No oophorectomy intent*	No	No	No	No	No
No personal history of cancer	No	No	No	No	No
No/insufficient family history of cancer	No	No	No	No	No
Not married	No	No	No	No	No
Oral contraceptive use	No	No	No	No	No
Short counselling session	No	No	No	No	No
Young age	No	No	No	No	No
Absence of guidelines*	Yes	Yes	Yes	Yes	Yes
Anxiety	Yes	No	No	No	Yes
Black racial identity	Yes	Yes	Yes	Yes	Yes
Clinician practice*	Yes	Yes	Yes	Yes	Yes
*Relevant only to American women.					

Table 6.3: Ethical principles in conflict with potential barriers to post-test care (continued)

Potential barrier	Respect for autonomy	Beneficence	Non-maleficence	Justice	Likely problematic?
Hispanic ethnicity	No	Yes	Yes	Yes	Yes
Insufficient income	Yes	No	No	Yes	Yes
Insufficient insurance*	Yes	No	No	Yes	Yes
Insufficient resources	Yes	No	No	Yes	Yes
Lack of familial support	Yes	No	No	No	Yes
Lack of patient knowledge	Yes	Yes	Yes	No	Yes
Lack of patient navigation	Yes	Yes	Yes	No	Yes
Lack of support groups	Yes	Yes	Yes	Yes	Yes
Lack of time	Yes	No	No	Yes	Yes
Low confidence in overcoming barriers	Yes	No	No	No	Yes
No clinician recommendation	Yes	Yes	Yes	No	Yes
No genetics consultation	Yes	Yes	Yes	Yes	Yes
No post-surgery psychological counselling	Yes	Yes	Yes	Yes	Yes
Poor clinician-patient relationship	Yes	Yes	Yes	No	Yes
Rigid surgical guideline use	Yes	Yes	Yes	Yes	Yes
Unhelpful location	Yes	No	No	Yes	Yes
*Relevant only to American women.					

6.3.3.1 Barriers to post-test care that are likely unproblematic

As in Sections 6.3.1 and 6.3.2, some of the 16 items in this category reflect the reality that not all post-test care is equally necessary, especially for lower-risk carriers. For instance, it makes sense that BRCA carriers at lower risk for breast cancer are less likely to pursue mastectomies than their higher-risk counterparts (Chapter Four). Likewise, BRCA carriers with weaker family histories of cancer and/or no personal histories of cancer (Chapters Four and Five) may elect post-test care less frequently because they have lower mutation penetrance. The Chapter Four observation that BRCA2 carriers are less likely to undergo oophorectomies than BRCA1 carriers may be explained by BRCA2 carriers typically being at lower risk of ovarian cancer than BRCA1 carriers. Another Chapter Four finding, the association of low perceived risk of ovarian cancer with declination of oophorectomy, is unproblematic as long as the woman accurately understands her actual risk.

Furthermore, women are not obligated to pursue recommended courses of action, so there is nothing problematic about a woman knowingly rejecting post-test care. A number of possible barriers introduced in Chapter Four simply indicate that post-test care may not be especially relevant or helpful to some BRCA carriers. For example, younger BRCA carriers may not be ready to consider permanent surgical procedures or even breast screening. Single and/or childless BRCA carriers, as well as oral contraceptive users who may have delayed childbearing, may wish to put off oophorectomy in particular until they have completed their families. Women with low cancer-related distress, low decisional conflict, competing life concerns, low perceived use for screening, or no intent to have oophorectomies should all be at liberty to decline care as long as they are fully informed.

Two final potential barriers dealt with how care is organised: A lack of multidisciplinary care was viewed as a general barrier to post-test care (Chapter Five), and shorter counselling sessions were associated with lower MRI uptake (Chapter Four). As long as women are appropriately orientated towards post-test care and armed with adequate information, the manner of delivery does not matter.

In sum, factors associated with declination of post-test care are not problematic when they reflect women knowingly rejecting post-test care, which sometimes happens because women have low-penetrance BRCA mutations. Additionally, differentially organised care is unproblematic as long as the quality is equivalent.

6.3.3.2 Barriers to post-test care that are likely problematic

Out of 20 barriers to post-test care that seem likely to be problematic, 13 were previously identified as barriers to counselling and testing. Organisational barriers include unhelpful clinician behaviours and healthcare system structures, whilst patient-specific personal and financial barriers involve various psychosocial, awareness, and demographic characteristics.

A dozen barriers involved violations of respect for autonomy, beneficence, and non-maleficence. Four repeated barriers arising in Chapters Four and Five were incompatible or absent clinician recommendations, poor clinician-patient relationships, and lack of patient navigation and knowledge; these items may indicate that clinicians have not adequately prepared their patients to accept or decline screening, medication, and/or surgery. Black racial identity and Hispanic ethnicity were also mentioned again in Chapter Four as characteristics associated with low uptake of oophorectomy, and as before, these systemic disparities also suggest possible justice violations. The remaining six barriers were new, and three concerned the presence and interpretations of guidelines. American women may find

the absence of USPSTF and CMS post-test care guidelines (Chapters Three and Five) affects which care their clinicians recommend and for which their insurers will pay, thereby constraining some of their choices and creating systemic disparities. American clinicians not offering twice-yearly CBE prevent women from deciding whether to follow the NCCN's CBE recommendation, although as Chapter Three discussed, there is no evidence that CBE reduces morbidity or mortality. Both American and British women may find their guideline-recommended management options limited if their surgeons object to operating on high-risk women at extreme ages (Chapter Five). Not consulting with genetics professionals (Chapters Four and Five) may leave BRCA carriers ill-equipped to make post-test care decisions and exacerbate systemic inequalities in genetic services. Lack of support groups and post-surgery psychological counselling (Chapter Five) also may affect BRCA carriers trying to cope with their positive test results in healthy ways and worsen outcomes

Five repeat factors breached respect for autonomy and justice. Insufficient resources (Chapters Three and Five) may limit which kinds of post-test care eligible women can elect, e.g., if there is variation in MRI availability. Once again, insufficient insurance (Chapters Three and Five) may constrain American women's post-care choices, and insufficient income (Chapters Four and Five) may hinder both American and British women's ability to afford out-of-pocket expenses. Lack of time and unhelpful locations, both discussed in Chapters Four and Five, round out the list of items that limit individual choice and manifest as systemic disparities.

The final three barriers only violated respect for autonomy. Two repeat barriers, anxiety (Chapters Four and Five) and lack of familial support (Chapter Five), and one new barrier, lack of confidence in overcoming barriers (Chapter Four), all hinder women's abilities to make decisions freely.

Overall, the likely problematic barriers to post-test care include organisational restrictions inside and outside of genetic services, as well as repeated social, financial, and cultural factors that arose in Sections 6.3.1 and 6.3.2. The barriers involving violations of all four principles – Black racial identity, Hispanic ethnicity, absence of post-test care guidelines, clinicians not offering CBE, rigid surgical guideline adherence, and lack of support groups, genetics consultations, and post-surgery psychological counselling – are once again particularly troubling.

6.3.4 Summary

Sections 6.3.1 through 6.3.3 reported the various barriers identified in Chapters Three through Five, separating them as 'likely unproblematic' and 'likely problematic' based on whether they violated any of Beauchamp and Childress's four principles. In practice, this delineation separated cases in which care was unnecessary or undesired from cases in which care was necessary and desired. Table 6.4 on the next page summarises the results of Sections 6.3.1 through 6.3.3, with items underlined if they occur across referral, counselling and testing, and post-test care. The two likely unproblematic factors occurring across all three domains are no personal history of cancer and no/insufficient family history of cancer, which makes sense given that risk of BRCA mutations is based on those two factors (Petrucelli et al., 2013). The four likely problematic factors occurring across all three domains are Black racial identity, lack of patient knowledge, poor clinician-patient relationships, and for American women, insufficient insurance. These four factors make sense given the systemic disparities in White and Black women accessing genetic services (Allford et al., 2014), the role that insurance plays in American healthcare (Roe & Liberman, 2007), and the importance of communication and pre-existing knowledge in facilitating patients' awareness and use of genetic services (Beene-Harris et al., 2007).

Table 6.4: Summary of likely problematic and likely unproblematic barriers identified in Chapters Three through Five

	Referral	Counselling and testing		Post-test care	
Likely unproblematic	No PH of cancer	Competing life concerns	Negative attitude to testing	BRCA mutation type	No multidisciplinary care
	No/insufficient FH of cancer	High religiosity/spirituality	No children	Competing life concerns	No oophorectomy intent*
		Lack of interest in testing	No family member tested	Low actual risk of cancer	No PH of cancer
		Low actual risk of mutation	No PH of cancer	Low cancer-related distress	No/insufficient FH of cancer
		Low cancer-related distress	No/insufficient FH of cancer	Low decisional conflict	Not married
		Low decisional conflict	Young age	Low perceived OC risk*	Oral contraceptive use
		Low perceived mutation risk		Low perceived screening use	Short counselling session
				No children	Young age
Likely problematic	Black racial identity	Anticipated negative reactions	Lack of patient navigation	Absence of guidelines*	Lack of patient navigation
	CMS guideline omission*	Anxiety	Lack of time	Anxiety	Lack of support groups
	Insufficient insurance*	Black racial identity	Language barriers	Black racial identity	Lack of time
	Lack of clinician knowledge	Concerns about stigma	Limited legal protections*	Clinician practice*	Low confidence in OV BAR
	Lack of education	Family-related guilt	Low family hardiness	Hispanic ethnicity	No clinician recommendation
	Lack of HBOC discussion	Hispanic ethnicity	Low self-efficacy	Insufficient income	No genetics consultation
	Lack of internet access	Insufficient income	Medical mistrust	Insufficient insurance*	No post-surgery PSY COUN
	Lack of patient knowledge	Insufficient insurance*	No clinician recommendation	Insufficient resources	Poor CLIN-PT relationship
	Lack of primary care access	Insufficient resources	No clinician referral	Lack of familial support	Rigid surgical guideline use
	Poor CLIN-PT relationship	Issues with FH forms	Poor CLIN-PT COMM	Lack of patient knowledge	Unhelpful location
	Uncritical use of guidelines	Lack of education	Poor CLIN-PT relationship		
	USPSTF guideline omission*	Lack of familial support	Social deprivation		
		Lack of patient knowledge	Unhelpful location		
	*Relevant only to American women. BRCA = breast cancer susceptibility genes 1 and 2. CLIN-PT = clinician-patient. CMS = Centers for Medicare and Medicaid Services. COMM = communication. FH = family history. HBOC = hereditary breast and ovarian cancer. OC = ovarian cancer. OV BAR = overcoming barriers. PH = personal history. PSY COUN = psychological counselling. USPSTF = United States Preventive Services Task Force.				

6.4 Relevance, effectiveness, and equity of access to services

In a perfect world, all currently unidentified BRCA carriers who have a strong family history of cancer would have the opportunity to receive a referral to genetic services; undergo genetic counselling and genetic testing, if they so choose; and subsequently elect their preferred BRCA carrier management options, if appropriate. As the previous section showed, though, potentially problematic barriers preventing high-risk women from utilising available services for BRCA mutations are widespread. Thus, it is unrealistic to assume every BRCA carrier will be identified under current risk-based assessment models, or that identified BRCA carriers will have the opportunity to pursue appropriate interventions. This reality raises important questions: Is it most ethical to prioritise the provision of BRCA services to (1) only the women individually identified as being at high risk; (2) a combination of women individually identified as being at high risk and certain groups of women who are, based on established research, likely to be at high risk; or (3) all women? Are certain barriers worthier of being addressed than others? Translated into the language used in Gulliford et al. (2002), how should relevance and effectiveness of services for different patient groups and equity of access be approached, measured, and improved?

6.4.1 Which approach to BRCA services should be used?

As discussed in detail in Chapter Three, both the United States and United Kingdom currently use risk assessment to determine which women should receive referrals to genetic services and gain access to counselling, testing, and post-test care. (There are, of course, some country-based differences in how genetic services and post-test care are organised and financed, how much clinician referrals dictate care, and how major guidelines are written and used in practice.) Clinicians aim to refer women with a significant family and/or

personal history of breast, ovarian, and a handful of related cancers, as that patient presentation is associated with familial BRCA mutations. Care for BRCA mutations is generally made both clinically effective and cost-effective by targeting the women most likely to have familial BRCA mutations for referral to genetic services; counselling and testing are subsequently offered to high-risk candidates, and appropriate post-test care is offered to identified carriers. However, barriers such as those described in the previous section may affect whether and how women pursue such care.

6.4.1.1 Population screening

In contrast, population screening, which was briefly discussed in Chapter Five, involves offering BRCA testing to all women in a given population. Neither the USPSTF nor the UK NSC has explicit numeric criteria, e.g., for sensitivity (rate of true positives) or specificity (rate of true negatives), that determine if a type of screening should be offered. However, Public Health England's criteria for population screening programmes include 'There should be a simple, safe, precise and validated screening test' and 'There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity' (2015b). It may therefore be useful to consider some data on mammography, a type of population screening recommended by both the USPSTF and UK NSC and discussed in Chapter Three. In systematic reviews commissioned by the USPSTF, researchers reported that mammography has a sensitivity between 77 and 95 per cent and a specificity between 94 and 97 per cent, as well as an estimated mortality benefit between 25 and 31 per cent (Humphrey, Helfand, Chan, & Woolf, 2002; Nelson et al., 2016). An independent panel commissioned by the Department of Health (England) reported a slightly lower mortality benefit of 20 per cent but a higher estimated sensitivity and specificity at 97 per cent each (Marmot et al., 2013). (As explained in Chapter Three, these different figures can be attributed to differences in which evidence was considered.)

Specific to population screening for genetic disorders, two additional resources provide helpful benchmarks. The first resource is a *New England Journal of Medicine* review article called 'Population screening in the age of genomic medicine'. The authors devote a section to population screening for genetic susceptibility for common diseases, among them hereditary hemochromatosis:

> Many consider hereditary hemochromatosis to be the key example of the need for population screening in the genomic era, but gaps in our knowledge preclude the recommendation of population screening for this disorder … The [CDC/NHGRI] panel concluded that population genetic testing for mutations in HFE, the gene for hereditary hemochromatosis, could not be recommended because of uncertainty about the natural history of the disease, age-related penetrance, optimal care for persons without symptoms who are found to carry mutations, and the psychosocial impact of genetic testing. (Khoury, McCabe, & McCabe, 2003, p. 54)

This CDC/NHGRI panel recommendation provides a set of conditions to consider when evaluating the suitability of population screening for HBOC. The second resource is a guideline from the UK-based Association for Clinical Genetic Science [ACGS], which issued its 'Practice guidelines for targeted next generation sequencing analysis and interpretation' in 2014. The group wrote that in order to replace a high-accuracy Sanger sequencing test, next-generation sequencing must be highly sensitive; in fact, the clinicians recommended a sensitivity threshold of 95 per cent (Ellard et al., 2014). This suggested threshold provides another yardstick against which population screening can be considered.

Mary-Claire King, who spearheaded the discovery of the BRCA1 gene in 1990, co-authored a *JAMA* viewpoint article arguing that all American women should be offered BRCA testing around age 30 as part of routine care (King, Levy-Lahad, & Lahad, 2014). Identified carriers, the authors suggested, could then pursue risk-reducing interventions before developing cancer. Providing BRCA testing in routine care would address certain barriers to genetic services, especially those barriers associated with receiving referrals. However, the data that King et al. drew on to support their proposal involved an AJ population in Israel, which

makes their argument less convincing when applied to American and British populations of all ethnicities. This is because AJ patients are more likely to have BRCA mutations than non-AJ patients, and moreover, the vast majority of harmful mutations found in AJ patients are limited to the three founder mutations (Rosenthal, Moyes, Arnell, Evans, & Wenstrup, 2015). Notably, King et al.'s proposal did not account for the clinical effectiveness of population screening in a non-AJ population, nor did it address the cost-effectiveness of population screening at all. The next few paragraphs describe studies investigating these aspects of population screening.

Warren-Gash, Kroese, Burton, and Pharoah (2016) simulated the effect of population screening using whole-genome sequencing in a hypothetical group of 100,000 British women. Four key metrics were reported in the study: identified BRCA mutations, prevented cancers, unnecessary interventions, and missed cancers. Per the model, whole-genome sequencing correctly identified 244 out of 320 pathogenic mutations, e.g., it had roughly 76 per cent sensitivity. Of those identified carriers, 132 were predicted to develop breast cancer; thus, if all identified carriers pursued interventions, population screening could have prevented 132 cancers whilst leading 112 women to undergo unnecessary interventions. Additionally, 41 unidentified BRCA carriers predicted to develop breast cancer would not have the opportunity to pursue interventions beyond population screening.

These particular results argue against using whole-genome sequencing in wholly unselected populations for a few reasons. First, whole-genome sequencing did not correctly identify an acceptable percentage of mutations. Whilst this model's 76 per cent sensitivity falls far below the ACGS's recommended sensitivity threshold of 95 per cent (Ellard et al., 2014), sensitivity estimates for comprehensive BRCA-specific testing are reliably north of 95 per cent (CDC, 2003). Second, it is currently difficult to predict how BRCA mutations affect

women with no family history of BRCA-related cancer, which was one of the CDC/NHGRI panel's reasons for not recommending population screening for hereditary hemochromatosis. This is because BRCA mutations are predispositional, not presymptomatic: The presence of a mutation alone does not determine if a woman will develop cancer. It is typically the combination of a mutation and a family history of BRCA-related cancer that suggests a mutation is actually harmful. Thus, it seems problematic to have 46 per cent of identified carriers undergo unnecessary interventions without even knowing if or how those mutations have increased their cancer risks.

Long and Ganz (2015) modelled the cost-effectiveness of universal screening using Myriad's comprehensive BRCA-specific test, which they estimated cost USD 4,000. Key metrics included prevented cancers, life years saved, and cost per quality-adjusted life year gained. For every 10,000 women tested, Long and Ganz predicted that compared to family history-based screening, universal screening would prevent an additional four breast cancers and two ovarian cancers. However, preventing these cancers would only increase those women's lives by two days, meaning the cost per quality-adjusted life year (QALY) gained would be an astronomical USD 1.7 million. (For context, the commonly used American cost-effectiveness threshold is USD 50,000 per QALY, whilst the accepted NICE threshold is between GBP 20,000 and 30,000 per QALY (NICE, 2013c; Neumann, Cohen, & Weinstein, 2014).) These findings suggest that universal screening may only become worthwhile if the cost of testing drastically decreases, and even then, the minute gains in life span for women without a family history of BRCA-related cancer may not be worth it.

To summarise, the status quo is to continue using family history-based risk assessment to guide testing, recognising that myriad barriers – including lack of patient and clinician knowledge and referrals – may prevent patients from accessing testing. The opposite of

targeted family history-based screening is population screening, which removes the issues of lack of patient knowledge and referrals and lessens the barrier of clinician knowledge. Combining the findings of the Warren-Gash et al. (2016) and Long and Ganz (2015) papers, however, neither whole-genome sequencing nor comprehensive BRCA-specific testing is suitable for universal use from a clinical and cost-effectiveness standpoint.

This is not to say that population screening for HBOC will remain infeasible, however, particularly when techniques besides whole-genome sequencing are considered. For instance, D'Argenio et al. (2015) reported that next-generation sequencing-based panel testing detected BRCA mutations with nearly 100 per cent sensitivity and 100 per cent specificity, which obviously exceeds the ACGS-recommended sensitivity threshold of 95 per cent. Also relevant are polygenic risk scores, or estimates of genetic effects across multiple markers (Dudbridge, 2013), which have been used for nearly a decade to model breast cancer risk (Machiela et al., 2011; Pharoah, Antoniou, Easton, & Ponder, 2008; Witte & Hoffmann, 2011). In the coming years, these scores may be better able to predict breast cancer risk in women without family histories of BRCA-related cancer, thus alleviating one of the CDC/NHGRI panel's major concerns. If the various criteria discussed earlier are satisfied – i.e., if (1) randomised controlled trials of panel testing in unselected populations demonstrate mortality or morbidity benefit, (2) the penetrance of BRCA mutations in women without family histories of HBOC is better understood through polygenic risk scores, and (3) models suggest panel testing would be cost-effective – then population screening for HBOC may indeed be appropriate.

6.4.1.2 Family history-based screening plus targeted population screening

A middle ground between these two screening approaches involves complementing family history-based screening with targeted population screening of certain high-risk groups. For instance, women whose ancestries are associated with high prevalence of BRCA mutations – e.g., AJ, Norwegian, Dutch, and Icelandic (NCI, 2015) – could all be offered testing. Likewise, some researchers advocate testing all ovarian cancer patients because of the high percentage of ovarian cancer patients with BRCA mutations and the potential to tailor treatments for those patients, a stance the NCCN guideline echoes (George et al., 2016; Høberg-Vetti et al., 2016; NCCN, 2016b). (Tumour profiling, which detects somatic mutations in tumour tissue, cannot currently replace the germline BRCA testing discussed throughout this thesis, but it can inform treatment selection and patient expectations [AstraZeneca ID-BRCA, 2015; Frey & Pothuri, 2017; Myriad Genetics, n.d.]. For instance, Hennessy et al. [2010] found that tumour testing could help predict which patients would benefit from PARP inhibitor trials, and Pennington et al. [2014] reported that somatic BRCA mutations are predictive of overall survival and platinum chemotherapy responsiveness. In the future, Frey and Pothuri [2017] suggest, clinicians may use tumour profiling to screen all ovarian cancer patients, either in lieu of germline BRCA testing altogether or as a form of 'triage' to determine who should be offered germline BRCA testing.) In theory, this strategy could alleviate some clinical and cost-effectiveness concerns related to population screening whilst reducing some barriers associated with current family history-based risk assessment.

Helpful in considering this hybrid testing strategy is a recent systematic review of the cost-effectiveness of different testing strategies. D'Andrea et al. (2016) reported that whilst population screening is cost-effective for AJ populations if carriers elect risk-reducing

surgeries (i.e., less than USD 30,000 per QALY), it is not cost-effective for cancer patient or unselected populations. The authors also say that current family history-based screening is likely cost-effective, though they recommend further analysis of risk assessment costs. In another study comparing BRCA testing strategies for AJ women, Manchanda, Legood, et al. (2015) found that population screening and risk-reducing surgeries actually saved GBP 2,079 per QALY gained as compared to family history-based screening. These results suggest that a combination of family history-based screening for non-AJ women and population screening for AJ women may be economically viable in both the United States and United Kingdom.

Similarly important is the question of how much mutations affect cancer risk in AJ women with no personal or family history of cancer. Manchanda, Loggenberg, et al. (2015) argue that studies such as Chatterjee, Kalaylioglu, Shih, and Gail (2006) 'indicate that Jewish BRCA1/BRCA2 carriers ascertained on a population basis and those without a strong family history of cancer have high risks for breast/ovarian cancer, though these estimates are clearly lower than estimates obtained from high-risk families/cancer genetic clinics' (p. 10). In alignment with this view, Metcalfe, Eisen, Lerner-Ellis, and Narod (2015) estimated breast cancer risk to be between 30 and 40 per cent for those with a 6174delT mutation (i.e., the founder mutation with the lowest penetrance [Antoniou et al., 2005]). As mentioned in Chapter Two, the average breast cancer risk in the general population is about 12 per cent, so even if they have no family history of cancer, AJ women with a mutation are expected to have at least 2.5 times the risk of a non-Jewish woman without a mutation. Moreover, the authors point to Metcalfe et al. (2012), which found that among BRCA carriers identified through AJ population screening, 11 per cent elected mastectomy and 90 per cent elected oophorectomy. These preventive surgeries slashed the group's breast cancer risk from 37

per cent to 21 per cent and ovarian cancer risk from 25 per cent to 7 per cent, which the researchers suggest will lower mortality.

Overall, current research tentatively supports a hybrid testing strategy of family history-based screening and AJ population screening as clinically effective and cost-effective. In the language of Gulliford et al. (2002), the groups of women to which BRCA services are particularly relevant and effective are (1) women considered high-risk because of their personal and family histories of cancer and (2) all women of AJ descent. Additionally, it is important to recognise that relevance and effectiveness may change over time as more technological advances occur and more research is published. Studies of population screening in other known high-risk ethnic groups, e.g., the Nordic and the Dutch, may suggest expanding ethnicity-based population screening beyond Ashkenazi Jews. In fact, the Netherlands routinely offers CHEK2 testing to non-BRCA-positive Dutch breast cancer families because CHEK2 mutations are found in up to 1.5 per cent of Northwest European individuals and associated with increased risk of contralateral breast cancer (Adank et al., 2015; Huijts et al., 2014). This is a good reminder that population screening for hereditary breast cancer may need to include non-BRCA mutations, further supporting panel testing (or more sensitive whole-exome sequencing) as a potentially viable future option.

6.4.2 Measuring and enhancing equity of access to BRCA services

Gulliford et al. (2002) pointed out that equity of access may mean both equal treatment for equal need and unequal treatment for unequal need. The concept of unequal treatment for unequal need aligns with the idea of BRCA services having particular relevance and effectiveness for high-risk American and British women. Additionally, it bolsters the argument that not every woman should have access to every type of care for BRCA

mutations. It is not inequity for average-risk women not to be offered population screening that would be economically and clinically ineffective. Likewise, it is not inequity when BRCA carriers are denied inappropriate management options, e.g., a 70-year-old carrier not receiving a mastectomy because her breast cancer risk has already decreased significantly.

The concept of equal treatment for equal need, however, is more complicated than simply saying that appropriate BRCA services should be offered to all high-risk women. One way to measure equity of access is to examine utilisation of services by high-risk women. Low utilisation of services, or differential utilisation between different high-risk patient groups, may suggest inequity of access. However, Chapter Four – specifically Section 4.4.1 – explained why utilisation of services for BRCA mutations is tricky to evaluate without context. If utilisation is impacted by problematic barriers to care, e.g., clinicians not referring high-risk women because they do not understand genetic testing, then that indeed suggests inequity of access. If, however, low or differential utilisation is driven by unproblematic patient choices or circumstances, such as a woman declining testing because she is not interested, then equity of access may not be a problem. (Incidentally, this is another reason why even clinically or cost-effective universal BRCA screening should not take place at birth or in childhood: There is no appropriate childhood clinical management that would necessitate early testing, and so a woman's right to choose whether to pursue care should be preserved until she is an adult.) Thus, this section will focus on the potentially problematic barriers identified earlier in this chapter that may lead to inequity of access, as well as implementable facilitators and service improvements identified in Chapter Five (and in a few cases, Chapter Four) that may redress those inequities. These facilitators and service improvements are listed in Table 6.5 and described in the accompanying text.

Table 6.5: Actionable facilitators identified in Chapters Three through Five

Referrals	Counselling and testing	Post-test care
Amended guideline referral criteria (CMS, USPSTF)*	Appeal of genetic counselling profession (CMS billing ability, increased pay)*	Adequately funded post-test care
Electronic health record alert	Counselling approaches (group, telephone, telegenetics, post-counselling risk estimate)	Letter for family members
Family history screening tool for breast services	Ease of coming to genetic services (proactive contact, online family history forms, online appointment scheduling)	Life insurance protections*
Genetics education for patients and clinicians	Free/subsidised testing programmes*	Support mechanisms (patient navigation and guidance, multidisciplinary care, psychological counselling, support groups)
Involvement of oncologists and surgeons	Genetics education for patients	Uniform guidelines/insurance standards for post-test care*
	Size/scope of genetic services (more staff, larger premises)	
	Testing approaches outside of genetic services (mainstreaming, research, direct-to-consumer testing)	

*Only relevant in United States. CMS = Centers for Medicare and Medicaid Services. USPSTF = United States Preventive Services Task Force.

6.4.2.1 (In)equity of access to referrals

Barriers to referral were previously divided along guideline ineligibility and eligibility, but 12 barriers considered between the two categories are problematic. There is almost certainly inequity of access anytime a high-risk American or British woman is denied the opportunity to even consider attending genetic services.

In the guideline ineligibility category, two policy-orientated barriers directly contribute to inequity of access: the CMS and USPSTF restrictions prevent some high-risk American women who are publicly and privately insured, respectively, from being referred. The obvious but politically complicated way to redress the CMS guideline-caused inequity would be through a US Congress amendment or a National Coverage Determination process (Jacques, 2008; Segovis, 2015), as mentioned in Chapter Three. An equally straightforward but somewhat easier fix for the USPSTF restriction would be to have HHS issue a clarification to expand the target population of the USPSTF guideline. As Chapter Three noted, HHS has previously expanded the target population to include women with a previous history of BRCA-related cancer, so there is precedent for amending the USPSTF guideline (DOL, HHS, and the Treasury, 2015).

The remaining barriers involved clinician behaviour and patient characteristics. Looking at these items holistically, a lack of referral is a likely symptom of a deficit in knowledge or experience (e.g., lack of clinical judgment) and/or a socioeconomic challenge (e.g., lack of internet access). The exception may be the racial barrier to referral cited in Chapter Five, although Black respondent USPT5 felt her surgical oncologist had simply internalised racial disparities in care rather than intentionally denying her care. Redressing major socioeconomic issues, such as lack of primary care, is beyond the scope of what genetics professionals can hope to achieve on their own. Thus, it makes sense that the more feasibly implementable facilitators identified in Chapters

Four and Five are systemic solutions aiming to better inform patients and clinicians about HBOC. These included genetics education for primary care clinicians and patients, electronic health record alerts telling clinicians to grant referrals, family history screening tools being used during routine breast care (e.g., mammogram appointments), and explicit involvement of oncologists and surgeons in the referral (and sometimes testing) process. Notably, these suggestions are all backed in the medical literature: Harris (2001) called for incorporation of computerised tools into clinical practice alongside better GP education about genetics, for example, and Rahman (2014) explained how oncologists are already being recruited to perform genetic testing through the Mainstreaming Cancer Genetics programme.

6.4.2.2 (In)equity of access to counselling and testing

The presence of 26 potentially problematic barriers to counselling and testing strongly suggests inequity of access, particularly when coupled with data on low utilisation of these services from Chapter Four. Whilst many barriers apply to how women access any kind of healthcare (e.g., language barriers or lack of income), several of these impediments are specific to genetic services (e.g., limited legal protections for American BRCA carriers). The facilitators discussed by empirical study participants in Chapter Five and reported in the literature in Chapter Four focussed on organisational and financial barriers specific to genetic services, rather than the personal barriers that affect how women access healthcare in general.

The most cited ideas for increasing uptake of genetic services involved better genetics education, streamlined administrative processes, more efficient counselling, more affordable testing, and increased capacity of healthcare professionals to conduct genetic testing. Unsurprisingly, these five facilitators relate to the lion's share of actionable barriers. First, genetics education for patients (Chapter Five) is an obvious remedy to patients lacking knowledge about genetics; indeed, Meilleur and Littleton-Kearney (2009) evaluated a range of genetics education tools and

concluded that some computerised interventions could quite effectively improve patients' knowledge of genetics. Moreover, educational tools could be tailored to address cultural factors such as medical mistrust, familial challenges such as family-related guilt, and psychosocial concerns such as negative attitudes towards testing. Second, streamlining administrative processes aims to reduce the burden on patients to reach out to genetic services and complete their paperwork. One method from Chapter Four is to call patients directly to schedule appointments, rather than waiting for patients to call themselves (Evans, Binchy, et al., 2009); given that the pilot test of this approach was effective, this suggestion is particularly promising. A second suggestion is to optimise online family history forms and appointment scheduling (Chapter Five), which fits with the trend towards Web-based scheduling systems (Zhao, Yoo, Lavoie, Lavoie, & Simoes, 2017). Third, several mechanisms cited in Chapter Four may make genetic counselling more efficient and effective. Pilot programmes examined telephone counselling and group counselling (Calzone et al., 2005; Schwartz et al., 2014), and other studies found that family information session attendance and the provision of post-counselling risk estimates helped women decide to attend testing (Kieran et al., 2007; Lynch et al., 2009). Fourth, even though lack of insurance and lack of income are not barriers specific to genetic services, one concrete way to improve financial access to genetic services for American women is by lowering the cost of testing. This may be accomplished by providing subsidised or free testing, e.g., through the programme that USCA6 described for low-income women (Chapter Five).

The fifth and final idea – increasing the capacity of healthcare professionals to conduct genetic testing – has the potential to increase utilisation of testing, reduce inconveniences associated with time and travel, shorten wait lists, and minimise the burden caused by a scarcity of genetic counsellors. Within genetic services, the UK counsellors in Chapter Five proposed hiring more counsellors and moving to larger premises, whilst the US counsellors focussed on fixing the CMS billing provision and raising genetic counsellors' salaries to grow the profession. Beyond

genetic services, participants also discussed the cautious employment of several types of counselling and testing approaches: mainstreaming, telegenetics, research-provided testing, and DTC testing.

6.4.2.2.1 Challenges in using different counselling and testing approaches

It is important to emphasise that trying to improve equity of access may unintentionally create other inequities of access if not approached properly. Chapters Three through Five have noted in different ways that broadening access to care may create unforeseen trade-offs. This theme will be revisited here in terms of how the different counselling and testing approaches mentioned above may affect equity of access both negatively and positively.

6.4.2.2.1.1 Mainstreaming

Mainstreaming may be the most straightforward way to enhance equity of access, as care is still provided in a healthcare setting and carried out in cooperation with genetics professionals. The danger, of course, is that non-genetics professionals might provide inadequate information, order improper tests, misinterpret results, and fail to consult with genetic services. Poorly implemented mainstreaming would likely be worse than no genetic testing at all, as patients would be misinformed about their actual risk. As noted in Chapter Five, however, US and UK genetics professionals voiced qualified support for oncologists providing testing – as long as they learned how to discuss genetic testing with patients, order and interpret tests appropriately, and consult with or refer patients to genetic services as needed, as in the Mainstreaming Cancer Genetics programme (Rahman, 2014; Slade et al., 2015). These stipulations could be addressed through medical education for all medical students and any practising clinicians interested in providing testing, clear links between genetic services and non-genetics departments, and regular review of cases in genetic services as a means of quality control.

Moreover, as clinical geneticist UKCA4 pointed out, mainstreaming may be central to the possibility of lowering the NICE-approved threshold for genetic testing. Any AJ population screening would also probably require mainstreaming support, given that genetic services likely lack the staff to provide counselling and testing to about 3.5 million American AJ women and about 114,000 British AJ women (Jewish Virtual Library, 2015; Manchanda, Legood, et al., 2015). Given the choice between serving fewer patients exclusively in genetic services and serving more patients in genetic services and relevant specialties, permitting mainstreaming and teaching non-genetics professionals to conduct testing responsibly seems the more ethical way to proceed. This view is further reinforced by existing non-cancer genetics examples of mainstreaming in clinical practice. Cascade testing for familial hypercholesterolemia, for example, has taken place successfully in lipid clinics instead of genetic services (Hallowell et al., 2011); so too has cystic fibrosis screening been a recommended part of American obstetrics and gynaecology practice for over 15 years (Collins & Guttmacher, 2001).

6.4.2.2.1.2 Research-provided testing

Research studies providing BRCA testing offer another possible way to increase equity of access, albeit on a much smaller scale than mainstreaming. Some women may find that research-provided testing removes major organisational and financial barriers, e.g., women may not need referrals in order to obtain services, and those meeting study criteria may be entitled to free counselling and testing. The wait time from study enrolment to testing may also be much shorter than the wait time from referral to genetic services appointments. However, research-provided testing is not without its own ethical issues, including (1) the challenges dual clinician-researchers face, (2) the risk of researchers mixing up samples, (3) the possibility of a protocol not testing for mutations exhaustively, (4) the negative feelings patients may have about research, and (5) the structural inequalities that may be perpetuated by such testing at systemic and individual levels. Each of these issues can be addressed during the informed consent process, however, meaning

that research-provided testing should be permitted as long as the informed consent process is comprehensive enough.

First, researchers who also serve as clinicians may find it challenging to navigate their dual identities and responsibilities. The primary goal of research is to create generalisable knowledge, not provide care for participants (Henderson et al., 2007). One example of this distinction is that test results may not be returned to participants in research, whereas test results should always be returned to patients in clinical care (National Library of Medicine [US], 2017). Hallowell, Cooke, Crawford, Lucassen, and Parker (2009) argue that concentrating too much on this distinction can confuse participants, however, and that the consent process should prioritise the risk/benefit profile of the procedures involved.

Second, because research laboratories are not subject to the same regulatory requirements as clinical laboratories (i.e., mandatory CLIA certification in the United States and voluntary accreditation in the United Kingdom, as discussed in Chapter Three), samples may be mishandled and thus participants may receive incorrect results. A National Heart, Lung, and Blood Institute working group declined to make a recommendation about returning results that were not analysed in a CLIA-certified laboratory for this reason (Fabsitz et al., 2010; Zhang, 2017). In the worst-case scenario, a BRCA-positive woman's sample could be mixed up with a BRCA-negative woman's sample: the first woman may be falsely reassured by a negative result, whereas the second woman may be falsely burdened by a positive result. As in the case of DTC testing, a clinician should order a confirmatory test in a CLIA-certified laboratory for the second woman before agreeing to any surgery, thus preventing the most irreversible consequences. However, the first woman may never undergo confirmatory testing and therefore never learn she is BRCA-positive, precluding her option to elect screening, medication, or surgery. Moreover, a falsely reassured BRCA-positive patient would be unable to talk to her family members about

genetic testing, so her result may have long-lasting repercussions. The potential for such sample swapping and its related outcomes should be disclosed during the consent process.

Third, the variants a research protocol examines may be different from the variants a commercial laboratory tests. This concern cuts two ways: if the research team is examining a new variant and believes it to be pathogenic, a commercial laboratory may not be able to confirm the result, and so a clinician may not be able to offer post-test care; and if the research laboratory is only testing a subset of known variants, then a harmful variant that a commercial laboratory would have detected may not be found. Here too, a thorough informed process could help participants understand exactly what kinds of variants are being tested through research.

Fourth, minority women may react negatively to research-provided testing because past medical research has been exploitative of minority participants, as support group member USPT2 suggested. Withholding research-provided testing from minority women to protect them from possible psychological discomfort would be paternalistic, though, and it could even exacerbate the existing racial disparity in usage of genetic services. Explaining what procedures will be done and why during the informed consent process may help minority women decide whether they feel research-provided testing is beneficial overall. This approach is also in line with current American efforts to incorporate underrepresented minorities, such as tribal citizens, in genetics research (Facher, 2017; Sahota, n.d.).

Fifth, research-provided testing may contribute to an improper allocation of resources for testing and post-test care. Health services may fail to budget for the number of women who actually need genetic testing and post-test care in clinical care because some of those women are receiving testing and post-test care in research, as discussed in Hallowell et al. (2009). Additionally, the concern registered by American genetic counsellor USCA6 about providing

women with discounted or free testing without the guarantee of post-test care applies here too. A woman may enrol in a study, find out she is BRCA-positive, undergo mammograms and MRIs for several years, and then find herself unable to continue screening once the study ends because she is in an under-resourced location or lacks the ability to pay for care. At the individual level, this testing decreases existing inequality by allowing that woman to find out she is BRCA-positive and receive several years of screening, but the possibility of discontinued care should be disclosed before the study begins. At the systemic level, one response to why research-provided testing does not increase inequality is that research studies may lead to more affordable testing and post-test care, and in the best-case scenario, contribute to a cure for HBOC.

6.4.2.2.1.3 Telegenetics

A relatively uncontroversial third way to provide care outside of genetic services is through telegenetics, as genetics professionals are simply providing counselling and ordering testing electronically instead of in person. For women who live far away from genetic services or cannot afford to take much time off from work, telegenetics may eliminate location and income-related barriers. US genetic counsellors USCA1 and USCA2 also pointed out that for community hospitals that cannot afford full-time genetics professionals, telegenetics may represent a low-cost way to provide expert counselling on demand. Notably, telemedicine has been successfully incorporated throughout places like Australia and the Canadian province of Manitoba for a variety of disciplines, including clinical genetics (Elliott et al., 2012; Fatehi, Martin-Khan, Smith, Russell, & Gray, 2015; M. Gill, 2011); in these cases, the technology has allowed providers to care for patients in rural, isolated communities.

Arguments against telegenetics involve both logistical concerns, e.g., poor internet connections, and quality concerns, e.g., inferior results to in-person counselling. Some studies have reported high patient satisfaction rates with telegenetics, but large-scale outcomes data on how

telegenetics impacts counselling and testing uptake are relatively scant (Buchanan et al., 2015; Hilgart, Hayward, Coles, & Iredale, 2012; Otten, Birnie, Ranchor, & van Langen, 2016). Whilst that evidence is being amassed, it seems reasonable that telegenetics should primarily be offered to women who would otherwise not have access to genetic services at all.

6.4.2.2.1.4 DTC testing

The fourth and final option discussed, DTC testing, is the most controversial. In theory, DTC testing enhances equity of access by allowing any woman to pursue BRCA testing in the convenience of her own home for a relatively low price. A high-risk woman unable to receive a referral – e.g., if her GP lacks the knowledge to refer her, or if she is American and lacks insurance – may benefit from the ability to order her own test. On the other hand, critics worry that women may misinterpret negative DTC results or take drastic measures based on false positive results. This negative reaction appears driven by a belief that genetic testing should only be done when accompanied by genetic counselling and clinician oversight, e.g., in a clinical setting. Thus, it makes sense that Color Genomics has not encountered pushback from clinicians or regulatory agencies, as Color includes counselling in its USD 249 kit and requires company-employed counsellors to authorise all orders (Color Genomics, n.d.).

In contrast, 23andMe, which requires neither counselling nor clinician authorisation, falls under greater scrutiny. Whilst the company has MHRA approval to offer testing for the AJ founder mutations in Britain, it does not have FDA approval to provide any BRCA reports in America. As the MHRA asserts, though, it is reasonable for companies like 23andMe to provide tests as long as they have appropriate protections in place. At minimum, tests should be required to be analytically and clinically valid, and the informed consent and results-giving processes should be thorough. Ideally, DTC companies should also work with regulatory agencies and local health authorities to develop a way to guide consumers who may require follow-up care in a clinical

setting (K. T. Edwards & Huang, 2014). This practical approach would recognise that although Color Genomics provides a more comprehensive test that is relevant to both AJ and non-AJ women, 23andMe still provides a valid service for AJ women unable to obtain founder mutation testing through other avenues.

6.4.2.2.1.5 Overall thoughts on offering genetic services outside the genetics clinic

Mainstreaming has the greatest potential to improve access on a large scale, but research-provided testing, telegenetics, and DTC testing also have the potential to expand access to certain groups of women. As illustrated in Sections 6.4.2.2.1.1 – 6.4.2.2.1.4, this sets up a trade-off between increasing the number of avenues to access genetic services and ensuring the overall quality of genetic services. Given the ubiquity of barriers currently inhibiting care for BRCA mutations that have been discussed throughout this thesis, though, offering genetic services outside the genetics clinic seems both appropriate and necessary. Moreover, increasing avenues to genetic services may empower patients by allowing them to choose their preferred care delivery model, rather than the only model available.

Importantly, choosing wider access as the more ethical option should not mean ignoring its potential effects on quality. Testing outside of genetic services should involve appropriate safeguards that may include, but do not require, genetic counselling. Developed with the input of genetics professionals, a thorough informed consent process could reasonably cover the risks, benefits, and scope of testing in clinical care, research, and DTC settings. For instance, one recommendation might be informing women that they have the option to pursue genetic services in a genetics clinic instead of through mainstreaming, research projects, telegenetics, or DTC testing. When more statistics on patient outcomes – both in terms of patient satisfaction and quality of counselling and testing outside of genetics clinics – are available, these could also be shared with women to facilitate their decisions. Ultimately, the informed consent process is

something familiar to patients and clinicians alike for all sorts of high-stakes decisions, and BRCA testing is not so different from patients being asked to consent to procedures like mammography or chemotherapy (Marshall, 2005; Myers et al., 2015; Pallarito, 2008), enrolment in nearly all research projects (Henderson et al., 2007), or even use of at-home pregnancy tests (K. T. Edwards & Huang, 2014).

6.4.2.3 (In)equity of access to post-test care

Once again, the sheer number of possibly problematic barriers to post-test care (20 in total) implies inequity of access, especially considering the wide variation in utilisation of post-test care options described in Chapter Four. Given the breadth of services that the term 'post-test care' includes, it is unsurprising that the range of facilitators and proposed service improvements found in Chapters Four and Five was quite comprehensive. In general, these suggestions related to the provision, costs, and awareness of different types of post-test care.

One interesting issue that emerged in the empirical study in Chapter Five is how to rectify inequity of access that arises when post-test care cannot be guaranteed after genetic testing. USCA6 explained how her previous workplace offered free testing to low-income, uninsured minority women, but that programme did not provide any free post-test care. Similarly, UK-based BRCA carriers may find themselves on the wrong end of a postcode lottery for MRIs if they live in a poorly resourced area. In these cases, women may have to cope with negative psychosocial responses to testing positive, as well as the knowledge that their preferred management options are not possible. As a result, USCA6 wondered if her workplace should have offered women in such situations testing at all.

Whilst well-meaning, withholding testing because of a guaranteed lack of access to post-test care for prevention and early detection of cancer would only exacerbate inequity of access. First, not

all barriers to post-test care are static. For instance, a US woman may obtain insurance that allows her to afford post-test care at a later date, and a UK woman may learn her local health authority has acquired funding for MRIs shortly after testing. Second, there are reasons to have BRCA testing beyond post-test care. Some women may test for familial benefit, particularly if they have potentially affected children or siblings. Other women may pursue testing for community benefit, especially if they are part of minority groups who historically have low usage of genetic services and high VUS rates. Third, testing may be time-sensitive, even if prevention and early detection are not the most urgent goals. Cancer patients may pursue treatment-focussed testing, e.g., testing that may inform patients' surgical decisions (as discussed in Section 6.3.1.1) or help clinicians tailor chemotherapy regimens based on patient and tumour characteristics (Levy et al., 2011; Stover & Winer, 2015; Trainer et al., 2010). Cancer patients may also wish to undergo testing as soon as possible, particularly if they are testing to benefit their families, so they do not have to worry about dying before testing can occur.

Given the ubiquity of this question, it makes sense that empirical study participants suggested ways to ensure access to post-test care, regardless of women's income. A popular proposal involved uniform guidelines for post-test care that are either adequately funded by public health authorities (NICE and CMS) or labelled as preventive care that private health insurers must cover (USPSTF). Support group member USPT1 also requested a US policy or law requiring life insurance policies to recognise that risk-reducing surgeries lower women's risk of cancer, in line with what Klitzman et al. (2014) suggested. Other respondents called for more and better psychosocial support mechanisms, e.g., ongoing support groups, patient navigation or multidisciplinary care, and post-surgery psychological counselling, as well as the routine provision of informational letters to give to their family members. As noted in Section 5.5.4, one helpful guide to organising these requests might be post-test drug access, as discussed in Doval et al. (2015); in this case, though, post-test access for women receiving testing to further research

for universities or companies like Myriad could include appropriate screening as well as support mechanisms. These suggestions are also a reminder that receiving inadequately supported care is another form of inequity of access that requires addressing.

6.5 Summary of country-based similarities and differences in access to care

In daily practice, access to care for BRCA mutations is similar in both the United States and United Kingdom, as demonstrated by the process maps drawn by US and UK genetics professionals and support group members in Chapter Five. Both countries use family history-based screening to determine which women receive referrals to genetic services, and neither country routinely uses population screening for any group. Both US and UK women identified as being at high risk for BRCA mutations are offered genetic counselling and testing, and if they test positive, they are subsequently offered appropriate post-test care options. Many of the problematic barriers and the facilitators that may redress inequity of access also apply to women in each country; for instance, a poor clinician-patient relationship is a universal hindrance, and patient education resulting in increased knowledge of genetics is a universal helper. However, there are systemic differences that result from how UK and US healthcare is organised, financed, and regulated.

At an individual level, Chapters Three through Five all described how vital it is for American women to have insurance to access genetic services, whereas free NHS care is the birth right of all British women. Whilst American women are sometimes able to self-refer to genetic services, British women must obtain referrals before being seen in genetic services; however, women who possess the knowledge to seek self-referral also likely have the wherewithal to request referral from their GP, so this may not be hugely problematic given that a GP appointment is free. Since wait times are one major constraint to UK access to genetic services, though, the added hoop of

receiving a referral may slow down a woman's ability to see a genetics professional by a few weeks. As the UK genetic counsellors suggested in Chapter Five, these wait times are the result of genetic clinics not being able to keep up with the volume of patients seeking genetic services.

At a systemic level, the NCCN and USPSTF guidelines generally have lower referral thresholds than the NICE guideline; initially, this finding makes it seem like more American women are eligible for referral than British women. As discussed in Chapters Three and Six, however, there are a few key caveats to this statement that may drastically affect access. One, a privately insured American woman is not USPSTF-eligible if she is symptomatic of or in treatment for BRCA-related cancer. Two, a publicly insured American woman falls under the jurisdiction of regional CMS guidelines, and she is not CMS-eligible unless she has a personal history of BRCA-related cancer. Three, clinicians in both countries are encouraged and even expected to use their clinical judgment to decide whether a woman should be referred, even if a guideline does not agree. The difference for a US clinician is that if a woman is not guideline-eligible, she may have to pay the full cost of counselling and testing on her own. That said, some US insurers allow referral for women at lower risk than the USPSTF or NCCN guideline threshold.

In terms of post-test care, Chapter Three described how the NCCN guideline permits a greater variety of care than the NICE guideline. This is because NICE applies a stricter evidentiary standard to NHS-funded care than NCCN does to insurer-funded care; for example, there is no evidence that ovarian screening is effective, yet the NCCN guideline permits it at a clinician's discretion. Privately insured American women are not guaranteed any post-test care for free, though, because the absence of USPSTF post-test care guidelines means there are no insurance standards. Because it is cheaper for insurers to pay for screening, chemoprevention, and/or risk-reducing surgeries than to pay for cancer treatment, many American women are covered for care anyway. On the other hand, British women clearly benefit by receiving NICE-approved care for

free, but if there is differential access based on where a woman lives (e.g., the perceived postcode lottery for MRIs mentioned in Chapter Five), that is hugely problematic.

A final point of discussion is the impact of US and UK anti-discrimination laws on access to care, which arose in Chapters Three and Five. Although the United States has a specific anti-genetic discrimination law, GINA, the United Kingdom offers superior protections to women in two ways. There are no protections against genetic discrimination for American women who (1) work in a company with fewer than 15 employees or (2) wish to buy life, disability, or long-term care insurance.

In sum, most of the problematic cases in which women do not access care could occur in either country. However, only US women are problematically constrained by insurance and legal limitations, and only UK women are problematically constrained by regional variations in health authority funding.

6.6 Conclusion

Access to care for BRCA mutations is potentially life-saving, yet there are a substantial number of US and UK women who do not access this care. In this thesis, I have sought to distinguish between situations in which these women may not want or need care and cases in which women want and need care but are unable to obtain it. In the latter case, I have suggested potential facilitators that could help women access care they want and need. I have also argued that it may be time to consider family history-based screening in addition to population screening for AJ women only, given clinical and cost-effectiveness data.

The main strength of this thesis was pairing a multi-dimensional model of access to care with a trio of mixed methods to capture different perspectives of each dimension of access. The

specific choice to use Gulliford et al. (2002) helped confirm the decision to conduct three interrelated studies, with the critical review in Chapter Three showing how regulatory mechanisms shape access; the scoping study in Chapter Four showing what some relevant academic literature says about barriers and facilitators to care; and the empirical study in Chapter Five showing what genetics professionals and support group members think about access to care, given their professional and personal experiences. The ethical analysis in this chapter was then able to connect these findings along the four dimensions of Gulliford et al., providing both a picture of how access to care for BRCA mutations works right now and also a view to how problematic gaps in access to care for BRCA mutations might be addressed in the future.

The main limitations of this thesis related to challenges in aligning all of the findings from the scoping and empirical studies within the Gulliford framework as neatly as intended. On one end of the spectrum, process mapping was a substantive part of the empirical study in Chapter Five, but it was more of a footnote about availability of services in this chapter. This minimisation occurred partly because the 24 participants had little variation in their maps and partly because any variation that was discussed was couched in terms of barriers and facilitators to care. On the opposite end of the spectrum, data on utilisation and outcomes of services were in short supply in Chapter Four, yet equity of access was an entire dimension of access requiring analysis in this chapter. Without sufficiently comparable quantitative data, the fourth dimension became a discussion of how to suss out whether low utilisation was the product of problematic barriers to care or the result of unproblematic personal choices and characteristics. Similarly, the Chapter Six section on relevance and effectiveness of services for different patient groups was informed by Chapters Three, Four, and especially Five but drew significantly on the literature on population screening in different groups. Including support group members from different locations, of different races and ethnicities, and with different clinical characteristics such as cancer status, BRCA test results, and carrier management choices could have given the third

dimension more practical context. Likewise, including other types of clinicians, such as GPs and oncologists, could have shed more light on how referrals happen in practice and what mainstreaming looks like now.

Future research directions for this thesis could seek to remedy the limitations listed above and make findings more applicable to daily practice. Building on the critical review of regulatory mechanisms, it would be interesting to analyse how closely US and UK guidelines are followed in practice by insurers and the NHS, respectively. Incorporating the additional suggested patient and clinician perspectives above in a future process mapping study would contribute a fuller understanding of how different kinds of patients access care for BRCA mutations. Attempting to estimate current utilisation of different kinds of care for BRCA mutations in the United States and United Kingdom, possibly using mailed questionnaires to primary care offices and genetic services, would also be a worthwhile research enquiry.

Additionally, these findings contain lessons for clinicians, patient advocates, and policymakers. For clinicians, Table 6.4 summarises quite clearly which kinds of women may be failing to obtain care for BRCA mutations and why, and Table 6.5 contains a variety of ways that those deficits in access may be addressed. Certain findings, such as the potential influence of a clinician recommendation on uptake of care, may be applied immediately; other findings, such as the negative relationship between medical mistrust and genetic testing uptake, may be addressed through longer-term minority outreach efforts. For patient advocates, these findings may help advocates determine where and how to use their resources, e.g., what topics support groups should discuss during upcoming meetings and what kinds of practices and policies they should lobby hospitals and healthcare systems to address. For US policymakers, the proposed changes and additions to regulatory mechanisms provide concrete ways they could attempt to improve women's access to care for BRCA mutations. For UK policymakers, the existing organisational

barriers to care, e.g., variability in MRI availability and long wait lists to attend genetic services, provide reasons to consider committing more resources to local health authorities.

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8 Appendices

8.1 Preliminary interview guide

Preliminary Interview Questions
Last updated 7-Feb-11

General goal of project: Semi-structured interviews: start off with beginning information (demographics – age, occupation, highest training, involvement in field) and brief description of project (reiterate content of one-page summary)

Background
Demographic details of respondent (age, position, education, years in post; experience working in multiple health care systems)

Introduction
{Reintroduce project based on one-page summary information}
Tell me about your job role (prompt: in relation to cancer genetics)

Interview content

- If interviewer has worked in multiple systems: Broadly speaking, have you seen any obvious differences between the two health systems?
    - How did you notice these differences? (Prompt: as consumer/patient, clinician, researcher, observer, relative…)
- Can you describe the typical patient pathway that a person has followed prior to entering your service?
    - What do you think about this pathway?
- In your experience, have the appropriate kinds of patients been referred to genetics services? Do you think that any other kinds of patients should be referred, but are not? Why haven't these patients been referred?
    - In general, do you think GPs and other clinicians who make genetics referrals know enough to make the correct referrals? What about in cases where a patient has a less common family history (e.g. a relative with male breast cancer)?
    - Have you encountered areas of genetics that GPs and other referring clinicians generally tend not to know, to the detriment of patient care?
- Which clinical guidelines do you use to help with these referrals? (If no explicit name, ask for description.) Do you think these should be changed?
        - If so, in what way, and why?
- Can you describe any difficult situations or scenarios you have encountered in your practice?
    - Have you experienced any situations in which you had to balance a patient's desire to not communicate relevant medical information to a family member with your obligation to warn?
    - What additional knowledge or guidelines, if any, would have helped you navigate that situation or scenario?
- What has your experience been with the content of counselling sessions?
    - Have you noticed anything in particular that seems to affect pre-visit expectations and/or post-visit satisfaction?
    - Have your patients usually had previous discussions about genetic testing with their relatives?
        - If so, do they emphasize the outcomes/results or their general experience with the process surrounding testing?
        - Have you experienced the tension between your patients' right not to know and your moral obligation to warn the patient or the patient's family?

    - Do you include a discussion of each of the following in general sessions? To what extent?
        - Communication of risk factors and behavioural coping strategies (with respect to individual and familial risk)
        - Pre-test discussion of post-test interventions (and the limited evidence associated with such interventions)
        - Expectation of having test immediately, testing children, effect on family
        - Appropriate communication of risk (percentages and ratio, comparison to baseline risk)
- How have the technological advances of the last decade affected your practice?
    - Has your practice transitioned to electronic patient records? If so, how does that affect the way you take down a patient's pedigree?
    - Have you discussed direct-to-consumer genetic testing with patients? With your department?
- Do you use measures such as the Cancer Worry Scale and Global Health Questionnaire? Why or why not?
- What are the main laws and guidelines that you refer to or use in your daily practices, if any?
    - Have there been any situations in which your awareness of the law or concerns about it have made a difference to the decision you made?
    - Can you give me a practice example?
- What role do you think advocacy groups play in genetic counselling/screening?
    - What role should they ideally play?
- Are there any questions you would like to know/that would be relevant to your practice?
- Groups that will be consulted (see below). Missing any stakeholders?
    - Clinicians (nurses, doctors – GPs, oncologists and gynaecologists, genetic counsellors, social workers)
    - Patients (inc. those who opted for and against testing)
    - Patient advocacy groups
    - Policy committees/policymakers (government and non-profit)
    - Public health interest groups/lobbying groups
    - Insurance companies (Medicare, private insurers in US; supplemental insurers in UK, NHS)
    - Genetic testing companies
    - Clinical trial researchers
    - Regional genetics laboratories
- Based on your experience, are there any other kinds of people I should speak to for expert opinions? (names, positions, e-mails)

8.2 Healthcare professional recruitment letter

Dear [Healthcare Professional Name/Group of Clinical Colleagues]:

I am writing to invite you to participate in the 'Ethical issues surrounding access to care for BRCA mutations' research study, which is being conducted by The University of Oxford's Ethox Centre and supervised by Professors Michael Parker and Anneke Lucassen. I located your contact information through [public online listing of clinicians at a research site/identification from another previously contacted clinical colleague].

The purpose of this study is to examine how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations. The empirical part of the project involves discussions with healthcare professionals and patient advocates/support group members through focus groups and interviews.

You may be eligible for this study if you meet the following two criteria:

- You are a healthcare professional who works with women who may be offered genetics services for hereditary breast and ovarian cancer (including primary care practitioners, oncologists, genetic counsellors, clinical geneticists, laboratory technicians, etc.), and

- You are located in or near one of four cancer genetics communities: Oxford and Southampton in the United Kingdom, or Baltimore/Washington DC and Philadelphia in the United States.

Your participation in this project is entirely voluntary. While there are no anticipated direct benefits to participants, indirect benefits may include contributing to a better understanding of the ethical issues that affect care for BRCA mutations. As the study findings will be fed back to interested participants, you may also be able to incorporate these findings into your clinical practice. There are no anticipated risks for participants in this study.

If you are interested in learning more about this study, please contact me via e-mail at caroline.huang@merton.ox.ac.uk.

Thank you for your time and consideration. I look forward to hearing from you.

Best wishes,

Caroline Huang, Doctoral Student and Principal Investigator
E: caroline.huang@merton.ox.ac.uk
T: +44 1865 287887 (UK), +1 302 383 0416 (US)

Ethics approval reference: MSD-IDREC-C1-2014-021
Version 2, 8-Jul-14

8.3 Support group member recruitment letter

Dear [Name of Patient Advocate Organisation/Support Group]:

I am writing to invite you to participate in the 'Ethical issues surrounding access to care for BRCA mutations' research study, which is being conducted by The University of Oxford's Ethox Centre and supervised by Professors Michael Parker and Anneke Lucassen. I located your contact information through [patient advocacy organisation/support group website].

The purpose of this study is to examine how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations. The empirical part of the project involves discussions with healthcare professionals and patient advocates/support group members through focus groups and interviews.

You may be eligible for this study if you meet the following two criteria:

- You are a patient advocate/support group member who advocates on behalf of, or speaks with, women who may be offered genetics services for hereditary breast and ovarian cancer, and

- You are located in or near one of four cancer genetics communities: Oxford and Southampton in the United Kingdom, or Baltimore/Washington DC and Philadelphia in the United States.

Your participation in this project is entirely voluntary. While there are no anticipated direct benefits to participants, indirect benefits may include contributing to a better understanding of the ethical issues that affect care for BRCA mutations. As the study findings will be fed back to interested participants, you may also be able to incorporate these findings into your patient advocacy and support group efforts. There are no anticipated risks for participants in this study.

If you are interested in learning more about this study, please contact me via e-mail at caroline.huang@merton.ox.ac.uk.

Thank you for your time and consideration. I look forward to hearing from you.

Best wishes,

Caroline Huang, Doctoral Student and Principal Investigator
E: caroline.huang@merton.ox.ac.uk
T: +44 1865 287887 (UK), +1 302 383 0416 (US)

Ethics approval reference: MSD-IDREC-C1-2014-021
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8.4 Healthcare professional participant information sheet





Ethical issues surrounding access to care for BRCA mutations
Healthcare professional participant information sheet

This study examines how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations. The project is being supervised by Professor Anneke Lucassen (University of Southampton) and Professor Michael Parker (University of Oxford) and carried out through The University of Oxford's Ethox Centre. The results will be used to make recommendations about how healthcare professionals and patient advocates/support group members can work towards appropriate access to care for BRCA mutations, and to fulfil the requirements of a doctoral thesis.

You are being invited to take part in this research study, and this information sheet is designed to help you decide if you would like to participate. It explains what is being done and how.

Please read this participant information sheet carefully. If you would like any further information or clarification, please see 'How can I receive further information?' at the end of the third page.

What is the purpose and value of the study?
The purpose of the study is to examine how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations from three angles: (1) critical review of policy documents, professional guidelines, and legal rulings governing access to care; (2) scoping review of how demographics shape barriers to and uptake of genetics services; and (3) empirical exploration of how healthcare professionals and patient advocates/support group members' daily experiences are impacted by documents, guidelines, and rulings, as well as patient demographics. The value of the study lies in the opportunity to shed light on which kinds of women do and do not have appropriate access to care, which could lead to better informed healthcare practice and policy.

Why have I been invited?
You have been invited because you are a healthcare professional who works with women who may be offered genetics services for hereditary breast and ovarian cancer (including primary care practitioners, oncologists, genetic counsellors, clinical geneticists, laboratory technicians, etc.) You are also believed to be located in one of four cancer genetics communities: Oxford and Southampton in the United Kingdom, or Baltimore/Washington DC and Philadelphia in the United States.

Do I have to take part?
Participation is voluntary. It is up to you to take part, and you are free to withdraw without giving a reason at any time without penalty by advising the researchers of your decision.

If I decide to take part, what will be involved?
You will be asked to participate in a one-off focus group with the principal investigator in a location convenient to you, typically on site at one of the foundation trusts or university healthcare systems. The focus group will begin with each participant individually completing a short paper and pencil task that asks you to think about how women are offered genetics services for hereditary breast and ovarian cancer. It will then progress to a semi-structured group discussion of your experiences with these women, any relevant policies or guidelines governing their access to care, and any barriers you perceive to women receiving care.

If you are unable to make a focus group but would still like to participate, the principal investigator will try to interview you separately using the same paper and pencil task and semi-structured discussion.

Each focus group or interview will take up to 75 minutes total (10 minutes for the paper and pencil task, and up to 65 for the discussion). If you agree to it, audio recording will take place during the focus group or interview.

What benefits and risks are anticipated for participants in the study?
While there are no anticipated direct benefits to participants, indirect benefits may include contributing to a better understanding of the ethical issues that affect care for BRCA mutations. As the study findings will be fed back to interested participants, you may also be able to incorporate these findings into your clinical practice or patient advocacy/support group efforts.

There are no anticipated risks for participants in this study.

Who is conducting the study and who funds it?
The study is being conducted by Caroline Huang (doctoral student in The Ethox Centre and the project's principal investigator) and under the supervision of Michael Parker (Professor of Bioethics and Director of The Ethox Centre) and Anneke Lucassen (Professor of Clinical Genetics at The University of Southampton). The study is primarily funded through the principal investigator's Rhodes Scholarship, awarded by The Rhodes Trust.

How will personal data be handled?
All information collected during the course of the project will be kept confidential in accordance with the Data Protection Act of 1998 and viewed only by the three project researchers. Responses to the interviews and focus groups will be anonymised prior to analysis and reporting. Audio recordings of interviews and focus groups will be deleted once they are transcribed and the transcripts have been anonymised. All data will be stored securely within university servers and/or locked filling cabinets within The Ethox Centre. After the study, data will be retained for the time required by the University (currently 3 years after publication of the work). The names of participants will be deleted at the end of the study.

What will happen to the results of the research study?
A report will be produced at the end of the study based on findings from the interviews and focus groups, alongside critical review of policy documents and systematic review of how demographics shape barriers to and uptake of genetics services. This will include recommendations for how healthcare professionals and patient advocates/support group members can work towards appropriate access to care for BRCA mutations. A copy of the report will be made available from The Ethox Centre's website.

Additionally, the results of the study will be used in the principal investigator's doctoral thesis. The University of Oxford is committed to the dissemination of its research for the benefit of society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with open access, meaning it will be available to every internet user.

Who has reviewed the study against ethical guidelines?
This project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.

If you have any concerns, please speak to Caroline Huang, the principal investigator [E: caroline.huang@merton.ox.ac.uk, T: +44 1865 287887 (UK) or +1 302 383 0416 (US)], or Michael Parker, her primary supervisor (E: michael.parker@ethox.ox.ac.uk, T: +44 1865 287885), who will do her or his best to answer your query. Either researcher will acknowledge your concern within 10 working days and give you an indication of how it will be handled.

If you remain unhappy or wish to make a formal complaint, please contact the chair of the Medical Sciences Inter-Divisional Research Ethics Committee at the University of Oxford (ethics@medsci.ox.ac.uk; Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD). The chair will seek to resolve the matter in a reasonably expeditious manner.

How can I receive further information?
Should you have any questions or like any further information before deciding whether to participate, please contact any of the following:

Caroline Huang [E: caroline.huang@merton.ox.ac.uk, T: +44 1865 287887 (UK) or +1 302 383 0416 (US)]

Michael Parker (E: michael.parker@ethox.ox.ac.uk, T: +44 1865 287885)

Anneke Lucassen (E: a.m.lucassen@soton.ac.uk, T: +44 2381 206841)

Ethics approval reference: MSD-IDREC-C1-2014-021

Version 2, 8-Jul-14

8.5 Support group member participant information sheet

Ethical issues surrounding access to care for BRCA mutations
Patient advocate/support group member participant information sheet

This study examines how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations. The project is being supervised by Professor Anneke Lucassen (University of Southampton) and Professor Michael Parker (University of Oxford) and carried out through The University of Oxford's Ethox Centre. The results will be used to make recommendations about how healthcare professionals and patient advocates/support group members can work towards appropriate access to care for BRCA mutations, and to fulfil the requirements of a doctoral thesis.

You are being invited to take part in this research study, and this information sheet is designed to help you decide if you would like to participate. It explains what is being done and how.

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Why have I been invited?
You have been invited because you are a patient advocate/support group member who advocates on behalf of, or speaks with, women who may be offered genetics services for hereditary breast and ovarian cancer. You are also believed to be located in or near one of four cancer genetics communities: Oxford and Southampton in the United Kingdom, or Baltimore/Washington DC and Philadelphia in the United States.

Do I have to take part?
Participation is voluntary. It is up to you to take part, and you are free to withdraw without giving a reason at any time without penalty by advising the researchers of your decision.

If I decide to take part, what will be involved?
You will be asked to participate in a one-off focus group with the principal investigator in a location convenient to you, typically on site at one of the foundation trusts or university healthcare systems. The focus group will begin with each participant individually completing a

short paper and pencil task that asks you to think about how women are offered genetics services for hereditary breast and ovarian cancer. It will then progress to a semi-structured group discussion of your personal experiences and the experiences of other women you have spoken to, any relevant policies or guidelines governing their access to care, and any barriers you perceive to women receiving care.

If you are unable to make a focus group but would still like to participate, the principal investigator will try to interview you separately using the same paper and pencil task and semi-structured discussion.

Each focus group or interview will take up to 75 minutes total (10 minutes for the paper and pencil task, and up to 65 for the discussion). If you agree to it, audio recording will take place during the focus group or interview.

What benefits and risks are anticipated for participants in the study?
While there are no anticipated direct benefits to participants, indirect benefits may include contributing to a better understanding of the ethical issues that affect care for BRCA mutations. As the study findings will be fed back to interested participants, you may also be able to incorporate these findings into your clinical practice or patient advocacy/support group efforts.

There are no anticipated risks for participants in this study.

Who is conducting the study and who funds it?
The study is being conducted by Caroline Huang (doctoral student in The Ethox Centre and the project's principal investigator) and under the supervision of Michael Parker (Professor of Bioethics and Director of The Ethox Centre) and Anneke Lucassen (Professor of Clinical Genetics at The University of Southampton). The study is primarily funded through the principal investigator's Rhodes Scholarship, awarded by The Rhodes Trust.

How will personal data be handled?
All information collected during the course of the project will be kept confidential in accordance with the Data Protection Act of 1998 and viewed only by the three project researchers. Responses to the interviews and focus groups will be anonymised prior to analysis and reporting. Audio recordings of interviews and focus groups will be deleted once they are transcribed and the transcripts have been anonymised. All data will be stored securely within university servers and/or locked filling cabinets within The Ethox Centre. After the study, data will be retained for the time required by the University (currently 3 years after publication of the work). The names of participants will be deleted at the end of the study.

What will happen to the results of the research study?
A report will be produced at the end of the study based on findings from the interviews and focus groups, alongside critical review of policy documents and systematic review of how demographics shape barriers to and uptake of genetics services. This will include recommendations for how healthcare professionals and patient advocates/support group members can work towards appropriate access to care for BRCA mutations. A copy of the report will be made available from The Ethox Centre's website.

Additionally, the results of the study will be used in the principal investigator's doctoral thesis. The University of Oxford is committed to the dissemination of its research for the benefit of

society and the economy and, in support of this commitment, has established an online archive of research materials. This archive includes digital copies of student theses successfully submitted as part of a University of Oxford postgraduate degree programme. Holding the archive online gives easy access for researchers to the full text of freely available theses, thereby increasing the likely impact and use of that research.

If you agree to participate in this project, the research will be written up as a thesis. On successful submission of the thesis, it will be deposited both in print and online in the University archives, to facilitate its use in future research. The thesis will be published with open access, meaning it will be available to every internet user.

Who has reviewed the study against ethical guidelines?
This project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.

If you have any concerns, please speak to Caroline Huang, the principal investigator [E: caroline.huang@merton.ox.ac.uk, T: +44 1865 287887 (UK) or +1 302 383 0416 (US)], or Michael Parker, her primary supervisor (E: michael.parker@ethox.ox.ac.uk, T: +44 1865 287885), who will do her or his best to answer your query. Either researcher will acknowledge your concern within 10 working days and give you an indication of how it will be handled.

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Caroline Huang [E: caroline.huang@merton.ox.ac.uk, T: +44 1865 287887 (UK) or +1 302 383 0416 (US)]

Michael Parker (E: michael.parker@ethox.ox.ac.uk, T: +44 1865 287885)

Anneke Lucassen (E: a.m.lucassen@soton.ac.uk, T: +44 2381 206841)

Ethics approval reference: MSD-IDREC-C1-2014-021

Version 2, 8-Jul-14

8.6 Consent form





Consent Form for Healthcare Professionals and Patient Advocates/Support Group Members

Title of study: Ethical issues surrounding access to care for BRCA mutations

Researchers:
Caroline Huang, Doctoral Student and Principal Investigator
E: caroline.huang@merton.ox.ac.uk, T: +44 1865 287887 (UK) or +1 302 383 0416 (US)
Michael Parker, Professor of Bioethics, Director of The Ethox Centre, and Project Supervisor
E: michael.parker@ethox.ox.ac.uk, T: +44 1865 287885
Anneke Lucassen, Professor of Clinical Genetics at Southampton and Project Supervisor
E: a.m.lucassen@soton.ac.uk, T: +44 2381 206841

Purpose of the study: This study examines how ethical issues affect access to care for BRCA (breast cancer susceptibility gene) mutations.

Study declarations: Please initial the boxes below if you agree with the corresponding statements.

1. I have read and understand the information sheet provided to me about this study dated 8-Jul-14. I have had the opportunity to consider the information, to ask questions and request any additional details, and to have these questions and requests handled satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without penalty by advising the researchers of my decision. ☐
3. I understand that this project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee. ☐
4. I understand who will have access to personal data provided, how the data will be stored, and what will happen to the data at the end of the project. ☐
5. I understand that the research will be written up in the principal investigator's thesis and how personal data included in that thesis will be published and stored. ☐
6. I understand that audio recording will be used to assist with the accuracy of participants' responses and that I am free to request the equipment be switched off at any time during the interview. ☐

7. I understand that while direct quotations may be used in reporting the study, these will be anonymised. ☐

8. I agree to take part in the study. ☐

9. I understand how to raise a concern and make a complaint. ☐

……..	……	……..
Name of participant	Date	Signature
……..	……	……..
Researcher	Date	Signature

(copy for participant, copy for research files)

Ethics approval reference: MSD-IDREC-C1-2014-021

Version 2, 8-Jul-14

8.7 Process mapping handout

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

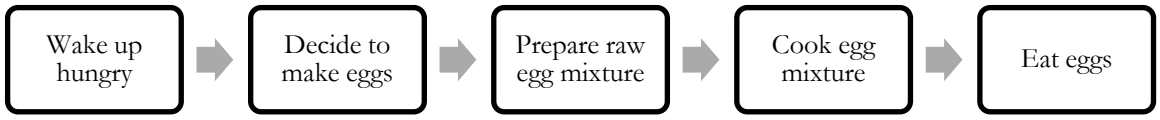
Date: _____ Participant ID: _____

(Optional but helpful to know)

Age: _____ City of residence: _____

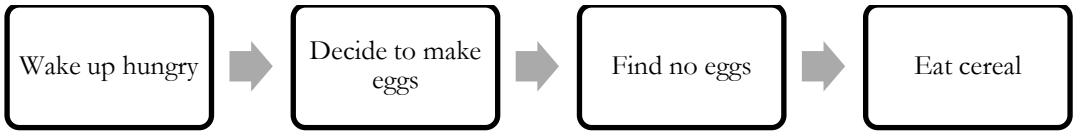
Race/ethnicity: _____ Highest degree attained: _____

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

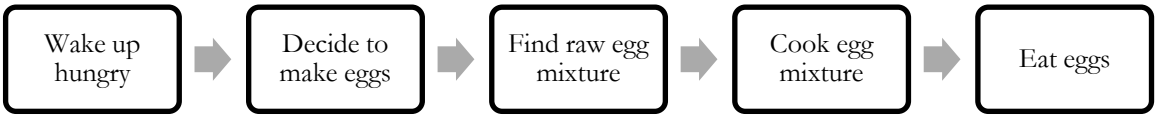


Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



The third person decided to make eggs and found her flatmate had already prepared an egg mixture for the two of them to share, so she was able to streamline the third step.



Finding no eggs and eating cereal instead could be called a 'barrier' to having eggs, since eating eggs is harder to do when there are no eggs in the kitchen. Likewise, finding an already-prepared mixture might be called a 'facilitator' to having eggs, since eating eggs is easier to do if someone has done part of the preparation for you.

With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

8.8 Focus group guide

Ethical issues surrounding access to care for BRCA mutations: Focus group guide

Group type: Site:

Number of participants: Date:

Start time: End time:

Thank you for participating in this focus group. The goal of this group is to hear your experiences of, and thoughts on, access to care for BRCA mutations. Your responses will help contextualise findings from the literature as well as real-world effects of current regulatory practices.

First, some ground rules to promote confidentiality.

- What is discussed in the focus group should not be discussed outside the focus group.
- Please try to use the numbers you have been assigned.
- Only one person speaks at a time.
- You are here participating voluntarily, which means you do not have to answer any question if it makes you feel uncomfortable.

Process mapping exercise for patient pathways (opening exercise)

To begin, we're going to start with an individual exercise. {Instructions are on the actual sheet.}

(1a) In words, what process do you think most people follow to receive care for BRCA mutations?

(1b) Was your second process map much different than the first? Why do you think that was?

(1c) When you think about the phrase 'care for BRCA mutations ', what kinds of care do you think would be included? Would the kinds of care discussed now change your map?

Who gets access?

(2a) What kind of people do you think access care for BRCA mutations? [If necessary: describe what you think the typical patient is like]

(2b) Do you think there are patients who need care they don't get? Why?

(2c) Do you think there are patients who get care they don't need? Why?

Factors determining access to counselling and testing

(3a) What kinds of things do you think determine access? Why?

(3b) Are you aware of any clinical guidelines that might affect access to care? Which ones? How do you think they might affect access?

(3c) Are you aware of any legislation, legal rulings, or industry agreements that might affect access to care? Which ones? How do you think they might affect care?

(3d) Can you think of any other ways that patients can access care other than through their doctors? [Should there be other ways to access care?] [If nothing: what do you think about direct-to-consumer? Participation through research? Self-referral to a genetic service?]

Barriers and facilitators

(4a) What things make it harder for individuals to access care? [Follow-up: are these different for counselling, testing, or post-test care (screening, medication, or surgery)?]

(4b) What things make it easier for individuals to access care? [Follow-up: are these different for counselling, testing, or post-test care (screening, medication, or surgery)?]

(4c) Share what is in the literature. Factors associated with uptake, including barriers and facilitators, fell into the following four categories: demographic (age, children, income, education), clinical (other types of care a person has received, relationship with clinician, referral), awareness (knowledge of genetics, knowledge of actual risk for a mutation), and psychosocial (anxiety about cancer, confidence in overcoming difficult situations). Do any of these findings surprise you?

Revisit process mapping exercise

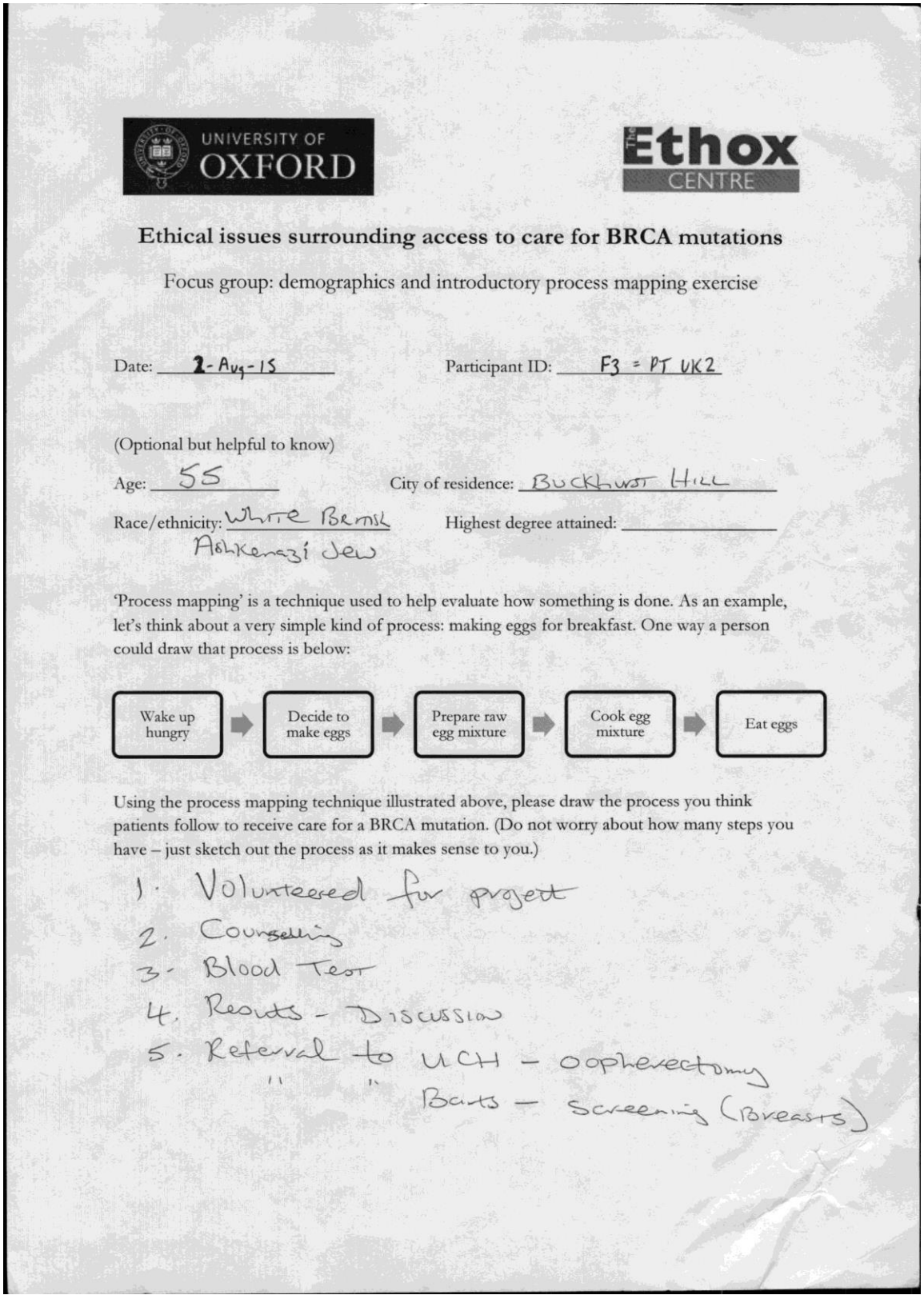
(5a) Given the discussion from today, would you change your second drawing of a pathway to care? If so, how would it change? If not, why not?

Additional questions from group

(6a) What else would you like to ask the group? Should I know anything else about your experience of accessing care?

8.9 Sample process maps

8.9.1 UK support group member UKPT2 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 2-Aug-15 Participant ID: F3 = PT UK2

(Optional but helpful to know)

Age: 55 City of residence: Buckhurst Hill

Race/ethnicity: White British Ashkenazi Jew Highest degree attained: _____

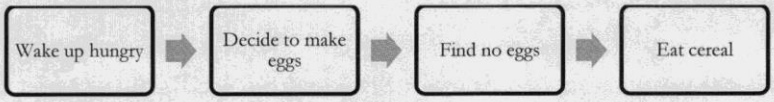
'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

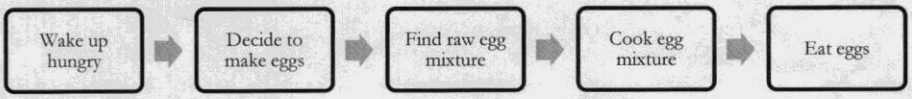
Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

1. Volunteered for project
2. Counselling
3. Blood Test
4. Results - Discussion
5. Referral to UCH - oophorectomy
   " " Barts - Screening (Breasts)

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



The third person decided to make eggs and found her flatmate had already prepared an egg mixture for the two of them to share, so she was able to streamline the third step.

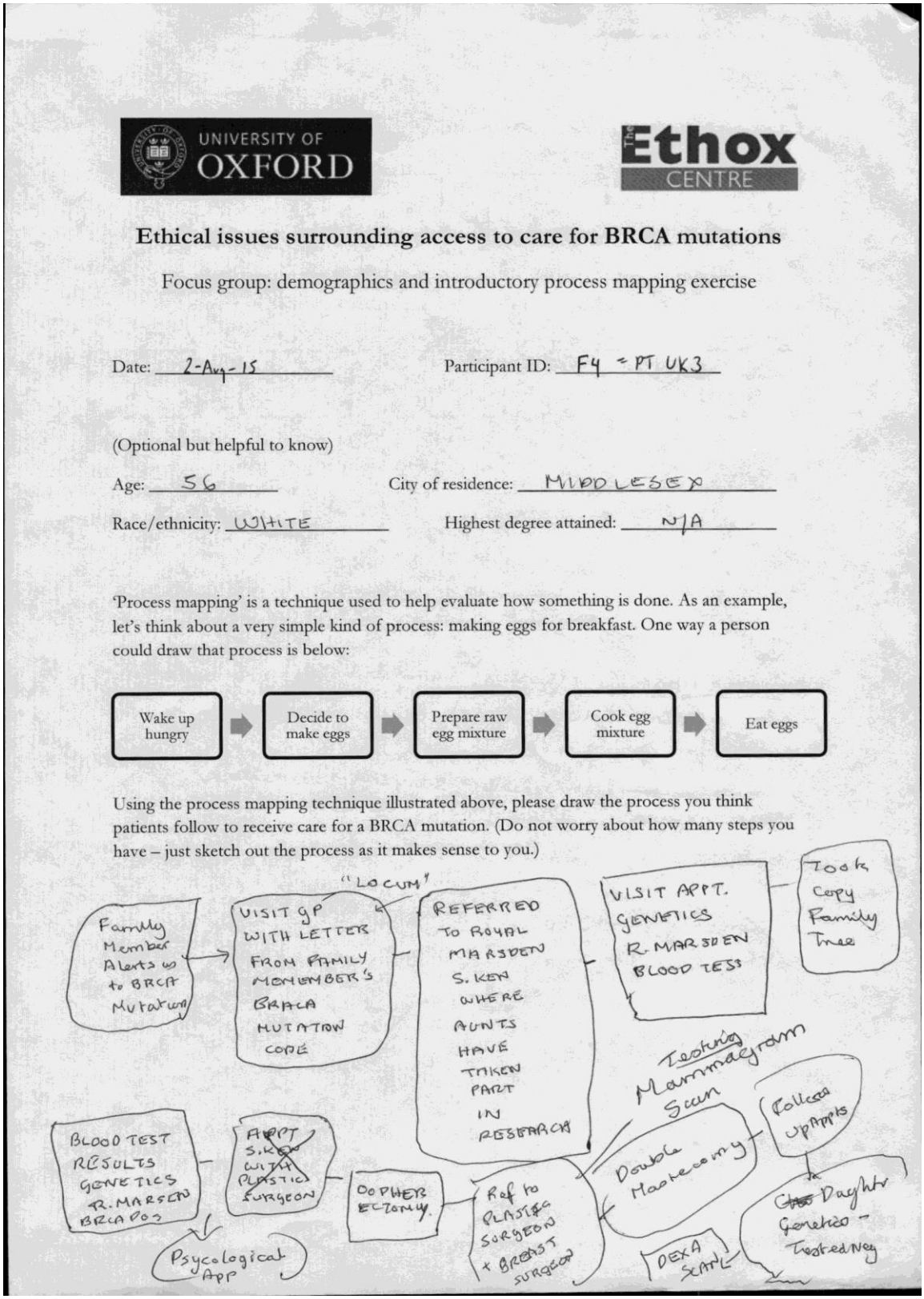


Finding no eggs and eating cereal instead could be called a 'barrier' to having eggs, since eating eggs is harder to do when there are no eggs in the kitchen. Likewise, finding an already-prepared mixture might be called a 'facilitator' to having eggs, since eating eggs is easier to do if someone has done part of the preparation for you.

With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

1. Believe there maybe a genetic problem.
B. 2. Approach GP who is NOT knowledgable on BRCA
3. GP reluctantly refers patient to a Genetic Counsellor
F. 4. Visit Genetic Counsellor who agrees to test
B. 5. Results are positive but only limited info is available.

8.9.2 UK support group member UKPT3 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 2-Aug-15 Participant ID: F4 = PT UK3

(Optional but helpful to know)

Age: 56 City of residence: MIDDLESEX

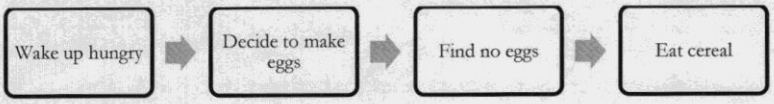
Race/ethnicity: WHITE Highest degree attained: N/A

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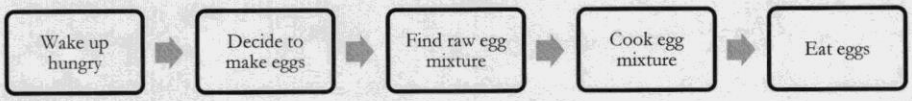
Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



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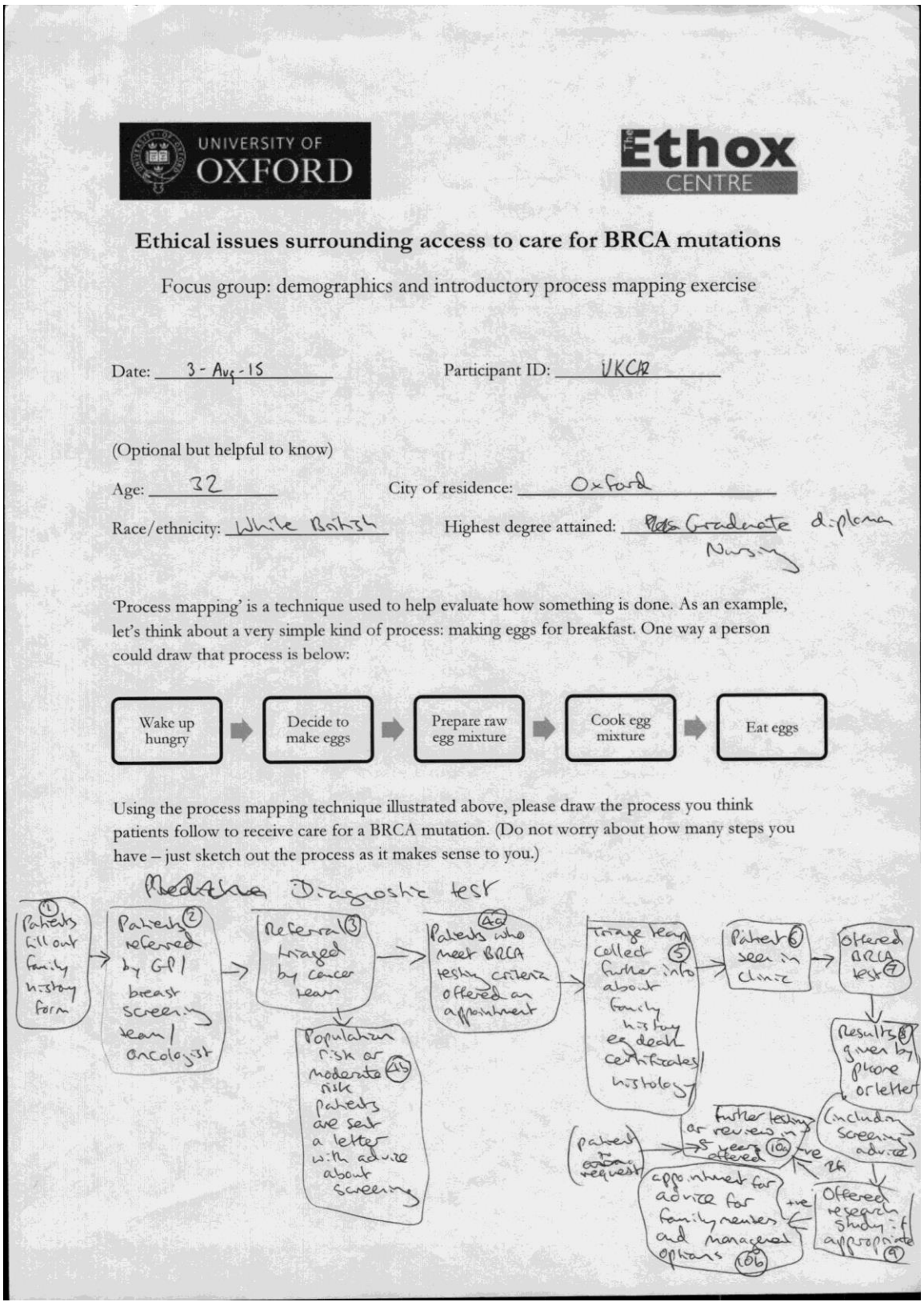
Genetics Appt (R. Marsden now swamped with enquiries since Angelina Jolie "effect") B

Genetic Blood Test + Result → Psychological Ass. of positive Person what next – surgery – surveillance

Meeting with consultants Plastics + Breast Surgeon – + Women's Surgery.

Surgery – Oophamtery + Double Mascotomy

8.9.3 UK clinician UKCA2 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 3 - Aug - 15 Participant ID: UKCA2

(Optional but helpful to know)

Age: 32 City of residence: Oxford

Race/ethnicity: White British Highest degree attained: Post Graduate diploma Nursing

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Pathway Diagnostic test

1 Patients fill out family history form

2 Patients referred by GP/ breast screening team/ oncologist

3 Referral triaged by cancer team

4a Patients who meet BRCA testing criteria offered an appointment

4b Population risk or moderate risk patients are sent a letter with advice about screening

5 Triage team collect further info about family history eg death certificates/ histology

6 Patient seen in clinic

7 Offered BRCA test

8 Results given by phone or letter

9 Offered research study if appropriate

10a Further testing or reviews in 5 years offered

10b Appointment for advice for family review and managerial options

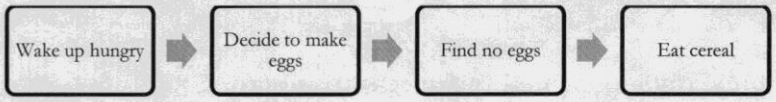
(including screening advice)

Patient requests

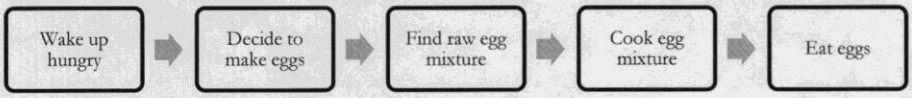
+ve

-ve

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



The third person decided to make eggs and found her flatmate had already prepared an egg mixture for the two of them to share, so she was able to streamline the third step.



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With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

(1)

B - Patient does not know how to get referral or what one is appropriate

F - GP/oncologist takes family history and checks against referral criteria routinely

(2)

F - oncologist orders test before referring appropriate patients

B - Referrer unaware of referral criteria/ how to refer

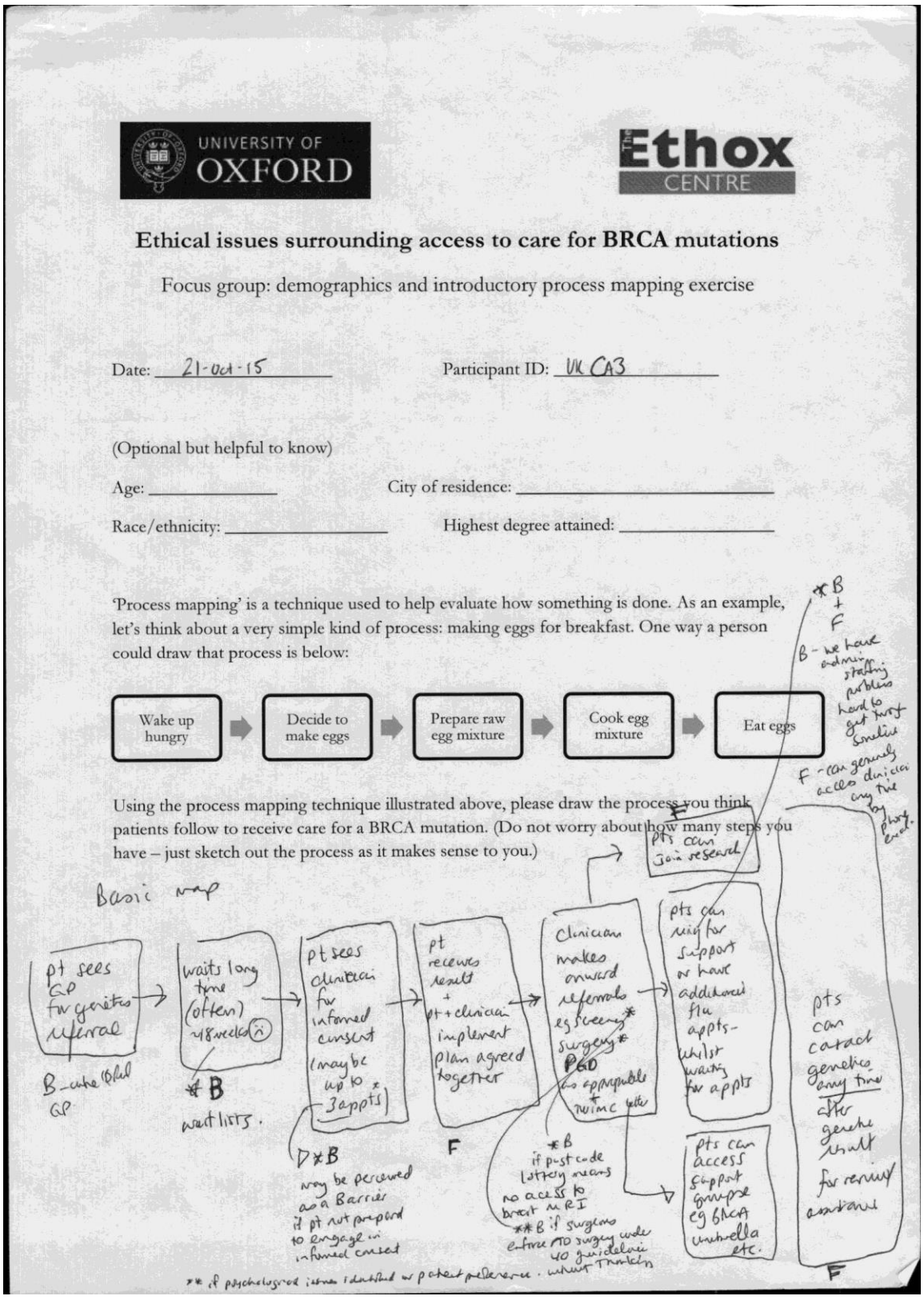
(5)

B - difficult to get info about other family members

(6)

B - waiting list

8.9.4 UK clinician UKCA3 (front only – did not draw on back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 21-Oct-15 Participant ID: UK CA3

(Optional but helpful to know)

Age: _____ City of residence: _____

Race/ethnicity: _____ Highest degree attained: _____

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Basic map

pt sees GP for genetics referral

B - cuts (Bld GP

waits long time (often) >18 weeks ☹

*B

wait lists.

pt sees clinician for informed consent (may be up to 3 appts) *

▷*B may be perceived as a Barrier if pt not prepared to engage in informed consent

pt receives result + pt + clinician implement plan agreed together

F

Clinician makes onward referrals eg screen* surgery* PGD as appropriate + RWMC refer

*B if post code lottery means no access to breast MRI

**B if surgeon enforces NO surgery under 40 guidelines

pts can wait for support or have additional flu appts - whilst waiting for appts

pts can access support groups eg BRCA umbrella etc.

pts can contact genetics any time after genetic result for review as needed

F

F

F - can generally access clinician any time by phone/email

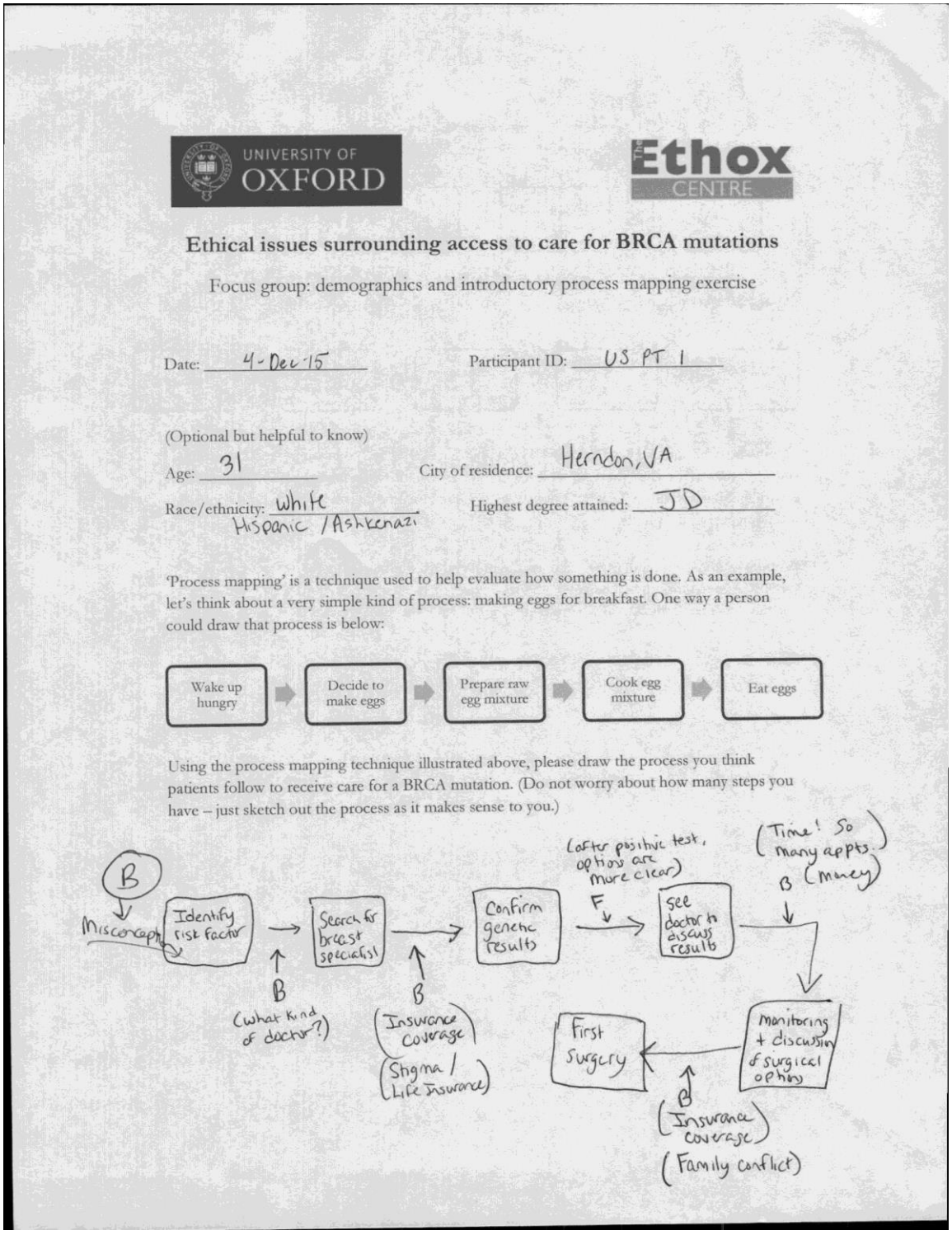
*B + F

B - we have admin + staffing problems hard to get appt sometimes

pts can join research

** if psychological issues identified or patient preference - refer to Thinklin

8.9.5 US support group member USPT1 (front only – did not draw on back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 4-Dec-15 Participant ID: US PT 1

(Optional but helpful to know)

Age: 31 City of residence: Herndon, VA

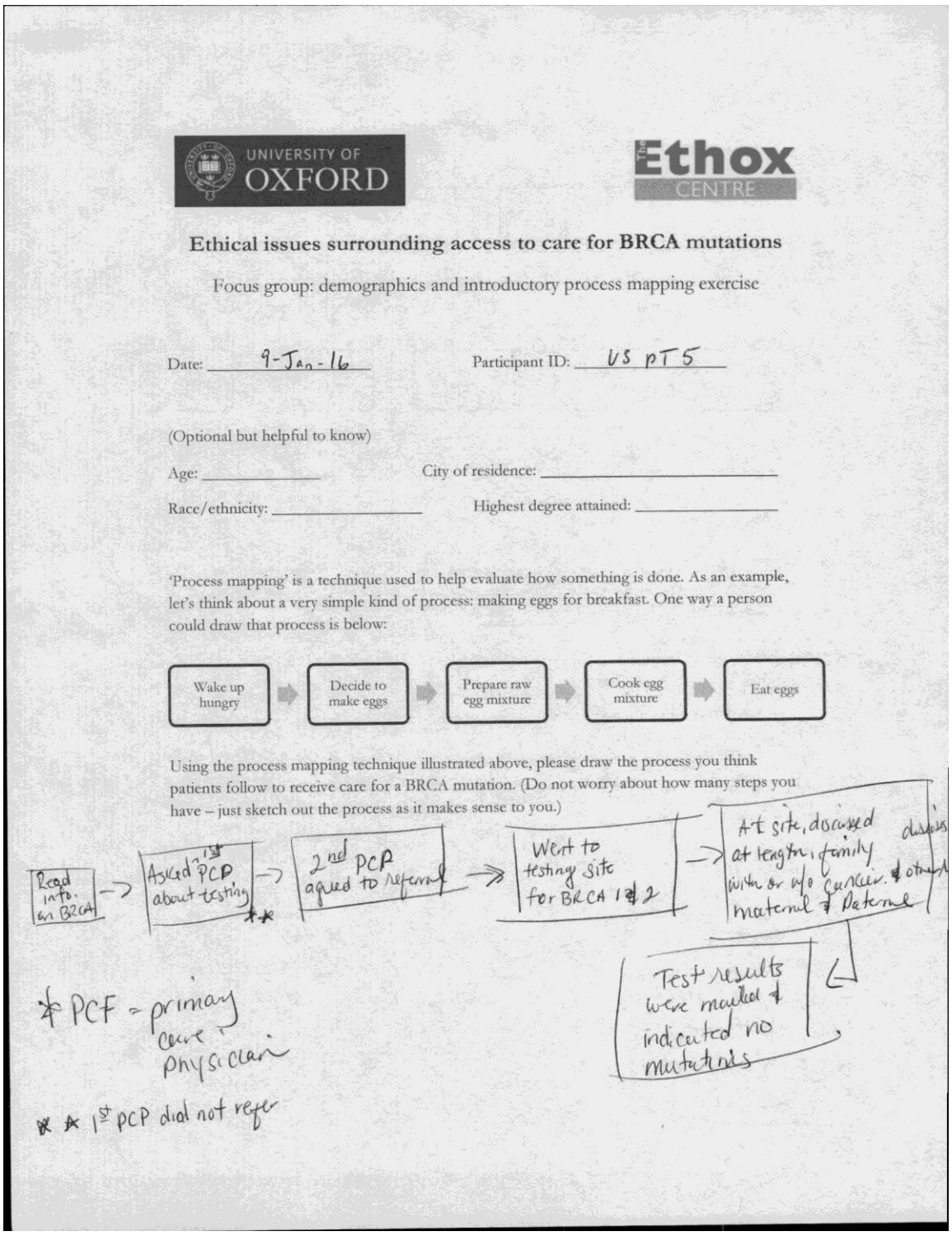
Race/ethnicity: White Hispanic / Ashkenazi Highest degree attained: JD

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

8.9.6 US support group member USPT5 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 9-Jan-16 Participant ID: US PT 5

(Optional but helpful to know)

Age: _____ City of residence: _____

Race/ethnicity: _____ Highest degree attained: _____

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

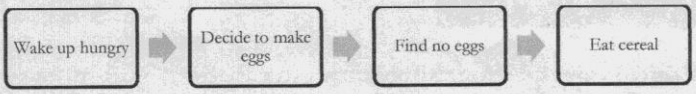
Read info. on BRCA → Asked 1st PCP about testing ** → 2nd PCP agreed to referral → Went to testing site for BRCA 1 & 2 → At site, discussed at length, family with or w/o cancer. & other maternal & Paternal

Test results were mailed & indicated no mutations

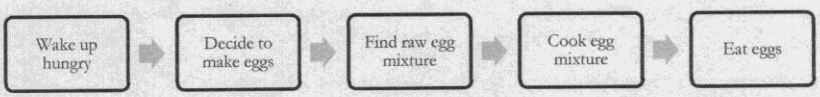
* PCP = primary care physician

** 1st PCP did not refer

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



The third person decided to make eggs and found her flatmate had already prepared an egg mixture for the two of them to share, so she was able to streamline the third step.



Finding no eggs and eating cereal instead could be called a 'barrier' to having eggs, since eating eggs is harder to do when there are no eggs in the kitchen. Likewise, finding an already-prepared mixture might be called a 'facilitator' to having eggs, since eating eggs is easier to do if someone has done part of the preparation for you.

With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

Read info on BRCA →

Asked 1st PCP for testing. He suggested testing be performed @ a later time (post mastectomy) Or since no family history, may not be necessary. I asked to be seen by another PCP (2nd PCP)

B

→ 2nd PCP was more understanding. She agreed that BRCA can be tested later but pre-surgery is also OK. I expressed discomfort w/ testing post surgery &/or having chemo/radiation w/o knowing BRCA testing

F

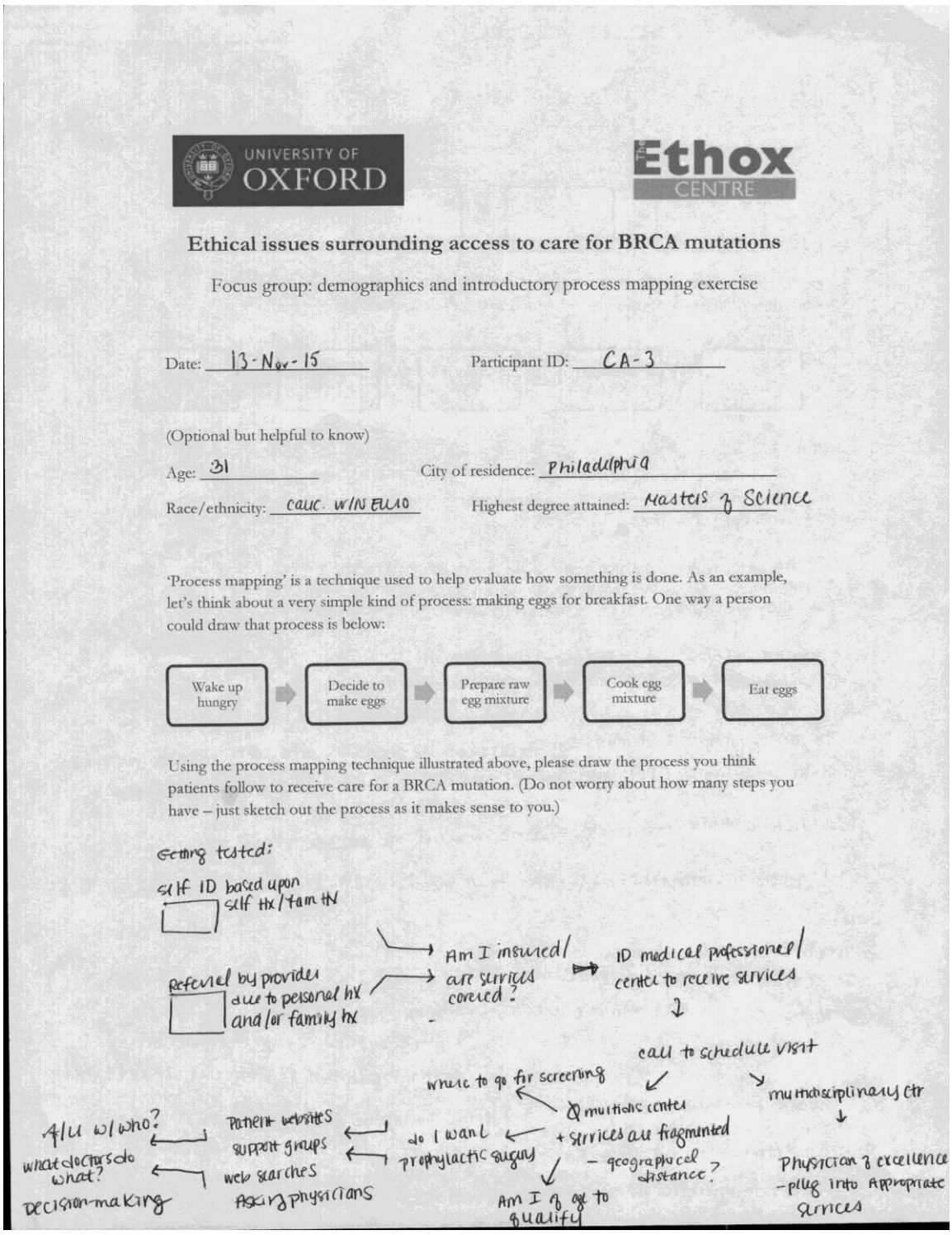
→ BRCA testing went well. The assistant was open to all questions & explained thoroughly

F

Post-Results, I asked about other genetic testing i.e. (LF) or any others & was denied

B

8.9.7 US clinician USCA3 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 13-Nov-15 Participant ID: CA-3

(Optional but helpful to know)

Age: 31 City of residence: Philadelphia

Race/ethnicity: Cauc. W/N Ellio Highest degree attained: Masters of Science

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry → Decide to make eggs → Prepare raw egg mixture → Cook egg mixture → Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Getting tested:

self ID based upon self hx/fam hx

referral by provider due to personal hx and/or family hx

Am I insured/ are services covered?

ID medical professional/ center to receive services

call to schedule visit

where to go for screening

Q multidisc center

multidisciplinary ctr

+ services are fragmented

- geographical distance?

Physician of excellence - plug into appropriate services

Am I of age to qualify

do I want prophylactic surgery

Patient websites

support groups

web searches

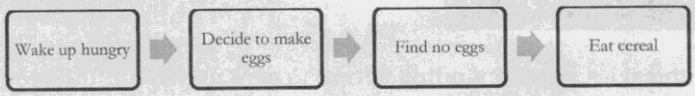
Asking physicians

f/u w/ who?

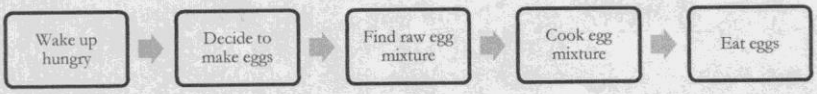
what doctors do what?

Decision-making

Returning to the breakfast example, imagine two other people also wanted eggs. The second person decided to make eggs, realised there were no eggs, and settled on cereal instead.



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With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

Potential barriers:

① insufficient insurance coverage – ∅ insured
– poorly insured
\ High deductible plans

③ general WHO status.

② lack of appropriate identification for services by providers who dln manage high risk families regularly (PCP, gyn, general internist), therefore, lack of referral

③ Misconceptions regarding genetic discrim. & genetic stigma

④ geographic barriers – ∅ close" to ↑ quality ctr or general services

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facilitators:

① nearby to major academic med ctrs.

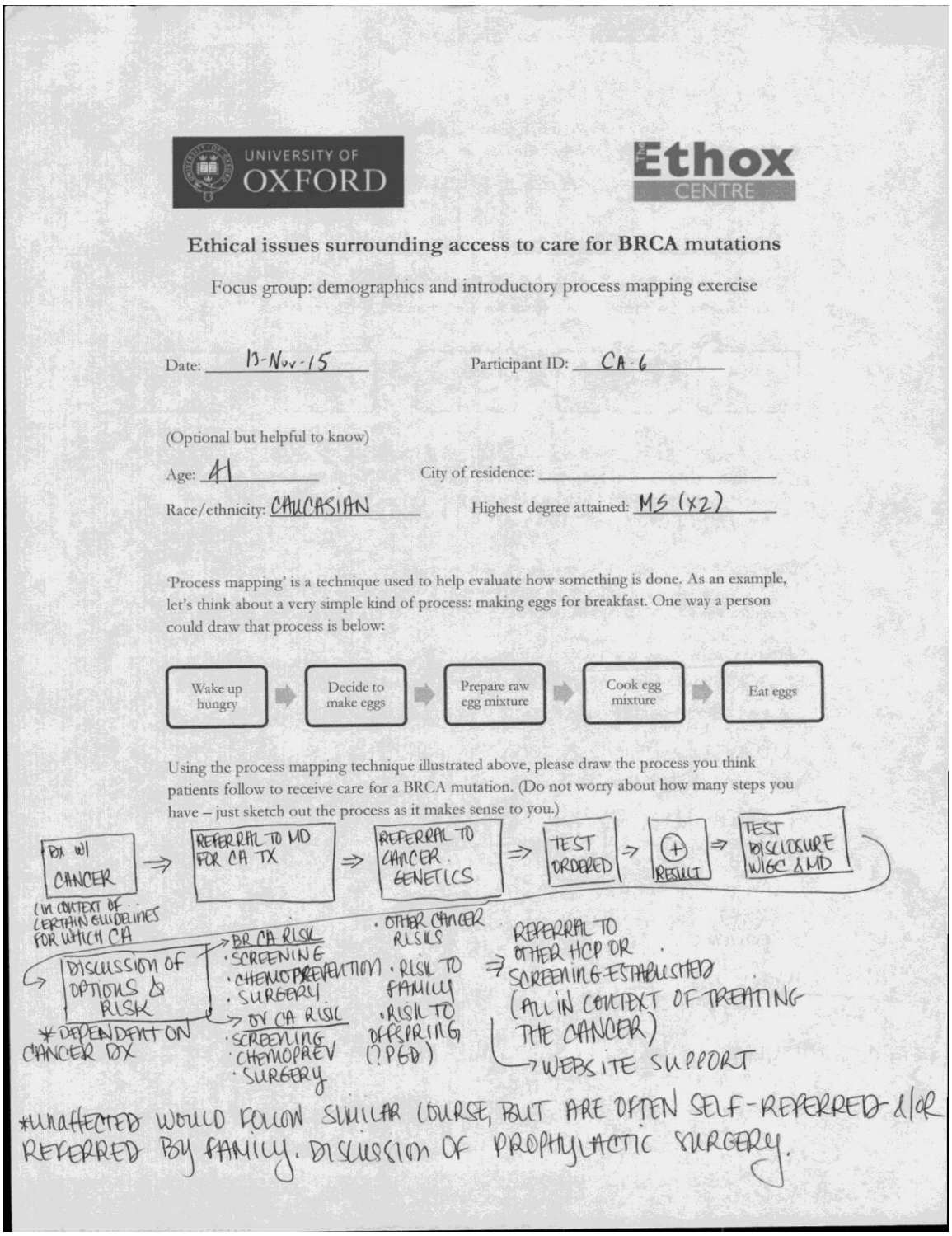
② Higher SES – more highly educated → more self advocacy
↘ plugged in w/ expert providers
↳ better equipped to seek out correct info

③ non-capitating insurance plans + having insurance in general

④ supportive family dynamics

⑤ Access to genetic services – genetic counselors to navigate issues if "all of the above"

8.9.8 US clinician USCA6 (front and back)



UNIVERSITY OF OXFORD

The Ethox CENTRE

Ethical issues surrounding access to care for BRCA mutations

Focus group: demographics and introductory process mapping exercise

Date: 13-Nov-15 Participant ID: CA-6

(Optional but helpful to know)

Age: 41 City of residence: _____

Race/ethnicity: CAUCASIAN Highest degree attained: MS (x2)

'Process mapping' is a technique used to help evaluate how something is done. As an example, let's think about a very simple kind of process: making eggs for breakfast. One way a person could draw that process is below:

Wake up hungry ⇒ Decide to make eggs ⇒ Prepare raw egg mixture ⇒ Cook egg mixture ⇒ Eat eggs

Using the process mapping technique illustrated above, please draw the process you think patients follow to receive care for a BRCA mutation. (Do not worry about how many steps you have – just sketch out the process as it makes sense to you.)

Dx w/ CANCER (IN CONTEXT OF CERTAIN GUIDELINES FOR WHICH CA) ⇒ REFERRAL TO MD FOR CA TX ⇒ REFERRAL TO CANCER GENETICS ⇒ TEST ORDERED ⇒ (+) RESULT ⇒ TEST DISCLOSURE W/GC & MD

DISCUSSION OF OPTIONS & RISK (*DEPENDENT ON CANCER DX)

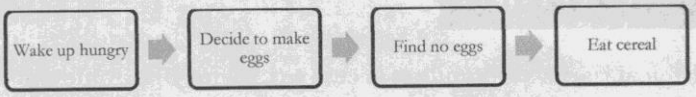
- BR CA RISK
  - SCREENING
  - CHEMOPREVENTION
  - SURGERY
- OV CA RISC
  - SCREENING
  - CHEMOPREV
  - SURGERY
- OTHER CANCER RISKS
- RISK TO FAMILY
- RISK TO OFFSPRING (?PGD)

⇒ REFERRAL TO OTHER HCP OR SCREENING ESTABLISHED (ALL IN CONTEXT OF TREATING THE CANCER)

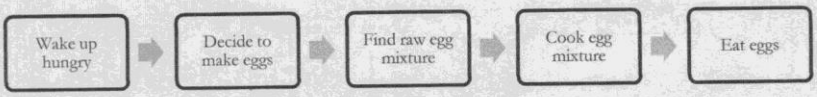
→ WEBSITE SUPPORT

*UNAFFECTED WOULD FOLLOW SIMILAR COURSE, BUT ARE OFTEN SELF-REFERRED &/OR REFERRED BY FAMILY. DISCUSSION OF PROPHYLACTIC SURGERY.

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With these things in mind, please re-draw the process you think patients follow to receive care for BRCA mutations, including any potential barriers or facilitators you think they might encounter. Put a 'B' next to any barriers to care and an 'F' next to any facilitators.

BARRIERS TO CARE
1. ECONOMIC (NO INSURANCE FOR TESTING NOR COUNSELING)
2. EDUCATION (NO HCP HAS DISCUSSED TEST W/ PT)
3. MISINFORMATION (PT TOLD THEY ARE NOT A CANDIDATE OR TEST NOT RECOMMENDED)
4. HEALTH MISINFORMATION ("I WAS TOLD IF I HAVE A BRCA MUT, I MUST HAVE B/L MASTECTOMY)
5. FEAR OF KNOWING
6. FEAR OF INSURANCE DISCRIMINATION
7. ACCESS (NO GC, MD TO DO TEST), PT DOESN'T WANT TO TRAVEL

FACILITATORS
1. LARGE ACADEMIC INSTITUTIONS W/ACCESS TO GENETICS
2. EDUCATIONAL PROGRAMS (COMMUNITY/MD OUTREACH)
3. FREE/DISCOUNTED TESTING
4. GINA LAW TO ALLAY FEARS OF DISCRIMINATION
5. GENETIC COUNSELORS!!!
6. ONCOLOGISTS/GYNS MAKING APPROPRIATE REFERRALS