The Ethics of Global Psychiatric Genomics: Multilayered Challenges to Integrating Genomics in Global Mental Health and Disability

A Position Paper of Oxford Global Initiative in Neuropsychiatric GenEthics (NeuroGenE)

Short Title: The Ethics of Global Psychiatric Genomics

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Abstract

Psychiatric genomics has the potential to radically improve the prevention and early intervention of serious mental and neurodevelopmental disorders worldwide. However, little work has been done on the *ethics* of psychiatric genomics – an oversight that could result in poor local uptake, reduced practical / clinical application, and ethical violations in this rapidly developing area of scientific research. As part of the Global Project of the Stanley Center for Psychiatric Research, Global Initiative in Neuropsychiatric GenEthics (NeuroGenE) based at the University of Oxford aims to embed ethical inquiry within scientific investigation and engage with fundamental ethical questions around a psychiatric genomics approach to mental and neurodevelopmental disorder. This position paper sets out the core aims of the NeuroGenE research programme and explores the importance of a cross-cutting research orientation in this field based on multidisciplinary methodologies which can ensure that efforts to translate and apply global psychiatric genomics in public policy and clinical practice are ethically grounded strategies, respectful of different cultures and contexts.

Keywords: psychiatric genomics, ethics, disability, mental disorder

Introduction / Rationale

Psychiatric genomics research has accelerated rapidly in recent years and now forms a core pillar of major scientific and mental health research programs. Through population wide association studies, psychiatric genomics examines the biogenetic causes for neurological traits underlying major psychiatric disorders, with the goal of generating a more nuanced psychiatric nosology and improve preventative and targeted treatments within a precision-medicine framework (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Sullivan et al., 2017). Thus far, genome-wide association studies have mainly targeted samples from European populations. Recognising the need to diversify representative populations, the Global Project of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard has embarked on an ambitious initiative to broaden sample collections of populations within sub-Saharan Africa, (Kenya, Ethiopia, Uganda, South Africa), Asia (China and Japan), and eventually South America, in order to probe the underlying biological mechanisms for mental and neurodevelopmental disorders (such as psychosis and autism).

In theory, psychiatric genomics presents a potentially transformative approach that could rapidly advance precision medicine in the field of psychiatry in the global context. As laudable as this aim is, how its goals and aspirations are to succeed in the global context is a significant concern for two reasons: first, psychiatric genomics will not be practically applicable if there is little engagement with a range of ethical issues that are raised in this approach; second, there is a risk that ethical violations could occur in research and application if these issues are not examined carefully. The *ethics* of psychiatric genomics from local and global perspectives has garnered little systematic attention thus far (Kong et al., 2017), though increased ethical attention on the implications of psychiatric genomics in the American context has been particularly welcome in current projects funded by the National Human Genome Research Institute's Ethical, Legal and Social Implications (ELSI) Research Program.

As part of the Stanley Global Project, the Global Initiative in Neuropsychiatric GenEthics (NeuroGenE) based at the University of Oxford seeks to fill in the notable gap in research around the bioethical implications of psychiatric genomics in the *global* context. In this paper we set out the core aims of the NeuroGenE research programme and promote a cross-cutting approach towards key debates within global mental health, genomics, and disability studies in addressing overarching research themes in the ethics of global psychiatric genomics, through the use of diverse methodologies and adherence to core guiding principles. A significant amount of work has already been carried out in the fields of global mental health and transcultural psychiatry. However, we clarify the unique ethical issues of global psychiatric genomics which warrant further special critical attention to ensure pressing ethical considerations – such as potential harms and putative benefits,

responsibilities and duties to disadvantaged, stigmatised individuals, local communities and cultures – remain foremost in future ELSI projects as well as practical and clinical applications.

Aims of NeuroGenE

NeuroGenE is a multilayered research and training programme focused on the ethics of psychiatric genomics within the global context. The ultimate goal of the programme is to ensure the responsible conduct and uses of scientific research, such that the research contributes to improvements in the treatment of and respect for persons facing mental health challenges, their families and their carers. An equally important, parallel goal is to identify how scientific research on psychiatric genomics can best respect and benefit local communities; including local stakeholders, practitioners, and scientific infrastructures.

The NeuroGenE project is structured along three related levels of research: (i) pragmatic inquiry; (ii) substantive inquiry; and (iii) policy / practice application. *Pragmatic inquiry* examines the ethical questions embedded within scientific investigation of psychiatric genomic data, including issues related to data collection and ownership, biobanking, and research procedure. *Substantive inquiry* critically examines deeper questions around the conceptual grounding, cultural translation, and normative implications of a psychiatric genomic lens to mental health within the global setting. These two levels of inquiry will feed into investigations on *policy / practice application*, exploring how an ethically grounded approach to psychiatric genomics should inform national and international policies in public health, as well as local practices of community mental health treatment.

Current Status of Research

The ethics of global psychiatric genomics intersects with the existing fields of research within genomics, global mental health, and disability studies. Alongside scientific research into the genomics of physical conditions, ethical discussions have explored core issues around the protection of research participants (e.g. community consent and consultation) and scientists in low-income countries (e.g. data-sharing and capacity-building), as well as the regulatory mechanisms of international collaborations (e.g. sample storage, ownership, and export) (de Vries et al., 2011). Questions of genetic identity, responsibility, and the ethics of return of results have also been part of bioethical discussions within the clinical context (Lázaro-Muñoz et al., 2018; Novas & Rose, 2000; Easter, 2012; Phelan et al., 2006; Miller et al., 2008; Knoppers et al., 2006; Jarvik et al., 2014).

Meanwhile, global mental health discussions readily identify the urgent need for collective action, investment, and innovative solutions to address chronic inequality and poor delivery of mental health care in the global context (Collins & Saxena, 2016; Patel et al., 2013). Gaps in treatment and care, both *within* and *across* countries – remain foremost in these debates, particularly with regards to

resource allocation, policy priorities, and service provision. Other strands of global mental health focus on the justification of a *global* mental health framework to *local* cultural contexts, beliefs, and social practices around mental disorder, sometimes questioning the portability of standard diagnostic tools and treatment recommendations (Sax, 2014; Read, 2009).

Recent research in disability studies echo this scepticism towards standard diagnostic tools, both for treatment and research, and highlight instead the systemic structures (i.e. public policy, laws, societal norms) that discriminate against and inhibit the full respect of persons with disabilities – including those with mental and neurodevelopmental disorders. Increasingly important in disability studies is the co-production of knowledge by persons with disabilities and survivors of psychiatry in alignment with a human rights lens that recognises their right to equal participation and structural accommodations (Charlton, 1998; UN Committee on the Rights of Persons with Disabilities, 2014; Dhanda, 2007; McDonald et al., 2013; Iacono & Carling-Jenkins, 2012; Wickenden & Kembhavi-Tam, 2014).

On one hand, critical engagement with these debates is crucial if the scientific research and application of global psychiatric genomics is to have sufficient ethical grounding: concerns around the genomics of psychiatric conditions will be similar to those of physical conditions in certain respects, whilst the investment and potential application of psychiatric genomics raises important questions around the resource distribution and local translation concerns within global mental health research. Moreover, engaging with core debates in disability studies will clarify the role and impact of psychiatric genomics in advocacy efforts to protect and promote the rights of individuals with mental and neurodevelopmental disorders.

On the other hand, each field of inquiry in isolation captures only a partial picture of the complex ethical challenges facing the research and practical application of psychiatric genomics. Capturing intersections in these three different areas is vital to articulate the unique substantive ethical challenges which emerge with this genomics focus in mental health and intellectual disability, as compared to that of physical conditions. Exclusive attention to the ethics of genomics draws particular focus on well-researched areas of genetic identity and data sharing issues. *Global psychiatric* genomics, however, raises singular additional questions beyond these issues, including the putative warrant of 'geneticising' behavioural phenotypes, the problematic ethical justification of early intervention / prevention of certain mental and neurodevelopmental conditions, the debatable portability and acceptance of psychiatric diagnostic categories and biogenetic models of mental disorder causation in the global context, and the particular stigma that is attached to mental disorder and intellectual disability. Overcoming these challenges will ultimately depend on detecting where the ethical faultlines lie in the first instance. This demands an original *cross-cutting* approach that generates *dialogue between these debates rather than a singular research orientation* (Fig.1).

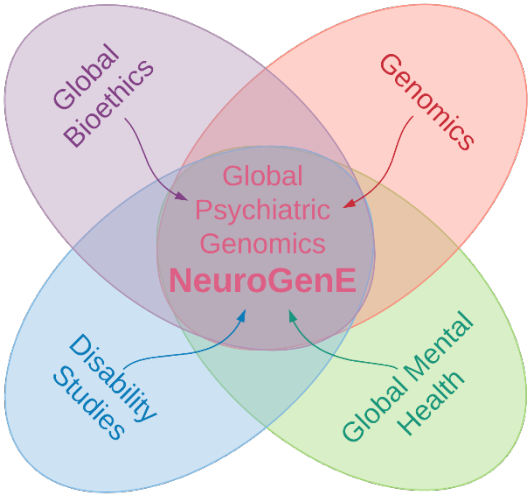

Figure 1: NeuroGenE Programme of Research

Importantly, these different areas of research have yet to be bridged in a single programme of bioethical inquiry. We maintain that a broadened intellectual orientation is necessary if innovative ethical inquiry and solutions are to be developed to confront these thorny issues in the context of global psychiatric genomics. As we discuss below, three major ethical faultlines are brought into sharp relief once a cross-cutting approach is adopted.

Early Intervention and Dimensional Approaches to Mental Disorder and Disability

Potential changes in psychiatric diagnostic classification to pursue early intervention and prevention strategies towards mental disorder and intellectual disability reveal a major faultline that is specific and unique to psychiatric genomics. Importantly, profound ethical implications around the diagnostic and early intervention aspirations of psychiatric genomics remain hidden until a cross-cutting approach is adopted, revealing uneasy tensions with the ethical orientation in disability research and advocacy.

Psychiatric genomics tracks important conceptual changes in mental health, moving away from dichotomous classifications of 'health' and 'disease/illness' and towards a more dimensional understanding which accommodates a spectrum of experiences between mental health to disorder and disability. As a 'symptom spectra' (Patel et al., under review), risk alleles for mental disorders can be present in *both* affected and unaffected people, whilst multiple disorders have common genetic aetiology and environmental risk factors (Owen, 2012). Not only do these findings invite greater nuance to diagnostic classifications of mental disorder, but the range of mental health interventions is also broadened to encompass early preventative strategies in addition to treatment and rehabilitation (Patel et al., under review).

At first glance, this dimensional approach appears consistent with recent changes to classifications of disability. The World Health Organization's International Classification of Functioning, Disability and Health (ICF) similarly charts health and disability along a multidimensional continuum based on a taxonomy of body functions, corresponding body structures, and contextual, environmental, and personal factors that impact on components of body functioning (WHO, 2002; Kostanjsek, 2011). Functioning and disability are conceived of as universal phenomena that all people experience over their life-span. Echoing this spectrum view is the UN Convention of the Rights of Persons with Disabilities (CRPD), a potentially transformative human rights framework that articulates the rights and obligations owed to individuals with disabilities, including positive societal, cultural, and state provisions to accommodate a diverse range of bodily and intellectual functionings. Recent disability studies and advocacy work has therefore focused on securing crucial protections for persons with disabilities – including those with mental and neurodevelopmental disorders – based around an ethos of respect for mind and bodily difference, protection of autonomy, non-paternalism, and participation in all areas of life.

Though both envisage mental health and disability on a spectrum, a cross-cutting perspective reveals fundamentally divergent ethical orientations embedded in the conceptual underpinnings of psychiatric genomics and disability. First, even within a dimensional approach to mental health, the criterion of functional impairment continues to be used as a threshold measure by which a person can be diagnosed with a disorder that *prima facie* warrants clinical treatment and rehabilitation (Patel et al under review). From the perspective of disability studies, however, this threshold concept of functional impairment might be viewed as discriminatory and prejudicial, where its application presumes the loss of decision-making competence, questions the authenticity of a person's deliberation and choices, or justifies (coercive or non-coercive) interventions. Indeed the ICF's concept of functionality has little to do with setting a threshold to separate 'prevention' from 'treatment', but instead provides the foundation for a tool to collect more accurate population-based disability statistics (via census and national survey) as a means of monitoring the international implementation of the CRPD (Oliver & Sapey, 2006).

The second tension touches on even more profound ethical questions around the commitment of psychiatric genomics to a prevention / early intervention approach to mental health care. Psychiatric genomics has a potentially crucial role to play in preventing, eliminating, and the early treatment of certain conditions: improved scientific understanding of underlying genetic mechanisms could help develop biomarkers and precision medicine in psychiatry, focused mainly on the early detection and prevention of mental disorder and disability. But through the lens of disability activism and research, such an aspiration of psychiatric genomics reflects a eugenics agenda that is not just ethically problematic, but should be abandoned altogether. From this perspective, *neurological difference* is increasingly recognised as *identity difference*, and efforts to 'fix' the individual's traits that are typically associated with differently functioning brains can be viewed as discriminatory

(Harpur, 2012). Such a view welcomes support and may even advocate for appropriate treatment, yet also critically challenges the concept of the individual being considered 'abnormal' with the expectation that they should immediately adjust to societal norms, either voluntarily or through coercive means (Oliver, 1996; Baker, 2011; Norbury & Sparks, 2013; Verhoeff, 2015; Jaarsma & Welin, 2012).

In sum, the aspiration to facilitate prevention and early intervention strategies means psychiatric genomics raises core questions around the societal and clinical acceptance of neurological disorders in different cultural contexts:

- Does the early intervention prism of psychiatric genomics imply (i) the pathologisation of certain behavioural conditions and (ii) the aspiration to *cure* individuals or *prevent* the development of certain disorders?
- How can prevention/early intervention lens of psychiatric genomics balance the imperative towards better life outcomes for people with mental and neurodevelopmental disorders on one hand, with respect for and acceptance of such individuals on the other?
- Would genomic responsibility suggest individuals and their family members are obligated to engage in preventative or early intervention strategies for mental and neurodevelopmental disorders?
- How does psychiatric genomics affect notions of personhood and personal identity amongst individuals with mental and neurodevelopmental disorders?

Dilemmas of the Global and the Local

Another major ethical faultline clusters around the dilemmas of navigating the *global* and the *local* at multiple levels of psychiatric genomics. These range from culturally specific issues around informed consent procedures, to questions of translation and cultural understanding of genomics and mental disorder, to fundamental issues around global equity and distributive justice. Particular ethical attention on these issues in the context of global psychiatric genomics is warranted for two important reasons. First, matters of the mind and brain functioning imply different, often incommensurable comprehensive conceptual frameworks and normative beliefs around the body, personhood, and identity. These divergent frameworks are often superficially acknowledged without systematic theoretical and philosophical engagement in global mental health and transcultural psychiatry; moreover, the status of these conceptual frameworks remains unclear, with worries that psychiatric genomics and global mental health replicates a unidirectional model of knowledge which accords no epistemic standing to cultural explanatory systems. Second, there are critical questions around how investment in highly advanced psychiatric genomics technologies helps fulfil local health and

research needs in a fair and equitable manner, where persistent under-resourcing of mental health remains the norm in LMICs.

The impetus to expand the collection of genetic samples to a global population acknowledges that contextualised data and the involvement of non-Western stakeholders in LMIC settings is much needed in psychiatric genomics research. However, the 'global' nature of psychiatric genomics discourse itself demands critical evaluation alongside these scientific initiatives. The wide variation between local belief systems around mental disorder (Foster, 1976; Keikelame & Swartz, 2015; Deribew & Tamirat, 2005) indicates that the biogenetic assumptions underlying psychiatric genomics research may have little resonance at both the *conceptual* level (frameworks of descriptive and normative concepts and beliefs) and the *practical* level (existing and normative practices and rituals) (Kong forthcoming). Additional contextual realities of different LMIC sites, such as the wide range of dialects / languages, lows literacy levels – especially amongst those with mental and developmental disorders (Owusu-Ansah, 2013; Deribew & Tamirat, 2005) – all contribute to the substantial translational challenges of psychiatric genomics.

The claim that translation and dissemination moves in a single direction, from 'global' scientific knowledge to 'local' beliefs, needs to be critically challenged if psychiatric genomics is to function as an asset to existing tools in local mental health systems and treatments which improve the lives of individuals. Collaboration between biomedical knowledge and indigenous perspectives, neither of which are static (Greene, 1998), may be necessary to improve cross-cultural translation and cultivate mutual understanding around mental health and psychiatric genomics (Kong, forthcoming; Keikelame & Swartz, 2015; Okello & Musisi, 2015). A major area of work in the NeuroGenE programme therefore explores ways in which the learning and translational process of psychiatric genomics is *multidirectional*, so that global psychiatric genomics engages seriously with local knowledge systems and beliefs around mental disorder in a reciprocal fashion. Core research questions include:

- To what extent can global psychiatric genomics become 'localised'?
- What does 'translation' mean in this project? To what extent can cultural / indigenous views be reconciled with biogenetic explanations of mental / neurodevelopmental disorder? Should 'reconciliation' be a goal of respectful scientific translation?
- How can these local conceptual frameworks and tools potentially enhance, not just the practical, clinical implementation of psychiatric genomics research, but Western frameworks of mental disorder and mental health practices?

Issues concerning justice and equity reveal the global-local dilemma in a different form. Significant attention has been paid to the structural and systemic challenges facing global mental health in recent years (Drew et al., 2011; Saraceno et al., 2007; Saxena, 2007; Jacob et al., 2007;

Collins & Saxena, 2016). Although mental health provision can be unequal *within* HIC settings, the most extreme disparities exist between HIC and LMIC settings, with many of the latter lagging behind significantly in terms of investment and prioritisation. The barriers to equity in global mental health care are especially daunting, ranging from poor infrastructure and lack of investment in community-based services, training programmes, and public mental health campaigns (Saxena et al., 2007; Chappell & Johannsmeier, 2009; Saraceno et al., 2007), to socio-economic and environmental factors of poverty physical and sexual abuse / exploitation, gender-specific issues (Belle, 1990; Patel et al., 2002), to restricted civil economic, political, and social rights, and institutionalisation (Drew et al., 2011). Despite multinational support to alleviate such barriers (WHO commission, 2008), the lack of tangible inroads in this area indicates two shortcomings: first, there is little consensus in terms of priority-setting with regards to where scarce funds can improve the lives of people with mental disorder, with solutions ranging from investment in human rights and regulatory frameworks (Burns, 2011), community-services (Alem et al., 2008), and government initiatives (Aikins et al., 2010). Second, the language of equity, global justice, and global health is often distilled through the prism of liberal rights-based language (Daniels, 2010), but whether it has sufficient normative power to express individual entitlements, empower advocacy work, and motivate systemic change in different cultural contexts is debatable (Flikschuh, 2014; Read et al., 2009; Gostin & Gable, 2004).

Questions of justice and equity are also deeply relevant to issues of global research collaboration, specifically around the *practices* of collaboration amongst stakeholders. How psychiatric genomics research grapples with such issues will determine the extent to which it navigates the global-local tension in an equitable fashion so that benefits accrue for local academic centres and individual researchers. Global scientific research programmes often encounter tensions between the pragmatic, cost-benefit interests of research and the imperative to include local expertise and knowledge. Funder expectations, government initiatives, familiarity with legal processes and existing collaborators, as well as the influence of scientific clusters (i.e. prominent academic researchers or centres) often justify why certain collaborators are favoured as opposed to others (Hennenmann et al., 2012). Yet the legitimacy and credibility of global health research often comes through the inclusion of less recognised stakeholders within LMICs, particularly given the increasing importance of local understanding and expertise in research design. This tension can mean the disproportionate benefit to high-income countries and research centres through inequitable practices of collaboration, such as the hierarchical division of intellectual labour, exclusion from tangible outputs through authorship and grant-writing policies, and the imposition of research agendas onto collaborators in LMIC (Engels & Rushenburg, 2008). Such unequal practices evoke deeper questions around the necessary mechanisms for a fair and ethically-grounded global research collaboration that encourages mutual respect, reciprocity, and shared ownership (Parker & Kingori, 2016).

These pressing political, economic, and social challenges in global mental health policies and research draw attention to three fundamental issues within the ethics of psychiatric genomics. First

are concerns of distributive justice and fairness: in the face of scarce resources in global and local mental health programs, critical reflection on the putative justification of financial investment in psychiatric genomics, particularly within LMIC settings, is essential. Second are concerns around the ethical appropriateness of liberal rights-based language that normative discussions of equity and justice often presuppose. Indeed, a genomics approach raises difficult questions as to *who* is the rights-holder and *whose* rights should be protected: the scientific research depends on population-wide samples to generate tangible findings, whilst the reciprocal benefits to individuals may be inconsequential or non-existent in the first instance. Finally, the nature of international scientific collaborations in the name of equity and social justice need to be scrutinised to better understand how diverse stakeholders interpret and enact these concepts from their different perspectives. These tensions are ripe for further bioethical research, exploring questions such as:

- What are the cultural and political realities in LMICs and what does equity and justice mean to different communities and various stakeholders within these communities and in scientific collaborations?
- Are there general principles of equity and justice in relation to global psychiatric genomics research and what obligations are generated out of these principles?
- How should equity and justice express itself in psychiatric genomics and mental health practices and policies?
- Does international scientific collaboration drive or hinder equity and justice; does it promote better outcomes and for whom? What mechanisms or procedures can be used to ensure global collaboration on psychiatric genomics itself is equitable and inclusive?
- How can the differing ideas and research trajectories come together whilst ensuring the intellectual integrity of all collaborators?

Further research into the ethical challenges of navigating the global and local will be vital to ensure psychiatric genomic research reflects an approach that balances respect for different cultural values and local conceptual frameworks (Munsaka & Charnley, 2013; Sax, 2014) with the pursuit of a just, equitable distribution of global mental health resources.

Combating Stigma

Psychiatric genomics raises important questions as to whether its advancement will potentially mitigate or worsen the problem of stigma facing those with mental and neurodevelopmental disorders and disabilities in different cultural settings. Such individuals are likely to experience stigma from multiple, intersecting angles: from the angle of mental disorder, they can be viewed as dangerous, uncontrollable, and unpredictable (Crisp et al., 2000; Phelan & Link,

1998); from the angle of disability, they can be perceived as helpless, less than human, and dependent (Fine & Asch, 1988). These negative perceptions often result in significant self-stigma, affecting self-perception through the internalisation of these harmful views and help-seeking behaviour (Corrigan et al., 2006; Link et al., 2001). Labelled as outsiders, persons with mental and neurodevelopmental disorders are often subject to discriminatory or even inhumane treatment. But mental health and disability advocacy often adopt divergent anti-stigma strategies, revealing a third major ethical faultline around the projected role of psychiatric genomics in combating stigma of mental and neurodevelopmental disorders.

Anti-stigma public health strategies in the West often emphasise the *physiological* or *neurological* basis of mental disorder so as to liken it to physical ailments. Biogenetic explanations of mental disorder are presumed to help reduce attributions of individual voluntariness and personal weakness, and in turn, social exclusion and rejection (Angermeyer et al., 2011), though the evidence is admittedly mixed, with some studies indicating heightened perceptions of dangerousness and immutability accompany such explanations (Read et al., 2006; Schomerus et al., 2014; Pescosolido et al., 2010). By contrast, anti-stigma campaigns in disability advocacy typically focus on the *social construction* of diagnostic labels and disability and downplay biological causes of impairment to confront discriminatory attitudes and empower individuals to advocate for their human rights and equal participation (Duffy & Kelly, 2017; Green et al., 2005).

The projected harms or benefits of psychiatric genomics in addressing stigma remain unclear as a result. The potential adaptation of psychiatric genomics to different cultural and religious beliefs in the global context further complicates existing tensions between social construction and biogenetic explanations (Norbury & Sparks, 2012; Marsh et al., 2011). From one standpoint, psychiatric genomics could have a substantial role in mitigating the stigma of persons with mental / neurodevelopmental disorder in non-Western contexts: emphasis on the inheritance of traits and genetic risks might displace indigenous explanations based on individual, familial, or gender-based moral failure, supernatural causes, or being cursed which fuels social distance and exclusion (Gureje et al., 2005; Read et al., 2009; Derebew & Tamirat, 2005). Equally, a psychiatric genomics lens could potentially exacerbate essentialist stereotypes and perceived differences among racial groups (Phelan et al., 2013; Foster & Sharp, 2002), where the racial distribution of certain disorders may negatively influence public perceptions (Duster 2003) or appear to validate racial prejudices (Condit & Bates, 2005). Key questions for further exploration include:

- Can genomic explanations of mental disorder help mitigate these stigmatising views? Can these help mitigate the subjective effects of stigma?
- Is there a danger that notions of genomic responsibility / citizenship could perpetuate essentialist understandings of race / disability / mental disorder?

- What does an ethically grounded strategy to combating stigma in LMIC contexts look like, particularly in the context of global psychiatric genomics?

Methodologies

NeuroGenE takes an expansive view about the methodologies that are needed to undertake this ambitious cross-cutting research agenda. Integrated within a multi-stage strategy, different methodologies will gradually establish an empirical and theoretical evidence base that will function as a vital resource for developing future practical and policy recommendations. Methodological details about each stage can be seen in Table I.

Table I: Stages of research and associated methodology deployed by NeuroGenE.

Stage 1	**Literature / systematic reviews and thematic analyses** of existing research in the areas of genomics, global mental health, and disability studies in order to survey, systematise, and evaluate the regulatory, legal landscape as well as ethics research in these respective areas as they bear on the issues within psychiatric genomics.
Stage 2	**Ethnographic, qualitative and participatory methodologies with stakeholders**. Local practitioners, individuals affected by mental and neurodevelopmental disorders, family members, and local advocacy groups, are consulted to explore (i) local knowledge systems, beliefs, and cultural meanings around mental health practices; (ii) the portability and translational challenges of global mental health and psychiatric genomics concepts; (iii) the perceived interests and priorities in mental health care by local stakeholders; (iv) lived experience of stigma. Case studies will be developed and a comparative analysis of this data will indicate relevant points of converging and diverging interests.
Stage 3	**Cultural and normative engagement with biomedical underpinnings** and methodological assumptions underlying psychiatric genomics. Cultural and normative theorising to critically examine points of contestation and open points of dialogue between cultural and scientific meanings.
Stage 4	**Conceptual and philosophical theorising** to probe the underlying ethical concepts, obligations, and principles (around distributive justice, equity, and human rights) which should guide global psychiatric genomics research and its application.
Stage 5	**Policy and practice recommendations** that are ethically grounded and context-sensitive, to address the gap between scientific translation and clinical practice and public health policy. Such policy recommendations will take both a short and long term perspective, with some recommendations relevant for immediate ground level change for persons with neurological disorders, whilst other recommendations support the development of future policy and practice.

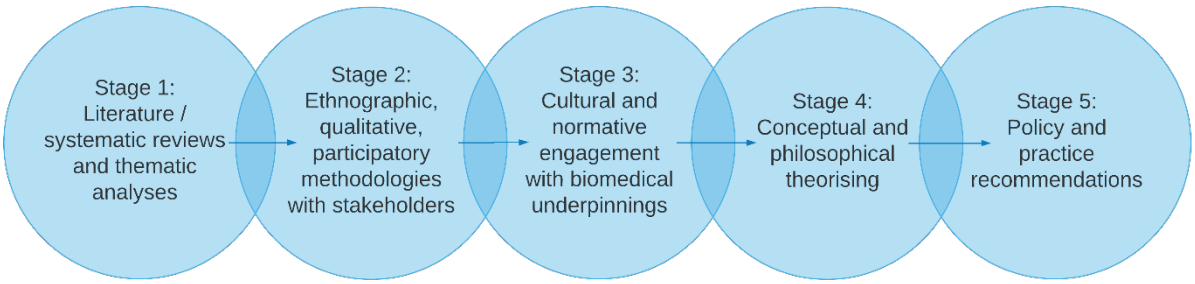

Figure 2: NeuroGenE Methodologies

These stages build on one another, but are not necessarily chronologically ordered and may be simultaneously undertaken; different ethical questions may also involve vacillating between the methodologies of early and later stages. However, the overall NeuroGenE strategy ensures that the final stage of policy recommendations and guidelines is substantively informed by prior stages. Systematic reviews from *Stage 1* will synthesise relevant global and country-specific data that will be used for purposes of comparison as well as provide a contextual survey of each potential site for fieldwork in subsequent stages, such as *Stage 2* which builds on the identified areas of intersecting ethical concerns through participatory engagement. *Stage 3* draws on the examination of cultural beliefs and indigenous conceptual frameworks and deploys systematic cultural and conceptual theorising to probe the presumed scientific objectivity of psychiatric concepts and diagnostic classifications in the global context. Contested even within Western contexts, post-colonial and LMIC settings raise unavoidable issues around the cultural and epistemological power of biogenetic psychiatry that warrant careful consideration. *Stage 4* engages in ethical theorising that reflects the nexus of local-global, cultural-scientific perspectives utilising the phenomenological, empirical, and conceptual data generated out of Stages 2 and 3. Together these stages will provide a crucial evidence base for practicable recommendations at *Stage 5* in which ethically grounded and culturally sensitive guidance is provided across the disciplines that are impacted by neuropsychiatric genomics.

Guiding Principles

Four core principles guide the NeuroGenE research programme: (i) reciprocity; (ii) collaboration; (iii) accountability; and (iv) capacity-building. These principles are operationalised at both procedural and substantive levels:

(i) the process of developing and generating research questions;

(ii) the practical ethos and virtues of researchers involved in NeuroGenE;

(iii) the obligations embedded within the overarching NeuroGenE research strategy and organisational structure.

The principle of *reciprocity* is an adaptation of deliberative practices of 'mutual reason-giving' (Gutmann & Thompson, 2002), but we understand the term to work inseparably with the principle of *collaboration*. Together they encompass the necessary intellectual orientation needed to generate areas of overlapping interests and aims amongst different cultural perspectives. Reciprocity and collaboration not only denote the equal status of stakeholders, but demand an equitable, mutually respectful, and trusting space for deliberation on the values, reasons, and motivations of different conceptual frameworks. This is crucial to mitigate the colonialism that can inadvertently shape the *intellectual sphere*: Western, medical and scientific frameworks or normative concepts assume their portability and tend to ignore the reality of non-Western beliefs, traditions and practices related to human identity, health and wellbeing (Kleinman, 1981; Kleinman, 2006; Kirmayer, 2012). The principles of reciprocity and collaboration embeds bi-directional knowledge production to facilitate the kind of cultural exchange that is demanded by a truly global orientation towards mental health and psychiatric genomics.

Reciprocity and collaboration with local stakeholders and service-users is also vital to avoid the exclusion and discrimination of persons with mental disorder and intellectual disability. This is to acknowledge that disabled persons organisations (DPOs) and survivors of psychiatry advocacy groups, with their emphasis on neurodiversity, acceptance, and accommodation, may ultimately have aspirations and goals that differ in a meaningful sense from those of psychiatric genomics. Persons with mental disorder and intellectual disability are too often treated as *subjects* or *objects* of research (Kachaje et al., 2014), yet they will have something fundamentally at stake with the widespread application of psychiatric genomics within a precision medicine framework. Direct engagement and dialogue with DPOs, mental health advocates, and service-users is necessary so as to probe how *they* believe their lives can improve through the research. Psychiatric genomics is unlikely to have little or no buy-in from local communities, or have practical relevance for different cultures or local stakeholders, unless reciprocity guides the entire process of learning, knowledge production, and practical translation.

The principle of *accountability* denotes interactions and processes where persons / entities are held to account for their choices, reasons, and justifications through a transparent and fair process. Accountability is applied in both *vertical* and *horizontal* senses: *vertical* accountability denotes responsibility to hierarchical decision-making bodies, such as NeuroGenE's Advisory Group that will be comprised of leading experts in relevant disciplines and strategic partnerships. But more important are the mechanisms of *horizontal* accountability within regional working groups and research partners, designed to encourage project collaborators to operate with transparency and mutual answerability, and exercise collective oversight of the research programme.

Capacity-building forms the fourth core principle of the NeuroGenE research programme. This includes mechanisms to strengthen capacity in bioethical research and, collaborative structures which will help lead to ethically grounded policy and practice recommendations as appropriate to

local contexts. NeuroGenE in conjunction with the Stanley GINGER programme will conduct training on the science and ethics of psychiatric genomics, through face-to-face sessions as well as online tools, targeting local researchers. Mentorship for local researchers will also be provided to develop, conduct, analyse, and publish their work. Other capacity-building activities include the formation of a global network of multidisciplinary researchers, within and across institutions. NeuroGenE is developing institutional research capacity through partnerships with different organisations, such as the University of Ghana, University of Zimbabwe, and African Mental Health Research Initiative (AMARI), as well as through the provision of postdoctoral training. Meanwhile, the programme provides support for enhancing research capacity of individual researchers who participate in the project's local working groups, such as the African Ethics Working Group (AEWG) comprised of individual academics from Moi University, Addis Ababa University, University of Cape Town, and Makerere University. Support mechanisms include core research, training and grant funding to enable the pursuit of individual and collaborative research projects at various levels of inquiry of the ethics of psychiatric genomics that will eventually feed into initiatives to enhance capacity within institutional review boards and amongst public health policy makers.

Conclusion

Global psychiatric genomics is rapidly advancing and has the potential to transform psychiatric nosology, public health policy, and the nature of clinical interventions. The NeuroGenE research platform establishes a vital cross-cutting, interdisciplinary programme of work around the ethical implications and challenges of psychiatric genomics within the global context. If different cultural contexts and people with mental and neurodevelopmental disorders are to accrue genuine benefits from advances in genomic technology, it is vital that substantive investigation into the ethical implications of psychiatric genomics adopts creative methodological strategies, engages in dialogue with different fields of study and relevant stakeholders, and fosters an orientation of intellectual openness and humility towards non-Western conceptual / value frameworks around mental health. We have provided reasons why such a bioethical research agenda should be prioritised as a matter of course for any scientific agenda, and should likewise inspire similar investigations within the ELSI Research Program.

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