Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2019 December ; 180(8): 543–554. doi:10.1002/ajmg.b.32736.

International Society of Psychiatric Genetics Ethics Committee: Issues Facing Us

Gabriel Lázaro-Muñoz[1], **Maya Sabatello**[2], **Laura Huckins**[3], **Holly Peay**[4], **Franziska Degenhardt**[5], **Bettina Meiser**[6], **Todd Lencz**[7], **Takahiro Soda**[8], **Anna Docherty**[9], **David Crepaz-Keay**[10], **Jehannine Austin**[11], **Roseann E. Peterson**[12], **Lea K. Davis**[13] **ISPG Ethics Committee**

[1]Baylor College of Medicine, Houston, TX, USA 77004

[2]Columbia University, New York, NY, USA 10032

[3]Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029

[4]RTI International, Research Triangle Park, NC, USA 27709

[5]University of Bonn, D-53127 Bonn, Germany

[6]University of New South Wales, UNSW Sydney 2052, Australia

[7]Hofstra University, Hempstead, NY, USA 11549

[8]University of North Carolina at Chapel Hill, NC, USA 27599

[9]University of Utah, Salt Lake City, UT, USA 84112

[10]Mental Health Foundation, London, UK SE1 2SX

[11]University of British Columbia, Vancouver, BC, V5Z4H4 Canada

[12]Virginia Commonwealth University, Richmond, VA, USA 23219

[13]Vanderbilt University, Nashville, TN, USA 37232

Keywords

psychiatry; genetics; ELSI; ethics; testing

Introduction

Psychiatric genetics research is improving our understanding of the biological underpinnings of neurodiversity and mental illness, and the importance of environmental factors in the development of mental illness.[1] This knowledge will be used in innumerable beneficial ways such as improving prevention, diagnosis, treatment selection and mental health care; education and psychological support related to personal risk and/or risk in relatives; and will

Corresponding author: Gabriel Lázaro-Muñoz, PhD, JD, MBE, One Baylor Plaza, Suite 326D, Houston, TX 77030, 713-798-2672 glazaro@bcm.edu.

Conflicts of Interest:
Todd Lencz has served as a consultant to Genomind, Inc. All other authors declare no conflicts of interest.

potentially help decrease blame and guilt that are often attributed to and experienced by individuals with mental illness. However, the products of psychiatric genetics research may also be used in numerous harmful ways. Psychiatric genetics may be prematurely integrated into clinical care, which can lead to clinical management decisions that are not evidence-based or in the best interest of the patient. As evidenced during the eugenics era, psychiatric genomics research may also be misused to advance an anti-social agenda and lead to increased fear and stigmatization towards individuals with markers associated with psychiatric disorders. Based on current technology, there is concern that knowledge about genomic variants associated with psychiatric disorders may be used for discriminatory practices in clinical and non-clinical settings, such as insurance, employment, financial loans and judicial proceedings.

Using psychiatric genetics in ways that maximize benefits and minimize harms to individuals and society depends largely on how the ethical, legal, and social implications (ELSI) of psychiatric genetics are managed. The International Society of Psychiatric Genetics (ISPG) is the largest international organization dedicated to psychiatric genetics (https://ispg.net/). Given its history, membership, and international reach, we believe the ISPG is well-equipped to contribute to the resolution of these ELSI challenges. As such, we recently created the ISPG Ethics Committee, an interdisciplinary group comprised of psychiatric genetics researchers, clinical geneticists, genetic counselors, mental health professionals, patients, patient advocates, bioethicists, and lawyers (https://ispg.net/membership/committees/). The mission of the ISPG Ethics Committee is to examine, discuss, educate, and provide recommendations to responsibly manage ELSI issues raised by the uses or potential uses of emerging knowledge and technologies in psychiatric genetics.

In this article, we discuss why psychiatric genetics researchers have a responsibility to contribute to the resolution of ELSI challenges in this field. We then consider key ELSI challenges in three contexts: research settings, clinical settings, and legal proceedings. For each of these arenas, we identify and discuss pressing psychiatric genetics ELSI dilemmas that merit attention and require action. This article is not a comprehensive discussion of all pressing psychiatric genetics ELSI issues, but is intended to highlight and review issues identified by the ISPG Ethics Committee that are of paramount importance for the ethical translation of psychiatric research into society. The goal of this article is to increase awareness about psychiatric genetics ELSI issues and encourage dialogue and action among stakeholders.

Role of Psychiatric Genetics Researchers in Addressing ELSI Issues

There are different perspectives of what social responsibility in science entails (Douglas, 2014; Sankar and Cho, 2015; Schienke et al., 2009). Most scientists are familiar with responsible conduct of research, which involves, among other things, ensuring scientific integrity, rigor and reproducibility, and respect for the contributions of others by not plagiarizing and employing fair authorship practices. Two other dimensions of social

[1]Neurodiversity refers to variation in psychological or neurological states and traits across human populations, while the concept of mental illness refers to poor health outcomes experienced by an individual on account of a pattern of behavioral, psychological, or neurological events.

responsibility in science are whether scientific endeavors are responsive to societal needs, and whether a particular line of research is worth pursuing when it may threaten important societal interests (Douglas, 2014; Sankar and Cho, 2015). Finally, another key dimension of social responsibility in science is the role that researchers, including ISPG members, should play in addressing the societal implications of scientific products (e.g., knowledge, technologies).

Researchers are one set of principal actors who generate psychiatric genetics products and make them part of society through publications, development of technologies based on this knowledge, public-private collaborations (e.g., direct-to-consumer genetic testing companies), expert testimony in court, and translation of the research into clinical care. Generating policies that optimize the benefits and minimize the potential harms of this knowledge for individuals and society requires the involvement of all key stakeholders (e.g., researchers, clinicians, patients, research participants, community members, policy makers) in order to provide adequate representation of their interests. In theory, researchers are the individuals with the best understanding of the capacity and limitations of the technologies they develop and apply. Without this perspective, it is difficult to craft sound policies that adequately balance the interest of stakeholders and maximize the net benefit of these technologies. Thus, researchers, individually or through professional organizations, have a responsibility to be a part of the discussion regarding how to promote the responsible development and use of the knowledge and technologies developed through psychiatric genetics research.

Psychiatric Genetics in Research Settings

Like many other areas of genetics research, psychiatric genetics research involves important ELSI issues that require attention. *Here, we focus on three key issues: an underrepresentation of racial and ethnic populations in genomic research that may perpetuate health disparities, potential challenges related to the return of results to research participants, and the need for increased stakeholder engagement.*

Increase the Representation of Diverse Populations in Psychiatric Genetics Research

There have been considerable advances in understanding genetic influences on psychiatric disease (Sullivan et al., 2018). However, individuals of diverse race, ancestry and ethnicity have been largely underrepresented in genetic research. Studies indicate that the overwhelming majority of participants are of European ancestry, whereas less than 20% of participants in genome-wide association studies (GWAS) are of non-European ancestry (Popejoy and Fullerton, 2016). Although this proportion is up from 4% in 2009 (Need and Goldstein, 2009) – largely due to contributions of cohorts of Asian ancestry – less than 5% of participants are from other populations such as African, Hispanic, or Indigenous peoples (Popejoy and Fullerton, 2016). These results highlight a significant gap in the study of genetic risk underlying psychiatric illness and raises concern that possible benefits of genomic research will not reach already-underserved populations. Here, we provide an overview of factors contributing to underrepresentation of non-European populations in psychiatric genetics research and the corresponding implications for this lack of diversity.

Research has identified several reasons for the under-representation of non-European participants in genomic research including lack of access to healthcare services and low-quality patient-physician relationships (Epstein, 2008). These factors are particularly impactful among historically marginalized populations and are known contributing factors in decisions to decline participation in genomic research (Kraft et al., 2018; Sabatello et al., 2018a; Sohn, 2017; Sierra-Mercado and Lázaro-Muñoz, 2018). Moreover, the extension of negative experiences in healthcare to research settings, including genomic research (King, 1998; Kraft et al., 2018); and a looming history of abuse of historically marginalized populations in genomic and other health research further reduce participation rates. The latter encompasses a range of incidents, from the harm inflicted upon African Americans in the Tuskegee Study of Untreated Syphilis in the Negro Male experiment, to the use, selling, and disclosure of information obtained from the HeLa cell line without adequate consent (Callier et al., 2014), and the various studies with American Indian and Alaska Native tribes that were conducted with some deception and disrespect for community norms (Garrison, 2013). Lack of knowledge of community needs and incongruence in researchers and community's views about research priorities may similarly reduce participation of diverse groups such as people with disabilities (Sabatello et al., 2019).

In addition, participation in genomic research on psychiatric conditions presents some unique challenges. Notwithstanding tremendous efforts over the past decades to re-conceptualize psychiatric conditions as brain and genetic-based conditions that are "like any other" disorders (Pescosolido et al., 2010), stigma associated with psychiatric disorders remains high (Phelan, 2005; Brannan et al., 2018). Consequently, there may be reluctance to participate in psychiatric genetic research (Mascalzoni et al., 2014). These concerns may be exacerbated among minority racial/ethnic populations who are already excessively surveilled and disproportionately diagnosed with psychiatric conditions (Grimm, 2007; Kreag, 2015; Sabatello and Appelbaum, 2016). Finally, underrepresentation of minority populations in genomic research may be due to far simpler reasons: studies suggest that although the interest in genomic research participation among minority groups may be high, they are too often not being asked to participate (Garza et al., 2017; Hartz et al., 2011; Millon Underwood et al., 2013; Wendler et al., 2006).

The challenges for diversity in genomic research are further augmented by a history of exclusion and limited attention in clinical settings and health research more generally. Psychiatric genomics studies are reliant on accurate phenotype definition and interpretation. Perhaps uniquely compared to other traits and disorders, psychiatric diagnostic criteria are descriptive and subjective, and as such are particularly vulnerable to biased interpretation and uneven application. Such biases may include for example race, age, gender identity or sexuality, and may lead to overdiagnosis, missed diagnoses or overlooked symptoms, or inappropriate diagnostic guidelines. For example, the rate of diagnosis of psychosis (and related disorders) in African-American and Hispanic/Latinx populations is consistently three times higher than in European Americans (Schwartz and Blankenship, 2014). Similarly, diagnosis of autism spectrum disorder (ASD) and other developmental disorders is substantially higher among children of foreign-born mothers in general, and of black foreign mothers in particular (Becerra et al., 2014).

The lack of racial, ethnic, and ancestral as well as other diversity (e.g., gender identity, disability) in genetic research not only impedes our understanding of etiological risk factors but will further contribute to health disparities, making this a serious public health and ethical concern. Heritability estimates of psychiatric disorders in populations of diverse ethnicity and ancestry are largely absent from the literature due to twin registries being primarily composed of families of European descent (Hur and Craig, 2013; Sung et al., 2006). Furthermore, heritability estimates vary as a function of the environment (Dick and Kendler, 2012; Turkheimer et al., 2003) and individuals from minority populations are disproportionately exposed to environmental stressors in comparison to socially-dominant groups (Williams et al., 2010). Therefore, etiological pathways or the relative contributions of genes and environment may vary across racial and ethnic strata. Greater representation of racially and ethnically diverse samples in registries is critically needed in order to increase our understanding of how contributions of genes and environment varies across development, across racial, ethnic, and ancestry groups, and how these factors may interact with putative environmental exposures.

Moreover, the fact that less than 20% of participants in GWAS are of non-European ancestry (Popejoy and Fullerton, 2016), raising questions of transferability of genetic findings from European ancestry populations to other groups. Because there are differences in allele frequencies and linkage disequilibrium (LD) patterns across global populations (Barrett and Cardon, 2006; Gravel et al., 2011; Lek et al., 2016), genetic associations detected in European ancestry populations cannot directly translate to other populations. Etiologically relevant variation is missed if diverse samples are not studied, and this has downstream ramifications for other research domains. For example, in pharmacogenetics, ancestry-specific differences in genetic variants associated with drug metabolism may prove some drugs more effective and/or safer in certain populations (Martin et al., 2017a). There are other advantages of incorporating data from diverse populations. Effect-size estimates derived from diverse ancestry cohorts tend to be more accurate than from single-ancestry cohorts (Carlson et al., 2013). Furthermore, the resolution of causal variant fine-mapping has improved through trans-ancestry meta-analysis (Consortium, 2014; Saccone et al., 2008), further highlighting the advantages of incorporating data from diverse human populations.

In addition, genetic risk prediction attenuates with increasing ancestral divergence between the discovery and target population (Martin et al., 2017b; Scutari et al., 2016) indicating that current polygenic risk scores based on Eurocentric GWAS are not equally predictive across populations. However, polygenic risk score profiling revealed improved prediction based on trans-ancestry meta-analysis (Li and Keating, 2014; Martin et al., 2017b), highlighting an advantage of incorporating data from diverse populations. In order for precision medicine initiatives to be successful, it is imperative that large-scale efforts are made to mitigate racial, ethnic, and ancestry underrepresentation in genetic studies so that all will benefit equally from scientific research and ensure that psychiatric genetics does not exacerbate long-standing health disparities.

There are ways in which the research community can promote diverse representation in cohorts. First, while a number of global consortia have been formed to redress the imbalance of populations represented in psychiatric genetic studies (CONVERGE consortium, 2015;

Pato et al., 2013; Wojcik et al., 2017), there is a need for extensive community engagement to address distrust in recruitment (see Stakeholder Engagement section below). Second, there is a need for developing policies that promote inclusivity. For example, several scientific funding agencies including the US National Institutes of Health and the Canadian Institutes of Health Research require diversity reporting and encourage the recruitment of diverse samples for genetics research. However, proposals that include recruitment of diverse samples often suffer during the peer review stage due to concerns that increased heterogeneity will reduce power to identify associated variants in genome-wide studies. Though this may be technically true, it is no longer a fatal flaw in study design. Moreover, this practice perpetuates the lack of diversity observed in research studies today. In today's era of team science, we are only limited by the data that individual investigators make available for meta-analysis. Until individual investigators begin recruiting diverse populations (which will no doubt be small at the outset), these issues will remain. Funding agencies can craft guidelines requiring peer reviewers not to penalize studies that seek to include diverse populations despite the possible consequences of inclusion (e.g., increased heterogeneity and reduced power). In addition, funding agencies can increase funding for proposals that seek to increase the pool of underrepresented groups in genomics research.

Return of Results

Debate over returning clinically relevant results to research participants has not received as much attention in the psychiatric genetics research context as it has in other areas of genetic research. However, the issue raises a myriad of ethical considerations that need to be addressed.

In general, studies indicate that patients with mental health disorders, their relatives, and clinicians overwhelmingly favor offering return of results for individual participants (Sundby et al., 2017). In a study published in this issue, Kostick and colleagues (2018) reported that the vast majority of psychiatric genetics researchers interviewed also support the return of at least some findings. However, return of results does not seem to be a common practice in psychiatric genetics research; 22% of researchers reported that they are offering return of results in at least one study (Kostick et al., 2018).

Recently, the National Academy of Sciences, Engineering, and Medicine in the United States published a report recommending, among other things, that "investigators and their institutions should routinely consider whether and how to return individual research results" (The National Academies of Sciences Engineering and Medicine, 2018). The report argues that when individual research results are intended for use in clinical decision making, they should be confirmed by clinically-certified laboratories to help ensure accuracy and analytical validity. However, if the research finding is not intended for medical decision making, the report argues that research laboratories should be allowed to return these research findings provided that oversight bodies develop a quality management system and documentation guidelines to help ensure proper tracking and validity of individual results (NASEM, 2018).

Debates regarding the management of clinical versus non-clinically relevant results and the kind of quality controls that research laboratories should have in order to return results are

ongoing and require attention from stakeholders. Some counterarguments to these proposals are that they would substantially increase the resources required, limit participants' access to research results, and that it may be enough to ensure that research laboratories clearly inform participants that individual results are not intended for clinical use because of the quality control limitations that research laboratories generally have (Wolf and Evans, 2018). If the participant would like to follow up on what seems to be a clinically relevant finding, the participant would need to do so through a healthcare system and get retested by a clinically-certified laboratory (Wolf and Evans, 2018).

The NASEM report is not intended to apply only to genetic research and does not address which specific types of genomic findings should be offered. However, in the genetics research context, working groups have gone further and argued that, at a minimum, researchers should offer findings generated in the course of research that are clinically valid, medically important and medically actionable (Jarvik et al., 2014). Similarly, in psychiatric genetics some have argued that researchers should consider offering medically actionable findings (e.g., pathogenic variants in ATP7B associated with Wilson Disease), clinically valuable findings such as those that may help confirm or reject a diagnosis (e.g., 22q11.2 deletion in a patient diagnosed with schizophrenia); or indicate moderate to high risk for severe health conditions even if non-medically actionable (e.g., pathogenic variants in *PSEN1* suggesting increase risk for Alzheimer's disease) (Lázaro-Muñoz et al., 2018). However, there is no consensus about which findings, if any, should ideally be offered to individual participants in psychiatric genetics research.

Returning genomic findings related to mental health disorders may accentuate certain challenges compared to non-psychiatric findings. For example, given high levels of mental health stigma, psychiatric genomics findings may be more likely than some non-psychiatric genomics findings to lead to self-stigma and discrimination in different spheres (Brannan et al., 2018). In addition, contrary to some monogenic disorders, to our knowledge, there are no proven preventive interventions to decrease the risk of developing a psychiatric disorder in individuals identified with pathogenic variants. Another issue that may complicate the return of results related to psychiatric disorders is that most of these findings are going to be common variants or polygenic risk scores which generally have low penetrance and are heavily influenced by environmental factors. Thus, explaining the implications of these findings to individual participants may be more complicated than explaining the implications for most non-psychiatric findings. This highlights the importance of ideally having genetic counselors or other clinicians involved in the return of clinically relevant results. The challenges do not end there, however, if individual participants receive clinically relevant findings, they may want to follow up with a mental health clinician to evaluate future steps.

Numerous studies indicate that most psychiatrists do not have sufficient training in genomics and are not familiar with genetic professionals in their area (Ward et al., 2019). The ISPG Residency Education Committee recently issued a statement that "Every psychiatrist should know the basic principles of genetics, the role of genes in psychiatric disorders and their treatment, the ways in which environment affects gene expression, ethical issues in the use of genetic information, and how to talk to patients and families about genetics" and that "Genetics education among psychiatric residents should become an essential part of the

emerging agenda for the development of a new cadre of psychiatric professionals for the 21st century (Nurnberger et al 2018).”

Moving forward, more research is needed to identify best practices for informed decision making about return and receipt of psychiatric genetic results. This includes better understanding of how to return these results; how to promote significant understanding of the implications of specific findings and the important role of the environment in promoting or hindering mental health; and what is the impact of returning results on participants. Will return of results lead to participants taking better or worse care of their mental health? Will it lead to better or worse clinical outcomes? How might return of results differ for psychiatric versus other medical conditions? Would return of results lead to adverse psychosocial or behavioral outcomes? How might return of results address health disparities rather than perpetuate them? In addition, it is important to explore the personal utility of genomic results for participants in research, which may be based on different sets of constructs than those that underpin determinations of clinical utility (Biesecker and Peay, 2013; Kohler et al., 2017).

Stakeholder Engagement

The challenges raised above, and many others, can be mitigated through stakeholder engagement. Stakeholder-engaged research integrates the expertise and perspectives of professionals and community members to address complex issues affecting specific populations (Davies et al., 2011; Jagosh et al., 2012; Joosten et al., 2015; Lavery, 2018; Goodman, MS, Sanders Thompson, 2017). Stakeholder engagement aims to incorporate multiple perspectives, with particular attention to the perspectives of the target community; achieve a more nuanced understanding of health, wellbeing, unmet needs, and preferences; develop acceptable study designs and improve participation rates; and inform data interpretation and dissemination of results.

There is evidence that engaging community members in the research process can improve the quality and outcomes of health promotion initiatives and research products (Balazs and Morello-Frosch, 2013; Goodman, MS, Sanders Thompson, 2017). Such engagement is a long-term, collaborative process that builds trust between researchers and the community (Butterfoss and Francisco, 2004; Quinn et al., 2013). In other mental health research areas, stakeholder engagement (e.g., mental health service user involvement) is well established (Kara, 2013; Minogue et al., 2005; Telford and Faulkner, 2004). In many fields, the involvement of community members in research has moved a long way from the traditional role of the community as providers of samples for research data. People who have experienced psychiatric conditions take on a range of roles including: reference groups which quality assure and contribute to research governance; academic researchers contributing to the collection and analysis of qualitative and quantitative data; to co- and principal investigators in large, well-funded research programs (Trivedi and Wykes, 2002). An example of the shift toward stakeholder engagement in the US, is the role that community members are playing in the governance and design of the *All of Us* Research Program (National Institutes of Health, 2018).

Engagement at all levels is particularly important where knowledge is emerging and whole new areas of evidence are being created. The nature and interpretation of that evidence will be directly affected by the actors who take part in its creation. These discussions have already taken place as part of broader thinking in psychiatry, philosophy and the nature of evidence-based and values-based practice (Crepaz-Keay, 2016; Rose et al., 2006). The ethical and social issues that emerge in psychiatric genetics research, in part, due to prevalent mental health stigma and varying views about what constitutes mental health conditions, make stakeholder engagement particularly important. However, engagement needs to be meaningful: it is not enough to include stakeholders into research decision-making and governance, there must be willingness to listen to stakeholder perspectives and mechanisms in place to integrate these perspectives into the research endeavors. Psychiatric genetics researchers are encouraged to use engagement approaches targeted to research on disorders and phenotypes that are highly stigmatized, and for patients and communities that are historically marginalized. To facilitate stakeholder engagement, researchers are also encouraged to collaborate with experts in stakeholder engagement and take advantage of a growing body of literature about stakeholder engagement approaches (e.g., resources on the Patient Centered Outcomes Research Institute website, www.pcori.org).

Psychiatric Genetics in the Clinical Setting

Psychiatric diagnoses are assigned using a categorical classification approach based on the symptoms the patient displays. Genetic testing can on occasion be used to confirm, establish or refine a psychiatric diagnosis, but it is not part of routine clinical care. Individual single-nucleotide polymorphisms (SNPs) do not have sufficient effect sizes for susceptibility to psychiatric disorders to be relevant in the clinical setting, but two alternative developments have greater potential for clinical utility: 1) the identification of pathogenic copy number variants (CNVs) that are associated with much greater relative risk (Marshall et al., 2017); and 2) the development of polygenic risk scores, representing the aggregate effect of thousands of potential risk alleles (International Schizophrenia Consortium et al., 2009; Ripke et al., 2014). Consequently, major efforts to establish such testing are now underway and more data are needed to demonstrate the clinical utility of psychiatric genetic testing.[2]

In the absence of genetic testing, psychiatric genetic counseling has typically relied on family and personal history combined with empiric risk data to inform risk assessment for patients and their family members (Austin et al., 2008; Ripke et al., 2014). Even in the absence of genetic testing, genetic counselling (or even discussion of risk) (Costain et al., 2014b) can lead to improved patient outcomes, including a better understanding of etiology, more informed choices about risk management strategies, more accurate perceived risk, less

[2]It is important to note that genetic tests have been used widely and successfully for several neuropsychiatric disorders, including developmental disorders (e.g., phenylketonuria or PKU (Mabry-Hernandez et al., 2008) Fragile X syndrome (Michelson et al., 2011), and Down syndrome or Trisomy 21, and some neurodegenerative diseases (e.g., Huntington's disease or HD (Huntington's Disease Society of America, 2003). The American Academy of Child and Adolescent Psychiatry recommends genetic testing as part of the medical assessment for children with autism spectrum disorder (Kaufmann et al., 2017; Volkmar et al., 2014; Kilincaslan et al., 2017). Research is underway to determine whether different genetic causes of ASD lead to different presentations and there are examples of ASD symptoms improving by addressing the underlying genetic deficits (Kaufmann et al., 2017). The FDA has recommended testing for HLA-B1502* in patients of Asian ancestry prior to the initiation of carbamazepine, as well as a lower maximum recommended dose for citalopram (20mg/day) in known CYP2C19 poor metabolizers (FDA, 2012, 2011).

stigma and greater patient empowerment (Austin and Peay, 2006; Costain et al., 2014a; Hippman et al., 2016; Inglis et al., 2015; Moldovan et al., 2017; Costain et al., 2014b).

Decision-making about whether to offer or undergo genetic tests that may currently inform psychiatric care is complex, for reasons including the fact that biological testing has not traditionally been part of routine psychiatric care, the complex genetic architecture of psychiatric disorders (e.g. potentially thousands of genes relevant, incomplete penetrance, phenotypic variability of identified risk factors, small to moderate effect sizes), the contribution of environmental risk factors, variation in age of onset and severity of the disease, and the differential availability of effective treatment (Ward et al., 2019). The ISPG put together a statement on genetic testing that provides helpful guidance for patients and clinicians (https://ispg.net/genetic-testing-statement/).

As well-powered GWAS enable the identification of individuals with polygenic scores indicative of high risk for psychiatric disorders, and penetrant pathogenic variants are identified, genetic testing may become a more routine part of psychiatric care (Khera et al., 2018). These developments may help improve risk prediction, diagnosis, recurrence risk estimation, and early detection through increased monitoring of symptoms and subsequent early intervention. Some recent evidence suggests that pharmacogenetics applications of polygenic risk testing may also play a role in precision medicine strategies in psychiatry (Amare et al., 2018; Chen et al., 2012; Lerman et al., 2015; Zhang et al., in press). The integration of genomic technologies into psychiatric care will generate key ethical challenges for clinicians who will have to make key decisions whether to offer these tests and how to manage the findings (Ward et al., 2019).

To enable responsible translation of genetic discoveries in psychiatry into improved clinical outcomes, research is required to systematically ascertain the important psychosocial, legal, behavioral and ethical implications of testing for genetic risk information in advance of the routine clinical implementation of this type of testing. Without reliable data, provided by rigorous research on which to base the development of sound service models, there is a danger that services may be ineffective or counter-productive and may become embedded in the health system that is not responsive to patient needs. Genetic testing in psychiatry may lead to psychological distress and, given high levels of mental health stigma, genomic findings may also be the basis for undue discrimination (Brannan et al., 2018). The current lack of robust prevention or risk mitigation approaches for at-risk individuals exacerbates psychosocial and practical challenges of integrating genetic testing into clinical care. These challenges may be particularly problematic for people with fewer resources (e.g., access to healthcare services, or poor environmental support). The implications of testing will also vary depending on whether the person tested has been diagnosed with a psychiatric disorder (diagnostic testing) or is currently unaffected (predictive genetic testing) (Meiser et al., 2008; Trippitelli et al., 1998).

Apart from some adult-onset neurodegenerative disorders, which are relatively well-studied in terms of the psychosocial implications of genetic testing (Meiser and Dunn, 2001; Rahman et al., 2012), there is currently a dearth of research on stakeholders' experiences with genetic testing for psychiatric disorders. With the exception of one study, which

examined the responses of individuals who had actually been genotyped for a putative risk allele (Wilhelm et al., 2009), all of the available studies involve hypothetical future genetic testing scenarios (Austin et al., 2006; Coors, 2005; DeLisi and Bertisch, 2006; Jones et al., 2002; Meiser et al., 2005; Wilde et al., 2011; Meiser et al., 2008; Trippitelli et al., 1998). It is known from the Huntington disease context that attitudes to hypothetical testing do not necessarily translate into actual uptake of genetic testing (Meiser et al., 2000). As such, it is necessary to conduct qualitative and quantitative research on individuals who are actually offered genetic testing for psychiatric disorders (CNVs as well as polygenic risk scores) in order to identify and understand the uptake of these tests.

To successfully translate progress in psychiatric genetic testing into beneficial clinical outcomes, more research is also needed to: 1) ascertain the psychological and behavioral impacts of receiving genomic testing results; 2) identify individuals most at risk of developing negative psychological and behavioral outcomes, thus allowing the precise targeting of interventions to such individuals; 3) assist clinicians in communicating highly complex testing results to their patients; 4) develop methodologically-sound decision aids to help patients make informed decisions about psychiatric genetic testing; and 5) develop innovative education and psychosocial counseling strategies to help patients understand their testing results and translate testing results into appropriate health behaviors.

Psychiatric Genetics in Courts

Although the use of psychiatric genetic information as evidence in judicial proceedings and other legal activities is not novel (Coffey, 1993), the development of powerful genomic technologies has given this a new impetus. In addition to ongoing work on psychiatric genetics in criminal proceedings, claims about psychiatric genetics have begun to enter civil courts such as child custody proceedings and tort litigation (Adacsi v Amin, 2013), and there is indication that such uses are likely to expand in the future (e.g., real property rights (Rothstein and Rothstein, 2016) and education (Sabatello, 2018)).

Whether criminal defendants can (and should) get “off the hook” on the basis of an argument that “my genes made me do it” has been widely debated in legal scholarship, raising questions about free will, justice, and proportionality of punishment for a crime for which “genetically predisposed” criminals may argue to lack the necessary blameworthiness as expected by law (Friedland, 2014; Johnson, 1998; Jones, 2003; Morse, 2011). To date, criminal defendants’ introduction of psychiatric genetic evidence (most recently, the *monoamine oxidase-A* (*MAOA*) gene) to absolve them from responsibility has been largely unsuccessful: both comprehensive studies of criminal cases in the U.S. (Denno, 2009, 2012) empirical studies using vignettes with experimental manipulation of neurogenetic evidence (Appelbaum and Scurich, 2014; Aspinwall et al., 2012; Scurich and Appelbaum, 2016) show that the impact of such evidence on trial outcomes is limited. However, emerging knowledge of psychiatric genetics may reopen this question (e.g., with increasing predictive value of polygenic risk scores and discovery of variants with relatively high penetrance), and may shift punitive policies into more rehabilitative approaches that tailor the treatment and rehabilitation programs of individual offenders’ to their genetic makeup and environmental backgrounds (Beaver et al., 2014). As scientists and healthcare providers will likely be

involved in developing and implementing such scientific developments, it is key that they are aware of the challenges, e.g., what are the implications for a defendant whose genetic makeup does not show responsiveness to medication (Sabatello and Appelbaum, 2017).

The possible uses of psychiatric genetic evidence in civil proceedings raises a host of other concerns about the means in which such genetic evidence may be obtained, its impact of judicial decisions, and overall, whether the use of psychiatric genetic evidence may bias judicial decisions and obstruct the administration of justice. Child custody proceedings can illustrate these dilemmas. Such cases are notorious for parental accusations of mental instability by the other parent and welfare authorities, and studies indicate that parents with psychiatric conditions are far more likely to lose custody of their child (Mental Health America, 2011). Given prevalent genetic determinism among the general population and the stigma surrounding psychiatric conditions, including increased perceptions of dangerousness when mental illness is attributed to genetics (Phelan, 2005; Phelan et al., 2006; Pescosolido et al., 2010), litigants may find it appealing to introduce such information as evidence about a parent's mental instability.

However, the collection and introduction of psychiatric genetic evidence about a parent involved in child custody proceedings raises important questions that need to be addressed. For example, should such data be collected from patients' medical records, which may lead to reluctance of people "at risk" to seek such testing? Should it be collected following a court order requiring a litigant to undergo psychiatric genetic testing, regardless of litigants' interest in (or anxiety about) learning their psychiatric genetic predispositions? How about collection through "genetic theft," where data is obtained from deserted property, such as cigarette butts, without the knowledge of the parent (Sabatello and Appelbaum, 2016)? Alternatively, should such data be obtained from discovery of the results of a litigant's biospecimen sample that was previously obtained in the course of a psychiatric genetic research that did not issue a Certificate of Confidentiality, which may deter research participation (Sabatello and Appelbaum, 2017) or through the use of samples from ancestry websites, as has been recently done to identify the alleged Golden State Killer (Ram et al., 2018; Springer Nature, 2018)? How to balance the various interests will require ongoing consideration and drafting of policies to ensure that psychiatric genetic data are neither abused in nor unduly impactful on judicial decisions.

As psychiatric genetic knowledge continues to emerge, judicial actors—from judges and jurors to researchers, healthcare providers, and other experts that provide testimony in courts—must develop an understanding of genetics and its possible uses and misuses. Moreover, it will be important to develop guidelines clarifying how psychiatric genetic evidence may be brought into judicial proceedings, considering power imbalances between litigants and balancing individual and societal interests. Psychiatric genetics researchers and mental healthcare experts have a key role to play in promoting a better understanding of the capacity and limitations of genomic knowledge and technologies and to promote the responsible use of psychiatric genomics in the legal system.

Conclusion

We have highlighted key psychiatric genetics ELSI issues in the research, clinical, and judicial domains. There are, however, many other issues that merit careful thought and community discussion but which we are unable to cover in depth in this paper. For example, how can psychiatric genetics researchers in aid in efforts to reduce stigma and increase awareness of neurodiversity? First, we can explicitly adopt stigma reduction as an important component of our mission as researchers studying highly stigmatized conditions. Second, we can be active and vocal community partners and early adopters of community preferred terminology in scientific and medical writing. Person-first language, which emphasizes the humanity of the person before their diagnosis (e.g., “a person with schizophrenia” instead of “a schizophrenic”), may be preferable (Jensen et al., 2013). However, there is not a “one-size-fits-all” solution. For example, some members of the autism community self-identify as and prefer the language of “Autistic person” rather than “person with autism.” Thus, in both clinical and research settings that afford personal interactions, asking the individual how they prefer to discuss their diagnosis helps to create a compassionate and destigmatized atmosphere. Though this is only a first step, we believe that psychiatric genomics researchers can be powerful allies to our community partners across the world by embracing destigmatizing language and appreciating neurodiverse identities.

Finally, very recent studies encompassing 100,000 to more than 1 million individuals have identified more than 1000 genome-wide significant loci associated with cognitive ability and/or educational attainment (Davies et al., 2018; Lam et al., 2017; Lee et al., 2018; Savage et al., 2018). The potential use of cognitive polygenic testing in educational settings (Selzam et al., 2017) and prenatal screening (Seidel, 2017) requires the psychiatric genetics community to take the utmost care in the conduct and communication of such research (Callier and Bonham, 2015; Sabatello, 2018). The Social Science Genomics Consortium (SSGAC) has provided a useful primer on the interpretation of cognitive genomics studies (https://www.thessgac.org/faqs), but further theoretical and empirical work is needed to understand the potential uses and abuses of cognitive genomics data, including the limits on predictive power, the implications for psychiatric disorders, and the role of public perceptions (and misperceptions).

Psychiatric genetics research holds great promise for improving the lives of those at risk for or experiencing a psychiatric disorder. As with most significant scientific advances, this research raises the prospect of great benefit and the potential for unintended harms. The goal of researchers in this field should not only be to advance the science, but to help maximize the benefits and minimize the potential negative impacts of this research for individuals and society. The ISPG Ethics Committee hopes to be an ally in these endeavors.

Acknowledgements:

We would like to acknowledge other members of the ISPG Ethics Committee for helpful discussions regarding the topics addressed in this manuscript: Laura Bierut, Weiyi Mu, Nicole Martinez-Martin, Consuelo Walss-Bass, Kevin McGhee, Manuel Mattheisen, Joseph McClay, Randell Libby. Lea K. Davis was supported by National Human Genome Research Institute (NHGRI) of the National Institutes of Health RM1HG009034 and the National Institute of Minority Health and Health Disparities U54MD010722; Anna Docherty was supported by NIH-National Institute of Mental Health (NIMH) K01MH109765; Gabriel Lázaro-Muñoz was supported by NHGRI

R00HG008689; Roseann E. Peterson was supported by NIH-National Institute of Mental Health (NIMH) K01MH113848. Todd Lencz is supported, in part, by NIMH R01MH117646. Maya Sabatello was supported by NHGRI K01HG008653.

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