Clinical Considerations

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Maximizing Near-Term Clinical Opportunities for Psychiatric Genetics

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Abstract

Over the past two decades, genomics research has been enormously successful in identifying specific genes, pathways, and mechanisms that play a role in the development of psychiatric and neurodevelopmental disorders. The translation of these findings into the clinical setting has been slow but steady. Current clinical advances range from identifying genetic etiologies for neurodevelopmental disorders to pharmacogenomic dosing guidelines for psychiatric medications. Many more advances can be anticipated, given the paradigm-shifting knowledge produced by the field. Principally, genomics research has produced neurobiological hypotheses that are likely to yield therapeutic advances only in the long term. Nonetheless, opportunities to improve clinical care also exist in the near term. This chapter evaluates and prioritizes these opportunities in terms of their feasibility and potential impact. Barriers to the successful translation of these findings are identified and areas for research highlighted to support their translation into clinical settings.

Introduction

This chapter is the result of an extended discussion between a group of psychiatrists, ethicists, medical geneticists, research geneticists, and genetic counselors, all of whom have extensive experience in their respective field. Our discussion was grounded on a common understanding that psychiatric genetic research, embedded in a human rights framework, can positively impact medical care, societal treatment, and quality of life for people with psychiatric

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illness and neurodevelopmental disorders. While our discourse was rooted in this shared perspective, it was also informed by our unique experiences, including lived experiences. As expected, consensus was reached on many themes, but for some issues, opinions diverged. In producing this report, we aim to represent the gestalt of our discussions fairly, including the diversity of perspectives. As such, the style of this chapter emphasizes the fluid nature of our discussions at the Forum. We are deeply indebted to the Ernst Strüngmann Forum for providing space for this debate and believe that there are multiple, exciting near-term clinical opportunities for psychiatric genetics.

We consider three layers of genetic information and will describe, for each, the status of clinical provision, the research gaps, and the potential for future implementation to improve clinical care and patient outcomes. We begin with a look at the potential return of rare variant genetic diagnoses for indications beyond childhood intellectual disability and autism spectrum disorder, for which a consensus already exists regarding clinical utility. Next, we look further ahead to the potential use of polygenic scores in clinical practice, identifying both the endpoints likely to have most utility and the substantial research gaps that need to be filled. We then consider the role of genetic counseling in the absence of testing and discuss provision of genetic education in the general population. Next, we discuss barriers to the application of genetics in clinical practice. Finally, throughout our discussions, themes of equity, diversity, and community engagement arose frequently. These themes are, therefore, presented as guiding principles for all future research and implementation.

Near-Term Opportunities and Challenges for Rare Copy Number and Sequence Variants

Currently, clinical care and access models for genetic testing and genetic counseling in psychiatric disorders are provided by medical genetic and genetic counseling professional organizations. In terms of clinical genetic testing, an established consensus exists to support the genetic testing of minors with intellectual disabilities and autism. The current best practice in the United States, Canada, and several European countries is to return an interpretation of rare and clinically relevant copy number variants (CNVs) identified through whole-exome sequencing or array-based technologies. We anticipate that whole-genome sequencing technologies will eventually replace whole-exome sequencing and array-based methods. Existing guidelines typically recommend clinical genetic counseling to occur at the point of care when genetic test results are returned. As of the writing of this chapter, we are unaware of any professional association guidelines that stipulate which patients who receive a psychiatric diagnosis, in the absence of intellectual disability or global developmental delay, should be offered genetic testing.

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Accordingly, we discussed what research would be needed to identify who else would benefit from clinical genetic testing, and the circumstances that would facilitate such a benefit.

Currently Available Genetic Testing in Clinical Psychiatry

Currently, most medical genetics professional societies provide guidelines and recommendations for offering exome sequencing or chromosome microarray to children diagnosed with global developmental delay (GDD), autism spectrum disorder, major malformations, or epilepsy (Finucane et al. 2021, 2022). The diagnosis of GDD requires a delay in reaching at least two early childhood developmental milestones, including fine or gross motor skills (e.g., delayed walking), cognitive development (e.g., intellectual disability), and social or communication (e.g., shared attention, speech, and language) milestones. GDD is common and is diagnosed in approximately 1–3% of children younger than five years of age (Bélanger and Caron 2018). Currently, an underlying genetic etiology can be discovered in approximately 40% of children with a diagnosis of moderate to severe GDD (Savatt and Myers 2021; Wortmann et al. 2022) and 24–45% of children with epilepsy (Sánchez Fernández et al. 2019). While current guidelines for offering CNV testing in children with GDD, epilepsy, and major malformations are appropriate, the uptake and implementation of these guidelines for minors who meet these criteria are inconsistent across healthcare systems and individual clinicians. For example, in the Netherlands, any clinician can request clinical testing, but reimbursement only occurs when the request is filed by a medical specialist in a hospital or a general practitioner. In the United States, clinical diagnostic genetic testing for patients with congenital anomalies, developmental delay, or intellectual disability is recommended by the American College of Medical Genetics and Genomics and the American Academy of Pediatrics. However, implementation varies greatly across states and institutions (Manickam et al. 2021; Miller et al. 2010), and many children who meet criteria are never tested. While many factors can contribute to this inconsistency (e.g., insurance status, access to clinical geneticists, reimbursement), one major barrier is that primary care providers may not be familiar with the guidelines for care and referral (Tremblay et al. 2018; Truong et al. 2021). Thus, the shift from clinical guidelines to a true standard of care is still ongoing and should be supported by research in implementation science.

Providing Clinical Genetic Testing Services to Adults with Developmental Delay and Intellectual Disability

As described above, consensus recommendations from professional societies and expert groups are available for the diagnostic workup of children with neurodevelopmental delay (Manickam et al. 2021; Sabo et al. 2020; Thygesen et

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al. 2018). Nonetheless, many children who meet the criteria are never offered genetic testing, and the technologies required for such a workup are relatively young. Together, these factors contribute to a substantial population of adults who would have met current criteria for genetic testing in their childhood but were never offered genetic testing, either because it did not exist when they were children or because the technology and counseling were not available to them. There is a growing body of evidence that the diagnostic yield in adult patients with intellectual disability is comparable to the pediatric population with intellectual disability; however, similar guidelines on clinical genetic testing for adults have been slow to emerge (Finucane et al. 2020).

Given the guidelines currently in place for children with GDD, should genetic testing also be offered to adults with GDD? Two primary reasons support this action. First, ethical principles regarding justice dictate that adults who would have met criteria for genetic testing as children have a right to the standard of care offered to children today. Second, early studies have found that carriers of CNVs associated with neurodevelopmental disorders, regardless of the level of neurodevelopmental delay, demonstrate increased rates of age-related disease (e.g., diabetes, hypertension, obesity, renal failure, and early mortality) and that carriers were twice as likely to seek hospital emergency services (Auwerx et al. 2022; Finucane et al. 2022). These studies highlight the importance of specific genotype-phenotype research across the lifespan for CNV carriers to inform continuing clinical management. Little is known about the long-term clinical management of patients who carry a neurodevelopmental CNV or other high-impact rare variant. We believe that this should be a priority area of research—one that could be filled by engaging adults who experienced GDD early in life and now choose to investigate the underlying genetic etiology as adults.

Given that existing studies have focused almost exclusively on children, additional work is needed to characterize the diagnostic yield from genetic testing in an adult population. These data are important for the continual development of clinical guidelines, as there will be populations of adults who may benefit from genetic testing for many years to come. In addition, it is critically important to understand the potential positive and negative psychosocial impacts of receiving a genetic diagnosis in adulthood. Ethical questions also arise. For example, a relative who serves as guardian for an adult, who experienced GDD as a child, may also be personally impacted by the decision to pursue (or not) genetic testing. In that situation, the potential exists for a guardian to make a choice based on the guardian's own interests rather than those of the ward. In this case, it would be important to include genetic counselors in the process to work with the family unit on understanding the potential risks and benefits of pursuing genetic testing (Morris et al. 2022). An evidence base should be built to maximize improved psychosocial and clinical outcomes in adults with GDD. Finally, studies should be prioritized to determine the impact of genetic

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testing on the clinical and health economics management of adult patients with qualifying disabilities.

Childhood, Early-Onset, and Adult Psychosis

Guidelines for genetic testing in individuals with intellectual disability are well established, yet no clinical guidelines exist for genetic testing in other early-onset psychiatric disorders. Emerging evidence suggests that children with early-onset psychosis benefit from a clinical genetics evaluation. For example, a recent study showed that the yield of chromosome microarray testing was identical in autism spectrum disorder and psychosis in children and adolescents younger than 18 years (Brownstein et al. 2022), and ethical analysis suggests equivalent benefits (Morris et al. 2022).

Key pieces of information are lacking in the population with early-onset psychosis, including the genetic testing yield by age at onset, level of premorbid cognitive functioning, and the additional clinical or family history modifiers that might increase the yield. For example, it is currently unclear whether children with early-onset psychosis and no history of GDD, but who have a sibling with epilepsy or autism, are more likely to have a positive genetic test than a child without these additional family history modifiers. In this population it is critical to assess yield, its clinical and family history modifiers, and whether there are any other factors (e.g., severity, chronicity, comorbidity) that could increase yield and trigger the offer of testing.

Finally, in adult-onset psychosis (≥ age 18) without a history of GDD, research is needed to determine whether there are clinical features (e.g., severity, chronicity, treatment resistance) that can serve as indicators for a rare genetic cause underlying the psychiatric disorder. Currently, no clinical guidelines exist for this population despite significant evidence that genetic counseling (even in the absence of genetic testing) increases empowerment and improves outcomes (Semaka and Austin 2019).

Additional Themes

Several themes emerged throughout our discussions. Preeminent among these was the need to increase representation of diverse genetic ancestries, as this will improve the interpretation of genetic testing results. Prior studies demonstrate that lack of diversity can result in a bias in which patients with increasing non-European ancestry are more likely to receive "variants of unknown significance" from high-throughput sequencing screens. This knowledge gap, in terms of clinical significance of some genomic variation, is an artifact of the limited investment in genomes from diverse ancestries over the past decades. Additional themes that emerged included the need for more systematic study of (a) the impact of genetic testing on subsequent clinical management of patients and (b) the impact of genetic counseling (with or without genetic testing)

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on the psychosocial well-being of patients. There was strong consensus that research should proceed under a community engagement framework that increases the presence of patient representatives and advocates at all levels of research. These issues are key translational areas in which linkages with clinical implementation science should be initiated early.

Near-Term Opportunities and Challenges for Polygenic Scores

Polygenic risk scores (PRSs) are per-person estimates of the cumulative genetic risk conferred by common single nucleotide polymorphisms, as opposed to rare genetic events. PRSs are estimated with respect to an index phenotype (e.g., depression, schizophrenia, externalizing behavior) that has been measured and tested for genetic association in large independent samples. They demonstrate imperfect, but measurable, average differences between groups of individuals with and without these index traits. While PRSs are not ready for clinical implementation in a psychiatry setting today (Araújo and Wheeler 2022; Lewis et al. 2022; Pereira et al. 2022), there is promise for their near-term use in certain identified contexts (e.g., differential diagnosis, screening, and prevention) (see Smoller, this volume). We recognize that PRSs are, *de facto*, already available to the public through direct-to-consumer genetic testing companies and third-party services (Peck et al. 2022). For certain cancers, PRSs are being utilized in some oncology genetic counseling clinics, and psychiatric PRSs may soon be included in genetic testing reports for psychiatric indications. These issues sparked a great deal of discussion on the type of research that could be instructive to implement PRS testing in clinical practice. We considered three classifications of patients: (a) genetically defined high-risk individuals, (b) phenotypically defined high-risk individuals, and (c) the general population. The research needed to determine PRS utility in each group is considered below.

Use of Polygenic Risk Scores in "Genetically Defined" High-Risk Populations

Individuals who are positive for clinical genetic screens (e.g., 22q11.2) may be at high-risk of developing a later psychiatric diagnosis. It is possible that a PRS for the "highest risk" psychiatric diagnosis may provide additional clinical utility. For example, in a child who has received a positive CNV test result but does not yet have a psychiatric disorder (e.g., a 22q11.2 deletion but no psychosis), the addition of a PRS for schizophrenia may meaningfully increase the positive predictive value of the initial genetic finding. Inherent in this hypothesis are two critically important issues. The first is whether the risk index is increased with addition of the PRS. The second is whether the increase is

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"clinically meaningful." We note, however, that there is little consensus on what constitutes a "clinically meaningful" increase in risk. We concluded that a "clinically meaningful" improvement in positive predictive value should impact at least one of the following domains: the time to diagnosis, clinical management, early intervention, surveillance and monitoring, or treatment selection. Either way, evidence shows that for families of individuals with the 22q11.2 deletion, genetic counseling regarding the chance for psychiatric manifestations can be helpful (Carrion et al. 2022).

The addition of PRS to CNV results could meet at least some of the clinically meaningful criteria. For example, a recent study found that among individuals with a 22q11.2 deletion, the rate of schizophrenia diagnosis (and thus the positive predictive value) increased from 20% (95% CI = 0.16, 0.24) at or below the 50th PRS percentile to 33% (95% CI = 0.222, 0.428) at or above the 90th PRS percentile. The 50th percentile represents the sample median PRS (also the mean for z-score scaled distributions). Equally important, the rate of schizophrenia diagnosis decreased from 20% to 9% in the lowest 10th percentile of PRS among 22q11.2 deletion carriers (Davies et al. 2020). This study, therefore, suggests that the risk for developing schizophrenia, relative to the "average PRS risk" given a 22q11.2 deletion, could be refined for patients at both ends of the schizophrenia PRS distribution. Similarly, much larger-scale studies have shown that PRS significantly improves the positive predictive value yield for breast cancer in individuals at high risk due to rare variants in *BRCA1/2* (Kuchenbaecker et al. 2017; Wray et al. 2021). Further research is needed, however, to replicate and test the generalizability of these findings. The additional benefits of genetic counseling required to understand the contribution from polygenic risk alongside rare variant risk (e.g., in CNV carriers) should also be evaluated. Finally, it is unclear whether clinical psychiatric management or surveillance recommendations would differ for those patients at the highest versus lowest decile of risk, nor have the potential negative consequences for patients and their treatment been explored systemically. These remain high-priority areas of future research.

Use of Polygenic Risk Scores in "Phenotypically Defined" High-Risk Populations

Patients who are "phenotypically defined" as high risk for a psychiatric disorder may be in a prodromal phase or may already have one or more conditions that increase their risk of developing a later psychiatric disorder. While there is clear evidence of the positive impact of genetic counseling and psychoeducation in helping patients adapt to a diagnosis already received (Ryan et al. 2015), there are fewer data on the best approach for helping patients adapt to genetic risk for a mental illness in the absence of that diagnosis (Carrion et al. 2022; Gerrard et al. 2020). In the case of a patient who is phenotypically defined at high risk for a major mental illness, there are additional ethical

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and practical considerations for communicating risk in a way that optimizes positive outcomes, patient autonomy, and patient-provider relationships, while minimizing negative consequences such as self-stigma, demoralization, therapeutic nihilism, and discrimination (Ryan et al. 2015). The group identified this as a critical area of genetic counseling research and elaborates on this subject below in the genetic counseling section of this chapter.

Use of Polygenic Risk Scores in the General Population

While a well-powered PRS for a highly heritable psychiatric disorder can index increased relative risk for developing a given disorder, the absolute risk in the general population remains low for disorders with a low prevalence (e.g., schizophrenia or Tourette syndrome). This reduces the predictive value of these tests. For example, the relative risk of developing schizophrenia for an individual with a PRS in the highest 1% of the distribution is 5.6 (compared to all others in the population), but the absolute risk is approximately 5% (Lewis and Vassos 2022; Trubetskoy et al. 2022). The utility of this knowledge for early diagnosis, prevention, or enhanced surveillance has yet to be determined. For common psychiatric disorders (e.g., depression, anxiety), the prevalence is higher but the heritability of the disorder is lower. The PRS explains less of the phenotypic variability between people, but given higher prevalence, absolute risks may be high.

We discussed the potential for PRS to be part of a tiered screening system aimed at promoting resilience and positive health behaviors. Given the potential for the PRS to influence *perceptions* of risk, the communication of the uncertainty inherent in PRS interpretation is critical to ensure the beneficial integration of genomic knowledge into the patient's view of their current and future mental health. Thus, research is needed to identify the most effective approaches to delivering the information given the clinical context of PRS screening. Understanding the psychosocial impacts of receiving such a score, and the role that clinical genetic counseling could play in mitigating any negative impacts, could further improve the benefit-to-risk ratio. Additional research is needed to determine which determinants of health (e.g., clinical, family history, social) increase risk and should thus be considered when prioritizing patients for screening. This will also inform the process of providing feedback to patients about their PRS.

Use of Polygenic Scores in Treatment Selection

Existing PRSs have primarily been trained on case/control labels for DSM constructs (e.g., major depression or schizophrenia). Thus, there is a need for further discovery research to guide treatment selection and predict treatment response (including presence of side effects). Existing genome-wide association studies (GWASs) of treatment response remain limited by sample size,

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outcome measurement, and design approaches. For example, treatment response phenotypes are often limited to "response versus nonresponse" of a single medication. A more valuable clinical use for PRS would be to distinguish which medication out of the many existing options might yield the best response.

Identifying the polygenic component to treatment response is challenging, and more robust polygenic predictors of treatment response are needed. As with GWAS of diagnostic labels, large sample sizes are key to success, but sample sizes for treatment response studies are currently low compared to case-control GWAS. Further studies focused on specific drugs or drug classes are needed to build relevant PRSs aimed at facilitating the prescription of decisions for a patient. Expanding the data sources with high-quality, individual-level response to treatment will be crucial to performing well-powered studies needed to identify genetic predictors of response to treatment. Limitations include lack of access to data from clinical trials (particularly from pharmaceutical companies), difficulties in determining response in real-world data, and confusion that arises from polypharmacy.

An open question is the extent to which genomic predictors for disorder risk are also predictive of treatment response. Current studies in depression show only modest overlap (Pain et al. 2022b), but confusion may exist since GWAS finds that people with high PRS are more likely to have severe, recurrent, or chronic disorder; this alone may account for poorer treatment response. There is an urgent need to develop novel data sources for treatment response, or surrogate measures, with validation of the measure and understanding of the biases, strengths, and weaknesses of each data source. Possibilities include:

- Exploiting electronic health record data using natural language processing to extract measures of treatment response.
- Using treatment-resistant cases, with the assumption that change of drug after a suitable prescribing period indicates a lack of response.
- Seeking innovative data sources, such as passive data collection from wearable devices or phone apps that can capture indicators of treatment response.

Equity in the Use of Polygenic Scores

As discussed above, we recognize that equitable translation of PRS is a barrier to current implementation. The Eurocentric history of GWAS discovery research has resulted in PRSs that are primarily tuned for performance in European-ancestry populations and which underperform in non-European ancestries. Clinical translation prior to equitable performance of such genomic tools will exacerbate health disparities. Thus, representation and equity must be a primary emphasis in any new discovery GWAS.

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The Impact of Genetic Counseling with and without Genetic Testing on the Clinical Management of Mental Illness

As defined by the National Society of Genetic Counselors, "genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease" (Resta et al. 2006). Genetic counselors provide genetic risk estimation, support decision making in relation to genetic testing, and obtain patient consent. They are involved in the interpretation and management of test results. Furthermore, they assist the patient in adapting to the genetic information and in managing the resulting psychosocial consequences (Patch and Middleton 2018). We believe that genetic counseling should be considered in two contexts: (a) counseling that accompanies genetic testing and (b) counseling in the absence of genetic testing.

Counseling that accompanies clinically recommended genetic testing, which can be ordered and interpreted by clinical geneticists or genetic counselors, aims to help people understand the results of their specific genetic test and the implications of those results. There was consensus in our group that clinical genetics services traditionally focus on rare disorders with Mendelian inheritance patterns. However, the genetic architecture of mental health disorders is complex and genetic testing is not routinely recommended. Hence, only a subset of those who might benefit from genetic *counseling* are referred to clinical genetic services for genetic *testing*.

Patients who do receive a genetic test result indicating the presence of an underlying genetic syndrome might experience changes in clinical management. Here, genetic counselors and/or medical geneticists can help patients and families adapt to these new healthcare needs. For example, young children with a 22q11.2 deletion will be referred to other areas of medicine (including cardiology to assess associated cardiac anomalies) and may benefit from referral to psychiatry services for surveillance for early psychosis symptoms. The positive predictive value of some rare genetic variants, especially when combined with additional genetic factors (i.e., PRSs), has the potential to provide increased clinical value (i.e., additional referrals or targeted surveillance). Information about underlying genetic causes can be beneficial for the planning of appropriate educational interventions, family support, and advocacy. In these contexts, genetic counselors and/or medical geneticists may also work with family members who seek family planning services or other recommendations (Butler et al. 2022). Early involvement and close collaboration of primary care, clinical genetics, and developmental pediatrics with child, adolescent, and adult psychiatry may help provide clinical care that can optimize outcomes.

Genetic testing may be absent in the counseling process when a patient has been offered genetic testing but declines or when genetic testing is not available. The latter is true in most cases. We agreed that patients with a psychiatric disorder would benefit from receiving general information on the genetic

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contribution to their disorder. However, we could not agree on how this intervention—in the absence of available genetic testing—should be delivered or what it should be called. Some argued that this falls under the umbrella of genetic counseling while others felt that the intervention was best described as psychoeducation.

In support of this first position, we reviewed the large body of evidence that supports the position that helping people understand the genetic contributions to disease has a positive impact on patients' lives, even in the absence of genetic testing (Morris et al. 2021; see also Austin, this volume). Genetic counseling provides a better understanding of how genes and environment contribute to the development of illness. This is particularly helpful to clinical management, as dispelling misperceptions related to etiology increases patient autonomy, reduces stigma, shame, blame, and guilt, and empowers patients to adopt healthy lifestyle changes that can reduce the chances of a psychiatric episode (Morris et al. 2021). For example, patients could work with a genetic counselor to understand how their genetic risk interacts with environmental risk and to identify factors that contribute to their own resilience (e.g., through sleep, physical activity, and medication adherence).

Acknowledging the limited resources available to provide genetic counseling, an alternative view is that this more specialized type of counseling should be reserved for patients who fulfill the criteria for being offered genetic testing or who specifically request genetic counseling for other reasons (e.g., questions about family planning or adoptions in the presence of family history of mental illness). Throughout our discussion, there was significant debate on the nomenclature used to describe genetic counseling in the absence of genetic testing. As previously indicated, there are currently no guidelines for psychiatric genetic counseling despite robust evidence of the positive and lasting impact that genetic counseling can have in helping patients change their beliefs about the origin of their psychiatric illness and their degree of control over their future. An alternative approach to prioritizing patients to be referred for genetic counseling was proposed, based on patient need. For example, in addition to those eligible for genetic testing, patients who have the lowest levels of empowerment could be prioritized for referral to a genetic counselor. Research suggests that this group benefited greatly after receiving genetic counseling in terms of increases in empowerment (Gerrard et al. 2020).

In terms of challenges related to the workforce, there is a general lack of education in psychiatric genetics among psychiatrists, psychologists, social workers, and other mental health professionals as well as a lack of interdisciplinary work among all relevant stakeholders. In some parts of the world, there are training programs for psychiatric counselors; however, opportunities to practice are limited as the creation of positions has not kept up with the supply of trained counselors (Dillon et al. 2022). The creation of genetic counseling positions is driven by demand for genetic counseling, as indicated by physician referrals, yet these tend to be driven by the availability of genetic

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testing (Chanouha 2022). In other parts of the world, there are few or no training programs for psychiatric genetic counselors. This has led to a workforce shortage and a reliance on clinical geneticists, psychiatrists, and primary care physicians to provide genetic information to patients.

The Impact of Genetic Education on Public Discourse Regarding Mental Illness

Genomic information is often perceived by the public as deterministic and immutable, which can lead to increased stigma and decreased sense of autonomy and control when an individual is diagnosed with a psychiatric condition. We identified the inclusion of information about the etiology of psychiatric conditions (including genomics) in public mental health campaigns as a priority area in public education. Key concepts that should be communicated to the public in awareness campaigns include the probabilistic nature of genetic variation, the spectrum nature of genetic risk (and phenotypes), and the complex interaction between genetics and environment throughout the lifespan (e.g., Ke et al. 2015). In addition, we recommend genomics education be included in schools alongside mental health education. Anticipating and addressing misconceptions is important when developing this type of awareness campaign, as is measuring outcomes to assess understanding and remaining gaps. Thus, partnering with patient representatives, mental health advocacy groups, national mental health institutes, and public mental health forums could provide avenues for these types of engagement and awareness campaigns.

Barriers to the Application of Genetics in Clinical Mental Health Practice

Multiple and diverse barriers inhibit adequate implementation of clinical genetics in clinical mental health practice at several levels: societal, healthcare organization, clinician, family, and patient. The specific issues experienced may vary, but the general barriers are similar regardless of the specific clinical genetic intervention under discussion. Table 12.1 lists barriers which cut across three forms of clinical genetic interventions: (a) clinical genetic testing and counseling, (b) genetic counseling in the absence of testing, and (c) increasing health literacy and genetic knowledge of psychiatric conditions.

Further barriers that cut across all classifications include institutional obstacles to implementation, poor diversity and representation, psychiatry-specific challenges to the use of genetic testing, and the potential for excessive medical conservatism. In terms of implementation, the lack of electronic health record support inhibits the integration of genetic information into the health record, needed to facilitate clinical management and inform (not confuse) clinicians and patients. Regardless of the type of clinical information being returned,

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Table 12.1 Barriers to the availability of clinical genetic services.

Societal	• Limited knowledge of genetics and misperception of genetic determinism • Fear that genetic explanations of mental illness will increase stigma • Disparities in access to clinical genetic services
Healthcare systems	• Inconsistent payment structures that sometimes disincentivize services • Limited human resources (e.g., clinical psychologists, psychiatrists, and psychiatric genetic counselors) • Limited workforce education on the role of genetics in psychiatry
Clinician	• Historical disconnect between psychiatry and clinical genetics • Failure to recognize the role of genetics in the context of complex psychiatric disorders, resulting in neglect of genetics in psychoeducation • Disagreement regarding role of genetic counselors in the absence of genetic testing
Family and individual	• Overestimation of absolute and relative risk • Concerns over genetic privacy and discrimination • Fears of eugenic motivations regarding clinical genetic services

patients from non-European ancestries are disadvantaged by the lack of ancestral diversity in existing genetic databases. Patients from non-European genetic backgrounds who meet criteria today for clinical testing are more likely to have variants that are currently of unknown significance. Additionally, PRS that are trained on genetic data collected from European-ancestry populations are not portable to non-European populations. Some of the barriers identified were unique to psychiatry, including the fact that psychiatric diagnoses remain stigmatized and that fears of the eugenic use of psychiatric genetic information are substantial.

Guiding Principles for Future Research and Implementation

Throughout our discussions, the need to improve education (clinical and public) was viewed as crucial. To aid progress, we propose a strategy that would build on existing pathways of information sharing and create a two-pronged awareness campaign aimed at both general and clinical audiences (see Figure 12.1). This campaign would utilize the World Health Organization and other groups to distribute educational materials developed by the International Society for Psychiatric Genetics (ISPG). Professional organizations, including the American (APA), European (EPA), and/or World (WPA) psychiatric associations could utilize these materials to educate professionals in training and practice, and potentially to develop clinical consensuses and practice guidelines. Other groups, preferably those with existing public awareness

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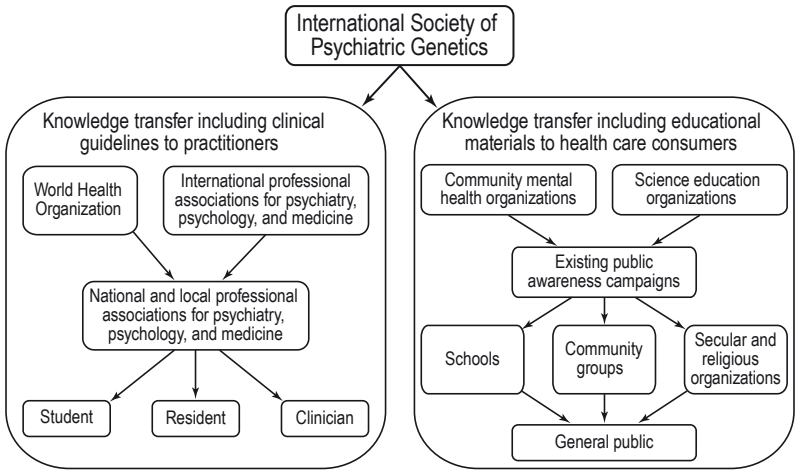

Figure 12.1 Strategy for psychiatric genetic awareness campaign.

campaigns, could use these materials to dissemination information on genetic risk and resilience to the general population, perhaps through schools and other community and faith-based organizations.

To support and optimize the near-term clinical opportunities for innovative psychiatric genetics, there are significant future research needs. In addition to innovation, future research must aim to remove existing barriers and be conducted according to the following principles. First, diversity in genetic data sets is paramount to facilitate equitable clinical use of genetic information. As described by Ronald et al. (this volume), capacity building must be a first principle of global diversity in psychiatric genomics, and we argue that capacity building for genetic research should not ignore the eventual goal of clinical implementation for the communities in which a research program is being established. Second, patient representatives must be meaningfully engaged at every level of research from discovery to research aimed at clinically oriented outcomes. This is both an ethical imperative and an essential design aspect of sustainable and relevant research programs. Third, experts in the field of implementation sciences and health economics should be consulted and ideally embedded in research teams that confront the challenges of psychiatric genetics translation described here. Finally, scientific communication experts, such as genetic counselors, are essential to the field, as they can advise on how to communicate effectively. This does not, however, absolve the psychiatric genetics community of the responsibility to learn how to communicate their own work to the public effectively. Further high-priority areas include:

1. Critical needs in translational psychiatric genomics: (a) Evaluation of clinical genetic testing in psychiatric disorders, including evaluation of the use of PRSs. Currently, it is unclear how much the incremental

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increase in risk provided by additional genetic information in the form of PRS might change clinical management. (b) Both existing and future data collections are needed to address the paucity of large-scale genomic studies of treatment response, further articulated below. (c) Studies aimed at assessing and positively impacting psychosocial consequences of genetic testing and risk stratification are needed, as the delivery of information can influence health behaviors in both positive and negative ways. Thus, best practice guidelines for delivery of genomic information related to mental health are essential.

2. Evaluating clinical genetic testing in general psychiatry: Studies are needed to identify the added value of genetic testing in psychiatric disorders for which there are currently no recommendations for testing (e.g., adult-onset psychosis). For example, the first episode of psychosis may initiate a battery of tests ranging from cognitive assessments to brain imaging, yet it is still unclear whether the addition of genetic data to those batteries can decrease the time to diagnosis or guide clinical management in situations with poor diagnostic specificity. Clinical trials are needed to determine whether diagnostic delay can be shortened and treatment selection improved. Importantly, these studies need not be limited to genomic data but may instead evaluate decisions based on risk or response calculators that incorporate genetic and nongenetic factors. Although risk calculators may be most useful when addressing questions of differential diagnosis, response calculators could be helpful in guiding management decisions.
3. Research on the clinical use of genetic testing to encompass patient-oriented outcomes and experiences: Treatment decisions are often made before a clear diagnosis has emerged. Thus, best practices are needed to guide interventions for at-risk patients. This could include interventions that promote positive attitudes toward mental health and avoid stigmatizing children and families. Indeed, the very definition of successful risk reduction is itself an active area of research. How should risk reduction be measured? Is there a role for genetic counseling and/or psychoeducation in risk-reduction strategies? Outcome studies are needed to determine whether individuals with positive genetic test results would benefit from additional genetic information in the form of PRS. These studies should assess the positive and negative predictive values of the addition of the PRS to the knowledge already conferred by the presence of the rare variant. In each case, patient engagement is critical to identify outcomes that are most important. For example, it may be a higher priority for families to learn whether the incorporation of the PRS can aid in treatment decisions and avoid diagnostic prognostication.
4. Improving genomic studies of treatment response: Genomic studies of treatment response for psychiatric conditions are lacking, in part due to

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limited collections in which genotype and treatment response are both measured at scale. Existing large-scale samples of genotyped patients with longitudinal treatment response data should be available within electronic health records; however, these data are rarely standardized and are often embedded as textual descriptions in the clinical notes of the care provider. Thus, developing tools in the electronic health record for efficiently recording treatment responses to psychiatric medications should be a priority for learning healthcare systems, as these data could inform a myriad of studies. Furthermore, new data collection efforts should consider the ethical application of innovative approaches to the collection of treatment response data that allow for both active (ecological momentary assessment) data collected (e.g., from mobile phones) and passive monitoring (e.g., of activity, sleep levels, voice modulation) from wearables. This could provide richer context for genetic studies of treatment response.

5. Large GWAS of treatment response to generate PRS: This may be more informative in guiding treatment selections than PRS which primarily measure genomic predisposition to develop particular psychiatric conditions. Again, clinical data from electronic health records coupled with large-scale biobanking efforts could be extremely useful; however, they are not without problems (e.g., polypharmacy, formulary differences, and variation in medication adherence), all of which can complicate interpretation of outcome data. Thus, it is important that clinical trials also include the collection of genetic data from participants, and that these data are shared with researchers under precompetitive research agreements. Again, inclusion of diverse patient populations at every step of the research process will be critical in guiding decisions on identifying multiple outcomes, all of which constitute important responses to treatment.
6. Best practices for delivery of genomic information in a psychiatry setting: More studies are needed that aim at assessing and positively impacting psychosocial consequences of genetic testing. These studies should identify contextual modifiers (i.e., social determinants) and develop best practices to enhance positive effects and reduce negative effects of genetic testing. As mentioned, though PRS interpretation is not currently supported in clinical workflows, many patients have access to their PRS through direct-to-consumer products, and patients are beginning to bring these genetic test results to their providers for interpretation. Thus, despite the lack of clinical guidelines on genetic testing in general patient populations, best practice recommendations are needed for clinicians to counsel patients effectively on existing PRS results brought into the clinical setting. This includes referral guidelines, approaches to genomic education, and guidelines on *how* and *who* should counsel patients to help them understand their PRS

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(NSGC, in press). Best practice guidelines are likely to differ based on the patient population.

Conclusion

Psychiatric genetics holds promise for improving prediction and diagnosis of psychiatric conditions, as well as the selection and implementation of effective treatment. In the short term, utilization is likely to remain focused on children and adults with neurodevelopmental disorders and might extend to children and adolescents with early-onset psychosis. Fulfilling the promise of psychiatric genetics for other disorders awaits the development of a more robust research foundation for the use of genetic information (including PRS) in clinical settings, including studies aimed at assessing their added value for clinical decision making. Of key importance is the development of ancestry-diverse databases for the interpretation of genetic findings, necessary for the equitable use of genetic testing, and the provision of enhanced training for mental health professionals in psychiatric genetics. An understanding of one's diagnosis (including the potential genetic contribution) should include psychoeducation and/or genetic counseling. Thus, it is important that all providers be trained to deliver high-quality information to patients and families. Finally, public education on genetics, including the genetics of psychiatric disorders, is essential to improve understanding of genetic test results and to reduce such negative consequences as stigma and discrimination.

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