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Integrating Genomics into Psychiatric Practice:

Ethical and Legal Challenges for Clinicians

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Abstract

Psychiatric genomics is a rapidly growing field that holds much promise for improving risk prediction, prevention, diagnosis, treatment selection, and understanding of the pathogenesis of patients' symptoms. However, the field of psychiatry (i.e., professional organizations, mental health clinicians, educational institutions) needs to address numerous challenges to promote the responsible translation of psychiatric genomics technologies and knowledge. The goal of this article is to review how clinicians currently encounter and use genomics in the clinic, to summarize existing literature on how clinicians feel about the use of genomics in psychiatry, and analyze foreseeable ethical and legal challenges for the responsible integration of genomics into psychiatric care at the structural and clinic levels. Structural challenges are defined as aspects of the larger system of psychiatric practice that constitute potential barriers to the responsible integration of genomics for the purposes of psychiatric care and prevention. These structural challenges exist at a level where they can be intervened upon by professional groups that set standards and regulate the practice of psychiatry and genomics. Clinic-level challenges are day-to-day issues clinicians will face when managing genomic tests in the clinic. We discuss the need for action to mitigate these challenges and maximize the clinical and social utility of psychiatric genomics, including: expanding genomics training among mental health clinicians; establishing practice guidelines that consider potential clinical, psychological, and social implications of psychiatric genomics; promoting an integrated care model for managing genomics in psychiatry; emphasizing patient engagement and informed consent when managing genomic testing in psychiatric care.

Keywords

Genomics; Psychiatry; Ethics; Clinical; Practice Guideline; Education; Medical

INTRODUCTION

Psychiatric genomics is a rapidly growing field that holds much promise for improving risk prediction, prevention, diagnosis, treatment selection, and understanding of the pathogenesis of patients' symptoms.[1–6] However, the field of psychiatry (i.e., professional organizations,

Conflict of Interest

The authors have no conflicts of interest to declare.

mental health clinicians, educational institutions) needs to address numerous challenges to promote the responsible translation of psychiatric genomics technologies and knowledge. In this article, we examine foreseeable ethical, legal, and practical challenges for the translation of psychiatric genomics into clinical practice.

Many psychiatric conditions are highly heritable, with the highest rates seen in schizophrenia (0.81), autism spectrum disorder (0.80), and bipolar disorder (0.75).[1] Nevertheless, for years, researchers studying the genetic foundations of mental health disorders struggled to obtain reliable findings.[4,6–8] Recently, the emergence of multinational research consortia, such as the Psychiatric Genomics Consortium,[9] have powered successful large-scale genome-wide association studies (GWAS) for psychiatric disorders.[2,10] Despite these early successes, the clinical utility of SNP arrays used for GWAS is limited. Although more than 140 genomic loci reliably associated with schizophrenia have already been identified in GWAS, these genomic loci contribute a small amount to the overall risk of developing schizophrenia.[11,12] Furthermore, only a handful of copy number variants (CNVs) have been linked to psychiatric disorders, such as 22q11.2 (schizophrenia, ADHD, autism spectrum disorder) and 17p11.2 (autism spectrum disorder),[13,14] and the prevalence of CNVs among patients with psychiatric disorders is relatively low.[5,14] Moreover, the most recent estimated heritability based on single nucleotide polymorphisms (SNPs) identified in GWAS is modest (45% for schizophrenia, 37% for obsessive compulsive disorder, 21% for bipolar disorder, and just about 8% for major depressive disorder and substance use disorders).[2] Finally, while GWAS have identified genomic markers that: may predict response to antidepressant, lithium, stimulant, and antipsychotic therapy (e.g., 4p15.1, 9q33.3); identify individuals at risk for antipsychotic-induced weight gain (e.g., *MC4R*) and; predict the risk of severe cutaneous side effects in patients taking Carbamazepine (e.g., HLA-A*3101), most studies have been limited by their relatively small sample sizes.[15,16] Given the limitations of GWAS, at the moment, collecting information on family history remains the most reliable way of predicting disease risk and treatment response.

Despite these limitations, the success of large-scale GWAS and the decreasing cost of array-based and sequencing-based (whole genome and exome sequencing; WGS/WES) genomic tests have revitalized psychiatric genomics and led to a redoubling of efforts to examine the genomic architecture of other psychiatric disorders, using large samples of cases and controls.[2,17] An examination of the critical ethical, legal, and practice challenges that psychiatrists will face as psychiatric genomics research is translated into clinical care can help identify and generate potential solutions that maximize its clinical and social utility.

Researchers and private enterprises are actively attempting to translate emerging knowledge about psychiatric genomics into clinically useful information to improve mental illness care and prevention.[5,18–20] In addition, clinicians are already encountering genomics findings in their practice, for example, when patients bring in their personal results from participating in a research study or, more commonly, from direct-to-consumer genetic testing. Within the next decade or two, genomics data will likely be ubiquitous in psychiatric practice. To integrate genomics in a way that promotes the best interest of stakeholders such as at-risk individuals, patients, patients' relatives, and mental health clinicians, the field of psychiatry must address critical structural and clinic-level challenges.

Structural challenges are defined here as aspects of the larger system of psychiatric practice that constitute potential barriers to the responsible integration of genomics for the purposes of psychiatric care and prevention. These structural challenges exist at a level where they can be intervened upon by professional groups that set standards and regulate the practice of psychiatry and genomics (e.g., the American Psychiatric Association (APA), the International Society of Psychiatric Genetics (ISPG), psychiatry residency programs, continuing education programs). Clinic-level challenges are defined as day-to-day issues that clinicians will face when managing genomic tests and responding to specific types of findings in the clinical setting.

The goals of this article are to review how clinicians currently encounter and use genomics in the clinic, to summarize existing literature on how clinicians feel about the use of genomics in psychiatry, analyze foreseeable ethical, legal, and practical challenges for the responsible integration of genomics into psychiatric care at the structural and clinic levels, and to provide recommendations about how these challenges may be addressed.

GENOMICS IN PSYCHIATRIC CLINICS TODAY

Many psychiatrists already encounter genomic technologies in their practice, and soon this will be the reality for most. As genomic knowledge and clinical applications develop, psychiatrists themselves may eventually order genomic tests on a regular basis, and use these results to aid in risk prediction, diagnosis, prognosis, and treatment selection for mental disorders (Table 1). In a 2014 study (n=372), 14% of psychiatrists reported having ordered a genetic test in the past 6 months, and 36% started conversations about genetic testing with their patients over the same period.[21] These psychiatrists were recruited via email from the American Medical Association (AMA) master list and 57% worked primarily in private practice. According to a separate article based on the same sample, the most commonly ordered tests by psychiatrists are pharmacogenomics tests (47% of genetic tests ordered), such as those analyzing cytochrome p450 genes, and the remainder are diagnostic or predictive tests for a variety of conditions, such as Alzheimer's disease (10%), Fragile × syndrome (6%), Down syndrome (4%), and Huntington's disease (4%).[22] Although the vast majority of tests ordered by psychiatrists are for neuropsychiatric conditions, a minority (10%) reported ordering tests for other medical conditions, such as breast cancer,[22] and 18% discussed prenatal genetic testing for non-psychiatric conditions with their patients.[21]

As patients and the general public become increasingly aware of the use of genomics in clinical practice,[23] psychiatrists will be under mounting pressure to order testing or to incorporate genetic findings into their practice. Already, 42% of psychiatrists report having had a patient ask them about genomics testing over the past six months[21] and 29% report having received commercial advertising from genetic testing laboratories.[22] Psychiatrists also encounter genomic test results when their patients get direct-to-consumer (DTC) genomic testing and bring the results to the clinic in hopes of having their clinician help interpret findings or evaluate if they may inform their clinical management. In a recent study, nearly 15% of psychiatrists reported having been asked about DTC genomic testing by patients.[22] Psychiatrists may confront a similar situation when their patients participate in research that involves genomic testing in which researchers return clinically relevant

findings to participants, a rising practice in genomics research,[24] and then participants bring these findings to the clinic.[25–29] Other patients may request the use of emerging psychiatric pharmacogenetic tests with the hope of finding more effective medication to manage their symptoms and/or reduce risk for severe side effects.

CLINICIANS' ATTITUDES AND CONCERNS ABOUT GENOMICS IN PSYCHIATRY

Ambiguity about How to Integrate Genomics into Practice

A number of studies have examined psychiatrists' attitudes regarding genetic testing in psychiatric care.[21,22,30–33] These studies suggest most psychiatrists believe genetics has a strong to moderate influence on mental health[21,32] and that more genetic tests should be ordered in their practice.[22] Moreover, psychiatrists appear to be optimistic about the role that genetics testing may play in clarifying diagnosis and guiding treatment.[30] One study (n=352) recruited psychiatrists attending a continuing education course on psychopharmacology, 21% of these psychiatrists reported their primary work activity was hospital or inpatient psychiatry and 52% reported that it was outpatient psychopharmacology. In this sample, the majority (83%) of psychiatrists reported that they feel it is their role to discuss and advise patients about the relation of genetic information to mental health disorders and 87% routinely obtain family histories of psychiatric illness.[30] These studies indicate a recognition among clinicians of the potential value of psychiatric genomics and a willingness to integrate it into their practice.

Despite their enthusiasm about the promise of genetics in psychiatry, many clinicians report a lack of confidence about *how* to apply genomics in clinical practice.[30] Psychiatrists also disagree on who should be tested. When asked about a theoretical genetic test to detect risk for schizophrenia, over 73% of 64 surveyed clinical psychiatrists (members of the NY State Psychiatric Society) favored administering it to patients with chronic schizophrenia and first-episode psychosis.[31] However, there was little consensus about the use of this test with other populations: 48% of these psychiatrists stated that they would test the rest of the family if one person tested positive, 41% would test adolescents and young adults with social problems, and others would test all psychiatric patients (22%) and all newborns (20%).[31] Approximately a quarter of respondents felt that no one should be tested. There was likewise no clear consensus on how genomics findings should be used. Notably, when asked whether they would prescribe "preventive medication" if people tested positive on this theoretical risk for schizophrenia genomic test, 100% of clinicians favored such an approach whereas only 52% of psychiatric genetics researchers—a group which included MDs, MD/PhDs, PhDs, and holders of other college degrees—agreed with this approach.[31]

Ethical Reservations about Genomics in Psychiatry

Mental health clinicians also express ethical concerns about integrating psychiatric genomics into practice. Almost half of psychiatrists and neurologists surveyed in one study reported concern that patients would be subject to psychological harm as a result of undergoing genetic testing.[22] Another study reported that psychiatrists believe genomic results could carry decreased "expectations for children who carry high-risk genes" (63%) and "increased

stigmatization" (35%).[30] In this study, clinicians also expressed concern that increased knowledge about psychiatric genetics may lead to denial of insurance (91%) and employment discrimination (78%). In addition, psychiatrists face medicolegal and ethical issues when managing genetic findings. A small, but significant number of psychiatrists report having encountered privacy concerns when discussing genetics findings with patients. According to one survey, 8% of psychiatrists have had patients ask them not to document genetics findings in their medical record,[22] and in this sample, 5% of psychiatrists reported having actually excluded genetic information from the medical record.[21]

Psychiatrists must strike a difficult balance between maintaining the trust necessary for an effective clinician-patient relationship (therapeutic alliance) and addressing concerns about potential legal liability for not including medical findings in patients' records. One might suppose that the above privacy concerns would have been allayed by the Genetic Information Nondiscrimination Act (GINA) of 2008, which protects against genomic-based discrimination in health insurance and employment. However, the fact that these last two studies were published six years after GINA was passed suggests that concerns about potential misuses of genomic information persist.[34] Furthermore, clinicians may be unaware of GINA regulations or how to manage genomic information consistent with GINA in practice,[35] as we discuss in more detail below. Patient and clinician concerns about the privacy of genomic information may be explained, in part, by lack of public visibility of genomic anti-discrimination laws[36] or the fact that GINA only protects against genomics-based discrimination in the context of health insurance and employment. Thus, existing anti-discrimination regulations may not protect against other concerns that clinicians may have such as the use or misuse of genomic results in other areas (e.g., life and disability insurance, education; mortgage and other lending scenarios).[37,38] In fact, 47% of 394 psychiatrists and neurologists somewhat or strongly disagreed with the statement: "Legal protections against genetic discrimination are adequate".[22] These findings suggest the need for further guidelines, legal protection, and educational campaigns about the implications of genomic findings in order to minimize the risk for genomics-based mental health stigma and other unintended consequences of genomic testing in psychiatric care and prevention.

STRUCTURAL CHALLENGES

The field of psychiatry must address a series of key structural challenges in order to promote the responsible integration of genomics into psychiatric care and illness prevention. These challenges, described in turn below, impact the field of psychiatry as a whole and will likely require collaborative solutions across organizations that help set standards for psychiatric practice and education.

Lack of Training in Genomics

Psychiatrists across multiple studies report they do not feel they have the expertise necessary to manage genomic testing and findings. In a sample of 45 psychiatrists recruited using the AMA master file (58% reported their primary practice was outpatient psychopharmacology, 13% hospital or inpatient psychiatry, and 29% had multiple responses), over 90% reported not feeling competent or prepared "to offer genetic tests and interpret the results."[32] The

authors replicated this result in a subsequent sample of 135 psychiatry residents and 100 educators,[39] noting a lack of training in psychiatric genomics. A total of 39% of educators and 55% of trainees from this study reported that their respective residency programs placed "little or no emphasis" on psychiatric genetics. Moreover, when educators were asked to rate their programs' readiness to provide training in this area, nearly half (46%) responded that there were "few or no" faculty with expertise in genetics or genomics at their respective institutions. Other studies similarly reflect gaps in genomics knowledge among clinicians, including a study that found that fewer than 1% of 352 psychiatrists surveyed answered 9 multiple choice questions about genetics correctly and the median number of correct answers was 4.30,* In a more recent study, most psychiatrists overestimated or underestimated the contribution of genetics to various disorders including depression and anorexia.[21] One study[32] found that 87% of psychiatrists were not aware of medical geneticists or genetic counselors in the geographic area where they practice, and most did not know whether genetic testing or counseling is covered by the majority of insurance plans in their geographic area.

Absence of Professional Guidelines and Legal Standard of Care

As shown in Table 1, there are a number of potential uses for genomic testing in psychiatry; however, available evidence suggests that psychiatrists disagree as to when and with which populations it would be appropriate to use genetic tests.[31] A critical structural challenge faced by psychiatrists is the lack of a clear standard of care and professional guidelines for the use of genomic testing and management of findings. Currently, the only guidelines focused on the use of genomics in psychiatric care are the ones offered by the ISPG. The ISPG's Genetic Testing Statement offers general recommendations on the use of genetic tests to assist in the diagnosis and identification of high-risk individuals, and to guide treatment. It also briefly addresses the report of incidental or secondary target findings and some of the psychological, ethical, and clinical implications of genetic testing. ISPG advocates for additional research initiatives, education programs, and privacy safeguards, but does not discuss in detail the management of specific psychiatric genomic findings.[40] However, this is a short document that is limited in scope and not meant to provide the in-depth guidance the field currently needs. It is possible that future revisions will expand on the current guidelines to address these issues in more detail. American College of Medical Genetics and Genomics (ACMG) has released recommendations that promote the examination of 59 secondary target medically actionable genes when clinical genomic sequencing is conducted, and has offered guidelines about the management of genomic information with pediatric patients for whom the ACMG discourages testing for late-onset conditions unless it is in the child's best medical and overall interest.[41–48] In theory, the ACMG recommendations apply to psychiatric practice, but do not address the particularities of the field. As such, psychiatrists and courts attempting to incorporate genomics or to judge

*For context, two of the questions included in this survey were: 1) "Which of the following statistics indicates the likelihood of linkage between a marker and a disease gene?" a) Penetrance; b) Lod score; c) Concordance rate; d) Relative risk; e) Family based association ratio. 2) "A disabling neurological disease transmitted in an autosomal recessive manner is found to have a carrier frequency of 1/40 in a given population. If two people from this population marry, what is the likelihood that they would have a child with the disorder?" a) 1/12,800; b) 1/6,400; c) 1/3,200; d) 1/600; e) None of the above. These examples are provided with permission from the corresponding author.[29]

the adequate use of genomics in the clinic are currently navigating mostly unchartered terrain.

Certain aspects of psychiatry generate unique challenges. Psychiatric genomics has progressed immensely in recent years but it is at a relatively early stage compared to other fields of genomics. Psychiatric disorders are also highly polygenic and multifactorial, complicating interpretation and management of findings. This makes them significantly different from the mostly Mendelian disorders addressed in ACMG recommendations. There is little research about the psychological and social impact of genomic information on patients or individuals at risk for a psychiatric disorder. Further, there is a high degree of mental health stigma that increases the risk for discrimination based on psychiatric genomic findings. As guidelines are developed and adopted in practice, they will help establish a much needed standard of care to guide clinicians.[49] However, these guidelines need to address the particularities of psychiatric practice. It would be useful if professional organizations such as the APA, the ISPG, or others established committees to periodically evaluate the state of psychiatric genomics and release recommendations that can help inform and guide clinicians and patients about the responsible use of genomic testing in psychiatry.

Lack of Evidence of Clinical Utility before Implementation

Genomic tests are already making inroads into psychiatric practice, despite substantive questions about their clinical utility. For example, pharmacogenetics tests could theoretically help clinicians minimize trial and error by selecting medications and dosages that are more likely to be effective and less likely to cause severe side effects. Evidence suggests a substantial willingness to use these tests. For example, one study shows that psychiatrists are more likely to order pharmacogenetics tests (47%) than any other type of genetic test, in contrast to the percentage (2%) ordered by neurologists.[22] Despite this willingness, and select findings that the use of pharmacogenomic testing may improve clinical outcomes,[18,20] critics contend that there is simply not enough evidence at this time to support the use of this testing.[50] A similar example comes from the U.S. Department of Veterans Affairs, which awarded contracts to companies such as Assurex Health to make their pharmacogenomics GeneSight® Psychotropic test available for use in VA facilities nationwide.[51] A couple of years after this contract was awarded the VA issued a report concluding that current evidence does not support that using GeneSight® Psychotropic reduces remission of depression symptoms more than usual care.[52]

While some psychiatrists and institutions may be enthusiastic about pharmacogenetics, surveys reveal skepticism among a significant number of psychiatrists, with some asserting that pharmacogenomic testing is being “overhyped” and “overused.”[53] At best, clinicians using these tests may be misspending limited health care resources and patients’ money, given that these tests are generally not covered by insurance because they consider these investigational and lack sufficient evidence of clinical utility.[54–57] At worst, psychiatrists using pharmacogenetic tests are potentially putting patients at risk by making clinical management determinations with no solid evidence for clinical utility.

Debates continue over whether and how pharmacogenetic testing should be regulated to avoid these risks.[58,59] The FDA has proposed a regulatory framework for these tests,[60] but

has not issued a final guidance. Moreover, this framework may not apply to previously marketed tests that become "grandfathered."[61] Professional organizations and government institutions can help raise awareness and provide guidance by circulating information about emerging pharmacogenetic tests and their clinical utility. This would bring relevant and curated information to a wider audience of clinicians and patients, while also relieving some of the burden of evaluation from clinicians alone. Relying solely on clinician discretion is especially problematic considering the evidence cited above showing clinicians' lack of knowledge and confidence about how to manage these tests in practice. Federal healthcare agencies like the Centers for Medicare and Medicaid Services (CMS) could also promote evidence-based genomics medicine by requesting data of clinical utility as a requirement for coverage.[62,63]

CLINIC-LEVEL CHALLENGES

Mental health clinicians constantly have to manage novel technologies (e.g., drugs) or novel applications of biomedical technologies. Some could argue that genomic testing is just one more biomedical technology; however, the amount of genomic information that may be generated by these tests, the complexity of the information, and the impact it can have on many aspects of clinical practice (Table 1) suggest that we should carefully examine and address the kinds of day-to-day challenges genomic testing will raise. These challenges, detailed below, include ethical, legal and practice issues related to the management of genomic findings that may help inform risk prediction, diagnosis, prognosis and treatment for psychiatric illness, along with management of health risks unrelated to mental health.

Risk Prediction for Asymptomatic Individuals

If genomic variants could help reliably identify individuals at risk for a disorder, limited health care resources could be better allocated to provide services to these individuals. In addition, reliably identifying individuals at risk could help improve clinical outcomes by monitoring symptoms and intervening as soon as an individual meets criteria for a psychiatric disorder. In the case of psychotic disorders, research suggests that shorter duration of untreated psychosis (DUP) is associated with improved clinical outcomes.[64,65] Shorter duration of untreated symptoms is likewise associated with improved outcomes for depression.[66] The ability to identify a group of individuals who is at risk for psychiatric disorders could also help researchers study and develop clinically useful interventions for these at-risk populations, which may delay or prevent the onset of psychiatric disorders.[67–69]

It is likely that most genomic tests in clinical psychiatry will be performed in patients with active psychiatric symptoms. However, clinicians may offer (or individuals may request) genomic tests for asymptomatic people, for example, someone with a family history of psychiatric disorders who wants to know if she is at an increased genomic risk. If tests in these individuals reveal an increased risk for a disorder, psychiatrists will likely be called upon to determine whether these individuals are candidates for early interventions, and whether, when, and what kinds of early interventions should be offered. Psychiatrists might feel compelled to offer clinical interventions to individuals testing positive in an attempt to prevent or delay the onset of illness, much in the way some psychiatrists currently offer

preventive psychotherapy and even pharmacotherapy to individuals that meet ultra high risk criteria for psychosis.[70–72] If psychiatrists do not comply with patient requests to provide "preventive" pharmacotherapy, patients could potentially "shop around" for a clinician who will prescribe these medications. Offering "preventive" pharmacotherapy is ethically problematic for a number of reasons. The penetrance of currently known genomic variants associated with psychiatric disorders is generally low. As such, while asymptomatic individuals testing positive for genetic variants associated with psychiatric disorders may be at an increased risk compared to the general population, it is still unlikely that they will ever meet criteria for a disorder. Further, there is little research to suggest that medications help prevent psychiatric disorders in asymptomatic individuals or even those with subthreshold symptoms, and the risks of offering such interventions could outweigh the projected benefits, especially if a drug carries substantial risk for adverse effects, as in the case of antipsychotics.[72]

Even in cases where risk prediction could confer potential clinical benefits, it presents certain ethical and clinical problems for psychiatrists, including a potential for negative emotional responses to arise among asymptomatic individuals who learn about their risks for psychiatric disorders. When testing asymptomatic populations, psychiatrists should be prepared to provide support to individuals receiving results, whether it is in the form of office-based supportive therapy or referrals to specialists, such as genetic counselors. As most psychiatrists do not routinely refer to genetic counselors nor are they usually aware of how and where to direct referrals,[32] in order to act in the best interest of these individuals, psychiatrists who order these tests should make an effort to educate themselves about the availability of these services.

Identifying asymptomatic individuals at risk for psychiatric disorders also raises concerns about the use of this information outside of the medical realm. For example, as noted above, in the United States, GINA[34] protects against genomic-based discrimination in health insurance and employment. However, it does not provide protection in any other aspects of life such as disability and life insurance, or even mortgages and student loans.[37,38] Given the potential for discrimination, psychiatrists should try to safeguard genetic information by ensuring compliance with HIPAA, securing electronic medical records against threats from hackers, and being mindful of which genomic test they order (e.g. WGS vs a more limited test that still generates the necessary genomic information) and what information they document in the medical record. Finally, because of HIPAA's minimum necessary standard, which requires that covered entities such as clinicians limit unnecessary access to patient's health information, and GINA's ban on the use of genetic information by health insurance companies and employers, psychiatrists arguably have both an ethical fiduciary obligation and a legal obligation to remove any genomic information when these parties request medical records.

Together, clinicians and patients must weigh the prospective clinical benefits of testing against the potential emotional and social harms, especially in those cases in which patients have no current symptoms of mental illness. Because testing asymptomatic individuals carries substantial risks and currently yields few benefits, clinicians should use caution in initiating genetic testing in asymptomatic individuals. If testing is pursued, and an

asymptomatic individual is identified to be at increased risk, regular monitoring of symptoms, as well as psychoeducation and psychotherapy, currently seem more appropriate than pharmacological interventions.

Using Genomics to Substantiate Diagnosis

The vast majority of psychiatrists believe genomic testing will play a role in the diagnosis of autism, bipolar disorder, major depression, and schizophrenia.[21] There are currently no biomarkers that can definitively establish a diagnosis of mental illness. However, genomics findings may be used to substantiate diagnoses. For example, copy number variants such as 3q29 or 22q11.2 deletions could, in theory, be used to help substantiate a diagnosis of schizophrenia because of their association with the disorder.[5,14,24, 73,74] As psychiatric genomics and neuroscience advance, it is not a leap to suggest that psychiatrists will increasingly use biomarkers as they formulate their diagnoses.

However, the increasing use of genetic testing for diagnostic purposes presents several challenges. Positive genetic testing results could promote the inaccurate view that patients' behaviors are a product of their genes (genetic essentialism), leading to a sense of determinism that could prove to be dispiriting to patients and their providers.[75–77] By emphasizing biological factors, such findings could lead patients to engage less with psychotherapy, an outcome that would be particularly problematic in cases in which that is an effective treatment. To minimize some of these risks, it will be essential for clinicians to understand and carefully explain to patients the complex interplay between biological and psychosocial factors.

Genetic testing for diagnostic purposes may also lead to increased stigmatization and discrimination.[37,78,79] Research suggests that when people know an individual's mental illness has a significant genetic component, this decreases the perception that a patient is to blame for the symptoms, but potentially intensifies stigma by increasing the perceived seriousness and persistence of the disorder, the perception that the individual is dangerous, and the desire for social distance.[78,79] Therefore, patients whose disorder is identified to have some genetic component are likely to be exposed to increased stigma, unless widespread changes occur in understandings about genetic determinism. Clinicians and patients must weigh the social risks of genetic testing against its potential diagnostic value.

Because genetic testing results may promote genetic determinism and stigma, could potentially generate emotional distress, and limit adherence to treatment (i.e., psychotherapy), psychiatrists face ethical challenges in deciding how to employ testing in their practice. First, psychiatrists need to decide whom to test. Ideally, professional organizations will generate guidelines and training to help psychiatrists make these determinations, as discussed above; however, in the clinic, psychiatrists will have to make final determinations about whether to offer genetic testing to specific individuals based on the overall interests of the patient. Given that genetic findings may suggest information about relatives, another source of challenge regarding whom to test is whether genomic findings may generate disputes or distress among family members. For example, parents may feel guilty because they believe they "passed on" pathogenic variants that led to symptoms, children may feel their parents are culpable for "passing on" those genes, and

some relatives may not want to know the results of a patients' genetic testing because of the potential implications it may have for them.

Psychiatrists also face ethical considerations when disclosing genetic results to patients. Patients themselves may experience self-stigma and share the view that a psychiatric disorder with genetic components is more serious and persistent.[78–83] For this reason, invoking the principle of nonmaleficence, some psychiatrists may consider that in exceptional circumstances, particularly if the patient is currently debilitated, it may be in their patients' best interests not to immediately disclose the results of genetic testing to the patient.[84] On the other hand, in the vast majority of cases, psychiatrists will likely favor disclosing these findings out of a respect for patient autonomy[84] or because they believe that sharing such information could foster a stronger patient-physician relationship, or "therapeutic alliance." Given the potential for these competing interests to complicate clinical decision-making, more research is needed on how patients respond to positive genetic findings, what may be the appropriate time to disclose this information, and how it should be disclosed.

A greater understanding of patient and clinician attitudes and the impact of disclosing genetic findings may facilitate evidence-based recommendations on the use of diagnostic testing, which could reduce variation in clinical practices. However, even with recommendations in place, to some extent, psychiatrists will always need to make these decisions on a case-by-case basis. One way to mitigate this decision-making burden is to seek greater patient input as these issues arise. Psychiatrists should use the informed consent process as an occasion to discuss patients' attitudes about genetic testing, explore with them the implications of positive results, and offer them the choice of whether or not to be informed of the findings. Such a discussion would help clinicians and patients make decisions that are more in line with the patients' values and interests, and may have the added benefit of fostering a stronger therapeutic alliance.

Using Genomics to Characterize a Psychiatric Condition

As noted above, there are currently no biomarkers that can be used to establish a diagnosis of mental illness. However, several psychiatric conditions are associated with known neuropathologies.[85] Using currently available genetic tests, psychiatrists may identify the neuropathological basis of certain of these psychiatric disorders. Clinicians may assess for Lesch-Nyhan syndrome in a patient with intellectual disability and prominent self-injurious behaviors,[86] Huntington's disease in a patient with early-onset neurocognitive disorder,[87] or Fragile × syndrome in a patient with ADHD and abnormal physical features.[88] Occasionally, genomics testing may call into question an already existing diagnosis. For example, testing may reveal that a patient previously diagnosed with schizophrenia in fact likely suffers from Wilson disease, a rare genetic condition that may cause psychotic symptoms and may be managed with copper chelating agents and diet.[89]

Psychiatrists face ethical and legal issues when deciding when to order tests for rare genetic conditions. Since failure to assess for these conditions may cause clinicians to miss treatable conditions, such as Wilson disease, some clinicians may be inclined to order these tests on a routine basis.[5] While probably unusual, some may be reluctant to order a test that could

reveal diagnostic error, especially in cases where psychiatrists are concerned that a misdiagnosis has led to improper medical treatment and may constitute grounds for a medical malpractice lawsuit. In either case, psychiatrists run the risk of performing a disservice to their patients. On the one hand, overuse of genetic testing may subject patients to unnecessary treatment (due to false positives) and may drive up to cost of healthcare, inconsistent with the ethical principles of nonmaleficence and justice. On the other hand, avoiding such testing may result in important information being withheld from patients, violating patients' autonomy, clinicians' fiduciary duty to look after the best interest of the patient, and the ethical principle of compassion. Psychiatrists should rely on their clinical judgment to avoid these extremes. It may be useful for psychiatrists to rule out medical etiologies particularly in patients with atypical presentations, positive family histories, or unexplained medical symptoms, but psychiatrists should avoid falling into the trap of practicing genetic "defensive medicine."

Prognosis

Currently, clinicians predict prognosis based on known risk factors. For example, it has long been known that schizophrenic patients with healthy premorbid social functioning and acute onset of illness fare better than those with more pronounced negative symptoms and gradual onset of illness.[90] With advancements in genomics, researchers may soon be able to identify genetic biomarkers that predict worse outcomes or more severe phenotypes, just as oncologists now use biomarkers to predict disease outcome and guide treatment choices.

As is the case with genomic testing to substantiate diagnoses, issues of stigma apply to the use of prognostic tests – perhaps doubly so in the case of prognostic testing given that it claims to predict not just the presence of but the persistence of disease. The use of testing to predict prognosis also has strong implications for treatment. Approximately 30% of patients with schizophrenia do not respond effectively to treatment[91–94] and ongoing studies may identify genomic correlates associated with treatment-resistant psychosis.[5,24] Suppose, for example, that genetic testing reveals that a subset of patients with newly diagnosed schizophrenia is at risk for treatment-resistant schizophrenia. Such a finding may prompt psychiatrists to consider a trial of Clozapine, a second-generation antipsychotic which is associated with better outcomes, but is typically not used as a first-line agent due to the increased need for monitoring and higher risk of adverse effects.[95–97] In such cases, clinicians departing from the standard of care may be protected under what some refer to as the "reasonable innovation rule," which allows clinicians in the U.S. some degree of flexibility when they depart from the standard of care to conduct clinical innovations even if these innovations caused harm to patients.[98–101] The purpose of this rule is to allow clinicians to innovate to address a patient's unique needs but, among other things, clinicians need to have carefully considered alternatives, and any available literature or evidence to suggest the innovative intervention might work. It is unclear how courts will view the use of genetic testing to determine prognosis or make determinations about other aspects of care. Guidelines from professional organizations would help provide guidance. However, because genetic information could be applied in so many different ways in psychiatric practice, clinicians are encouraged to obtain more training in genomics and examine how the location

where they practice manages these clinical innovation cases. This will help psychiatrists make informed decisions about how and when to use emerging genomic technologies.

Treatment

Although there is still work to be done to evidence the clinical utility of pharmacogenetics tests in psychiatry, in theory, pharmacogenetics has great potential to help guide treatment by predicting both treatment response and medication tolerability. For patients who are treatment naive, such findings may aid clinicians in choosing a suitable first-line medication. On the other hand, pharmacogenetic findings pose unique challenges in patients who have already been prescribed medication. For example, genetic testing may reveal that the medication a patient has been prescribed is likely to be less effective or generate severe side effects compared to others. For patients who are not in remission and for whom a change in treatment is indicated due to lack of response, such findings might suggest alternate treatment approaches. However, for patients relatively stable on their current regimen, pharmacogenetic findings that suggest another medication would be more effective or less likely to produce severe side effects will pose a significant dilemma for clinicians. If, on the basis of pharmacogenomics testing, providers proposed medication changes which ultimately were unsuccessful, this would lead to unnecessary inconvenience and suffering. Conversely, if providers opted not to make a switch in the face of such findings and patients subsequently experienced severe side effects, disease recurrence or worsening of symptoms that, for example, led to a suicide attempt, some could argue this would constitute negligence, and could also negatively affect the clinician-patient relationship.

When using pharmacogenetic tests, it will be critical to involve the patient in the decision-making process, or the patient's legally authorized representative if the patient lacks decision-making capacity. This is particularly important in situations where a patient is relatively stable in their current medication regimen. Given the probabilistic nature of genetic testing, even with the development of increasingly sophisticated tools to guide treatment selection, psychiatrists will continue to face difficult decisions in their day-to-day practice. By involving patients in the process, clinicians can mitigate potential harms, prescribe treatments that are more consistent with patients' values, and strengthen their therapeutic alliance.

CONCLUSION

In the sections above, we have sought to describe the nature of key challenges genomics may raise in psychiatric practice. Here, we synthesize and elaborate upon some of the recommendations made above to promote responsible decision-making about genomic testing and management of results. First, to the extent that the integration of genomics into clinical practice is hindered by lack of genetics training, we propose that such training become a priority for medical schools, residency programs, and continuing medical education courses.[102] Given recent breakthroughs in psychiatric genomics, psychiatry residency programs may have more incentives to offer comprehensive genetics training to residents, and residents may eventually seek out programs that offer this training. A more

immediately feasible route is to increase continuing medical education courses in psychiatric genomics.[103]

Second, as psychiatric genomics knowledge quickly develops and genomic testing increasingly enters psychiatric practice, there will undoubtedly be a period of uncertainty about what constitutes responsible use of these technologies. However, professional organizations could help minimize this uncertainty and promote responsible use of genomics by releasing well-informed and carefully crafted practice guidelines. Such guidelines would help to establish a standard of care and would go a long way in addressing clinician concerns regarding proper practice and legal liability related to the use of genomics findings.

Third, given the complexity of genomic information and the potential for genomics tests to reveal information related to both psychiatric and non-psychiatric conditions, psychiatrists should continue to support the integrated care practice model, in which psychiatrists work collaboratively with other clinicians. Already, the ACMG recommends that when clinical genomic sequencing is performed, laboratories should analyze those genes potentially associated with a patient's symptoms along with 59 genes that may reveal risk for non-psychiatric conditions (e.g., colon cancer, Long QT syndrome) for which medical interventions exist.[41,43] Therefore, if psychiatrists order genomic sequencing they may have to manage findings that fall outside their areas of practice. In these cases, and even when clinicians identify genomic findings with implications for mental health care, psychiatrists should ideally involve colleagues such as medical geneticists and genetic counselors to ensure optimal clinical management.[5]

Fourth, psychiatrists should place special emphasis on patient engagement, choice and informed consent when ordering genomic testing. Given potential medical and social harms, it is imperative that clinicians take the time to educate their patients about the risks and benefits of genetic testing when they obtain informed consent. In addition to the standard elements of legally valid informed consent, this process should include, at minimum, the following three elements: an explanation of the science underlying the test being ordered, including an acknowledgment of any limitations the test may have; a review of its clinical applications; and a discussion of the ethical and legal implications of testing (i.e., stigma, privacy concerns). Clinicians should take special care when obtaining informed consent in cases in which the use of genetic testing could dramatically alter the course of treatment, generate results that may be particularly stigmatizing, or may foreseeably cause other harms.

The genomics era promises a lot for psychiatry. However, effective psychiatric practice, perhaps more than any other medical field, depends heavily on a deep understanding of the patient as an individual, and of disorders as having potentially complex etiologies and treatment trajectories that cannot be reduced solely to genetics. Diagnostic and treatment approaches that rely too heavily on genomics and other biomarkers have the potential to depersonalize psychiatric practice and erode the doctor-patient relationship. It is ultimately the responsibility of professional organizations to set proper guidelines and of individual psychiatrists to responsibly integrate novel technologies while maintaining their therapeutic alliance with patients and retaining the humanism that has for so long animated their profession.

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Table 1

Current and potential applications of genomic testing in psychiatric practice

	Current Uses of Genomics Testing		**Potential Applications of Genomics Testing**	
Clinical Activity	Treatment	Diagnosis	Risk Prediction	Prognosis
Genomic Testing Facilitates	Reduction in medication trial and error; maximization of clinical response and/or minimization of severe side effects	Differential Diagnosis	Prevention, early detection, early intervention, decreased duration of untreated disorder, improved clinical outcomes	Clinical management
Examples	For a patient identified as a *CYP2C19* poor metabolizer, the maximum recommended dose of citalopram is 20 mg due to increased risk of cardiac arrhythmia. If genomic testing reveals such information, psychiatrists may prescribe a different medication or follow the FDA guideline of no more than 20 mg to decrease the likelihood of severe side effects.	If a patient diagnosed with schizophrenia is found to have a mutation in the *ATP7B* gene, this suggests the patient has been misdiagnosed, and actually suffers from Wilson disease, which may present with psychotic symptoms.	An asymptomatic research subject or patient with attenuated psychosis syndrome is identified with a 22q11.2 deletion, a copy number variant associated with schizophrenia. A psychiatrist could offer increased monitoring of symptoms, and depending on symptoms, could offer early interventions such as psychotherapy, social skills training, or even prophylactic pharmacological intervention if symptoms worsen.	Genomic tests may soon reliably identify variants associated with treatment-resistant depression or schizophrenia. If a patient is identified with variants that suggest an increased risk for treatment-resistant schizophrenia, clinicians could consider a more aggressive treatment approach such as prescribing clozapine at an earlier stage in treatment.