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Preventing Discrimination Based on Psychiatric Risk Biomarkers

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Abstract

Recent studies have identified genomic and non-genomic psychiatric risk biomarkers (PRBs; *e.g.*, genomic variants, blood analytes, gray matter volume). PRBs may soon become a powerful tool for improving psychiatric care and prevention. PRB research and its translation to clinical care, however, may prove to be a double-edged sword. Mental health stigma and discrimination are already widespread, and data caution that biological explanations of psychiatric disorders can exacerbate these stigmatizing attitudes, increasing the desire for social distance and heightening the perceived dangerousness of the patient. As a reaction to the Human Genome Project and historical concerns about eugenics, the international community mobilized to establish legislation to prevent genomic discrimination. But in most countries, these laws are limited to few contexts (*e.g.*, employment, health insurance), and very few countries protect against discrimination based on non-genomic risk biomarkers. Like genomic PRBs, non-genomic PRBs provide information regarding risk for stigmatized psychiatric disorders and have similar—and in some cases greater—predictive value. Numerous large-scale neuroscience and neurogenomics projects are advancing the identification and translation of PRBs. The prospect of PRB-based stigma however, threatens to undermine the potential benefits of this research. Unbridaled by nonexistent or limited PRB anti-discrimination protections, the threat of PRB-based stigma and discrimination may lead many to forego PRB testing, even if shown to have clinical utility. To maximize the clinical and social benefits of PRB-based technologies, educational campaigns should address mental health and PRB stigma, and lawmakers should carefully consider expanding legislation that prohibits PRB-based discrimination.

Keywords

stigma; genomics; genetics; mental health; law

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CONFLICTS OF INTEREST

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INTRODUCTION

Developing biomedical risk assesment technologies are enhancing our capacity to identify individuals at risk of mental illness. These technologies are based on measurable psychiatric risk biomarkers (PRBs) that represent a contributing point in a pathway that can lead to psychiatric disorders. Recent studies have identified blood-, neuroscience-, and genomics-based biomarkers, among other markers capable of generating increasingly reliable and accurate risk assessments (Kambeitz et al., 2015; Koutsouleris et al., 2012; Perkins et al., 2015; Ripke et al., 2014, 2011). PRBs could improve psychiatric care and prevention in multiple ways. An individual identified as at risk for a psychiatric disorder could be offered increased monitoring of symptoms—possibly leading to early detection—decreased duration of untreated symptoms, and improved clinical outcomes (Kane et al., 2016; Perkins et al., 2005). These biomarkers could also help prevent or delay the onset of disorders if interventions are shown to be effective in asymptomatic or sub-threshold populations with relevant markers (McGlashan et al., 2004; McGorry et al., 2002). PRBs could also help inform the allocation of limited healthcare resources by targeting those at increased risk for psychiatric disorders. This could lead to more cost-effective ways of addressing the staggering emotional, social, and economic impact of psychiatric disorders that include the cost of hospitalization, treatment, reduced labor, and consequences of economic homelessness (Insel, 2008).

There are numerous ongoing research efforts focused on the identification of reliable biomarkers and the development of risk models for psychiatric disorders (Debost et al., 2017; Koutsouleris et al., 2015; Perkins et al., 2015; Sullivan et al., 2017). The possible incorporation of risk biomarkers in psychiatric care and prevention, however, is not without obstacles; several social challenges must be addressed to allow the responsible translation of these predictive technologies into clinical care. Management plans and policies aimed at protecting against unintended consequences of novel biomedical technologies most often emerge as a reaction to observed or imminent harms once technologies are in use. To avoid this reactive approach, and to maximize the clinical and social utility of PRB technologies, it is essential to preemptively address foreseeable potential misuses and harms.

This article has two goals. First, we seek to examine how the identification of more reliable PRBs and improved risk prediction models poses as a double-edged sword. PRBs could improve psychiatric care and prevention, and potentially reduce misconceptions of afflicted individuals being somehow at fault for their disorders (Kvaale et al., 2013b). Conversely, risk biomarkers may also exacerbate mental health stigma and lead to increased discrimination in numerous spheres of society. Laypeople often turn to genetic explanations when trying to make sense of others' behaviors (Parrott et al., 2005; Shostak et al., 2009), triggering essentialist thinking. Genetic essentialism is the notion that phenotypes, including behavioral phenotypes, are largely or entirely determined by an individual's genetic makeup, with little consideration to penetrance, gene-gene, or gene-environment interactions (Dar-Nimrod and Heine, 2011). Neuroessentialism attributes one's psychological phenotypes to be defined by the brain and its related activity (Schultz, 2015). This school of thought is particularly relevant for PRB research and translation given that essentialist thinking has been associated with greater endorsement of social stereotypes (Bastian and Haslam, 2006),

and neurogenomic and neurological correlates of mental health are seen as essence-like (Haslam, 2011; Dar-Nimrod and Heine, 2011). Therefore, individuals may overestimate the predictive power of PRBs and attribute negative mental health related stereotypes to people whom these biomarkers have identified as being at risk (Bastian and Haslam, 2006; Dietrich et al., 2004; Kong et al., 2017; Phelan, 2005). This article also examines what may be done to minimize the risk of discrimination based on PRBs. Specifically, we argue that the international community should carefully consider expanding legislation that prohibits discrimination based on genomic information to cover more social settings (*e.g.*, employment, insurance, mortgage and other lending companies), and banning discrimination based on non-genomic PRBs. The goal of expanding biomarker anti-discrimination laws would be to minimize the potential social harms associated with psychiatric risk prediction, regardless of which type of PRB is used, and maximize the benefits and uptake of PRB testing, if shown to have clinical utility.

DEFINING GENOMIC AND NON-GENOMIC PSYCHIATRIC RISK BIOMARKERS

We begin by laying out some important concepts, to help make clear our working definition of PRBs and draw a distinction between genomic and non-genomic PRBs. Risk biomarkers may be genomic (*e.g.*, 22q11.2 deletion associated with risk for schizophrenia) or non-genomic. For example, gray matter volume, blood analyte levels, and traumatic brain injury, can be non-genomic PRBs, as long as they are clinically valid biological indicators of risk for psychiatric disorders. In this paper, we differentiate between genomic and non-genomic biomarkers in order to facilitate discussion about relevant anti-discrimination laws and policies around the world. As we discuss in more detail below, a number of countries have already adopted limited genomic anti-discrimination laws that would cover genomic PRBs, but in all likelihood, these laws would not extend to non-genomic PRBs.

For the purposes of establishing what health conditions are covered when we use the term PRBs, we define “psychiatric” as information related to those disorders on the DSM-5. Thus, our definition of “psychiatric” includes conditions like dementia caused by Alzheimer’s disease and alcoholism. As a consequence, PRB anti-discrimination laws would cover a broad array of brain-related conditions. Simultaneously, having a discrete definition of the term “psychiatric” when discussing PRB anti-discrimination laws will facilitate debate, research, and enforcement should these laws be enacted (Rothstein 2007). Furthermore, including all disorders covered on the DSM-5 would help avoid the illogical result of protecting against the use of risk biomarkers for some stigmatized psychiatric disorders, but not extending protection to other stigmatized neuropsychiatric conditions, for example, protecting PRBs related with depression but not those associated with dementia caused by Alzheimer’s disease. Concededly, drafting a perfectly comprehensive definition of PRB is likely an unattainable goal, but our proposition would cover risk biomarkers for most stigmatized psychiatric conditions.

By focusing on biological risk factors, PRB anti-discrimination laws would not cover non-biological risk factors such as history of alcoholism, violence, or speech patterns. Ideally,

these non-biological risk markers should also be protected if they can be used to discriminate against someone as a consequence of their predictive value. Examining possible protections for non-biological risk markers in detail, however, falls beyond the scope of our paper. Here, we focus on the development of risk biomarkers for psychiatric disorders, and advocate for why the international community should carefully consider protecting against discrimination based on these.

PSYCHIATRIC RISK BIOMARKER TECHNOLOGIES

Risk biomarkers for each psychiatric disorder will generate unique questions. We use schizophrenia risk biomarkers to illustrate the potential implications of PRBs on mental health stigma and discrimination. As we discuss in more detail below, there is arguably more information about risk biomarkers for schizophrenia than any other psychiatric disorder, which facilitates our discussion about the technologies and types of PRBs in current use (Bergen and Petryshen, 2012; Fusar-Poli et al., 2013; Lichtenstein et al., 2009; Ripke et al., 2014; Sullivan et al., 2017). Not all psychiatric disorders are stigmatized to the same extent, however. For example, some evidence suggests that schizophrenia may be more stigmatized than other psychiatric disorders (Pescosolido et al., 2010), but there is ample evidence of high levels of stigma for many psychiatric disorders including depression, Alzheimer's, and substance abuse disorders (Batsch and Mittelman, 2012; Pescosolido et al., 2010; Schomerus et al., 2011).

In recent years, the identification of blood- and neural-based risk biomarkers for psychotic disorders has advanced more than for other disorders in great part due to the development of the ultra-high risk (UHR) criteria. These criteria identify individuals at an increased risk for psychosis mostly based on subthreshold symptoms (Yung et al., 2004, 2006). Individuals who meet the UHR criteria have approximately a 30% chance of transitioning to frank psychosis within two years (Cannon et al., 2008; Fusar-Poli et al., 2012a). Individuals meeting UHR criteria have become a standard cohort for studies seeking to identify biomarkers associated with risk for schizophrenia.

Nevertheless, to maximize the benefits of identifying at-risk individuals and minimize the potential harms, it is important to more precisely identify which at-risk individuals are more likely to transition. Approximately 30% of UHR individuals will transition to frank psychosis, but that still leaves 70% of UHR individuals who will not. Resources and early interventions are more likely to generate net benefit if researchers could better identify those at highest risk; the 30% of individuals that do transition. To improve the capacity to discriminate which UHR individuals are more likely to transition to frank psychosis, researchers have examined blood- and neural-based risk biomarkers.

Schizophrenia risk biomarkers have been uncovered by conducting baseline blood- or neural-based testing of individuals soon after being identified as UHR. After a period, usually between one to four years, researchers assess which individuals transitioned to frank psychosis and identify which baseline biomarker measures distinguished UHR individuals who transitioned versus those who did not (Koutsouleris et al., 2015; Perkins et al., 2015; Santoro et al., 2015; Yung et al., 2006). The identification of genomic biomarkers for

schizophrenia has relied mostly on examining diagnosed patients and comparing them to controls. Important recent breakthroughs in this area have come from large-scale genome-wide association studies (GWAS) (Franke et al., 2016; Ripke et al., 2011, 2014). There are ongoing large-scale GWAS for other disorders, but they have not yet reached the sample size of schizophrenia GWAS and have not uncovered as many genomic risk loci (Sullivan et al., 2017).

Multiple biological processes and molecules have been identified as potential risk biomarkers for schizophrenia. For example, the North American Prodrome Longitudinal Study (NAPLS) identified 15 blood-based biomarkers using an analyte multiplex screen that helped to discriminate which individuals who meet the UHR criteria are more likely to transition to frank psychosis (Perkins et al., 2015). A few studies have applied multiplex blood screens to UHR individuals, as well as individuals at familial high-risk, and found changes that strongly implicate immune-related plasma signatures in the etiology of schizophrenia (Lizano et al., 2016; Stojanovic et al., 2014), a hypothesis consistent with findings from GWAS studies (de Jong et al., 2012; Ripke et al., 2014; Shi et al., 2009). As predictions using blood-based PRBs become more reliable, it is likely that they may be coupled with other biomarkers to provide a more accurate risk assessment for psychotic disorders.

For more than a decade, numerous studies have found that UHR individuals' baseline gray matter volume measures can help predict later transition to frank psychosis (Borgwardt et al., 2007; Dazzan et al., 2012; Fusar-Poli et al., 2012b, 2013). Replicating some of these findings has been challenging. Recently, however, researchers have used machine learning to stratify UHR individuals' risk for transitioning to frank psychosis using baseline measures of gray matter volume from various brain regions (Koutsouleris et al., 2012, 2015). Combining the UHR's symptom-based and this neuroanatomical-based predictive approaches can distinguish three UHR groups with different risk levels. A high-risk group has an 87.5% transition rate and a median transition time of 147 days; an intermediate risk group with a transition rate of 37.5% and median transition time of 1,456 days; and a low risk group with a transition rate of 8.3% and median transition time of 1,514 days (Koutsouleris et al., 2012, 2015). Subjects were followed for over four years, and transition to frank psychosis was defined as symptoms that occurred daily and persisted for longer than a week (Koutsouleris et al., 2015). The increasing capacity to discriminate between different risk levels using blood- and neural-based tests is critical for advancing research on potential preventive interventions and will later be key in helping determine the appropriate clinical management of individuals at risk for psychosis.

Schizophrenia's tendency to occur in families (Kendler and Diehl, 1993) has long been a signal of its potential heritability, which is now estimated to be between 64% to 81% (Lichtenstein et al., 2009; Sullivan et al., 2003). GWAS have uncovered more than 150 genomic loci associated with schizophrenia (Ripke, 2013; Ripke et al., 2011, 2014; Sullivan et al., 2017). It has been estimated that over 8,000 single nucleotide polymorphisms (SNPs) contribute to risk for schizophrenia and that an intricate networking of these SNPs contributes to its heritability (Bergen and Petryshen, 2012; Ripke, 2013). Genomic loci associated with schizophrenia can be used to compute genomic risk scores (Purcell et al.,

2009). These risk scores for schizophrenia currently have low predictive value (Lu et al., submitted; Sullivan et al., 2017). But it is possible that the combination of genomic risk scores along with other predictive tools, such as blood-based PRB testing or neuroimaging, could prove to have significant predictive value (Franke et al., 2016). The presence of some rare copy number variants is more predictive of schizophrenia than high genomic risk scores (Kirov et al., 2014). For example, a 22q11.2 deletion or 3q29 deletion has an estimated penetrance for schizophrenia of 12% and 18%, respectively, and could potentially be combined with other risk factors such as UHR criteria or other biomarkers to improve predictive models (Kirov et al., 2014).

As PRB research progresses, researchers will identify more reliable biomarkers that can independently or—more likely—in combination, improve risk assessment at an individual level (Fusar-Poli et al., 2013). Given the amount of progress and resources invested to advance risk biomarker science for psychotic disorders, it may be possible to have reliable schizophrenia risk prediction in common use within the next decade. Reliable measures for other disorders may take longer. As predictive biomarker tests for all psychiatric disorders prove to be useful, however, they will likely make a quick transition from research to clinical settings and perhaps other spheres of society. The discovery of risk biomarkers and development of predictive models will help improve psychiatric care and prevention, but it may also increase stigma and discrimination against an already highly stigmatized population.

PSYCHIATRIC RISK BIOMARKERS, STIGMA, AND DISCRIMINATION

Stigma occurs when “elements of labeling, stereotyping, separation, status loss, and discrimination co-occur in a power situation that allows the components of stigma to unfold” (Link and Phelan, 2001). Research suggests that mental health stigma is high (Angermeyer and Matschinger, 2004; Bharadwaj et al., 2017; Baba et al., 2017; Corrigan et al., 2000, 2001, 2004; Phelan, 2005). Even among primary care providers, negative stereotypes toward people with schizophrenia and other psychiatric disorders are widespread (Kapungwe et al., 2011; Mittal et al., 2014). Therefore, the possibility of being identified as at risk for a highly stigmatized psychiatric disorder such as schizophrenia, and the gaps in anti-discrimination protection, will likely lead many to forego PRB testing and greatly hinder the potential benefits of PRB research and translation. Moreover, studies suggest that the identification of biological correlates of mental health disorders may increase stigma and discriminatory actions. PRBs are biological correlates that indicate risk for highly stigmatized health conditions, thus, it is likely that the mere peresence of PRBs will be enough to give rise to stigma and generate discriminatory actions against those identified with these risks factors.

Evidence of Mental Health Stigma and its Implications

Individuals with psychiatric disorders are a highly stigmatized population (Corrigan, 2004, 2006). Discrimination toward those labeled with a psychiatric disorder often stems from stereotypes that elicit negative social responses (“discriminatory actions”) toward a specific social group (Krueger, 1996). Stereotypical characteristics commonly maintained by the public toward people with psychiatric disorders include blame, incompetence, and violence

(Brockington Hall et al., 1993; Corrigan, 2006; Hamre et al., 1994; Link, 2011). Furthermore, those diagnosed with psychiatric disorders are paid less (Alexander and Link, 2003), have less chances of obtaining and keeping employment (Alexander and Link, 2003; Bordieri and Drehmer, 1986; Farina and Felner, 1973; Farina et al., 1973; Link, 1982), and often do not receive the same insurance benefits (Druss and Rosenheck, 1998; Druss et al., 1998; Link, 2001). Therefore, life opportunities are often cut short for those with psychiatric disorders.

The employment rate for individuals with schizophrenia in many countries is much lower than the employment rate for the general population. For example, the employment rate in the United Kingdom varies between 4% and 31%, with the average falling far below the 75% to 80% employment rate of the general population (Marwaha and Johnson, 2004). Similar differences are observed in other European countries and the United States (Marwaha and Johnson, 2004). International studies have concluded that low rates of employment are not inherent to schizophrenia, and barriers such as a stigma and discrimination play a key role (Marwaha and Johnson, 2004).

Research suggests that people with psychotic disorders are often aware that they are undervalued by members of society and often report experiencing daily indignities including perceived unfair treatment and active avoidance by other people (Link and Phelan, 2014). Individuals with psychiatric disorders often internalize stigmatization, producing self-stigma, and interpret psychiatric disorders in a way that devalues their sense of self (Link, 1987, 2001). There is evidence that individuals experiencing prodromal symptoms of psychosis are already stigmatized, and the stress associated with mental health stigma, including self-stigma, during this prodromal stage can increase the rate of transition to schizophrenia (Baba et al., 2017; Rüsch et al., 2015). Self-stigma can also cause demoralization that results in lack of motivation to pursue employment or other life opportunities (Corrigan, 2004). Furthermore, people who are labeled as mentally ill often seek to avoid stigma by concealing their disorder (Corrigan and Matthews, 2003) or denying mental health status altogether (Corrigan, 2004), both of which significantly impede access to mental health care. Self-stigma has been shown to be a barrier for individuals seeking mental health care (Clement et al., 2015), due to the prospect of social disapproval and reduced self-esteem (Corrigan, 2004; Fenton et al., 1997). Less than 30% of a surveyed population consisting of mentally ill individuals sought treatment (Regier, 1993), while another study showed that less than 40% of people with a psychiatric disorder received treatment within the past year (Kessler et al., 2001). Regardless of diagnosis or degree of disability, people labeled as mentally ill are often stigmatized more harshly than those suffering from other health conditions (Corrigan et al., 2000; Phelan, 2005; Weiner et al., 1988).

Evidence that Biological Correlates of Psychiatric Disorders Can Exacerbate Stigma and Discrimination

Anti-stigma campaigns often promote medicalized understandings of psychiatric disorders and utilize the biomedical model for the purpose of reducing stigma (Kvaale et al., 2013b, 2013a; Read et al., 2006). There is evidence, however, that endorsement of biological

explanations may also run the risk of exacerbating stigma by triggering essentialist thinking (Boysen, 2011; Boysen and Gabreski, 2012; Haslam, 2011, 2013; Phelan, 2005; Schnittker, 2008), which deepens social divides and diminishes desire to cross them (Carr et al., 2012; No et al., 2008). One systematic review concluded that public understanding of the biological components of psychiatric disorders has increased since 1990; but this has not helped minimize the stereotype that individuals with schizophrenia are dangerous, and social acceptance of individuals with schizophrenia has actually decreased (Schomerus et al., 2012).

Other studies suggest that when people are provided with biological explanations of a psychiatric disorder they are less likely to blame individuals for the disorder but are more rejecting, discordant, and frightened of the individual (Kvaale et al., 2013a; Mehta, 1997; Phelan, 2005; Walker and Read, 2002). Those who endorse biological explanations for mental health disorders, instead of psychosocial causes like a stressful life event, have a greater desire for social distance from individuals with a psychiatric disorder (Dietrich et al., 2004). One study with 1,241 respondents used vignettes to examine attitudes towards individuals with a ruptured disc, or different psychiatric disorders (i.e., schizophrenia or depression) that participants were told were “due to genetic factors” or “definitely not genetic” (Phelan, 2005). This study showed that participants desired more social distance from the individuals with psychiatric disorders—whether or not the condition was described as having a genetic component—than those described to have a ruptured disc. Furthermore, compared to participants who were told the psychiatric disorders were “definitely not genetic,” those participants who were told the disorder was “due to genetic factors” perceived the psychiatric disorders as more serious, persistent, and were more likely to believe that the individuals’ siblings and children would have the disorder (Phelan, 2005). Other studies suggest that genetic explanations of schizophrenia increases perceived dangerousness (Schnittker, 2008). More recent meta-analyses also support these findings (Kvaale et al., 2013a).

Although we believe it is unlikely, it may be possible that PRBs—contrary to biomarkers associated with the presence of a disorder—do not exacerbate stigma. PRBs may decrease stigma, for example, by leading to the perception that psychiatric disorders are similar to other somatic disorders. We are unaware of any research that has directly examined attitudes toward subthreshold or asymptomatic individuals with PRBs. The studies described above examined stigma towards individuals with a mental health disorder and whose disorder has some kind of biological component. The high level of mental health stigma, together with the fact that psychiatric biomarkers can exacerbate stigma towards individuals with diagnosed psychiatric disorders, however, suggest that biological markers indicating increased risk (not presence) for stigmatized disorders may also lead to stigma and discriminatory actions. It is necessary for countries fund research to directly examine whether PRBs are, in fact, stigmatizing. It would also be important to understand exacly how it is that this information serves to increase stigma. For example, future studies could use vignettes to compare people’s attitudes (*e.g.*, desire for social distance, perceived dangerousness) toward individuals identified with PRBs against individuals identified with risk biomarkers for somatic conditions such as cancer. This will promote the development of well-informed and responsible anti-discrimination policies.

As PRB research progresses and begins to be translated to clinical settings, the tendency for laypeople to endorse biological explanations of psychiatric disorders will likely continue to rise (Schnittker, 2008). The endorsement of biological explanations—perhaps due to lack of sufficient understanding of genomic and non-genomic PRBs—seems to lead to essentialist thinking and negative stereotypes, which in turn lead to increased stigma and potential discrimination. The way the media communicates scientific findings further complicates this problem. A recent study showed that media reports of neuroscience discoveries were plagued with essentialist claims (Racine et al., 2010). To optimally address the increase in essentialist thinking and potential discrimination that can come from advances in PRB research and translation, different stakeholders need to take action. Governments need to invest in science education. Media outlets need to be more careful about accurately reporting PRB findings. Clinicians, on the other hand, will likely need to make an effort to carefully explain PRB findings in a way that helps patients understand the implications and limits of genomic and neuroscience data. Nonetheless, cultural changes through education may take a long time. Even if entities understand the limits of genomic and non-genomic PRBs, they may still use PRBs to discriminate against individuals at risk for psychiatric disorders if they believe PRB tests are useful to advance their interests, as we discuss below. There are multiple reasons to believe that numerous entities would be interested in using PRB information in ways that would discriminate against those at risks for psychiatric disorders. In most countries, however, the laws and regulations currently available to protect against discrimination based on PRBs are inadequate.

INADEQUATE PROTECTION AGAINST DISCRIMINATION BASED ON PSYCHIATRIC RISK BIOMARKERS

When evaluating the adequacy of protections against PRB discrimination, it is important to consider that many groups will likely have an interest in using genomic and non-genomic PRB information. For example, employers could use information about risk for schizophrenia to decide on job placement in cases where the safety of the employee or others could be affected by schizophrenic symptoms. Employers may also use PRB information to decide on promotions for administrative positions involving high-stakes decision making in which the individual will be under significant stress (Levin, 2013). Health insurance companies could use this information to raise premiums, given the potential need for psychiatric care and the costs associated with treating comorbidities (*e.g.*, substance abuse, cardiovascular disease, diabetes) often affecting these patients (APA, 2013; Giusti-Rodríguez and Sullivan, 2013). Life insurance companies could use this information during the risk-assessment process, given that the life expectancy of patients with schizophrenia is approximately 15–20 years less than the general population (Tandon et al., 2009). Disability insurance and long-term care insurance companies would be interested in this information because treatment options for schizophrenia are frequently ineffective or have intolerable side effects. Approximately 30% of patients suffer from treatment-resistant psychosis (Lieberman et al., 2005; Lieberman and Stroup, 2011; Suzuki et al., 2011) and this can impair an individual’s ability to work and require medical care for an extended period. Mortgage and student loan lenders may use the predictive value of this information to adjust interest rates based on risk for schizophrenia, given that the condition could affect an

individual's capacity to repay. While these practices may not currently be in place, as inexpensive predictive testing such as blood tests become more reliable, these uses for PRB information will become feasible in many countries.

Genomic discrimination is an internationally recognized phenomenon, generally defined as disparate treatment of asymptomatic individuals on the basis of their genotype rather than their phenotype, or against symptomatic individuals whose health condition has a genomic component (Otlowski et al., 2012). Worries about the illegality of genomic discrimination are rooted in privacy concerns, as well as the idea that discrimination based on immutable characteristics is considered unfair and socially unacceptable (King et al., 2006). In response to trepidations about the potential misuses of genomic information, governments have played a key role in limiting its use (Otlowski et al., 2012).

The completion of the Human Genome Project (HGP) in 2003 prompted legislative action around the world expressly prohibiting genomic discrimination (Table I). For example, several European countries including Austria, Belgium, Denmark, France, Germany, along with serveral others, enacted laws prohibiting health insurance companies from using genomic information to set premium costs (Otlowski et al., 2012). Denmark, Austria, Bulgaria, Estonia, and other countries were more preemptive in their actions and enacted similar laws before completion of the HGP. Genomic discrimination in employment is prohibited by legislation in countries such as Israel, Spain, Bulgaria, and others (Table I). In 2008, the United States adopted the Genetic Information Nondiscrimination Act (GINA) (GINA, 2008; Roberts, 2010). GINA is a federal statute aimed at preventing the discriminatory use of genomic information on the part of the health insurance industry and employers (Slaughter, 2013).

The scope of protection for each legislative response and the forms of medical data protected varies by country. Germany's Human Genetic Examination Act (Gendiagnostikgesetz - GenDG [Draft Human Genetic Examination Act (Genetic Diagnosis Act - GenDG)], 2009) passed in 2009, prohibits discrimination based on genomic information for life, disability, occupational disability, and pension insurance contracts that do not exceed a value of 300,000 euros. Portugal is broader in its protections, prohibiting genomic discrimination in employment, health and life insurance, education, and adoption, without limitations based on contract value (Lei n.° 12/2005 [Personal Genetic Information and Health Information]; Soini, 2012).

On a supranational level, genomic discrimination has been treated as a human rights issue (King et al., 2006). The Council of Europe's European Convention on Human Rights and Biomedicine took a broad approach to banning genomic discrimination, and all countries that signed on to the agreement committed to enacting legislative protections against genomic discrimination (Bombard et al., 2010). Table I summarizes the range of protections granted by international legislative responses to genomic discrimination, as well as by a few broad anti-discrimination constitutional and statutory protections that may cover non-genomic PRBs.

Despite the important protections afforded by these laws, they are not all-encompassing. Furthermore, some countries such as Australia, India, China, New Zealand, most South American and African countries, and many others, have not enacted specific legislation targeting genomic discrimination (Joly et al., 2017; King et al., 2006). In fact, Australian law allows for genomic-based discrimination by life insurers under specific circumstances (Joly et al., 2017). Similarly, countries like the United States, Germany, Sweden, Switzerland, and the United Kingdom allow genomic information to be factored into a risk assessment for obtaining life, disability, or long-term care insurance (Rothstein, 2009). Outside of the contexts of insurance and employment, both the United States and the European Union have been quite liberal about allowing corporations and governmental agencies to make use of genomic data. In the United States, GINA does not protect against genomic discrimination within the military or outside the employment or health insurance contexts. Hong Kong has used genomic information from volunteers to create facial composites for public interest campaigns, and the Kuwaiti government has introduced a law that would make DNA sample collection mandatory for all citizens, visitors, and permanent residents for contribution to a law enforcement database (Joly et al., 2017).

Notably, the vast majority of these protections extend only to genomic information and have not been interpreted to cover non-genomic biomarkers. While some have argued that all biomarkers are a product of genes, blurring the distinctions between genomic and non-genomic biomarker data (Yesley, 1998), the narrow statutory language in legislation such as GINA does not legally protect the results of tests that do not “detect genotypes, mutations or chromosomal changes” (GINA, 2008). Therefore, there is nothing in these laws to cover individuals identified with non-genomic biomarkers (Lakhan et al., 2010). Only Albania’s Law On Protection From Discrimination enacted in 2010 and Article 328b of Switzerland’s Code of Obligations contain provisions that could be interpreted as protecting all types of PRBs in some contexts. Albania protects against discrimination based on health status and genetic predispositions. In Switzerland, an employer may only manage employee data that is relevant to job performance. In theory, PRBs do not affect job performance. Some could argue, however, that if the manifestation of a PRB could impact job performance and the likelihood of the poor health outcome is sufficiently high, then the PRB does, in fact, become relevant to job performance.

An important factor in promoting the legal protection of genomic information has been the idea of genomic sequencing as an immutable characteristic: people have no control over their genotype, and therefore discrimination based on such characteristics is generally considered unfair (Hoffman, 2010). Beyond any ethical or human rights arguments, many countries have determined that allowing genomic discrimination in certain contexts, such as employment and health insurance, is poor public policy. Arguably, implicit in the enactment of GINA and similar anti-genomic discrimination legislative pieces is a determination that society has more to gain (*e.g.*, decrease in health care expenditures because of disease prevention, increase in labor participation) from the promotion of participation in genomic research and the use of genomics in medicine than from allowing employers or health insurance companies to discriminate based on this information. Non-genomic biomarkers (*e.g.*, blood analytes, gray matter volume) can be as predictive and, in some cases, even more predictive of disease than genomic biomarkers (Koutsouleris et al., 2015; Lu et al.,

submitted; Perkins et al., 2015; Sullivan et al., 2017). The promotion of non-genomic biomarker testing in research and clinical care may also generate significant health care benefits and decrease expenditure. Furthermore, non-genomic biomarkers are also generally perceived as immutable characteristics, and any control an individual may have over their expression does not differ meaningfully from the control an individual would have over genomic markers (Hoffman, 2010).

Nevertheless, of the legal protections outlined in Table I, almost all countries listed solely shield against the misuse of genomic information—including psychiatric genomic biomarkers—in certain contexts, and do not reach non-genomic risk biomarkers (United States District Court for the Northern District of Alabama, 2013). Legislative priority given to genomic anti-discrimination laws, as opposed to other risk biomarkers, may be explained by historical concerns about eugenics and the widespread attention that genomics and possible genomic discrimination received during the planning and execution of the HGP (Garver and Garver, 1994; Juengst and Watson, 1991; Malinowski, 2003). In fact, most laws aimed at preventing genomic discrimination were enacted after the HGP began in the early 1990s (Table I). During this time, the HGP's leaders also decided to allocate 5% of the project's budget to examine ethical, legal, and social implications (ELSI) of the HGP, including concerns about genomic discrimination (Juengst, 1996; Juengst and Watson, 1991). Recognizing the importance of addressing these issues, the US National Human Genome Research Institute continues to fund the ELSI program and other countries have similar programs. Today, it may be time to turn our attention to how non-genomic biomarker anti-discrimination legislation—particularly for PRBs—can help maximize the benefits and minimize the potential unintended consequences of big science projects focused on brain function and disorders.

Similar to how the HGP fueled genomics research, and concerns about its ethical, legal and social implications, today, the E.U. Human Brain Project, U.S. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, and other large-scale neuroscience and neurogenomics research projects such as the Psychiatric Genomics Consortium, aimed at developing neurotechnologies, knowledge, and clinical applications of neuroscience knowledge present a similar situation and together, involve a much larger investment of resources than the HGP (Frégnac and Laurent, 2014; Insel et al., 2013). These projects will likely serve as catalysts for the identification of more neural- and blood-based health risk biomarkers, including PRBs. Smaller initiatives and research programs, including NAPLS, aim to identify other PRBs such as blood-based markers that are not covered under laws that ban discrimination based on genomic information (Addington et al., 2012). As we discussed above, there is a high degree of mental health stigma and evidence that biological correlates of psychiatric disorders may increase stigma and discrimination. This highlights the need to address the gaps left by current international legislation aimed at preventing genomic discrimination.

ARGUMENT FOR INCREASED PROTECTION AGAINST PSYCHIATRIC RISK BIOMARKER-BASED DISCRIMINATION

Given the limited existing legal protections against the discriminatory use of genomic PRB information and the almost non-existent protections against the discriminatory use of non-genomic PRB information, it is critical that international governments turn their attention to finding ways to promote the fair use of all PRBs. As we have established above, there is legitimate concern that the development of more reliable PRB technologies and the endorsement of biological explanations of psychiatric disorders will exacerbate stigma and discrimination in several spheres of society. Gaps in the protections against PRB discrimination will not only harm individuals who get tested and are discriminated, but will also deter individuals from undergoing PRB testing. This may ultimately undermine the potential benefits of psychiatric genomics and other omics research, as well as neuroimaging-based predictive psychiatric research. It is, therefore, important to consider the value of and arguments for introducing anti-discrimination legislation covering all PRBs.

The international community has recognized the right to privacy as a fundamental human right that is “solidly embedded in international human rights law as well as in national constitutions, legislation, and jurisprudence” (Hendriks, 2001). Legislation regulating genomic information around the world has been tied to a fundamental right to privacy (King et al., 2006). That is, there is an entitlement to the protection of personal genomic data and therefore a corresponding duty on the part of governments to protect against unwanted intrusions, disclosures, and improper discovery by third parties (Hendriks, 2001). The privacy implications of genomic and PRB data are analogous. Therefore, if legislation to prevent the misuse of PRB information is not promoted, the same fundamental, internationally recognized human right of privacy would be put at risk by potential misuse.

Another compelling reason to prohibit the use of PRB data to make adverse determinations about asymptomatic individuals at risk for psychiatric disorders is that, much like sex and skin color, genomic and most non-genomic PRBs are immutable characteristics over which people have little or no control. Immutability is a unifying principle underlying legally, and often constitutionally, protected traits (Hoffman, 2010). For the same reason, genomic and non-genomic PRB information that can help explain why an individual is suffering from a psychiatric disorder, prognosis or recurrence of symptoms should not be used to take adverse actions against an individual. It is beyond the scope of this article to discuss how the manifestation of these disorders should be managed. Laws in many countries protect against discrimination based on disability, and the definition of disability often includes manifested psychiatric disorders, although the societal settings in which these laws apply are often limited (ADA, 1990).

Legislation and policies should ideally treat all biomarker risk information equally. But given the internationally recognized problem affecting the prevalence and care of psychiatric disorders, and the high levels of mental health stigma around the world, it would likely be much more feasible to gain swift international governmental support for narrow anti-discrimination laws specific to PRBs, as opposed to sweeping risk biomarker anti-discrimination laws. In arguing for narrowly tailored legislation targeting PRBs specifically,

we note that there is international precedent for the special treatment of information related to mental health. In the United States, the Health Insurance Portability and Accountability Act (HIPAA) allows mental health clinicians to keep psychotherapy notes separate from patients' medical record to protect the privacy of the sensitive information disclosed during conversations between patients and clinicians (Annas, 2003; HIPAA, 1996). While this rule has some limits, it is one of the few instances in which American law treats one type of medical information differentially (HIPAA, 1996). In fact, data shows that when asked whether special privacy protections should be implemented for certain medical conditions, peoples' concerns for the protection of their mental health data ranks second only to data on abortion history and more highly than genetic information or data on HIV/AIDS status (Kass et al., 2003). Of the forty-two country members of the World Health Organization, twenty have adopted specific mental health legislation, in recognition of the unique challenges and stigma attached to this particular realm of medicine (World Health Organization, 2008). To be sure, legislation has also treated medical information other than mental health exceptionally (*e.g.*, genetics, HIV/AIDS, child abuse) (The Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, 1990). We note the exceptional treatment of mental health in these instances only to illustrate that there is precedent for doing so, and not to imply that mental health is the only exception worth making.

Managing genomic information differently than other types of medical information, referred to as genomic exceptionalism, has been criticized on several different fronts. PRB-specific legislation may likely face similar criticism. Some have argued that genomic anti-discrimination legislation is problematic because it only addresses one aspect of risk biomarker-based discrimination and may lead lawmakers to forego more sweeping anti-discrimination legislation entirely (Rothstein, 2007, 2009). Others argue that there is no justification for treating genomic information differently than other types of medical information because it does not provide predictive information that is qualitatively different than cholesterol level or smoking status (Evans and Burke, 2008). However, even those who argue against genomic exceptionalism have recognized that genomic exceptionalism "makes sense in some circumstances...for example, when genetic risks related to mental illness or other behavioral conditions have the potential to stigmatize individuals or groups" (Evans et al., 2010). Furthermore, the focus of discussions surrounding prospective anti-discrimination legislation should be on the net benefits of such regulation, and not on whether there is a clear qualitative way to distinguish the type of medical information provided by PRBs versus the information gathered from other somatic risk biomarkers such as blood pressure. If we believe that PRB information may be used to discriminate against those who use these tests, that PRB testing can become a valuable tool to promote psychiatric care and prevention, that the potential for PRB-based discrimination may lead many of those who could benefit from PRB testing to forego the use of these technologies, and that PRB anti-discrimination legislation can help promote the use of PRB testing, then there is a forceful policy argument to be made for the benefit of promoting these regulations, regardless of arguments about semantic differences between the information PRBs provide and the information obtained from other biomarkers.

An obstacle the proponents of laws targeting genomic discrimination had to overcome when lobbying for regulation was that anti-discrimination legislation usually takes place as a

reaction to a history of discrimination against a particular group. By contrast, genomic discrimination legislation was preemptive, targeting a foreseeable likelihood of discrimination (Roberts, 2010). Future discrimination patterns based on PRB status is a legitimate concern given the widespread international prevalence of mental health stigma, the fact that PRBs would indicate risk for those stigmatized conditions, and the expected interest that third party institutions will have for using PRB data to make determinations about individuals at risk for psychiatric disorders. It is foreseeable that PRB-based discrimination will likely become a problem in many societal contexts. Governments, and other regulatory bodies should not wait until individuals are negatively affected by these technologies to react to these harms with belated legislation. By being proactive in addressing anticipated unintended consequences of biomedical advances, societies can help prevent future harms and promote the responsible translation of these advances to the clinic.

Widespread educational campaigns on mental health and the treatment of individuals diagnosed with psychiatric disorders would be the ideal way to address problems of misinformation, stigma, and potential PRB discrimination. But the rate at which these technologies are developing, and the potential for imminent and systematic discrimination based on the misuse of the valuable information promised by these technologies, make presenting a timely and successful educational campaign challenging. While swift and comprehensive legislative action would serve to preempt discrimination, lessons from legislation enacted to prevent genomic discrimination teach us that governmental regulations typically suffer from several limitations. It has been pointed out that existing regulatory models for preventing discrimination often lack public visibility, are narrow in their protection, and involve complex administrative procedures (Joly et al., 2017). An ideal solution to preventing PRB-based discrimination would involve both investment into a far-reaching educational campaign about mental health, including PRBs, and efficient and targeted anti-discrimination legislation.

Countries around the world should carefully consider adopting broad prohibition of discrimination based on actual or presumed PRB status. In parallel, countries including the United States should consider that these changes may also take the form of amendments to laws already in place, such as the GINA, to include protection for PRBs. PRB anti-discrimination laws should ideally cover all private employers and any person who offers goods and services, including all types of insurance and banks. In countries where there are genomic anti-discrimination laws, this may just require amending those laws to expand the conditions and contexts covered to include PRBs, as defined above. There is a lack of research, however, about the social and economic impact that PRB anti-discrimination laws would have in these contexts. Thus, it is essential that governments invest in research to clarify these unknowns and implement well-informed policies. Governmental use of PRB data should only be allowed in exceptional situations, when the government has a compelling interest at stake and PRB data can meaningfully contribute to protect the government’s interest. PRB testing promises to eventually decrease the staggering amount of global resources spent on mental health, the negative social consequences related to psychiatric disorders, and (most importantly) help minimize the suffering of individuals identified to be at risk and their families. Therefore, the likely benefits of encouraging PRB

research, development, and use far outweigh the benefits to be gained from allowing broad use of PRB data by private entitites and governments.

CONCLUSION

PRBs have great potential to improve psychiatric care and prevention. However, as we discussed above it is likely that PRBs will also give rise to stigma and discriminatory actions. A substantial body of research evidences a high degree of mental health stigma around the world, the presence of PRBs would link individuals to these highly stimatized health conditions, and research suggests that biological correlates of psychiatric disorders increase stigmatizing attitudes and beliefs. Specifically, these biological correlates—probably due to misinformation and misinterpretation—lead to a desire for social distance, and an increase in both the perceived severity of the condition and the perceived dangerousness of the patient (Kvaale et al., 2013a; Phelan, 2005). These stigmatizing attitudes and beliefs, in turn, increase the risk for discriminatory actions.

Numerous entities such as employers, insurance, and lending companies will likely be interested in using PRB information, and there is little protection against the discriminatory use of genomic, and particularly non-genomic PRB information. Therefore, a population already vulnerable to stigmatization and discriminatory actions is further exposed to potential discrimination for using PRB testing technologies that could benefit their health. Unless all stakeholders, including patients, patient advocates, psychiatric researchers, and clinicians participate in promulgating ethical and policy standards for the use of PRBs, discoveries in this area may be undermined by social and legal risks associated with the generation of PRB information. Governmens should carefully consider expanding legislation to prohibit PRB-based discrimination to promote the uptake of evidenced-based PRB testing, and maximize the promise of genomic and non-genomic PRB research.

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Table I

Anti-discrimination protections for psychiatric risk biomarkers. Legislative pieces were interpreted based on clearly stated protection in employment, health, life insurance, and disability insurance.

International Anti-Discrimination Legislation Relevant to Psychiatric Risk Biomarkers			**Social Spheres Protected**			
Protections for genomics-based psychiatric risk biomarkers						
Country	**Legislation Title**	**Year**	***Employment***	***Health Insurance***	***Life Insurance***	***Disability Insurance***
Austria	Austrian Gene Technology Act	1995	✓	✓		
Belgium	Insurance Law	1992		✓	✓	✓
	The Anti-Discrimination Law	2007	✓			
Bulgaria	Bulgarian Health Act	2004	✓	✓	✓	✓
Canada	Genetic Non-Discrimination Act	2017	✓	✓	✓	✓
Denmark	Health Act No. 546	2005	✓	✓		
Estonia	Human Genes Research Act	2000	✓	✓	✓	✓
France	Act of 4 March 2002	2002	✓	✓	✓	✓
Germany	Human Genetic Examination Act	2010	✓	✓	✓*	✓*
Israel	Genetic Information Law of 2000	2000	✓	✓		
Mexico	Federal Law to Prevent and Eliminate Discrimination	2014	✓			
Netherlands	Medical Examination Act	1998	✓	✓	✓**	✓**
Portugal	Law n°12/2005 of 26 January 2005	2005	✓	✓	✓	
Spain	Spanish Constitution of 1978	1978	✓			
Sweden	The Genetic Integrity Act	2006	✓	✓		
United States	Genetic Information Nondiscrimination Act	2008	✓	✓		
Protections for all psychiatric risk biomarkers						
Country	Legislation Title	Year				
Albania	Law n°10 221 on Protection From Discrimination	2010	✓	✓	✓	✓
Switzerland	Article 328b of the Code of Obligations	1993	✓			

*Germany prohibits use of genetic information for life and disability insurance contracts up to a pre-specified amount.

**The Netherlands prohibit use of genetic information for life and disability policies up to a pre-specified amount. (Otlowski et al. 2012)