PHENOTYPES FOR PREDICTION: GENE EXPRESSION AND GENETIC EXCEPTIONALISM

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ABSTRACT

In the wake of the post-genomics era, United States legislators enacted the Genetic Information Nondiscrimination Act (GINA) of 2008 in an effort to combat looming threats of discrimination and to relinquish citizen’s fears of genetic testing. GINA, like other questioned nondiscrimination laws before it, only protects genotypes. Multiple scholars have insisted these provisions are unjustified and only serve to reinforce genetic exceptionalism, or the idea that genetic information is inherently different than other health information and should be treated as such. In this article we will use gene expression assays to show the dichotomy drawn between genetic and non-genetic information is flawed, as properties often claimed to distinguish these categories are common to both. Furthermore, we will contest that phenotypes such as gene expression have greater predictive utility than genotypes due to their ability to account for various environmental influences. Finally, we will provide potential negative consequences of GINA’s scientific and definitional oversights, and show that for nondiscrimination health policy to be effective it must be constructed with scientific accuracy and transparency as a top priority.

Keywords: Gene expression, genetic exceptionalism, Genetic Information Nondiscrimination Act (GINA)

1. INTRODUCTION

Genetic information, no matter how unsophisticated compared to today’s standards, has been used for decades to improve healthcare. Now with the completion of the Human Genome Project, the creation of HapMap and the advent of genome-wide association (GWA) studies, it is no surprise that the era of personalized and genomic medicine may be approaching. However, no discipline has been able to fully unlock the genetic and genomic mysteries surrounding disease and reach the pinnacle that is patient-tailored therapy. This has left practitioners and scientists questioning whether or not this vision of futuristic medicine will ever be attained [1-2]. Our notion is that both the genetic predisposition and the influence of the environment will act in concert to initiate a disease state and then set the course for its progression; concentration on the genetic component will be necessary but not sufficient to explain this disease progression. Ongoing advances in high-throughput genomic technologies such as gene expression microarrays will be instrumental in gaining deeper insights into the environmental triggers for genetic predispositions for disease. This is because we can directly measure the transcriptional program in the nucleus following receptor activation from chemicals and hormones circulating in the blood. Therefore, any mutations in the receptor protein or the signal transduction enzymes leading to abnormal or pathological transcriptomes can now be characterized in great molecular detail. Furthermore, through using an integrated approach of data mining, text mining and sophisticated multivariate statistical and clustering tools on the large amounts of data currently being uploaded and made freely available to researchers, it will become feasible to identify the key molecular players in disease progression [3] and the link to environmental factors.

Currently, advances in pharmacogenomics that seek to predict patient level response to drug treatment may be limited, but great progress has been made in the realm of genomics using high-throughput data. GWAs have lead to the discovery of casual risk variants in cancers such as colorectal, prostate, and chronic lymphocytic leukemia [4-6]. Similarly, gene expression assays have become exceptionally popular by assisting treatment decisions in breast cancer [7]. As might be expected, these methods all come with their respective obstacles and criticisms [1-2, 8].
While some of these obstacles have come from the lack of sufficient scientific knowledge, others have arisen from the clinical side of medicine through the political/social/ethical sphere. In fact, the latter can often be as difficult to circumvent as the former. The inability to attain public acceptance of genetic and genomic medicine, even in cases where testing has shown to be highly beneficial [9], has stimulated legislative intervention [10] and created an interesting medical anthropological puzzle.

Adequate delivery of medical treatment at the patient level will require integration of both public health policy and healthcare advances stemming from genomics. The increased prediction of the environmental causes for initiation of diseases through specific genetic mechanisms will pose a major challenge for all players in healthcare to ensure that genetic information and any related policies are (1) appropriately defined in concordance with scientific evidence, and (2) implemented fairly across all societal and health groups. Mainstream use of clinical gene expression necessitates a detailed analysis of the non-scientific and scientific factors associated generally with genetic and non-genetic testing and specifically with gene expression. In this article, we will examine the interplay between the social, legal, and ethical components of predictive genetic testing with the science of clinical gene expression assays. Using the Genetic Nondiscrimination Act of 2008 we will show how legislative measures can miss important details when making efforts to alleviate the public’s concerns of discrimination. The putative harms of these scientific oversights in conjunction with common misconceptions about genotypic tests (e.g. genetic exceptionalism) will then be examined. Finally, we will conclude with suggestions on how to view disease, genetic information, genetic tests, and health information in general, which will maximize transparency and help develop fair, scientifically cognizant, health-related nondiscrimination legislation.

2. CLINICAL USE OF GENE EXPRESSION ASSAYS

Researchers are investigating new ways in which genomic phenotypes can be disseminated to better understand the nature of disease as well as to treat patients more efficiently and effectively. One of these methods is gene expression. Gene expression is often considered an “intermediate phenotype” and is measured by analyzing the relative amount of gene transcription within a particular cell type [11]. The transcriptional activity of a cell is important due to the assumption that transcribed genes will be translated into functional polypeptides and proteins. This is a substantially dynamic process that can be highly influenced and regulated by environment, cellular demands, and disease [12]. Due to its implications for identifying, classifying and determining treatment for disease states, as well as being a cost-effective way to produce large quantities of data, gene expression analysis has become exceptionally popular in biomedical research.

Gene expression assays can be conducted in a variety of ways. The most common is through microarray, which screens tens of thousands of transcripts for altered regulation. While microarray use is integral in both hypothesis- and discovery-driven research, analysis of gene expression in the clinical setting typically involves assays investigating many fewer genes and has an increased emphasis on validation [13]. One such test, Oncotype DX® (Genomic Health Inc., Redwood Falls, CA), is likely the most widely used gene expression assay in oncology. Oncotype DX uses real-time polymerase chain reaction (RT-PCR) to analyze a 21-gene (16 experimental and 5 reference) assay that predicts the 10-year recurrence rate of estrogen receptor positive, lymph node-negative breast cancer. The resulting test gives a Recurrence Score (RS) between ranging from low (0) to high (100) probability of recurrence [14]. This data is used to help determine the costs (both physically and financially) and benefits of aggressively treating cancer with chemotherapeutics. Multiple clinical studies have shown that Oncotype DX is a better predictor of 10-year cancer recurrence than any other combination clinical pathological markers [15]. However, some have contested the unique clinical utility of Oncotype DX by showing that histopathological markers can account approximately two-thirds of the variation predicted by Oncotype DX [16]. Regardless, Oncotype DX has been ordered for more than 85,000 patients and integrated into the guidelines of both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) as a standard clinical practice [13, 17-18].
Other predictive gene expression assays are pushing their way into mainstream use as well. MammaPrint® (Agendia, Amsterdam, NL) is an FDA approved 70-gene signature used to predict the likelihood of relapse (within 5 years) of lymph node-negative breast cancer (≤ 5 cm) in patients < 61 years of age [18-19]. Unlike OncoType DX, MammaPrint uses a microarray platform to investigate expression levels. While the FDA has set the aforementioned eligibility guidelines, the current European MINDACT trial should provide sufficient evidence necessary to better understand the prediction capabilities of this test [20]. Further details of both MammaPrint and OncoType DX as well as other prospective prognostic gene expression assays for breast cancer can be viewed elsewhere [18].

Other investigations are showing gene expression signatures are not limited to predicting relapse in cancer patients but can also assist in early diagnosis of other diseases. Analysis of blood samples of patients with autoantibody positive arthalgia predicted future development of arthritis [21]. Ten of the 109 at risk patients that were sampled developed arthritis within 7 months of undergoing the analysis [21]. Identification of high-risk patients will presumably allow patients to undertake preventative measures to thwart disease onset and perhaps allow physicians to provide earlier treatment.

Expression profiling may also be able to identify early onset and progression of diseases with well-know genetic pathologies. Huntington’s disease (HD) is an autosomal dominant neurodegenerative condition that results from mutation of the Huntingtin gene (HTT). Symptoms of HD typically begin during mid-life and often leads to death within 15-20 years. Multiple gene expression studies have identified genes that are differentially expressed among healthy controls, symptomatic HD patients, non-symptomatic HD patients, and patients with other neurological disorders [22-23]. These expression disparities not only provide potential therapeutic targets and early treatment options, but may also present a way of stratifying individuals with HTT mutations on a gradient ranging from asymptomatic to symptomatic.

3. GENETIC DISCRIMINATION

While many ethical aspects of genetic analyses cause for concern, none have had such a substantial effect on public opinion as genetic discrimination. The repercussions from this distrust of genetic analyses have been well documented [24-26]. Fear of genetic discrimination has prohibited advancements in science and deterred public health [25]. In a 2007 survey, 93% of Americans believed that researchers should be able to conduct genetic tests in order to improve disease prevention, diagnosis, and treatment. However, 92% expressed concerns with the ability of this information to act as a detriment to their overall wellbeing through various modes of discrimination [27]. Clinical trends in patient decision-making have also quantified these fears. Studies many individuals who meet BRCA1/2 testing criteria, which determines if patients are predisposed to hereditary breast cancer, forgo testing due to discriminatory concerns [9, 27].

In addition to BRCA1/2, there are currently over 1,500 genetic tests can indicate predisposition to health conditions, predict patient response to drug therapeutics, and provide disease diagnosis [25, 28] However, the lack of use by patients does not necessarily come from ignorance of testing but is often preferentially bypassed. Patients fear that participating in genetic testing might cause them to choose between maximizing their health and remaining insured [29]. For example, identifying BRCA1/2 mutations are often critical in early detection and prevention of hereditary breast cancer [30]. Those positive for these mutations may choose more aggressive treatment such as a prophylactic mastectomy to prevent breast cancer from ever occurring. Individuals who are more predisposed to a particular condition may also be able to alter lifestyle choices to help curb the progression from genetic predisposition to disease [31]. If patients are unwilling to utilize these technological advancements for fear of adverse reactions not associated with their health, scientific resources are squandered and public health is jeopardized.

Patients are not the only individuals concerned with the protection of genetic information. Healthcare professionals such as physicians and genetic counselors worry about genetic prejudice against their patients [32]. 52.4% of California physicians of mixed specialties feared their cancer patients could experience either increased premiums or coverage denial based on their genetic test results. Interestingly, these results did not seem to be confined to cancer
patients as 52% of these physicians say these same difficulties apply to their non-cancer patients as well [24]. Conversely, not all individuals believe that there is a legitimate risk for discrimination [32]. Some have asserted that these fears are unfounded since there has been little or no documentation of health insurers’ misuse of genetic information [33]. When there have been so few cases of insurance-based genetic discrimination it may currently be unjustifiable to have insurers operating under volatile procedures and regulations [34].

Proponents of genetic anti-discrimination are quick to identify that fear of genetic testing and avoidance of genetics-related research studies is a real ailment in our society [25]. Although those who oppose legal intervention claim most cases of discrimination are anecdotal and hearsay, there are documented instances of genetic inequity and some even have stimulated legal action [26]. In the 1970’s, insurance companies discriminated against African Americans who were carriers of the genetic mutation for sickle-cell anemia by increasing their premiums or denying coverage outright [29]. The Burlington Northern Santa Fe Railroad was responsible for what was likely the most infamous misuse of genetic information. Perhaps in an effort to reduce the burdensome cost of employees’ health coverage, Burlington covertly conducted genetic analyses on its workers, screening for genetic predispositions to diabetes, alcoholism, and a rare genetic form of carpal-tunnel syndrome [26]. One individual who refused to be tested was threatened with termination if he did not submit a blood sample. The actual non-speculative purpose of collecting this information was never made certain, but its potential for discrimination is unquestionable. This case was ultimately settled outside the courtroom, casting a mysterious shroud over how the legal system would rule on such an overt abuse of genetic information [35].

Many of the documented acts of discrimination have come against individuals with predisposition to HD, which is likely due to its completely penetrant nature, or essential guarantee for carriers to one day become symptomatic for the disease. On two separate occasions Jolene Hollar was denied a life insurance policy due to her family history of the disease. One insurer specifically required that Hollar test negative for the HD mutation before offering her an insurance policy [26]. Similarly, predisposition to this disease has led to prejudice outside the medical field. Because of her heightened risk for HD, a woman from North Carolina was prevented from adopting a child [36]. Given these claims, it is not surprising that many susceptible to HD avoid being tested for the gene [37]. While certainly not the only barrier to predictive testing, widespread fear of genetic discrimination has repeatedly shown itself to be a factor in patient decision-making [9, 38].

4. THE U.S. SOLUTION: GENETIC INFORMATION NONDISCRIMINATION ACT

In an attempt to derail current and looming threats of genetic discrimination, most U.S. states enacted laws in an attempt to allay fears and protect citizens. Because these laws were often limited in scope and varied greatly from state to state, they we deemed inadequate by many patients, advocates, and legislators. With aspirations personalized medicine on the horizon, lawmakers began to believe an overarching federal framework was needed to ensure protection to all who reside in the U.S. In 1995, Representative Louise Slaughter (D-NY) introduced the first genetic information bill in the U.S. House of Representatives. In 1996, Senator Olympia Snowe (R-ME) introduced a similar bill in the Senate that called for the prevention of genetic discrimination by health insurers. While both were unsuccessful, they set the foundation for thirteen years of advocacy that culminated in 2008 when the Genetic Information Nondiscrimination Act of 2008 (GINA) was passed by both the House and Senate and subsequently signed into law by George W. Bush. Dubbed by senator Edward Kennedy (D-MA) as, “The first major civil rights bill of the new century” [25], GINA promised not only to alleviate fears of genetic testing but also to increase individuals’ willingness to participate in genetic and genomic studies. Implementing GINA likely has as much relevance to alleviating fears as it does to prevent actual acts of genetic discrimination [25]. By boosting the participation rate in genomic studies, both legislators and scientists hoped to see an increase in the discovery and development of new biomedical technologies.

GINA was drafted to provide protections against genetic discrimination from both health insurers and employers. As many others have sufficiently discussed the legislative details of GINA [25-27, 35], comprehensive coverage will not be provided here. Importantly, GINA now defines genetic information as any “analysis of human DNA, RNA,
chromosomes, proteins, or metabolites that detects genotypes, mutations, or chromosomal changes” [10]. More generally, GINA provides protection for an individual’s genotype but not phenotype [39]. Much to the satisfaction of advocates, family history is now covered under the umbrella of GINA’s legal protections. GINA’s provisions for health insurers, Title I, went into effect May 21, 2009. Title II, which places limitations on employers, was enforced starting on November 21, 2009 [10].

5. OVERVIEW OF GINA BENEFITS

- Health insurers may not underwrite based on genetic information in both group and individual health plans.
- Family history is included in the definition of genetic information.
- Insurers may not request or require an individual to undergo a genetic test, nor can they request or require this of a family member.
- Employers operating businesses with 15 or more employees may not make hiring, firing, promotional or job description decisions based on genetic information.
- It is illegal for employers, employment agencies, labor organizations, and training programs to request, require, or purchase genetic information from its current or potential employees and they also cannot request the genetic information of a family member [10, 25-27, 35].

6. KEY DEFINITIONS IN GINA

- Genetic information is defined as information regarding, “(I) [An] individual’s genetic test, (II) the genetic tests of family members of [an] individual.”
- Genetic test is defined as, “An analysis of human DNA, RNA, chromosomes, proteins, or metabolites, that detects genotypes, mutations, or chromosomal changes.”
- Genetic tests do NOT include, “(I) … analysis of proteins or metabolites that does not detect genotypes, mutations, chromosomal changes; or (II) an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition that could reasonably be detected by a health care professional with appropriate training and expertise in the field of medicine involved.”
- “Manifested disease,” while mentioned many times throughout GINA, was never specifically defined [10, 39].

7. GENETIC EXCEPTIONALISM

According to Rothstein, with the genomic revolution legislators had three options regarding genetic discrimination: (I) ignore the issue within legislation; (II) establish legislation to limit how all health information is used and disclosed; or (III) provide legislation that treats the use and dissemination of genetic information differently from all other types of health information [40]. The recent passage of GINA shows that U.S. lawmakers have opted for the third. Perhaps legislators, like other individuals, truly believe genetic information is special since it is predictive and, for the sake of argument, immutable. This belief is likely a large contributor since it has been continually substantiated in pro-GINA literature [25-26, 35, 41]. Or possibly, legislators opted to take the path of least resistance, assuming that some protections would be more beneficial than none [40].

These and other justifications for GINA are grounded in genetic exceptionalism, or the ideology that genetic information is somehow special relative to other forms of medical information. However, not all support this ideology, or agree that offering some protection is better than offering none at all. Genetic nondiscrimination legislation is capable of placing unequal financial burden on those in the health insurance market who are pre-symptomatic or even symptomatic for diseases that are either not genetic or have yet to be attributed to specific
genetic underpinnings [42]. If Americans are being divided into different risk pools based on GINA (genetic and non-genetic), the non-genetic risk pool may experience the brunt of medical expenses reflected in higher premiums and denied coverage [42, 43]. Opponents of GINA now fear that health insurers prohibited from using genetic information will opt to have more stringent coverage criteria for other types of health information. This has been a reported consequence of some European nondiscrimination laws [43-44]. So while legislators may be justified in fearing economic backlash by outlawing underwriting based on broader forms of health information, protecting only genetic information is not necessarily benign to its non-genetic counterparts. It must be stated that this is currently speculative, and how much influence GINA will actually have on the insurance market is relatively unknown. Nonetheless, it is important for legislators, patients, and health providers alike to acknowledge that the vast majority of factors that determine health status are not necessarily under an individual’s control, making it unjustifiable to burden one group with the health costs of another [42].

Other individuals shy away from economics and instead question the effectiveness of genetic nondiscrimination legislation by attacking the basic premises of genetic exceptionalism. When analyzed with more scrutiny, arguments for genetic exceptionalism are a variation of two central themes: (1) genetic information can predict future health status; and (2) genetic information is heritable. However, other factors both biological and socioeconomic are also highly predictive of future health status. Families without health insurance or with lower incomes are more prone to adverse health conditions [40]. It is important to mention children, as they have no legitimate control over whether or not they have health insurance just as they cannot control their genotype.

Furthermore, insurers are still allowed to underwrite on the results of routine analyses such as cholesterol tests [45]. While the genetic basis of cholesterol levels are not as well understood as says BRCA1/2-related hereditary breast cancer or HD, researchers have still identified biomarkers, both genetic and non-genetic, that identify individuals at an increased risk of obesity [46-48]. As scientists continually link diseases and health conditions to genetic factors of varying penetrance, the distinction between genetic and non-genetic starts to become lost. Especially when using such a scientifically unintelligible dichotomy, it is incredibly difficult to morally argue that discrimination against various forms of medical information is acceptable as long as it is not “genetic” [39].

8. GENE EXPRESSION IS HERITABLE

U.S. legislators have constructed definitions of “genetic information” and “genetic test” that certainly reside in scientifically murky waters, which is perhaps best exemplified by looking at gene expression. As mentioned previously, gene expression is an intermediate phenotype that reflects interactions between genetic structure and the environment, and may arguably be the closest biological process to genotypes while still remaining a phenotype. The differences in these categorical definitions does not mean these expression phenotypes and genotypes do not share properties. Through GWA studies researchers have found many single nucleotide polymorphisms (SNPs), or in essence, genotypic mutations, that are highly correlated with expression levels of certain genes [49-50]. Some studies have noted that expression variation in a substantial number of genes can be mapped to genomic regions or quantitative trait loci, which infers that genotypic alterations in that region may be causing the observed phenotype [51-53]. Such studies are called expression quantitative trait loci (eQTL) mapping [50]. Multiple investigations of eQTLs have shown they can be highly heritable [8, 50, and 53].

It should be said that GINA protects any analysis of RNA that can detects genotypic alterations. However, will GINA protect associations that are not as unambiguous as specific DNA alterations casually connected to phenotypes like in the case of HD? Using eQTLs in conjunction with disease association studies can connect assortments of SNPs (haplotypes) and expression levels of particular genes with disease. The major caveat that must be recognized is that these are associations that often uncover candidate non-coding regions containing many SNPs and the specific SNP(s) or genotypic variant(s) that drives the increased risk of developing a pathological phenotype is unknown [50]. This proposes questions about how such studies could be misused to stratify and discriminate against risk groups. If comprehensive disease association and eQTL studies use gene expression to identify candidate genotypic variants increasing the risk of disease for certain population of individuals, would it eventually
be possible to infer that certain gene expression levels on average are indicative of disease predisposition in that population, and can subsequently be used in place of genetic markers? Since expression levels are currently not considered genetic information and causal variants cannot always be identified from these studies, it is difficult to say if GINA would protect against these practices. Perhaps these concerns are purely speculative and will not come to fruition. Regardless, with the rapid advancement of scientific knowledge and creation of large publicly accessible GWA and eQTL databases [8], these potential scenarios need to be acknowledged and addressed. Whether GINA will protect against potential misuse of eQTL disease association studies or not, the implications of expression analyses are clear. Gene expression is often a heritable trait but is offered no legislative sanctuary under GINA.

9. GENE EXPRESSION IS PREDICTIVE

While gene expression can be heritable and used in conjunction with genetic variants to identify disease risk, it can also be used solitarily to predict risk, onset, progression, and recurrence of disease [18-23, 54]. Due to this predictive nature, these assays inherit the same ethical dilemmas carried by any genotyping assay predicting the future risk of acquiring a currently latent disease. Yet under GINA, assays evaluating expression signatures of malignancies are not covered since expression doesn’t detect a genotype and cancer being “manifest” presupposes an individual’s qualification for the assay. Underwriters may then consider recurrence when establishing policies or adjusting patients’ premiums. Take for example three women eligible for Oncotype DX, which again provides a recurrence score (RS) that predicts the likelihood of relapse within 10 years in lymph-node negative, estrogen receptor positive breast cancer. Patient one chose not to undergo the Oncotype DX assay. Patient two’s results had a low RS indicating relapse is less probable. The third patient had a high RS predicting significant risk for breast cancer relapse. This information was used complementarily with other factors to establish a therapeutic plan. All three women decided full treatment including aggressive chemotherapy, which was successful, and all were in remission within one year. Health insurers must now make post-treatment coverage decisions for all of these patients. Patient one will likely obtain coverage as any breast cancer patient would prior to the implementation of Oncotype DX. The second individual would likely be treated much like patient one due to her low RS value. The most interesting scenario lies with patient three. At this juncture it is difficult to determine her coverage relative to the other patients. Nevertheless, due to her increased risk for relapse, she may be prone to face increased premiums, reduced coverage or to be denied coverage altogether.

Regarding predictability, these affairs are hardly different from those encountered by sheltered genetic information. One might argue that GINA should not harbor expression assays since they often pertain to manifested diseases as is the case with cancer recurrence prediction. However, manifest disease, even when ignoring the dubious dichotomy it seeks to fabricate, becomes irrelevant to this conundrum as recent findings suggest expression can predict risk in asymptomatic patients [22-23]. If left unaddressed, these emerging scenarios regarding phenotypic assays in disease prediction, prevention and personalized medicine could deter public health and scientific development as much if not more than genotypic information.

10. DISCUSSION

Despite that some of these concerns are only associative to GINA and the U.S., the underlying issues that have created a detachment between legislation and science and lead to GINA’s passing are far less ethnocentric. Both Australia and the United Kingdom have reported cases of genetic discrimination with Australia’s experience being with health insurance and employment and the United Kingdom’s with life insurance [55-56]. Many European countries have also established genetic nondiscrimination laws, but they are not without their respective imperfections [43]. In some cases, poor definitions of “genetic” and “genetic test” have allowed insurers to continue using genotypes in their underwriting practices [43, 57]. Due to their lacking effectiveness, many of these laws have failed to alleviate discriminatory fears [43, 58]. Recently, the German Federal Parliament has passed the Human Genetic Examination Act [59]. Unlike GINA, this enactment includes protections for diagnostic and predictive genetic analyses. It also adds regulation to frequently cited ethical issues surrounding new-age genetics such as
direct-to-consumer testing by requiring facilities to obtain accreditation in order to perform any genetic test [59]. However, like GINA and other predecessors, its definition of “genetic analysis” is limited in scope and may encounter difficulties now as well as when further advancements in medical science are attained.

Unfortunately, GINA’s definitional obstacles are not limited to “genetic” terms. Failing to effectively define “manifest disease” has further convoluted what information will be safeguarded. It seems as if legislators treated disease in the same binary fashion as genotypes. However, disease is not a simple on or off switch. Determining whether or not symptomatic individuals can be considered as having “manifest disease” can be quite arbitrary. Some have even suggested that disease is, in essence, indefinable [60]. Disease should be recognized in a manner that truly represents its pathology, and that is a continuum. While it is desirable, especially when attempting to establish legislation, to stamp a condition as present or absent, current discoveries in biology and medicine are making these distinctions decisively blurry if not absent altogether.

Genetic nondiscrimination legislation has been widely supported for its proposed ability to complement new and revolutionary scientific discoveries. While few would disagree that at certain places on this continuum we can definitively state whether or not an individual is afflicted with a disease, attempting to define the exact point where a disease becomes manifest is counterintuitive to evidence currently being generated by medical science. In the absence of legislation such an argument would likely be irrelevant or have no true utility. However, given that GINA’s implied definition of “manifest disease” is in many ways an arbitrary concept, it follows that it will be legally permissible to discriminate against individuals on arbitrary grounds. Most importantly, this legislation might cause a quintessential “passing of the buck” with regards to which tests patients will avoid. GINA has been frequently cited as legislation that will allow U.S. citizens to discover if they are at risk for a condition and subsequently implement preventative measures. Intriguingly, many new and old diagnostics incorporate the same promise, but are not accompanied by the protected term “genetic.” Prior to GINA individuals not only feared genetic information, but also other sources of information that could propagate discriminatory backlash [61-62]. In this post-GINA climate, patient behaviors with regards to new non-genetic prognostic tests will help determine if patients’ accumulating fears are a result of discrimination based on genetics or simply discrimination derived from prediction.

The aforementioned misconceptions about so-called unique genotypic properties likely emanate from genetic determinism [40, 61], or the idea that genotypes have complete influence over phenotypes. Though this phenomenon has long been rejected by mainstream science, remnants of its ideologies circulate throughout society. While completely and highly penetrant genetic disorders exist, providing legislation that protects only genotypic information and not other health variables may only serve to reinforce fallacious beliefs about both genetic exceptionalism and determinism. It is important to educate people on the intricate interplay between genotypes and the environment, especially when environmental factors can influence the onset of completely penetrant disorders such as HD [63-64].

Simply stated, genotypes alone are often not enough to either construct firm diagnoses or make accurate predictions about future health status. In oncology, gene expression studies demonstrate that even in cases of known gene fusions and chromosomal translocations there is great heterogeneity on the expression phenotype as measured by mRNA levels that is in some part due to the cancer microenvironment [65]. This link between the cancer microenvironment and the gene signature is often more predictive of treatment and disease outcome than the genetic predisposition itself [66-67]. We expect that as gene expression signatures become widespread they will be used in place of the genetic markers as the signatures essentially report the outcome of the interactions of the environment with the genetic machinery. Quandary certainly has and will continue to arise from this type of information as clinical outcome has roots in both the genetic abnormality and the environmental influence. Protecting only genotypes will become increasingly difficult to justify if a preponderance phenotypic markers continue to show significant predictive value independent of or complementary to genotypes. Perhaps more research will swing the prognostic value in favor of genotypes. Considering its inability to account for environmental interactions, whether at the macroscopic or microscopic level, it is the belief of these authors that it will not.
While we have presented arguments against legislative efforts that potentiate genetic exceptionalism, we are not suggesting apathy towards genetic discrimination. Genetic discrimination does pose a potential harm to individuals; however, it is our belief, and the belief of others [40, 61, 68], that this threat is no greater for genetic information than other forms of health information. Tests and information should be regulated in the absence of genetic exceptionalism. Some have proposed defining a genetic test as one that can identify predispositions to future disease and can be passed from parent to child, regardless of whether or not it directly insinuates a genotype [68]. Excluding the passing infectious agents such as HIV from mothers to children, such a definition more accurately reflects current scientific knowledge and would subsequently include a broader range of predictive markers, including gene expression. When investigating potential harms stemming from a predictive test, instead of using intangible “genetic” and “non-genetic” designations Green and Botkin suggest evaluating four categories: “(1) the degree to which information learned from the test can be stigmatizing; (2) the effect of test results on others; (3) the availability of effective interventions to alter the natural course predicted by this information; and (4) the complexity involved in interpreting test results” [68]. Utilizing these definitions when constructing nondiscrimination legislation would prevent adverse consequences for non-genotypic conditions and promote scientific accuracy and advancement by including provisions that foster predictive phenotypes.

In this article, we have provided potential harms of using genetic exceptionalism to guide nondiscrimination health law. Using gene expression, we have provided specific examples where phenotypes are both heritable and predictive, and can often predict more information in a greater number of disease contexts than genotypes. Commonalities between phenotypes and genotypes cause gene expression assays to have many of the putative harms surrounding genetic testing without any of the legal protections. Importantly, GINA is not necessarily neutral as it could shift health insurance market forces similarly to what was evoked by some European nondiscrimination laws [43-44]. If GINA causes individuals exhibiting non-genetic predictive markers to bear the costs of those with genetic markers, patients may then avoid predictive phenotypic tests such as gene expression.

Furthermore, we contested the idea of “manifest disease” as it currently implied in GINA and proposed that disease be more accurately viewed as a continuum rather than binary. Due to its dynamic predictive power, we postulate that expression profiling will be used to monitor various diseases all along this continuum and will be of greater overall utility than genotypes. Both the scientific endeavors and the process of crafting legislation must take into serious consideration the complex interaction between the cellular environment and the genetic predispositions to disease to yield improved diagnosis and prognosis of disease states. As its clinical validity increases, health policy must follow to assure individuals they will not be punished for adopting scientific advances such as gene expression to improve their health.

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