The problems of liminal states, line drawing, and false dichotomies

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ABSTRACT

This commentary focuses on the tenuous line between health and disease and the conflicting characterizations of genetic predisposition that sometimes place it on one side of that line, and sometimes on the other. For example, GINA uses the line between health and disease to distinguish between, respectively, the healthy (including, those with genetic predispositions), who are shielded from discrimination, and those with 'manifested illness,' who are not. At the same time, some have argued that the Americans with Disabilities Act protects individuals with genetic predispositions, relying on a label akin to disability, as opposed to health, to characterize this group. Similarly, courts have described genetic predisposition as a disease of sorts to justify insurance payment for medical intervention. Attempts to fit genetic predisposition neatly into the binary world of health or illness can be problematic because this dichotomy doesn't capture the complex continuum between those states. Some individuals reside in yet another 'liminal' state when they develop mild symptoms or biomarkers, placing them somewhere between genetic predisposition and actual disease manifestation. As a result, they may be unprotected under existing frameworks. Liminal states are therefore problematic not only with respect to insurance reimbursement, but in other areas as well.

KEYWORDS: genetic testing, prevention, insurance discrimination, employment discrimination, pre-disposition

Prevention for Those Who Can Pay nicely describes the tenuous line insurers draw between prevention and treatment and how this can limit coverage for preventive care for individuals with genetic pre-dispositions—those 'in the liminal state between health
As commentators and policymakers promote precision medicine and genetic analysis as valuable tools to improve health, they emphasize the preventive value of learning about genetic risks. Prince persuasively shows, however, that the false dichotomy between prevention and treatment and between health and disease results in significant limitations in the current system of insurance reimbursement for preventive care associated with genetic pre-dispositions. Since insurance coverage is the key to health care access for many people, these barriers to insurance reimbursement are deeply problematic. Prince rightly notes that learning about a genetic pre-disposition without having access to preventive care not only eliminates the benefits of obtaining information about risk factors associated with preventable conditions, but also can lead to affirmative psychosocial harms.

Prince’s focus on the liminal states between health (prevention) and disease (treatment) in the context of insurance coverage of preventive care is a far too overlooked reality. Yet the complications that arise when systems impose this binary structure in the context of clinical genetics are not new and have been at the root of many issues surrounding genetic analysis. In efforts to maximize the benefits of genetic testing while minimizing the collateral harms, policymakers have struggled to describe what it means to have an identified genetic mutation in terms of this binary structure. Concerns about the possibility of discrimination on the basis of genetic risk have led some to characterize genetic pre-disposition as lying on one side of the tenuous line between health and disease and sometimes on the other.

The first approach stems from the argument that is unjust to treat individuals who are merely pre-disposed to a particular illness as if they were actually ill. Working within the binary structure of health and disease, the common theme has been that individuals with genetic pre-dispositions lie on the side of health, as opposed to disease, and therefore should be treated in the context of insurance and employment like individuals who are not ill. Many state non-discrimination laws as well as the federal Genetic Information Nondiscrimination Act (‘GINA’) quite explicitly use the line between health and disease to distinguish between, respectively, the healthy (including those with genetic pre-dispositions), who are shielded from discrimination, and those with disease manifestation, who are not.

At the same time, motivated by similar concerns about genetic discrimination in employment, some, including the US Equal Employment Opportunity Commission (‘EEOC’) have argued that the Americans with Disabilities Act (‘ADA’) should be

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1 Anya E.R. Prince, Prevention for Those Who Can Pay: Insurance Reimbursement of Genetic-Based Preventive Interventions in the Liminal State Between Health and Disease, 1 J. Law Biosci. 365 (2015).
2 See eg Francis Collins, The Language of Life: DNA and the Revolution in Personalized Medicine (2010); Leroy Hood & Stephen H. Friend, Predictive, Personalized, Preventive, Participatory (P4) Cancer Medicine, 8 Nat. Rev. Clin. Oncol. 184, 184 (2011). Even the President shares hopes in his budgetary plan to allocate ‘hundreds of millions of dollars for a new initiative to develop medical treatments tailored to genetic and other characteristics of individual patients’. Robert Pear, Obama to Request Funding for Treatments Tailored to Patient’s DNA, NEW YORK TIMES, Jan. 24, 2015.
3 Prince, supra note 1, at 367, 387.
4 See 29 U.S.C. § 1182(a)(3)(B) (2008); 42 U.S.C. § 2000ff-9 (2008); Sonia M. Suter, The Allure and Peril of Genetic Exceptionalism: Do We Need Special Genetics Legislation, 79 WASH. UNIV. LAW Q. 669, 711 (2001) (describing state legislation that limits protections to ‘asymptomatic, predictive, or predisposing genetic information’).
read to protect individuals with genetic pre-dispositions.5 This claim, however, relies on characterizing the liminal state of genetic pre-disposition as something akin to disability, as opposed to health. Admittedly the ADA does not just protect those who are ‘actually’ disabled. In its definition of disability, the statute includes not only those with an ‘impairment that substantially limits’ a major life activity, but also those who have ‘a record of’ or are ‘regarded as having such an impairment’.6 Even so, the argument that an employment disability law should be read to protect individuals with genetic pre-dispositions places genetic risk closer to the side of disease than health.7 Rather than emphasize how someone with a genetic pre-disposition is like a healthy person, these efforts align the pre-disposed individual with the protected class of disabled individuals. In other words, the strategy to protect against discrimination in this context forces an interpretation away from the health side of the binary structure.

Similarly, to justify insurance payment for medical intervention, some courts have described genetic pre-disposition as a disease. In Katskee v. Blue Cross/Blue Shield, for example, the Nebraska Supreme Court addressed the question that Prince takes on—whether an insurer should pay for preventive care.8 Based on her family history, Katskee had been diagnosed with ‘breast–ovarian carcinoma syndrome’, which gave her ‘at least a 50-percent chance of developing breast and/or ovarian cancer’.9 As a result, her physician recommended prophylactic surgery (hysterectomy and bilateral salpingo-oopherectomy). The insurer, Blue Cross/Blue Shield, argued, however, that such treatment was not covered under the policy because Katskee did not have a bodily illness or disease and therefore the treatment was not medically necessary. At issue, therefore, was whether someone with a pre-disposition to cancer should be treated as healthy or ill. The court ultimately concluded that even though she was merely pre-disposed to breast/ovarian cancer, Katskee’s ‘physical state ... significantly deviate[d] from the physical state of a normal, healthy woman’ because of ‘a different or abnormal genetic constitution’ and therefore her condition ‘constitute[d] an illness within the meaning of the policy’.10

These examples illustrate how uneasily genetic pre-disposition rests on the tenuous line that divides health and disease. When the structure is set up to benefit those who are healthy, the tendency is to characterize this state as healthy. When the protections benefit those with illness or disability, however, the incentives cut the other way. This

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5 See 2 U.S. EEOC Compl. Man., Order 915,002, at 902, 945 (1995). But note the caveats discussed below.
6 42 U.S.C. § 12102 (2) (1990).
7 See Suter, supra note 4 at 746 n.405 (noting that this approach “labels” genetic and other predictive information as a disability’).
8 515 N.W.2d 645 (Neb. 1994).
9 Id. at 647. At the time, genes associated with inherited forms of breast and ovarian cancer had not yet been identified. As a result, the diagnosis was based entirely on family history. Id. at 651 (noting that there was ‘no conclusive physical test ... which would demonstrate the presence of the condition’).
10 Id. at 652, 653. The court makes a leap in assuming the presence of genetic changes related to breast and ovarian cancer in Ms. Katskee. Noting that the ‘hereditary occurrence of this form of cancer is related to the genetic makeup of the woman’, the court reasons that ‘genetic deviation has conferred changes which are manifest in the individual’s body and at some time become capable of being diagnosed’. Id. at 651. It is likely that her family history was based on a gene in affected relatives that conferred a strong predisposition to cancer, like the BRCA genes. Without analyzing her genes, however, there was only a 50% chance that Ms. Katskee had actually inherited the predisposing gene. If she hadn’t inherited it, however, she would not have had the kind of ‘genetic deviations’ (at least with respect to breast and ovarian cancer) to which the court referred.
tension reflects the fact that our social structures, laws, and insurance reimbursement system, as Prince shows, presume a binary world of either health or disease, when in fact there is a complex continuum between health and disease, with genetic pre-disposition lying somewhere within that continuum.

Of course, as Prince notes and has noted in prior work, the characterization problem is even more complicated because various states can exist between health and illness besides just genetic predisposition. Policy makers have focused on the vulnerabilities of those whose predisposition to disease is detectable through genetic tests. There are, however, other asymptomatic individuals who may have indications of predisposition based on non-genetic tests. Whether the disease will ultimately manifest in either category of individuals depends on other genes and environmental factors. Genes can be altered through methylation (epigenetics), which can affect gene expression. Environmental factors and other genes can affect epigenetics, RNA expression, as well as protein and metabolite levels, all of which may play a role as to whether disease will ultimately manifest. Predisposed individuals who ultimately become ill do not simply go from being presymptomatic one day to ill the next. Instead, the path from predisposition to illness is usually gradual and may involve a variety of changes at the cellular and molecular level that will slowly accumulate and intensify until they have full-blown symptoms.

What this means is that some individuals with genetic predispositions may begin to develop mild symptoms or biomarkers, which can increasingly be detected via advances in transcriptomics, proteomics, and metabonomics. In other words, other tests—which are not precisely speaking ‘genetic’ tests—may indicate that an individual has started down the path from pre-disposition toward disease. These individuals may not have sufficient symptoms to be deemed ill, and they may never ultimately reach the disease state, but the presence of these symptoms makes them potentially something more than merely pre-disposed to the condition. The continuum from health to disease therefore includes pre-disposition and ‘pre-disease’. Genetic pre-disposition is one liminal state and pre-disease is another.

While Prince’s focus in this piece is on the way liminal states between health and disease create problems for insurance reimbursement, they present problems in other contexts. Even though genetic pre-disposition sits precariously on the line between health and disease, policy makers have recognized it as a distinct state with respect to discrimination (even if they try to align it sometimes with health and other times with disease). The second liminal state—between pre-disposition and disease—however, is rarely included in these policy efforts. As scholars (including Prince) have noted, individuals with identifiable changes at the RNA, protein, or epigenetic level may not be protected from discrimination in the way that those with pre-dispositions based on genetic tests

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11 Prince, supra note 1, at 370; Anya E.R. Prince & Benjamin E. Berkman, When Does Illness Begin: Genetic Discrimination and Disease Manifestation, 40 J. L. Med. ETHICS 655, 657 (2012) (noting ‘the continuum from genetic predisposition to manifested symptoms’); see also Mark A. Rothstein, GINA, the ADA and Genetic Discrimination in Employment, 36 J. L. Med. ETHICS 837, 838 (2008) (describing ‘the continuum from genotype to expressed disease’).

12 See generally Eric D. Green et al., Charting a Course for Genomic Medicine from Base Pairs to Bedside, 470 NATURE 204 (2011).

13 Rothstein, supra note 11, at 839.

14 Prince, supra note 1, at 370.
are.\textsuperscript{15} They are not ‘well’ enough to be treated as healthy and not ‘ill’ enough to receive disability protection.

The GINA approach, for example, protects against discrimination based on genetic information for asymptomatic individuals, but not for those with manifested disease, even if they both have genetic mutations. Although the statute itself did not offer a definition of disease manifestation, the Department of Health and Human Services (‘DHHS’) and EEOC regulations, provide, however, that

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manifestation or manifested means, with respect to a disease, disorder, or pathological condition, that an individual has been or could reasonably be diagnosed with the disease, disorder, or pathological condition by a health care professional with appropriate training and expertise in the field of medicine involved. For purposes of this subchapter, a disease, disorder, or pathological condition is not manifested if the diagnosis is based principally on genetic information.\textsuperscript{16}
\end{quote}

In other words, the protections are based on changes at the DNA, genetic level and seem to exclude protection for people with only mild symptoms or certain identifiable biomarkers associated with pre-disposition.

Under the ADA approach, however, even though some have tried to argue that those with genetic pre-dispositions should be protected under the ‘being regarded as having … an impairment’ prong,\textsuperscript{17} commentators are skeptical that courts would ultimately interpret the provision in that way.\textsuperscript{18} If they are right, individuals in this liminal state between pre-disposition and disease would not be protected under the ADA because such a state would not constitute ‘a substantial limitation of a major life activity’.

The upshot is that the inattentiveness to this other liminal state creates a potential gap or, to use Prince’s phrase from another piece, a ‘doughnut hole’ in protection against genetic discrimination.\textsuperscript{19} Prevention for Those Who Can Pay, therefore, is a continuation of Prince’s earlier work in showing the deficiencies of the binary framework of illness and health. Such a construct falsely suggests that we can easily determine whether we are on the disease or health side of the dividing line. But it also creates inequities for individuals who are very similarly situated: Under the EEOC’s and DHHS regulations’ definition of ‘manifested’ illness, a person with a genetic pre-disposition and no outward symptoms would be protected under GINA, whereas a person with a genetic pre-disposition, no outward symptoms, and an identified biomarker would not. This means that once someone finds out they have a genetic pre-disposition, they could move from protected to unprotected status simply by undergoing a ‘non-genetic’ test that indicated the presence of biomarkers. Prince therefore argues for a broader definition of manifested illness that would protect this second group as well.\textsuperscript{20}

While she is right that there are challenges with the regulations’ current definition of manifested illness, the underlying problem is the effort to draw such sharp and tidy lines between health and disease \textit{and} between genetic and non-genetic information when

\begin{footnotes}
\item[15] Prince & Berkman, \textit{supra} note 11, at 657; Rothstein, \textit{supra} note 11, at 839.
\item[16] 45 C.F.R. § 160.103 (2013); 29 C.F.R. § 1635.3 (g) (2010).
\item[17] See text accompanying notes 5, 7.
\item[18] Prince & Berkman, \textit{supra} note 11, at 657; Rothstein, \textit{supra} note 11, at 839.
\item[19] Prince & Berkman, \textit{supra} note 11, at 657; see also Rothstein, \textit{supra} note 11, at 839.
\item[20] Prince & Berkman, \textit{supra} note 11, at 661.
\end{footnotes}
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health states and health information exist on a continuum. Broadening the definition of manifested illness does not change the fact that the GINA model attempts to distinguish not only between health and disease but also between genetic and non-genetic information. These distinctions, as I and others have argued, are hard to sustain and ultimately inequitable.  

With respect to health insurance discrimination, at least, the Patient Protection and Affordable Care Act has eliminated these problematic dichotomies by prohibiting health insurers from discriminating based on pre-existing conditions. In other words, the ability to obtain health insurance is not based on health or illness or genetic or non-genetic risks. If one is to be intellectually consistent, the arguments against genetic discrimination in insurance inevitably argue for access to health insurance irrespective of risk, whether one is at risk of colon cancer because of a genetic mutation, whether one is at risk of colon cancer because of large adenomatous polyps, or whether one actually has colon cancer.

The false dichotomies, however, still exist with respect to employment nondiscrimination where those who are pre-disposed based on polyps would not be protected by GINA or the ADA, but those with a genetic mutation would be protected by the former and those with cancer would be protected by the latter. And yet the spirit of both GINA and the ADA is to protect the ability of people to have access to employment if they are ‘otherwise qualified’. This should apply whether you have a genetic mutation, a biomarker, or cancer itself.

In the context of insurance reimbursement, Prince tries to break down the dichotomy between prevention and treatment with respect to genetics. While her call to mandate insurance coverage for predictive genetic testing and medically appropriate follow-up interventions is much needed, it runs the risk of reinforcing the genetic/non-genetic dichotomy. Instead, her arguments should be part of a broader effort that attempts to ensure that insurance reimbursement allows individuals to reap the full benefits of predictive assessment writ large, not just in genetics. Not only should we urge policy makers to find value in genetic predictive testing and intervention as opposed to just treatment, we should urge them to find value in other forms of pre-disease and pre-disposition assessments. In short, the goal is to find ways to encourage people to gather information to learn about health risk and to engage in preventive care without causing them psychosocial harms. One way to do that is to avoid drawing lines that lead to false dichotomies.

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21 See eg Suter, supra note 4; Mark Rothstein, Genetic Exceptionalism and Legislative Pragmatism, 35 Hastings Ctr. Rep. 27 (2005).
22 Patient Protection and Affordable Care Act, Public Law 111, 148 (2010).
23 See Suter, supra note 4; Rothstein, supra note 21.
24 See Russell Korobkin & Rahul Rajkumar, The Genetic Information Nondiscrimination Act—A Half-Step Toward Risk Sharing, 359 New Eng. J. Med. 335, 335 (2008) (suggesting the inequities in only protecting some of these individuals from discrimination).