

What is a genetic test, and why does it matter?

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How the term 'genetic test' is defined, matters for social policy. The past few years have witnessed many efforts to enact legal barriers specifically against genetic discrimination. To the extent that information derived from genetic tests receives special protection, both enthusiasts for genetic medicine and those who stress its perils have an incentive to adopt a broad interpretation of genetic testing. However, the consequences have not always been those anticipated.

Genetic testing is the subject of much popular and scholarly commentary. But what exactly is a 'genetic test'? As with the allied terms 'genetic characteristic' and 'genetic information', there is no agreed-upon definition¹. The term 'genetic test' is used in a bewildering variety of ways. It may be restricted to tests for conditions that are inherited, or that have a clinical purpose, or that involve the analysis of genes and chromosomes. But it may also encompass non-heritable cancers, or non-clinical purposes (such as DNA profiling), or the analysis of proteins or other gene products^{2,3}. This terminological tangle in part reflects the fact that where to draw the line between genetic and other medical tests is not simply a technical matter. There are complex and subtle political interests involved. A consideration of the history of the first 'genetic test' – for the recessively-inherited metabolic disorder phenylketonuria (PKU) – illuminates some of these interests.

How the test for PKU became a genetic test

Individuals affected with PKU lack a liver enzyme that is necessary to metabolize phenylalanine, an essential amino acid found in all dietary proteins. If untreated, the phenylalanine accumulates in the blood and tissues, usually resulting in severe cognitive and psycho-social deficits. However, if the condition is detected at birth, infants can be placed on a special diet which, although onerous, prevents the worse consequences of the disease. Since the mid-1960s, newborns in Britain and the USA have been routinely tested for PKU; today, screening programs are nearly universal (Figure 1).

The PKU control program has become an exemplar for genetic medicine in general, and genetic testing in particular. Advocates of other screening programs frequently trade on its success⁴. However, when screening began in the 1960s, PKU was thought of simply as a treatable form of mental retardation. The etiology of the disease was not considered important. Indeed, the fact that PKU was a genetic disease received virtually no attention in state legislative hearings, nor was it mentioned in any of the statutes establishing newborn screening programs⁵. While the test does incidentally provide genetic information that may be relevant to reproduction, its primary aim has always been the identification of affected newborns for the purposes of treatment. Moreover, the 'Guthrie' test used to diagnose the disease is a bacterial inhibition assay, not a DNA-based test.

But characterizing the Guthrie test as a genetic test serves several interests. It has become

a truism that our ability to diagnose genetic diseases has vastly exceeded our ability to treat them effectively. A definition of genetic testing that is broad enough to include the test for PKU narrows this 'therapeutic gap'. It thus provides a rejoinder to critics of genetic testing, whether they are motivated by opposition to abortion or by concern that attention is being deflected from environmental causes and cures for disease. However, because genetic tests are subject to greater scrutiny and regulation than other medical tests, an inclusive definition appeals not only to enthusiasts for genetic medicine, but also to individuals with concerns about the safety and utility of tests and their broader social consequences.

Impact of the human genome project

Developments in genomics, and especially the Human Genome Project (HGP), have focused both scholarly and media attention on social and ethical issues in genetic testing. In the

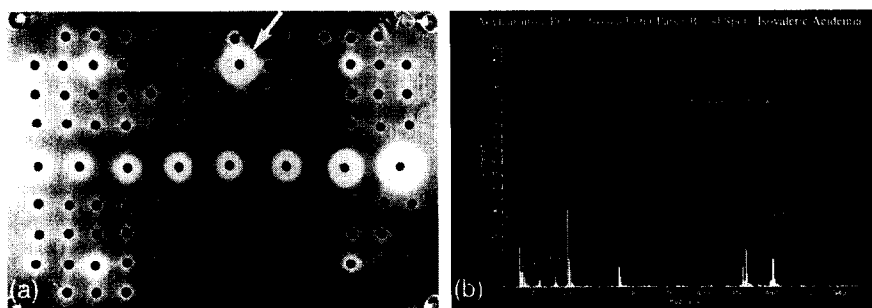


Figure 1 By 1970, infants in developed countries routinely were tested for a small number of metabolic disorders, using bacterial inhibition assays or so-called Guthrie tests. PKU affects about 1 in 10 000 ethnic Northern Europeans and is caused by mutations in the enzyme phenylalanine hydroxylase (PAH). There is a range of similar rare metabolic disorders, and a different bacterial test is used for each. The principle behind the test is that the presence of high levels of a metabolite in the blood inhibit the growth of a specific strain of co-cultured bacterium, and a positive result is detected by a clear ring around the blood sample spot (a). Optimal results are obtained from samples taken 48–72 h after birth, when the characteristic metabolite has had time to accumulate to measurable levels. The accuracy of this test is compromised by early discharge of newborns from hospital. The introduction of a highly sensitive tandem mass spectrometry technique (MS/MS) to measure metabolites in blood samples within 24 h of birth overcomes this problem (b). Although MS/MS has potential advantages over traditional screening methods, it has also prompted concerns that the technology will be used to test for conditions that are untreatable and/or poorly understood, and may result in an increase in false-positive results. While the Guthrie tests and the MS/MS technique detect genetic disorders, they are not in themselves DNA tests³².

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USA, the Ethical, Legal and Social Issues (ELSI) program of the genome project has funded numerous conferences and research projects, one of which resulted in an influential model Genetic Privacy Act, and created both a Task Force on Genetic Testing and a Task Force on Genetic Information⁶. In the UK, where potential dangers from genetic testing have also received extensive media coverage, both an Advisory Commission on Genetic Testing and a Human Genetics Advisory Commission (HGAC) were established. Thus, genetic tests tend to be intensively scrutinized – at least relative to other medical tests⁷. It is notable that there have been well-publicized committees created to advise on genetic testing – but no comparable committees on other medical testing.

The aim of raising standards in respect to the quality of medical tests, and ensuring their appropriate use in clinical practice, is thus served by expansive interpretations of genetic testing. This point was recently brought home to me when I was commissioned to write a background report on the history of newborn screening for the Task Force on Genetic Testing. My draft included an aside to the effect that newborn screening does not specifically involve genetic technology. Some members of the committee were upset, for the comments had unwittingly strengthened the hands of those arguing for less government oversight. If the test were not 'genetic', it would fall outside the committee's purview.

The wider social consequences of genetic testing – especially the prospect of what has come to be called 'genetic discrimination' – have also been the subject of countless studies, reports, position papers and declarations, which usually condemn the discriminatory use of genetic information. For example, the United Nations' (UN) Universal Declaration on the Human Genome and Human Rights proclaims that, 'no one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity'⁸, while the Council of Ministers of the Council of Europe Convention on Human Rights and Biomedicine has condemned 'any form of discrimination against a person on grounds of his or her genetic heritage'⁹.

Some of these efforts have obviously been vacuous, and many others have been defeated. In the UK, where concern focuses primarily on discrimination in life insurance and employment, the HGAC recommendation of a two-year moratorium on genetic testing for insurance purposes was rejected by the government¹⁰. In the USA, numerous efforts to pass federal antidiscrimination laws have failed, and the two existing laws that directly or indirectly address the issue [the American with Disabilities Act (ADA) and the Health Insurance Portability and Accountability Act (HIPAA)], are riddled with loopholes. While activity at the state level has been intense – in 1997, over 150 bills were filed in state legislatures, and at least 31 states have enacted some kind of genetic discrimination law – the

scope and degree of protection afforded is also minimal^{11,12}. Indeed, Philip Reilly concludes that state antidiscrimination statutes are most relevant to the small and declining fraction of individuals (10–15%) who purchase individual health insurance, a segment of the population that is also relatively well-off¹³.

Converging interests

Insurers have an obvious interest in opposing or weakening anti-discrimination legislation, but who has an interest in promoting such legislation? Advocates of course include politicians and reporters, but also researchers, clinicians and entrepreneurs. That is because barring discrimination would remove a roadblock to research and to its clinical and commercial applications.

Far fewer people than anticipated have made use of genetic tests¹⁴. The low uptake is partly a reflection of the tests' uncertain value. Since nearly all 'genetic diseases' involve complex and little-understood interactions among genes and between genes and environment, their predictive value is generally low. That is why few insurers or employers currently use them. Moreover, uptake is affected by the availability of methods to prevent or treat the condition, and many predictive tests have little benefit beyond providing information on risk¹⁵.

But another factor in the low uptake of genetic testing is fear that information derived from these tests will be used against individuals and their children. Mark Rothstein notes that genome scientists, entrepreneurs and members of the public all demand that the confidentiality problem be fixed immediately to eliminate barriers to testing¹⁶. Surveys show that most people say they will not have genetic tests if the results are made available to insurers or employers¹⁷. This attitude is naturally a matter of concern to companies with large investments in the development and marketing of tests (such as those for colon and breast cancer susceptibility genes), which so far have been used by only a small fraction of the potential candidates.

It has also been a matter of concern to genetics professionals. According to the HGAC, many clinical geneticists think that anxieties about obtaining insurance are deterring patients from having genetic tests from which they would benefit, and also that these anxieties would lead patients to seek 'over-the-counter' tests, whose results would not be shared with their physicians.

Enthusiasts for testing often link their critiques of genetic discrimination to strong claims for the value of testing. According to President Clinton's health-care adviser, 'If you do not increase the public's confidence that privacy will be protected and misuse of genetic information will be prohibited, it will undermine the public support for research in this area that has extraordinary potential for diagnoses and treatment'¹⁸. Exaggerated claims also appear in the scholarly literature; for example: 'Scientists can now predict with some certainty whether an individual is predisposed to certain diseases. However, people

are refusing to take the tests to learn their genetic predispositions. As ridiculous as it sounds, people are passing up the chance to determine what conditions they may possess and are foregoing treatment to help these ailments for fear that the genetic information will be used for discriminatory purposes'¹⁹.

Rationales

While many statutes aim to prevent insurance companies from taking the results of genetic tests into account in their underwriting decisions, insurers remain free to discriminate based on information from other medical tests. Indeed, as is often noted, commercial insurance is inherently discriminatory²⁰. Thus, the question arises: What is special about DNA? What are the grounds for distinguishing genetic tests from non-genetic medical tests²¹?

One rationale is that genetic tests provide more precise results than other medical tests. A second is that such tests may also be informative about relatives. A third is that they uniquely foretell the future; genetic information is sometimes equated with a 'future diary' that chronicles the most private aspects of a person's life²². A fourth (related) claim is that they disclose people's most basic and immutable characteristics. But as various commentators have noted, these distinctions do not withstand close analysis. Genetic tests are not always completely (or even highly) predictive, many medical tests provide familial information, and genes do not constitute our 'essence'. Moreover, diseases do not neatly divide into genetic and non-genetic.

The logic of the distinction: what is a 'genetic disease'?

The concept of 'genetic disease' (like the related terms 'genetic characteristic', 'genetic disability', and so forth) has progressively expanded, thus eroding the distinction between genetic and other medical conditions. There are at least two dimensions to this expansion.

First, the category of 'genetic disease' has come to encompass cancers that are not inherited on the grounds that, in the end, all cancer involves a disorder of DNA. That is, while most cancer occurs in somatic rather than germ cells, and is thus not transmitted from parent to offspring, it always involves a breakdown of normal genetic regulation, which makes it a 'genetic disease'²³.

Second, a condition with any genetic component, however marginal, now tends to be labelled a 'genetic' condition. That perspective is reflected in the many antidiscrimination statutes that cover any statistically increased risk of development of a disease. Thus, the category of 'genetic disease' includes not only the classic single-gene disorders, such as PKU or cystic fibrosis, but multifactorial ones, to which many genes and environmental factors contribute, and where the genetic contribution may be both slight and poorly-understood. The situation is analogous to the 'one drop rule' in the USA, according to which anyone with any black ancestry – even a single drop of 'black blood' – is considered black. Indeed, as Eric Juengst notes: 'It is becoming

commonplace for proponents of genome research to point out that, to the extent that all our physiological responses to the environment and its insults are products of our genes, all disease is genetic disease²⁴.

If the new nosology prevails, the boundary between medical tests and genetic tests will lose all meaning. Every medical test will become, *ipso facto*, a genetic test. Even if efforts to subsume all disease into the category of genetic disease fail, the boundary will remain fuzzy. Moreover, as a practical matter, isolating 'genetic' from other information in medical records is exceedingly difficult, if not impossible²⁵.

Social significance of protecting genetic information

The distinction between genetic and other medical tests is socially, as well as logically, problematic. As Joseph Alper and Jonathan Beckwith note, in the USA, efforts to protect against specifically genetic discrimination narrow the focus of health-care reform, and may deflect attention from the fact that the availability of health insurance is affected by all forms of medical testing, of which genetic testing constitutes only a small part²⁶.

Efforts that privilege genetic tests also reinforce a deeply-held cultural bias about genes. In general, people think that a condition with a genetic cause is neither preventable nor treatable²⁷. The literature on genetic discrimination is rife with claims that genetic information is special because genes are immutable (akin to race and sex) and fundamental to our being. In a seminal 1995 essay, Susan Wolf argued that the focus on genetic discrimination 'entrenches genetic bias', producing the broader and deeper harm of 'geneticism'; that is, equating individuals with their genes²⁸. Her fears are exemplified by the reporter who argued that: 'Our DNA can't be changed. If work demands that a worker quit smoking, then that worker can make a choice. There is no choice with genetic makeup ... our DNA does represent a large part of who we are, and who we must always be'^{29,30}.

Genetic antidiscrimination legislation also weakens one constraint on the premature or otherwise inappropriate use of genetic tests, which is one reason it appeals to those with disciplinary or commercial interests in testing. It is notable that when President Clinton proposed federal legislation to ban insurers from using genetic information to deny or limit coverage to people who purchase their own policies, he warned that some people refused testing out of fear that the results would be used against them. Genetic tests could 'save millions of lives and revolutionize health care' he declared, and people ought not to have to choose between saving their health insurance and taking a test that could save their lives. His specific example was the reluctance of women to be tested for mutations in the breast cancer-predisposition genes. Soon after, it was reported that the mutations were in fact rare in the general population and the test is warranted only for women with strong family histories of the disease³¹. Thus for many

reasons, it would seem that the cost of statutes aimed at specifically curbing genetic discrimination would exceed what has, to date, been their very meager benefits.

Notes and references

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