ON DEFINING THE GENETIC TEST

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"Although genetic testing has now become a major risk classification issue, it's ironical that few understand what genetic testing means."

Introduction

Intense debates over genetic testing are taking place in the insurance industry and elsewhere. Yet few—including many who are involved in these debates—have a good understanding of what genetic testing actually means. This lack of understanding leads to unnecessary and nonproductive argument. Irrational public fears can result from inaccurate understanding. Faulty legislative language not only fails to accomplish intended goals, but can cause considerable unintended damage.

As far as the issue of genetic testing is concerned, definitions drive legislative strategy. The wording of such definitions is critical. Not only do opposing sides on this issue define genetic testing differently, but differences of opinion among those with common interests lead to distinctly different definitions. This paper strives to frame the issues and derive a legislative definition for genetic testing that meets the major needs of the life insurance industry, while also recognizing basic concerns of the consumer. In the process, it provides readers with an understanding of the meaning and significance of alternative language and an ability to critique definitions proposed by others.

Thoughts communicated in this article represent the personal opinion of the author and are not intended to represent the position of Lincoln National Reinsurance Cos. or any other entity.

Some basics

The majority of those in the insurance industry and elsewhere in society who are having to deal with the challenging genetic testing issue have limited knowledge of the science of genetics. In recognition of this fact, a glossary has been written to introduce readers to often-used terms and describe the major types of genetic disease. Readers may find it helpful.

Why even try

Why even try to gain an understanding of what genetic testing means? Imagine that someone suggests to you that life insurers now need to add a question on Part II of their applications inquiring whether the proposed insured has ever had an abnormal genetic test. Do you think that most applicants will understand what is meant by abnormal genetic test? For this reason, states are not apt to approve such a question. Even if they did, the legal value of such a question is likely to be nil.

A state has a pending bill that would restrict the right of a life insurer to use genetic tests. Again, how does one define a genetic test? What definition is used by the sponsor of such legislation?

Say a genetic privacy act is introduced in the US Senate intended to safeguard the confidentiality of genetic information. What is genetic information? Gender is genetic; is gender information to be protected? Eye color is genetic; is eye color included?

Polls show that many people actually “fear” that their personal genetic information may get into the wrong hands and somehow be used against them. What thoughts go through people’s minds when the term genetic test is used? Are misconceptions about genetic testing contributing to the public’s concerns? Would people have less anxiety over this matter if they had a better understanding of genetic testing?

Although genetic testing has now become a major risk classification issue, it’s ironical that few understand what genetic testing means.

Legislative definitions

Bills have been introduced in many states aimed at restricting the right of health (and in some cases life) insurers to access and use genetic test information. The striking diversity of language used in these bills sends a variety of messages. Here are three:

1. Ohio’s HB 71 bars health insurers who offer basic health (medical expense) insurance from using results from any “genetic screening or testing” in their underwriting and defines this as: “a laboratory test of a person’s genes or chromosomes for abnormalities, defects, or deficiencies, including carrier status, that are linked to physical or mental disorders or impairments, or that indicate a susceptibility to illness, disease or other disorders, whether physical or mental, which test is a direct test for abnormalities, defects, or...
deficiencies, and not an indirect manifestation of genetic disorders."

2. Minnesota's S 259 that applies to health insurance defines a genetic test as a: "presymptomatic test of a person's genes, gene products or chromosomes for the purpose of determining the presence or absence of a gene or genes that exhibit abnormalities, defects, or deficiencies, including carrier status, that are known to be the cause of a disease or disorder, or determined to be associated with a statistically increased risk of development of a disease or disorder. Does not include a cholesterol test or other test not conducted for the purpose of determining the presence or absence of a person's gene or genes."

3. New Hampshire's HB 576 defined a genetic test as a: "test examination or analysis of an individual's genes, gene products or chromosomes for abnormalities or deficiencies, including carrier status, that are linked to physical or mental disorders or impairments or that indicate a susceptibility to illness, disease, impairment, or other disorders, whether physical or mental, or that demonstrate genetic chromosomal damage due to environmental factors and any report, interpretation or evaluation of such material."

ACLI definition

With a need to try to influence the wording of state statutes, the American Council of Life Insurance has constructed its own definition of genetic testing. At the request of the working group of the ACLI task force on genetic testing, the genetic issues committee of the ACLI Medical Section met June 12, 1993, and agreed on the following: a genetic test is a "test of human DNA used to identify the presence or absence of abnormalities, e.g. mutations, in genes which are associated with disease or illness."

ELSI definition

The National Institutes of Health working group on ethical, legal, and social implications (ELSI) of the Human Genome Project has established a task force on genetic testing. This task force recently developed the following working definition for a genetic test: a test for "the analysis of human DNA, chromosomes, proteins or other gene products to detect disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes. Such purposes include prediction of disease risks, identification of carriers, monitoring, diagnosis or prognosis, but do not include tests conducted purely for research."

This task force had its first meeting this past April. Item one on its agenda dealt with the definition of genetic testing. In a summary statement of this meeting, it was said that "the definition (of genetic testing) is critical to the scope of the task force's work and its recommendations."

Broad vs narrow

The concept of broad vs. narrow becomes important in the context of restrictive legislation.

The broadest definitions encompass virtually all biochemical, hematological or other sorts of tests. Narrow definitions, focus exclusively on the sort of DNA-based tests that are now beginning to flow from new genetic discoveries and technology.

Restrictive legislation utilizing broad definitions threatens to prevent the private life insurance industry from using results of time-honored tests. Even legislation of a narrow nature, if improperly worded, could serve to legalize antiselection and severely limit the insurer's ability to classify risk.

Public's concerns

To the extent that legislation is needed, it should address the major concerns of the public.

The public is concerned about genetic privacy. One of the reasons that genetic test information is viewed as being especially sensitive is that genetic disorders are shared by first degree relatives. What George discovers about himself may apply to his brother Harry, and to his children as well as Harry's children. Society also tends to be concerned with prediction of future events. Most people can understand the need to test to discover present disease— or to diagnose the cause for symptoms that someone may be experiencing. They find it much less acceptable to do DNA-type tests in an attempt to predict future disease. For one thing, many do not want to know what will happen in years ahead, especially if the news is not good. And people don't tend to trust these sorts of predictions either.

Gene products

Most geneticists believe that eventually it will often be easier and preferable to test for the protein product of a mutated gene than it is to test for abnormal gene itself. Given these circumstances, it makes good sense to include mention of gene products in the definition. The problem is that a gene product can include virtually everything. PSA (prostate specific antigen) might be considered a gene product. And cholesterol. And countless other things. So, when a law is proposed that indiscriminately says life companies cannot use tests for gene products, insurers have good reason for concern.

Evolutionary shift in thinking

People have commonly thought of genetic disease as referring exclusively to inherited disease or, in the case of chromosomal disorders, disease that is acquired during embryonic development. This is no longer so. More and more, people are begin-
ning to realize that common cancers and most other nonhereditary diseases have a genetic basis as well.

Genetic, DNA-based, tests are now often performed for acquired disease. Acquired disease is somatic rather than germline. This means that not all cells in the body are affected. Somatic disease affects selective tissues only. But it's still genetic.

The 1993 report of the National Institutes of Health task force on genetic information and insurance made this very point when it said that "as a practical matter, it will become increasingly difficult to deal with genetic information as special and separate from other forms of health related information because diseases are increasingly understood as having both genetic and environmental components."

Dr. Francis Collins, director of the National Center for Human Genome Research, has said that "all disease except trauma is genetic," meaning that all disease results from changes that take place in the DNA of a cell. Those changes may be inherited. Or they may be acquired as a result of some environmental factor, or purely by accident.

Dilemma

Assuming all disease can now be considered as genetic, it follows that legislation that essentially bars the use of genetic information by life insurers could have catastrophic results. ACLI spokespersons have made this point repeatedly. Legislation of this nature could preclude insurers from ordering any attending physicians statements or using many of the tests that insurers are accustomed to using. This type of legislation would make no sense—not unless the sponsors wanted to do away with medical underwriting altogether.

Even though people like Dr. Collins make a valid point when they say that all disease is genetic, the fact remains that most people—and certainly this applies to geneticists and those representing special interest groups—will continue to equate genetic disease with inherited disease, i.e. with disease that is due to DNA mutations passed down from parents to offspring. Genetic testing for inherited disease is what concerns people. And it is these concerns that will drive continued legislative activity.

The fact that all disease is genetic should not be ignored. Insurers need to understand, however, that there are limitations—and even downsides—in placing too much reliance on this argument. Additionally, the more insurers make this point, the greater the risk of locking themselves into a broad interpretation of genetic information not intended by original sponsors.

Spectrum concept

Although not found in textbooks and presumably not a notion that would be endorsed by geneticists, the concept of a four-part spectrum of genetic disorders provides a logical mechanism for understanding and analyzing alternative legislative definitions and strategies. Here is that spectrum:

1. No increased risk of disease in spite of a genetic mutation: At one end of the spectrum there are those with an identifiable gene abnormality, but absent any increased risk of that mutation leading to a genetic disease. The carrier state (see Appendix A) is the prime example of a genetic abnormality not associated with increased risk of disease. Another example would be the female carrier of an X-linked mutation such as the gene for hemophilia. She herself is not at risk of getting hemophilia.

2. Predisposed, i.e. at increased risk of developing a genetic disease: This second position on the spectrum consists of those whose genome predisposes them to a genetic disease. We are talking about multifactorial genetic disorders (see Appendix A) where a combination of gene mutations and environmental insults are needed in order for disease to develop. The presence of one or more of these inherited mutations predisposes or places a person at increased risk, but a host of events must take place before disease occurs. Predisposition is not synonymous with disease; people with genetic predispositions do not have genetic disease. Without other mutated genes or absent certain necessary environmental factors, many—arguably a majority—of those with genetic predispositions will not go on to develop disease.

3. Presymptomatic, i.e. already has a genetic disease—but is not yet symptomatic: Once this third segment on the spectrum of genetic disorders is reached, one is dealing with actual disease. The presymptomatic individual has disease; he simply has not yet developed disease symptoms. In the absence of reduced penetrance (see Appendix A), all who are presymptomatic will eventually develop outward signs of disease. With reduced penetrance, risk of future clinical disease is less than certain and the situation takes on characteristics of multifactorial disease. Although the terms predisposition and presymptomatic are sometimes confused, they are in fact very different. Our four part spectrum forces a distinction to be made between genetic predisposition and presymptomatic genetic disease, and this may be its major benefit.

4. Symptomatic disease: At segment four of our spectrum of genetic disorders we find overt genetic disease. Any sort of disease that has a genetic basis, be it single gene disease, multifactorial, chromosomal or acquired (see Appendix A), falls into this final portion of the disease spectrum when associated with clinical signs and symptoms.

Two basic types of tests

Genetic tests can be grouped into one of two basic types. There are tests used for diagnostic (or screening) purposes. And there are other tests used for prognostic (or therapeutic) purposes.
Test categories (based on spectrum of disease and type of test)

By combining our four-part spectrum of genetic disorders with the two basic kinds of tests, one derives the following chart, creating six basic test categories. Because of their distinctive characteristics, genetic testing discussions that make reference to these specific categories are considerably more meaningful than discussions that fail to make such distinctions.

<table>
<thead>
<tr>
<th>Spectrum of genetic disorders</th>
<th>Type of test</th>
<th>Carrier</th>
<th>Predisp.</th>
<th>Presympt.</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
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</tr>
<tr>
<td>Prognostic</td>
<td>N/A</td>
<td>N/A</td>
<td>(5)</td>
<td>(6)</td>
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Category one (diagnostic/carrier): It is generally agreed “carriers” present no increased morbidity or mortality risk. Consequently there is no controversy with results of category one tests.

Category two (diagnostic/predisposition): In terms of public policy debate, genetic test category two is perhaps most contentious. Here we are talking about people who are genetically at increased risk of developing a multifactorial disease (see Appendix A), but who may never develop such disease.

Many in the life insurance business would maintain that it is the category two type of test that will eventually be most important to risk classification. The value of risk factors we use today, such as build and blood pressure, may well be exceeded by the value of tomorrow’s genetic risk factors. And we can’t forget that when test results are favorable, people will want to receive underwriting credit.

While the above is certainly true, there are significant negatives associated with the life insurer’s use of category two genetic information. Most people are believed to possess a handful of genetic defects that predispose them to a serious disease. Most will never know what mutations they possess because there is no test, nor any occasion to test for such mutations. Knowledge that genetic predispositions are universal prompts some to challenge the fairness of penalizing those who accidentally find out that they are genetically predisposed to a multifactorial disease.

Furthermore, some question how the insurer can quantitate the importance of a predisposing gene when it typically takes other genes plus environmental factors to generate disease? Variable age at onset and a broad spectrum of clinical severity contribute even more to the problematical nature of genetic changes associated with multifactorial disease.

A compelling case is made by insurers that there is little difference between using the results of a genetic predisposition test versus time honored underwriting impairments such as cholesterol. Elevated cholesterol predisposes to atherosclerosis. Actuaries have no problem in quantifying the risk imparted by an elevated cholesterol. Likewise the actuary is capable of analyzing the relative importance of complex genetic predisposition factors.

While the above is true, differences do exist. (1) High cholesterol can be treated; mutated genes cannot. (2) As a medical risk factor, cholesterol is widely trusted and used by the medical profession. Not so with most genetic tests. Genetic tests are currently investigational. (3) Actuaries are armed with clinical and insured lives cholesterol data and know what effect various blood levels have on relative mortality. Such data does not exist for DNA mutations involving multifactorial disease, and the complexities of biological variation may preclude actuaries from ever being able to quantitate such information.

Many are predicting that numerous genetic predisposition tests will come on line in the next decade. Assuming this happens and people learn what scientists assume to be an increased risk of getting disease, physicians will be working with these people to change their life-style or otherwise modify their environment in an effort to reduce, or even eliminate, their added risk.

The significance of the above scenario cannot be overstated. Billions of public and private dollars are being spent on human genome research. One of the major goals of this research is to discover ways to test people for genetic conditions for which they can then intervene to reduce their risk and thus prevent or forestall future disease. Some view life insurers as standing in the way of society’s ability to reach this goal. It is said, for example, that people often refuse to be tested for fear that results will be used against them by their life insurer. Although reliable evidence to support this accusation appears lacking, this argument is repeatedly and effectively made.

If the genetic revolution does create the capability of intervening and thus reducing the risk of future disease, our nation’s mortality should improve. Life insurers and those they serve ultimately stand to gain. In this context, it is argued that it is in the life insurer’s best interest to do everything it can to encourage predisposition testing and primary intervention. Critics say that the specter of life insurance underwriters using such information to discriminate against individuals diminishes public acceptance of these tests and reduces their future potential benefit to society.

Category three (diagnostic/presymptomatic). There are two general categories of presymptomatic disease. One deals with presymptomatic, typically late-onset, single-gene disease. The other involves presymptomatic acquired disease.

First let’s look at presymptomatic single-gene disease. In a manner that is somewhat analogous to the man who is discovered to have prostate cancer by virtue of his elevated PSA (prostate specific antigen) test, certain single-gene diseases can be discovered by using genetic tests. Huntington’s disease is a prime example. If a young person has a positive DNA-based test for Huntington’s, it is reasonable to consider that he or she has
Huntington’s disease. He isn’t going to get Huntington’s in 10 years or in 20 years. He has it now. It’s presymptomatic. But it is as real as the prostate cancer that has yet to become clinically manifest. Signs and symptoms of Huntington’s are certain to eventually develop, most likely around age 40.

And then we have presymptomatic nonhereditary genetic disease. Take presymptomatic cancer for example. A genetic test to detect this disease is analogous to doing a chest X-ray for early evidence of a lung tumor or running an electrocardiogram for silent coronary artery disease. This has nothing to do with heredity. We are not talking about the possibility of siblings or children having the same genetic mutation. Such testing is done in an attempt to make an earlier or more accurate diagnosis, using the newest of technology.

Although category three tests do not possess many of the characteristics that make category two tests so controversial, both deal with those who are asymptomatic. Concerns about genetic privacy and the fairness of risk classification are intensified under such circumstances.

Category four (diagnostic/symptomatic). Test category four overwhelms all other categories in size and clinical significance. Not only does this include the millions of Americans who have symptomatic multifactorial diseases like coronary artery disease and hypertension, but it includes the huge number with symptomatic acquired genetic disease as well. Common cancers are the primary example of acquired disease.

One would hope that people will generally equate the insurer’s use of the results of DNA-based diagnostic tests for symptomatic genetic disease to the insurer’s use of ordinary tests for traditional diseases. Except for the universal need to protect confidentiality, category four genetic testing touches no raw nerve and should precipitate relatively little controversy vis-a-vis categories two and three.

Categories five and six (prognostic/presymptomatic and prognostic/symptomatic). Categories five and six involve prognostic tests: tests intended to define the natural history of a disease. Results of these tests, among other things, help the physician to know how aggressively to treat a given disease. Yes, some tests simultaneously diagnose and define prognosis too.

Disease examples

The following disease examples are intended to demonstrate the utility of specified test categories.

Category one (diagnostic/carrier). Sickle cell trait: Those with the trait have mutations in only one of their two globin genes and are called “carriers.” They do not have the autosomal recessive disease called sickle cell anemia. Those with sickle cell trait have normal life expectancy.

Category two (diagnostic/predisposition). Familial Alzheimer’s disease: persons who carry Apo E 4 alleles on chromosome 19 are believed to be at increased risk of developing Alzheimer’s.

Category three (diagnostic/presymptomatic). Huntington’s disease: The finding of an expanded sequence of “CAG repeats” in the Huntington’s gene located on chromosome four indicates that progressive neurodegenerative disease is almost certain to develop, usually before age 50. The penetrance for Huntington’s disease (HD) is at or near 100 percent meaning that virtually everyone who has this mutated gene will develop signs and symptoms of the disease. Disease is late-onset; typically people with the Huntington’s gene remain asymptomatic for the first 35 or 40 years of life. Then symptoms appear and progressive deterioration is expected from that point forward.

Category four (diagnostic/symptomatic). Duchenne muscular dystrophy: Early symptoms of this X-linked disease can now be confirmed as being due to DMD using genetic tests.

Category five (prognostic/presymptomatic). Cystic fibrosis: Mutation-specific penetrance and expressivity data, once it is accumulated, should greatly increase the opportunity to predict, in early life, the clinical significance of many of the nearly 500 mutations already found on the cystic fibrosis gene, and thus the severity of disease that will develop in the future.

Category six (prognostic/symptomatic). Breast cancer: Mutant-allele-specific amplification (MASA) testing is now being done on lymph nodes to detect micrometastasis in tissue that is histologically negative.

The sorts of distinctions shown above are frequently not neat and clean. A common reason why categorization of a particular test can be difficult is lack of complete understanding of that test. Nevertheless, having to go through this exercise creates a better understanding of the nature and significance of the genetic-based test in question.

Defining a genetic test

A workable legislative definition must reflect a compromise between satisfying societal concerns on the one hand and protecting legitimate business needs of the commercial life insurance industry on the other.

As mentioned, the public is concerned with genetic privacy. Hereditary data that affects multiple family members is of special concern. Prediction of future events, especially if perceived to be unreliable, is another major concern that people have. Life insurers are primarily concerned that denying insurers access and the right to use genetic test results would, in effect, legalize anti-selection. Insurers must retain the right to use results of tests in categories three through six. As previously stated, category one tests are not in question. From an insurer’s standpoint, the only question pertains to test category two.
Life insurers would prefer no restrictive legislation, in this sense insurers have a zero tolerance for any definition of genetic testing. However, assuming some continued legislative initiatives are inevitable, the following compromise definition is recommended. This attempts to satisfy certain societal concerns and yet protects the major interests of the life insurance industry:

A genetic test is “a laboratory test for inherited disease-related alterations of human DNA or chromosomes (or for ‘gene products’ used to identify those same abnormal genes or chromosomes) that predispose an individual to a disease for which they as yet manifest no symptoms or other clinical evidence of that disease. Those who are presymptomatic for genetic disease are not included.”

This definition confines itself to category two. It refers to gene products, but does so in a specific manner. It targets inherited disease and excludes acquired disease by inference. It specifies that the person being tested be asymptomatic (thus excluding test categories four and six). And it says that the test is seeking to identify alterations that predispose to disease. Presymptomatic disease is specifically excluded (excludes test categories three and five).

Also, the above definition makes no mention of the genetic “carrier.” As previously stated, carriers present no increased morbidity or mortality risk. A comment about carriers could certainly be appended to this definition.

This definition falls short of satisfying all the desires of the public and is certain to be criticized by outsiders. It fails to protect insurance access to results of category two tests and will consequently be criticized by insurance people as well. The test of a true compromise is that it be universally unpopular. This recommendation will surely meet that test.

It’s interesting to note which test categories are included in previously cited definitions. Minnesota’s definition is relatively narrow, appearing to include only categories one, two and three. All others, including those of Ohio, New Hampshire, ACLI and ELSI, include all six test categories and are broad definitions.

Conclusion

No issue has ever held the potential importance to risk classification that genetic testing holds. Many legislative battles are anticipated in years to come. Their cumulative outcome will dictate whether risk classification survives or whether risk classification—and thus America’s private insurance industry—is crippled.

What has been said in preceding paragraphs will not help to define future political outcomes. Hopefully, however, the ideas expressed in this paper will help those involved in legislative debates to focus on relevant issues.

References

8. Beerring SE (1994) Lecture, Indiana University Medical Center, October 12