Foreword

The study papers included in this report were prepared to provide an initial background resource for further discussion, analysis and debate within the American Council of Life Insurance on some of the potential implications of genetic testing for the life insurance business. Accordingly, these papers are not intended to reflect viewpoints, recommendations or policy positions that the Council may express or adopt with respect to genetic testing in the future.

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Executive Summary

The science of genetics studies the mechanisms by which parents transfer biological characteristics to their offspring. On a molecular level, genetic information is stored within the chromosomes of cells as DNA (deoxyribonucleic acid). Genes are specific portions of DNA that direct the production of proteins that function as structural materials in the body.

The entire complement of genetic material within the chromosome is known as the genome. The human genome may contain as many as 100,000 genes.

Tests that can identify genes are known as genetic tests. At present genetic tests are available for only a relatively small number of the estimated 3,500 human disorders that have a genetic component. But technology is rapidly being developed that will soon permit the identification of many of the genes responsible for health and illness. Researchers predict that genetic testing will probably become standard practice within the medical community by the year 2000.

Genetic tests will be able to identify two different types of genetic conditions: diseases with a genetic predisposition and genetic diseases.

Diseases with a genetic predisposition have some genetic component. The disorder may or may not ever develop depending on a variety of personal and environmental factors. Disorders within this group include cancer, coronary heart disease and diabetes. Many common diseases have a genetic predisposition and contribute significantly to the morbidity and mortality of an insurance pool.

In genetic diseases the genetic component is so overwhelming that its results are predictable and need no environmental interaction. Examples are cystic fibrosis, Huntington's disease and Duchenne muscular dystrophy. Individual genetic diseases are rare compared to diseases with a genetic predisposition, but collectively they are also an important cause of morbidity and mortality.

Genetic tests may be of great benefit to society. But any use of genetic tests by insurers would present complex ethical, medical, and social issues that insurers would have to take into account.

Insurers already obtain some genetic information from applicants through questions about family history and laboratory tests such as those for blood cholesterol. As attending physicians begin to perform genetic tests more commonly, insurers may ask additional questions in the application about a personal or family history of genetic disease. Insurers may request details of prior genetic tests, and perhaps have genetic tests performed during the risk selection process. If, at some future time, insurers decide that they must order at least some genetic tests of their own, it will be important to remember that such an action carries with it the responsibility to anticipate future consequences. In particular, a decision to initiate genetic testing must be part of a deliberate, coordinated effort by a company's medical director(s), underwriters, actuaries, attorneys and government relations personnel. Such a decision cannot be made in a haphazard, poorly planned fashion.

Most genetic tests will not provide an absolute answer about whether a disorder will occur. From an underwriting perspective, it would usually be necessary to interpret the results of genetic tests within the context of other traditional risk selection parameters such as age, gender, current health status, occupation, and health enhancing factors such as exercise and avoidance of tobacco and excessive amounts of alcohol.

Genetic tests will be different in some ways from other diagnostic tests. In certain cases technology will outpace knowledge, i.e., laboratories will be able to perform genetic tests long before their diagnostic or predictive abilities can be validated. Insurers and their laboratories must insist that genetic tests satisfy high standards before they can be used. The issues here extend well beyond the relatively straightforward matters of accuracy and technical skill. Harm might be done to public and government relations if an insurer were to begin to order genetic tests before their significance had been confirmed and generally accepted by the medical community.

Part I

Public and Government Relations Issues

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This section of the report includes the following sections:

A. Introduction

B. Two Different Types of Genetic Tests

C. Genetic Tests and Adverse Selection

D. Private and Public Insurance

E. Group Insurance

F. Confidentiality

G. Counseling

H. Informed Consent

I. The Role of Laboratories

J. Arguments Supporting Use of Genetic Tests for Risk Classification

K. Concluding Remarks

so at rates that do not properly reflect their known risk. If a large number of such applicants bought insurance, or if large amounts of insurance were purchased, the ensuing claims would markedly exceed projected losses. Everyone in the insurance pool would suffer.

Consider the following scenario. It applies equally to tests for genetically predisposed diseases and for genetic diseases.

> A man applies for an individual life or non-cancelable disability insurance policy. He has previously had a genetic test performed by his own physician. The results are unfavorable. The test suggests a significant likelihood of premature death or disability. If the insurance company does not learn about this test result, and no other unfavorable risk factors are known in this case, the insurer issues a policy on a standard basis.

The above scenario violates the principle of equity. This applicant, who has an above average potential for claim, has bought insurance at standard rates. This situation is analogous to that of an older person who misrepresents his age and obtains insurance at the rate of a much younger person.

Although the applicant in the above scenario would be pleased with his purchase, it would be unfair to other policyholders. True, the man currently seems to be in good health. But his unfavorable genetic test has identified a significantly increased risk. Furthermore, under existing regulations, coverage cannot be cancelled once it has been purchased. Nor can the premium be increased relative to other policies issued to individuals with similar coverage. This man's insurer will probably pay him benefits that are disproportionate to the premiums he has paid.

This case exemplifies unfair discrimination against other policyholders in the pool, who have measurably different risks of death or illness and deserve to be charged accordingly. Unfair discrimination affects healthy individuals who deserve to pay standard insurance rates. Such discrimination also affects people who are making additional premium payments because of a prior history of cancer, heart disease, diabetes or knowledge of an unfavorable genetic test that they have shared with their insurance company. All of these people would, in essence, be subsidizing the insurance coverage for the individual in the scenario. The attractiveness of insurance for everyone, healthy and impaired, would be lessened.

D. Private and Public Insurance

Many people believe they are entitled to both private life and private health insurance. They believe that everyone should have affordable insurance protection and that it should be made available to them regardless of age or health. Concurrent with these expectations are efforts by the federal government to shift as many health care expenses as possible to the private sector.

A report by the U.S. Office of Technology Assessment has fueled fears that private insurers might exclude significant numbers of people by ordering more tests on applicants. This report concluded that the use of "predisposition" tests (including genetic tests) to classify health insurance risks "may lead to substantial costs to government if private insurance becomes too costly or unavailable to selected individuals." The report also stated that the "use of medical tests in determining insurability. . . not only affects the balance between governmental and private sector financing of health care, but also can aggravate the problem of the uninsured and underinsured."[1]

Comments such as these may reflect misconceptions about private and public insurance programs. A brief discussion of the nature and purpose of these two different types of insurance will help clarify their relationships.

(a) *Private (Voluntary) Insurance.* Participation in a private commercial insurance plan is usually voluntary. The applicant chooses whether to belong and determines how much insurance protection he or she would like to purchase. All of the funds used to pay future claims against the insurance pool come directly or indirectly from premium payments. Therefore, risk classification is essential to ensure that the premium charged is proportionate to the risk assumed. The potential for adverse selection is very real and an important concern of the insurer. Finally, private insurance companies are businesses that are accountable to their

[1] **John H. Gibbons, *Medical Testing and Health Insurance*, (Washington, D.C.: Congress of the United States, Office of Technology Assessment, August 1988), p. iii.**

sive rise in premiums as more and more good risks decided not to purchase insurance. The relatively large base of good (standard) risks would be progressively eroded. As a result, it would become increasingly costly to subsidize poor risks, and premiums would increase again. Some companies would decide to stop offering coverage altogether since profits could no longer be expected.

The bottom line is that such legislative or regulatory mandates would force insurers to provide coverage for a large group of people at a price that would, because of adverse selection, be insufficient to cover claims. These additional costs would be passed directly to other policyholders with a subsequent decrease in insurance affordability and availability.

E. Group Insurance

There will be vigorous debate when and if employers begin using genetic tests. The possibility of such testing has raised concerns that people who are insured at their place of employment (where they are covered by commercial group insurance) may find that coverage jeopardized. A clear understanding of the differences between individual and group insurance is necessary to weigh the issues that will be prompted by this debate.

For individual life, disability and health insurance, an applicant applies for whatever amount of insurance coverage he or she wants within guidelines established by the insurance company. The applicant completes a form that includes medical questions, and medical tests may be ordered. Sometimes, the insurer will ask for an attending physician's statement. The premium is based on such factors as age, health history, general physical condition and occupation.

Group life and health insurance generally falls into two categories: medium to large groups containing 10-25 or more employees, and small groups of fewer employees.

Under a medium to large group life and health insurance plan, an employer buys a single policy for his or her employees. All employees can elect to take coverage. The employer typically pays part of the cost, thus giving employees an incentive to join. Benefit amounts are fixed by formula and individuals are normally not subjected to underwriting. (Possible exceptions are those who choose not to participate in the program when they first become eligible and those who withdraw from the plan and later request reinstatement.) Rather, the entire group is underwritten according to factors such as the number of employees, age and gender distribution, area of the country and prior health care costs for the entire group. Once a rate is established, it is typically adjusted ("experience rated") on a yearly basis depending on claims experience. If claims exceed expectations, rates increase. And vice versa. With such a large group, some workers are bound to be poor insurance risks. But the majority, who are good risks, tend to offset these few. This allows the insurer to offer coverage to the entire group at an affordable rate.

Small group life and health insurance is different. Small groups do not have the benefit of a large number of employees among whom the less healthy risks can be shared. Therefore, claims experience depends strongly on the health of the small number of individuals within the group. For example, if an insurer were unaware that one individual in the group was already ill or at significant risk of becoming ill when employed, the claims submitted by this one individual could far exceed the claims expected from the entire group. If this occurred with any frequency, the cost of insurance to this small group would become unaffordable. For this reason, the underwriting of small groups is quite similar to that used for individual insurance. Application forms, medical information, and, sometimes, testing and attending physician's statements may all be required.

The main differences between individual and group insurance are summarized in Table II, above right. The column headed "Group" refers to medium to large group plans.

The government is interested in the potential ramifications of genetic testing on society. Of particular importance to insurers are concerns about the disclosure of genetic test results to third parties. One government report recommended that: "Because of the potential for misuse as well as unintended social or economic injury, information from genetic testing should be given to people such as insurers or employers only with the explicit consent of the person screened. Further, the agencies in question should develop forms for specific rather than blanket consent, to prevent unnecessary disclosures and to ensure the screenee selective control over access."[4] Statements such as this serve to highlight the issue of confidentiality and its paramount importance to insurers.

G. Counseling

Genetic counseling is an evolving field that may become integral to health care with the development of new genetic testing techniques. Counselors may serve primarily as information givers, providing the knowledge for individuals to make informed health care decisions.

The nature and extent of genetic counseling could vary depending on the disorder. For disorders with a genetic predisposition such as cancer, heart disease and diabetes, counseling would consist primarily of discussions of risk reduction measures and general preventive health guidance. But with genetic diseases such as Huntington's disease, counseling could become much more involved. Issues that might have to be addressed include whether tests should be done, whether there is a cure or treatment, whether the disorder can be passed on to children, and whether the subject really wants to know now about a disorder that may not develop for decades.

Genetic tests deal with matters that are often highly personal, such as family planning and the likelihood of illness or premature death. The attending physician has traditionally been the first source of medical information about matters like these. Attending physicians may be called upon even more as genetic testing evolves.

Insurers and attending physicians have always had a good working relationship. For example, if an insurer discovers an abnormality during underwriting through a test or examination performed by the insurer, test results are generally passed on to the attending physician. He or she is then able to more quickly initiate any needed medical evaluation. And attending physicians have, with patient authorization, shared with insurers the past medical histories and test results of patients applying for insurance coverage. They have also provided medical counseling for their patients if an abnormality was detected by a test ordered by insurers. With the advent of genetic tests, insurers and attending physicians may find their relationship enhanced.

H. Informed Consent

Informed consent may occupy an important place in legal, ethical, and social discussions of genetic testing. The growing importance of personal independence and autonomy, the need to ensure confidentiality, the impact of genetic testing on health care, and the changing relationships between patients and health care providers will all figure prominently in discussions of confidentiality and consent.

Insurers will be drawn into these discussions because of fears that an applicant's right to self-determination may be violated if genetic tests are performed during risk assessment. If a point is ever reached where it becomes necessary to order genetic tests during underwriting, insurers will have to be certain that applicants have a full understanding of tests performed and implications for their future health and insurance status. Because the nature of genetic tests is still uncertain, it is not possible now to discuss specific types of informed consent that may be needed.

I. The Role Of Laboratories

Genetic tests will differ in some ways from other diagnostic tests. In certain cases technology will outpace knowledge. (Laboratories will be able to perform tests long before their diagnostic or predictive abilities can be evaluated.) It is difficult to predict the responses of both the medical community and insurers to this situation. Data from medical literature will be meager and inconclusive for many years. Will insurers discard proven risk selection practices because of the alleged superior predictive value of new tests?

[4] ***Screening and Counseling for Genetic Conditions*, (Washington, D.C.: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, February 1983), p. 42.**

It is worth noting that the private insurance industry was responsible for initiating studies that resulted in coverage for individuals with health impairments. Traditionally, these people had been unable to get coverage. Insurers concluded that they could offer insurance protection to many of them as long as risks could be evaluated and priced appropriately.

Because of today's increased testing during underwriting, concerns have already been raised that the large "standard" pool of applicants could be diminished slightly since these tests are identifying previously undiscovered abnormalities.[5] However, the definition of a standard risk could be expanded to maintain the high proportion of applicants that has usually been accepted for coverage on a standard basis.[6] This approach could also be taken to offset any shrinkage of the pool if genetic testing were to become the norm.

Argument No. 3: Genetic data will be evaluated in the context of other risk selection parameters. If genetic testing is undertaken, genetic test data would represent only one of the many factors needing consideration by insurers as they attempt to predict the probability of illness and premature death. The belief that genetic tests would often be the sole or primary determinant of insurability is mistaken.

Consider the case of a man who has had a series of genetic tests that have detected a heightened risk for a certain type of cancer. Such a determination would not necessarily mean that insurance would be declined or extra premiums charged. Many other factors would have to be evaluated. These factors would include physical condition, exercise, avoidance of tobacco and excessive amounts of alcohol, occupation and any history of health problems. Another factor would be whether the type of cancer to which the man was predisposed was a common or uncommon cause of mortality or morbidity relative to other illnesses that occur in a large group of insured persons. This type of cancer might develop so rarely that an adverse underwriting decision would not be necessary even if a significantly increased likelihood of its occurrence were detected. Age would be another issue, especially if the applicant had already passed the age at which the cancer would probably have developed.

Given all of these considerations, an applicant in otherwise good health might still receive insurance coverage at favorable rates because he was known to be an excellent risk —except for an increased likelihood of developing a certain type of cancer. And since the applicant would have been alerted to his heightened risk, he could try to avoid other factors that might further increase that risk.

Argument No. 4: Adverse selection is real. It is discussed in virtually all publications that deal with the social, ethical and economic ramifications of genetic testing. For example, authors discussing the usefulness of a genetic test to identify the gene responsible for Huntington's disease speak openly about the importance of "acquiring disability insurance" and the need to "buy extra insurance—before testing."[7] Others write that an important factor in deciding whether a test for Huntington's disease should be performed is whether the individual is "adequately insured" before the test is ordered.[8]

Critics of the possible use of genetic tests by insurers echo the common theme that testing would discriminate against people with genetic diseases.[9,10,11] Such comments highlight the impression that discrimination by insurance companies is bad or unfair. (Drawing distinctions is part of the traditional insurance process.) But these critics also indirectly state that it is "okay" to "discriminate" against those with a history of cancer, diabetes or heart disease by requiring a premium appropriate for the increased risk. These disorders, like genetic diseases, are usually no one's fault. Nevertheless, they believe that it is unfair to apply premiums in a similar manner to people with genetic diseases or diseases with a genetic predisposition.

It is not well understood that fair discrimination is precisely what insurance companies must, and, in fact, are expected to carry out. Insurers identify good and poor risks and charge premiums commensurate with those risks. In fact, it is because of this type of discrimination that insurance coverage can be offered to so many people at affordable rates.

[5] **Donald Chambers, M.D., "Medical Section Report," (Washington, D.C.: American Council of Life Insurance, Spring 1989), Vol. XIII, No. 1, p. 1.**

[6] **Harry Woodman, FSA, "Are all Substandard Risks Still Substandard?" (Seattle: Life Underwriting Education Committee, *On The Risk*, October/November 1988), Vol. 5, No. 1, p. 23–24.**

[7] **Alan Newman, "The Legacy on Chromosome 4," (Baltimore: *Johns Hopkins Magazine*, April 1988), p. 30–39.**

[8] **Sally Squires, "Do People Really Want To Know Their Medical Future: DNA and Destiny," (Washington, D.C.: *Washington Post*, October 4, 1988), p. 14–16.**

Part II

Genetic Testing: Analysis of Test Results

By Brian Kay, M.D.
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The impact of a genetic test can be projected only with a basic understanding of why medical tests are performed and what the tests can and cannot do. This part of the report covers these topics:

A. The Functions of Tests
Figure 1: Example of a Discrete Risk Factor
Figure 2: Example of a Continuous Risk Factor

B. Genetic Screening

C. Genetic Tests and Impairment Types

D. Criteria for Tests Used for Screening Purposes

does not fit for others. Most predisposition tests are of a continuous nature. And most diseases have many and varied causes.

The genetic test for Huntington's disease is consistent with the idea that wholes should be fully understood by examining their parts: Somewhere on the "short arm" of chromosome No. 4, a bit of DNA has an uncontrollable power to cause chorea and dementia. In this case, macroscopic results are explained by the properties of their microscopic parts. Occurrence of the disease results from definite, predictable causes. These reductionistic principles apply to the study of simple objects and, to a large extent, of discrete, overwhelming risk factors.

But continuous risk factors do not fit well into the reductionistic model. Hundreds of genes may be involved. Bodies are not unambiguous maps of their genes. There is no "gene" for a right foot or for an earlobe. Bodies cannot be atomized into parts, each constructed by an individual gene. Diseases, such as atherosclerosis and cancer, are almost always multifactorial, their development the result of many influences, each influence acting in a complex way. Organisms are much more than amalgamations of genes.[2]

B. Genetic Screening

Genetic screening can be defined as the systematic search for people with certain genotypes (genetic constitutions).[3] Diagnostic analysis of test results is important to understand abnormalities. Such analysis tells how well the test determines the presence or absence of disease. Because abnormal test results are one of the principal concerns of an insurance medical director, tests must be examined in a way that tells how often people with positive tests have disease and how often people with negative tests do not.[4] On this level, there are two important factors, the predictive value positive and the predictive value negative. Predictive value positive is the probability of disease if the test result is positive. Predictive value negative is the probability of absence of disease if the result is negative. The sensitivity and specificity of the test and the prevalence of the disease are used to calculate these probabilities. The final diagnosis is determined only after comparison to an accepted operational definition of the disease.

The seriousness of the disease in question is an important factor in deciding whether to conduct genetic testing. For life insurance, the disease's mortality should be known. For disability income insurance and health insurance, morbidity of the disease should be known.

Hence, criteria especially important for testing include sensitivity, specificity, prevalence of the disease in the population and the mortality/morbidity implications of the disease in question.

With respect to genetic testing, it may be that conventional tests have greater predictive power than genetic tests. For example, it may be that hyperlipidemia, though a separate risk factor for coronary disease, may be best monitored by studying lipoprotein levels rather than by knowing of a specific genetic defect. Such an approach would allow a look at the interaction between genetic predisposition and environmental factors.

C. Genetic Tests and Impairment Types

A genetic disease is any disease which has an inherited component. This includes disorders that may begin as early as childhood (e.g., insulin dependent diabetes); those whose onset often is in early adulthood (e.g., duodenal ulcers); and those whose onset may be in late adult life (e.g., atherosclerosis). Diseases with inherited components are responsible for most of the mortality and morbidity in the industrialized world.[5]

In theory, isolated effects of major genes, multiple genes or environmental variables could produce disease. However, predisposition to disease can come from both genes and environment. Most diseases result from the accumulation of environmental factors over time in genetically susceptible people.

There is a distinction between someone who *has* a disease and someone who has a predisposition to developing a disease. Further distinctions include:

(a) No current disease or predisposition to disease.

[2] **S. J. Gould, *The Panda's Thumb: More Reflections in Natural History*, (New York: W.W. Norton, 1980), p. 90–92.**

[3] **P. T. Rowley, *Frontiers in Genetic Medicine*, (Columbus: Ross Laboratories, 1987).**

[4] **A. W. DeTore, "The Evaluation of Abnormal Laboratory Results," (Los Angeles: *Journal of Insurance Medicine*, 1988), Vol. 20, No. 2, p. 5–9.**

[5] **J. I. Rotter, *Frontiers in Genetic Medicine*, (Columbus: Ross Laboratories, 1987).**

Part III

Genetic Data: Impact on Underwriting

By Mark E. Battista, M.D.
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This section of the Genetic Testing Committee's report focuses on practical life and health insurance underwriting issues. These are the issues that would be generated by the widespread availability of genetic data and the capacity to perform genetic testing.

This paper includes the following sections:

Figure 1: Range of Potential Impact of Adverse Selection on Mortality Experience

The hypothetical example assumes Life Insurer X has an average mortality experience of 1 per 1000 per year in its 20–30 year old insureds.
It also assumes that 50%* of those insureds who antiselected on basis of knowledge of a genetic condition die within first ten policy years.

Deaths/1000/Yr. Without Added Antiselection	Total Deaths Per 1000 By Ten Years	Antiselection Incidence Per 1000 Policies Issued	Extra Deaths Per 1000 By Ten Years	Total Deaths Per 1000 By Ten Years	Impact (Extra Mortality)
1	10	1	0.5	10.5	Minimal
1	10	10	5	15	50% Increase
1	10	25	12.5	22.5	100% + Increase
1	10	50	25	35	250% Increase

*NOTE: This figure might range from 5% to 50% depending on the nature of the genetic conditions prompting the antiselection.

However, if, with broader clinical use of genetic testing the incidence of adverse selection were to rise to 50 per 1,000, and if an additional 25 deaths occurred in the first 10 years, the 10 year total would swell to 35 per 1,000, a major increase. This figure could be diminished somewhat because current underwriting procedures would identify some of these applicants. Moreover, the number of additional deaths per 1,000 might, in fact, be considerably less than 25. At any rate, Figure 1 illustrates an approach to estimating the spectrum of extra mortality resulting from varying degrees of adverse selection.

In general, with no individual underwriting (and no individual risk classification), a company would be overpricing some risks and underpricing others. The overpriced risks would gradually leave the insurance pool, seeking better rates. The underpriced risks would tend to stay in the pool, which would be further expanded by additional underpriced risks buying new policies.

Insurers, of course, do medically underwrite individual life and disability products. Therefore, the number of overpriced and underpriced risks, and the extent of overpricing and underpricing, would be less than in a group insurance setting. In group settings, medical underwriting is not routine.

As insurers increase the accuracy of risk classification, they will be able to set prices more precisely. Moreover, more accuracy in risk classification generally correlates with lower risk capital requirements to fund mortality and morbidity risks. This is the result of greater certainty in projecting mortality and morbidity. Better risk classification could translate into lower prices for future applicants and higher returns on investment for stockholders and policyholders.

F. Practical Consideration for Insurers Contemplating Implementation of a Genetic Screen in Underwriting

Insurance companies already use genetic data. For example, many insurance applications request information about family history. To some extent, one might consider family history data a proxy for more specific confirmatory genetic tests. This would be similar to the use of T-Cell testing as a proxy for HIV antibody testing that took place in California in the past. Therefore, the issue is not so much whether insurance companies should obtain genetic data—many already do—but rather what additional data they should obtain, from which applicants and from what sources? The underlying issue of how much value genetic data will have in enhancing risk classification remains unanswered. Generally, however, the more relevant the medical data obtained, the more accurate the risk classification is likely to be. Thus the relevance of data is a central issue.

G. Genetic Data: Would it Add Value to Risk Classification?

It is important to define genetic data and the spectrum of conditions for which genetic markers are or may soon be clinically available. It is also important to study the relative feasibility of their use by the insurance industry. For example, genetic markers have been identified for cystic fibrosis, Huntington's disease, sickle cell anemia, hemophilia, phenylketonuria, polycystic kidney disease, retinoblastoma and other single gene diseases. Genetic testing relies upon technology ranging from chromosome analysis (Philadelphia chromosome, for example) to biochemical studies (PKU and Tay-Sachs carrier tests) to DNA probes (cystic fibrosis and sickle cell anemia). Assuming the technology for testing for the presence of these markers becomes sufficiently sensitive and specific as well as reasonably inexpensive, applicants with a marker for any of these diseases could be identified. At the other end of the spectrum is a whole range of conditions, such as coronary artery disease, which probably have a genetic component, and for which testing for genetic markers is or might become technically feasible. That would present another variable in risk classification.

H. The Potential Yield of Genetic Testing

The discussion above does not say whether genetic testing would improve risk classification. The length of time it takes for a disease to occur and the age distribution of proposed insureds are two important factors necessary to resolve that question. It may be that in the vast majority of cases, a particular disease would already have become manifest before the time of application. Other diseases which are late in manifesting themselves might be more suitable for testing. Even where the condition does lead to the presence of disease at a young age, testing might be useful depending on the actual age of the proposed insureds.

Another important factor in determining whether genetic testing for a particular condition would be useful is whether the condition can be identified using a non-genetic test already in use. For example, why use a DNA probe to identify those with sickle cell anemia? Hemoglobin electrophoresis would probably be an effective and less expensive test, particularly because the co-marker—hemoglobin S—can be detected almost as early as the DNA probe can identify the disease.

Sensitivity, specificity, predictive value and other factors that have an impact on the value of genetic testing have been addressed elsewhere.[4]

[4] **R. J. Pokorski, "The Genetic Testing Debate," (Los Angeles: *Journal of Insurance Medicine*, 1988), Vol. 20, No. 4, p. 57–61.**

Figure 2 places these categories along the spectrum of intrusiveness. In most cases, the degree to which the factors enhance the accuracy of risk classification will correspond to the degree of intrusiveness of the attempts to obtain data.

J. Obtaining Genetic Data

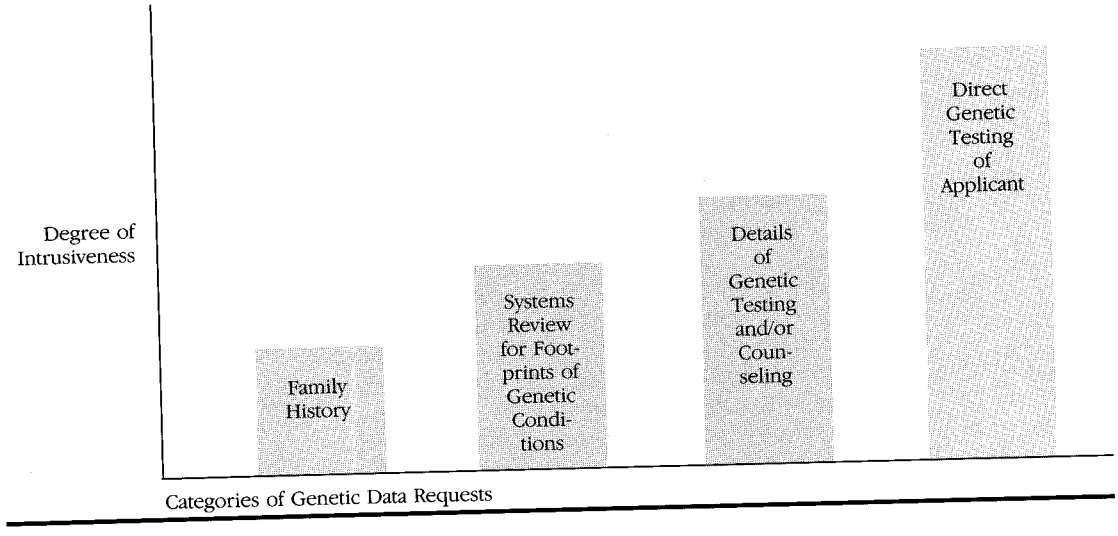
There are two basic methods of getting genetic data from applicants. The first way is indirect. The insurer could get records that document prior testing or other evidence of concern about a genetic condition. The insurer could also ask the applicant specific questions about his or her family's current or past history, or undertake a systems review.

Direct testing of the applicant, either on a for-cause or on a screening basis, would be a second approach.

Standard operating procedure currently includes asking applicants a range of questions covering past history and systems review. Therefore, the indirect approach described above really only extends an existing practice.

Similarly, insurers now get the applicant's permission to obtain either an attending physician's statement or copies of medical records. Therefore, getting records that document direct genetic testing falls within current practice, although special patient authorization could be needed. However, since much genetic testing and counseling is now done through specialized centers, test results might not be available through the attending physician. Requests for such results might meet resistance. There might be even more resistance if insurers requested genetic test results from employers or the military.

Figure 2: Degree of Intrusiveness of Categories of Genetic Data Requests



Part IV

Overview of Genetics

By William H. Alexander, M.D.
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This paper includes the following sections:

*Table I: Determining Carrier Status by Non-Genetic Means**

Example of Disease	Abnormality in Carrier
Agammaglobulinemia (Bruton type)	Ecto-5′-nucleotidase reduced lymphoblastoid cells
Alport syndrome	Microscopic hematuria
Anhidrotic ectodermal dysplasia	Reduced sweat pores, dental defects
Becker muscular dystrophy	Serum creatine kinase (less effective than in Duchenne)
Centronuclear myopathy (lethal type)	Muscle biopsy changes
Chronic granulomatous disease	Partial NADPH oxidase deficiency; discoid lupus-like skin lesions
Duchenne muscular dystrophy	Serum creatine kinase
Fabry disease	Skin lesions: a-galactosidase assay
Glucose-6-phosphate dehydrogenase deficiency	Quantitative enzyme assay and electrophoresis
Glycogen storage disease VIII	Reduced phosphorylase kinase
Hemophilia A	Factor VIII assays
Hemophilia B	Factor IX assay
Hunter syndrome (MPS II)	Enzyme assay on hair bulbs and serum
Lesch-Nyhan syndrome	Hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) assay on hair bulbs
Lowe syndrome	Aminoaciduria, lens opacities
Vitamin D-resistant rickets	Serum phosphate (may be clinical features)
X-linked congenital cataract	Lens opacities
X-linked retinitis pigmentosa	Pigmentary changes: abnormality of electroretinogram

*Modified after Milunsky, *Genetic Disorders and The Fetus* (1986)

tions. Table I describes some current non-genetic methods of determining carrier status for a few disorders linked to abnormalities of just the X chromosome. The magnitude of the human heritable burden becomes clearer when it is realized that 22 *other* chromosome pairs exist to which genetic disorders and carrier abnormalities can also be attributed. The challenge facing the geneticist is to develop better, faster, and more accurate means of recognizing early those with a genetic trait or disorder so that ultimately heritable disease may be prevented or even reversed by gene therapy.

The human genome is composed of 23 pairs of chromosomes, including one pair of sex chromosomes: XX for females, XY for males. Each chromosome is composed of deoxyribonucleic acid (DNA) in segments, called genes, which are also paired. The genetic DNA contains the code for a particular sequence of ribonucleic acid (RNA); the process of transmittal of DNA information to RNA is called transcription. The RNA sequence is then translated into the production of multiple copies of aminoacids, which finally are joined into longer cellular segments called proteins. It is the presence, absence or abnormal synthesis of

Some genes determine characteristics or traits in health and in disease. If a trait is expressed in the heterozygote then the trait is dominant (e.g., brown eyes); if the trait is expressed only if both paired genes are identical (homozygous), then the trait is called recessive (blue eyes, for example). If the effects of both alleles are seen in the heterozygotes (example: blood types A, B, AB, O), then the trait is a codominant one.

There are approximately 2,000 autosomal dominant traits known in man, some of which are abnormal. Table II lists some of the more common disorders known to be dominant traits (with an abnormal gene occurring on only one of the paired non-sex chromosomes) and their frequency in the population.

There are over 1,300 autosomal recessive traits known in man. Table III lists some of the more common of those disease traits (with an abnormal gene occurring on both of the paired non-sex chromosomes) and their frequency.

In 1911, E. B. Wilson assigned the color-blindness gene to the X-chromosome; thus the first gene assignment in man was an example of a sex-linked inheritance as opposed to an autosomal inheritance as described above. There are no human examples of Y-linked disease, but both X-linked recessive and dominant inheritance patterns are known. Table IV gives a few examples of X-linked recessive traits and their corresponding frequency in the population.

There are over 250 X-linked recessive traits in man. For all X-linked recessive disorders, heterozygote females (one normal gene, one abnormal) are clinically unaffected carriers, but transmit the abnormal gene to one-half of their female offspring (making them carriers) and to one-half of their male offspring (making them affected with the disorder). X-linked dominant disorders are rare—two examples are pseudohypoparathyroidism and vitamin D-resistant rickets.

*Table II: Autosomal Dominant Diseases**

Disease	Frequency/1,000
Dominant otosclerosis	3
Familial hypercholesterolemia	2
Adult polycystic kidneys	1.0
Multiple exostoses	0.5
Huntington's chorea	0.5
Neurofibromatosis	0.4
Myotonic dystrophy	0.2
Congenital spherocytosis	0.2
Polyposis coli	0.1
Dominant blindness	0.1
Dominant congenital deafness	0.1
Others	1.9
TOTAL	10/1,000

*Modified after Connor, Ferguson-Smith, *Essential Medical Genetics* (1987)

*Table III: Autosomal Recessive Diseases**

Disease	Frequency/1,000 births
Cystic fibrosis	0.5
Recessive mental retardation	0.5
Congenital deafness	0.2
Phenylketonuria	0.1
Spinal muscular atrophy	0.1
Recessive blindness	0.1
Adrenogenital syndrome	0.1
Mucopolysaccharidoses	0.1
Albinism	0.025
Others	0.3
TOTAL	2/1,000

*Modified after Connor, Ferguson-Smith, *Essential Medical Genetics* (1987)

*Table IV: Human X-Linked Traits**

Trait	Frequency/1,000 males
Red-green color-blindness	80.0
Fragile X mental retardation	.5
Non-specific X-linked mental retardation	.5
Duchenne muscular dystrophy	.3
Becker muscular dystrophy	.05
Hemophilia A (factor VIII)	.2
Hemophilia B (factor IX)	.03
X-linked ichthyosis	.2
X-linked agammaglobulinemia	.01
TOTAL	81.79

*Modified after Connor, Ferguson-Smith, *Essential Medical Genetics* (1987)

Cancer is a prime example of a multi-factorial disorder. Certain viruses are known to carry one or more specific genes, called oncogenes, that can be integrated into a host cell's DNA and have the ability to transform those cells into a tumor. Similar genes, called cellular oncogenes or proto-oncogenes, have been found in the genome of most animal species, including the human DNA. Normally, such oncogenes probably control cellular growth and differentiation. In addition, the proto-oncogenes are kept under control by other genes called anti-oncogenes or suppressor genes. Loss of a suppressor gene may facilitate the transformation process of an oncogene. The "double-hit" theory of tumorigenesis theorizes that the loss of control by the suppressor gene (possibly the heritable event) and the transformation of the oncogene by some carcinogenic stimulus (the environmental event), such as ultra violet light, viral infection, asbestos and tobacco tars leads to the transformation of the cells into malignant growths. In addition, specific chromosomal translocations and gene mutations are linked to the development of cancer in humans.

C. Current Genetic Techniques

The above defines and describes some of the heritable disorders challenging the genetic scientist. Details of some of the newer methods of attacking these problems are described below.

Currently, advances in genetic engineering are allowing for more accurate DNA diagnosis and, we hope, are opening the way for genetic therapy. The components of genetic engineering include the use of restriction endonucleases, DNA ligases and cloning vectors.

Restriction endonucleases are enzymes which cleave DNA in a sequence-specific manner, that is, at one particular site that is labeled the recognition site. Variable length fragments of DNA are produced, but all with the same coded sequence at their ends. These enzymes occur naturally in micro-organisms, probably as a protective mechanism against foreign DNA invasion. More than 200 restriction enzymes are known and can be used in the genetics laboratory today. DNA ligases are enzymes which join together DNA fragments.

One recently developed technique, called polymerase chain reaction (PCR), allows for rapid gene amplification. Small bits of genetic material from cells, viruses or bacteria can be chemically copied until enough are available to quickly make diagnoses of genetic diseases. Tests that were once impossible to run or that took days to perform can now be done in minutes.

Another technique that is important in the DNA diagnosis of genetic disorders is the use of restriction fragment length polymorphisms (RFLPs). Once the DNA is extracted from some nucleated cell (peripheral blood lymphocyte, skin fibroblast, amniotic fluid cell, etc.), it can be cut into fragments using the restriction endonucleases described above. For each individual, the number of recognition sites on his or her chromosomes for that particular enzyme varies, i.e., the exact number and size of fragments produced by use of the endonucleases is unique for the individual. The presence or absence of a particular recognition site is called a restriction fragment length polymorphism (RFLP).

The study of these RFLPs is very important in the DNA diagnosis of genetic disorders. For example, for some genetic disorders, it may be difficult to pinpoint the exact locus on the chromosome of the gene responsible for the disease. However, the gene mutation which caused the disease may also cause a loss or a gain of a recognition site for a restriction endonuclease and changes in the patterns of fragments can be studied to make the diagnosis of that gene disorder. Similarly, it may be possible to identify the disease (or carrier for a disease) because of the presence of a neighboring chromosomal endonuclease recognition site. The mutated gene is "linked" to the recognition site and linkage studies using RFLPs thus help make genetic diagnoses.

Currently, the most important and expanding work in medical genetics is tied to the use of DNA probes. If an abnormal gene can be sequenced, then a radioactive-labeled synthetic DNA analog of that gene (the probe) can be constructed, amplified and banked or stored until needed. The piece of synthetic DNA will hybridize with a denatured DNA sample taken from an individual to be tested for that genetic disorder, confirming that he or she has the disease (or confirming that he or she does not have the disorder if no hybridization occurs). Such probes already exist for the diagnosis of some prenatal disorders, to help confirm the diagnosis of some types of leukemia, and will soon be available as diagnostic tools for other tumors, such as colon and bladder cancer.

*Addendum 1**

Gene	Chromosome
Onc gene: Abelson strain of murine leukemia virus	9
ABO blood group	9
Aconitase, soluble	9
Acid phosphatase-I	2
Adenosine deaminase	20
Adenosine kinase	10
Alpha-fetoprotein	4
Aryl hydrocarbon hydroxylase	2
Adenylate kinase-I (soluble)	9
Albumin	4
Apolipoprotein A-I	11
Apolipoprotein B	2
Apolipoprotein E	19
Adenine phosphoribosyl-transferase	16
Arylsulfatase A	22
Arylsulfatase B	5
Argininonsuccinate synthetase	9
Antithrombin III	1
Beta-2-microglobulin	15
Becker muscular dystrophy	X
Complement component-3	19
Cataract, zonular pulverulent	1
Congenital adrenal hyperplasia	6
Catalase	11
Color-blindness	X
Cystathionine beta-synthase	21
Cystic fibrosis	7
Chorionic gonadotrophin, beta chain	19
Charcot-Marie-Tooth disease	1
Collagen I alpha-1 chain	17
Collagen I alpha-2 chain/ Osteogenesis imperfecta	7
Dentinogenesis imperfecta	4
Dihydrofolate reductase	5
Duchenne muscular dystrophy	X
Myotonic dystrophy	19
Epidermal growth factor, receptor	7
Elliptocytosis-I	1
Oncogene ERBB	7
Endogenous retrovirus-I	18
Esterase A4	11
Esterase D	13
Clotting Factor VII	13
Clotting Factor VIII	X
Clotting Factor IX	X
Clotting Factor X	13
Fumarate hydratase	1
Oncogene FMS (McDonough feline sarcoma virus)	5
Oncogene FOS: FBJ osteosarcoma virus	2
Duffy blood group	1
Acid alpha-glucosidase	17
Galactokinase	17
Galactose-1-phosphate uridyltransferase	9
Group-specific component	4
Growth hormone	17
von Willebrand factor/ disease	12
Alpha-galactosidase A	X
Glutamate oxaloacetate transaminase, soluble	10
Glucose-6-phosphate dehydrogenase	X
Glucosephosphate isomerase	19
Glutathione peroxidase-I	3
Glutathione reductase	8
Beta-glucuronidase	7
Hemoglobin alpha chain	16
Hemoglobin beta chain	11
Huntington disease	4
Hexosaminidase A	15
Hexosaminidase B	5
Hemochromatosis	6
Human leukocyte antigens	6
Haptoglobin	16
Hypoxanthine-guanine phosphoribosyltransferase	X
Harvey rat sarcoma-1 protooncogene	11
Isocitrate dehydrogenase soluble	2
Alpha-1-iduronidase	22
Interferon, fibroblast	9
Immunoglobulin heavy chain gene cluster	14
Gene (cluster) for kappa light chain	2
Gene (cluster) for lambda light chain	22
Insulin	11
Oncogene INT: putative murine mammary cancer oncogene	12
Inosine triphosphatase	20

Addendum 2

Glossary

ALLELE—one of several alternate forms of a gene occupying a given locus on a chromosome

AMINO ACID—an organic acid; the 20 amino acids are assembled into proteins

AMPLIFICATION—the production of additional copies of a DNA sequence, found as either extrachromosomal or intrachromosomal

ANTIONCOGENE (suppressor gene)—gene whose function is to control the transformation of an oncogene into tumorous growth

AUTOSOME—one of the non-sex chromosomes; 22 pairs in the human genome

BACTERIAL PLASMID—an autonomous self-replicating extrachromosomal circular DNA found in bacteria; non-bacterial DNA may be inserted for cloning purposes

CARRIER—genetic, person in good health whose chromosomes contain a mutant gene which may be transmitted to his or her children

CHROMOSOME—one unit of the genome; consists of a long molecule of duplex DNA and proteins; 23 pairs in the human genome

CHROMOSOME-SPECIFIC LIBRARY—set of cloned fragments, each fragment a chromosome; together representing the entire genome

CLONING VECTOR—a virus or a plasmid that is used to carry an inserted segment of DNA into a host for the purpose of producing multiple copies of the segment

CODOMINANT—alleles that both contribute to the phenotype

CONCORDANCE RATE—rate at which a trait occurs in two different individuals: a measure of the genetic contribution or heritability

CONGENITAL MALFORMATION—physical trait or disorder found at birth that may be hereditary, environmental or both

CONTINUOUS MULTIFACTORIAL TRAIT—trait that follows as bell-shaped curve in distribution in the population and is derived from both genetic and environmental factors

DEOXYRIBONUCLEIC ACID (DNA)—the genetic material found in chromosomes; in chemically linked sequences of nucleotides that code for the production of amino acids

DNA LIGASE—enzyme used to splice together DNA segments

DNA PROBE—a synthetic DNA analog of a gene that will hybridize with that gene, if present in a DNA sample from an individual being tested

DOMINANT TRAIT—a trait in which one of a pair of alleles is expressed in the phenotype in preference to the other

GENE—a segment of DNA on a chromosome which codes for the production of a particular protein product

GENETIC ENGINEERING—manipulation of genetic material; in particular, cloning methods

GENOME—the entire cohort of chromosomes for that species; 23 pairs of chromosomes comprise the human genome

GENOMIC DNA LIBRARY—a set of cloned fragments, each fragment part of a chromosome, together representing the entire genome

GENOTYPE—the genetic constitution of an organism

HETEROZYGOUS—description of an individual who carries two different genes for a particular trait

HOMOZYGOUS—description for an individual who carries two identical genes for a particular trait

HYBRIDIZATION—the technique by which two complementary nucleic acid sequences anneal with each other to form a duplex structure

Annex:

Principles of Insurance and Risk Classification

By Robert J. Pokorski, M.D.

Life insurance risks judged to be substandard are charged an extra premium that is determined by the magnitude of the extra risk. Examples of impairments and/or risk factors that increase the likelihood of an early life insurance claim are cigarette smoking (200 percent), significant hypertension (300 percent), diabetes mellitus (400 percent), and stable coronary heart disease (500 percent). These examples are illustrative only. The percentages in a given case might depend on many variables. For health and disability insurance, substandard risks may be accepted by charging an extra premium, applying an exclusion rider, adjusting the waiting period before a claim can be filed or otherwise modifying the terms under which benefits can be paid.

Six percent of applications for individual life insurance are accepted on a substandard basis. Approximately 15 percent of individually underwritten health insurance policies are issued on a substandard basis with either a rider or an extra premium.

(c) Declined—The risk presented is so great that the insurance company decides it cannot issue insurance to these individuals. Why? There is a point where yearly premiums for certain risks become so high that they appear to be unaffordable to most people. At this point, only a very small percent of those who are offered such insurance will accept. And these tend to be people who know more about their health problems than the underwriter was able to learn. So even if the premium were set quite high, it would probably be inadequate to cover claims.

Few life insurance companies elect to offer insurance when anticipated mortality exceeds a specified level such as 500 percent of standard. Those whose risk is judged to be greater than this are "declined" for insurance. Impairments with a mortality ratio greater than 500 percent include recently diagnosed cancer (approximately 20,000 percent), newly-acquired HIV infection without AIDS (4,400 percent), and AIDS (over 50,000 percent). About two percent of applications for individual life insurance are declined.

For health insurance, impairments that would increase premiums by over 100 percent would render the risk uninsurable by most health insurers (without restrictions on coverage). Six to seven percent of applications for health insurance are declined for health reasons.

Adverse selection, also known as antiselection, is one final consideration that is of great importance to insurers. Adverse selection is a well-known phenomenon. It occurs when people with a greater likelihood of loss than what they are charged for buy or continue insurance coverage to a greater extent than other people. Sometimes these applicants withhold significant information from the insurer and/or choose amounts and types of insurance that are most beneficial to themselves. For example, someone with a history of heart disease is more likely to apply for insurance and/or likely to apply for a greater amount of insurance coverage than would otherwise be the case because he or she knows that a claim is likely in the foreseeable future. If this important information goes unmentioned on the insurance application, the premium charged by the insurer will be insufficient to cover the risk involved. This premium deficit would be made up by the others in the pool who have already paid their fair share.

Adverse selection also occurs if the insurer is not permitted to obtain or use information that is pertinent to the risk being considered. In the example above, the premiums charged would be insufficient to cover the risk involved if the insurer was not permitted to ask the applicant and his or her attending physician whether there was a history of heart disease. Similarly, adverse selection and a premium incommensurate with the risk could occur if the insurer were not allowed to use this information once it was obtained.