# Understanding Gene Testing

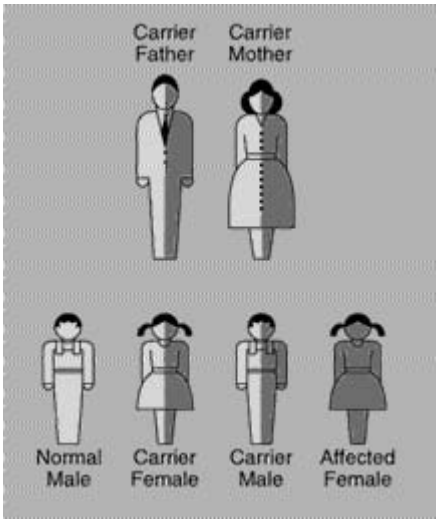
*How does heredity influence disease?*

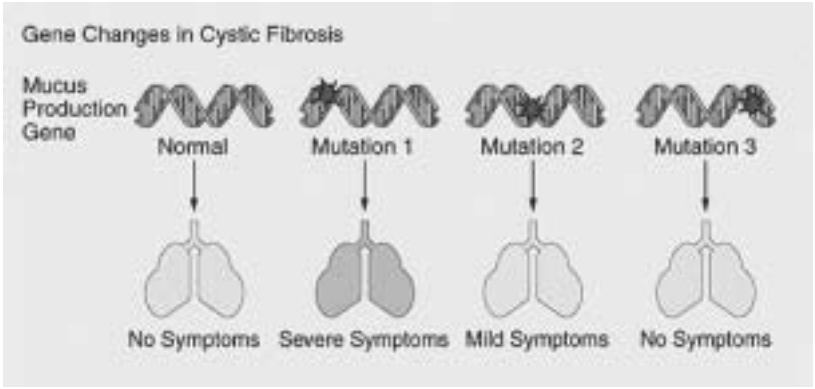
Genes come in pairs, with one copy inherited from each parent. Many genes come in a number of variant forms, known as alleles. A dominant allele prevails over a normal allele. A recessive gene becomes apparent if its counterpart allele on the other chromosome becomes inactivated or lost.

For example, in cystic fibrosis (a disease that seriously impairs breathing and digestion), the gene that causes abnormal mucus production and disease is a recessive allele. A person who inherits one copy of the recessive allele does not develop disease because the normal allele predominates. However, such a person is a carrier who has a 50-50 chance of passing the altered recessive allele to each of his or her descendants. When both parents are carriers, the chance is one in four that a child will inherit two of the recessive alleles, one from each parent, and develop disease. (This chance remains one in four for each pregnancy.) Although most recessive mutations are rare, a few, including those for cystic fibrosis and sickle-cell anemia, are fairly common in specific ethnic groups.

However, most diseases and traits don't follow simple patterns of inheritance; a variety of factors influence a gene's performance. To begin with, not all mutated alleles invariably lead to disease. Even with a dominant allele such as the BRCA1 breast cancer susceptibility gene, for instance, the risk of disease by age 65 is 80 percent, not 100 percent. This quality – an indication of the probability that a given gene mutation will produce disease – is referred to as penetrance.

Not only can different mutations in the same gene produce a wide range of effects in different individuals, as is the case with cystic fibrosis, but also mutations in several different genes can lead to the identical outcome, as is the case with some forms of Alzheimer's disease. Some traits require simultaneous mutations in two or more genes. And a phenomenon known as imprinting can determine which of a pair of genes, the mother's allele or the father's, will be active or silenced.




In diseases associated with altered recessive genes, both parents - though disease-free themselves- carry one normal allel and one altered allele. Each child has one chance in four of inheriting two altered alleles and developing the disorder; one chance in four of inheriting two normal alleles, and two chances in four of inheriting one normal and one altered allele, and being a carrier like both parents.

**Understanding Gene Testing**
*What is gene testing?*

Gene testing involves examining a person's DNA – taken from cells in a sample of blood or, occasionally, from other body fluids or tissues – for some anomaly that flags a disease or disorder. The DNA change can be relatively large: a missing or added piece of a chromosome – even an entire chromosome – that is visible under a microscope. Or it can be extremely small, as little as one extra, missing, or altered chemical base. Genes can be over expressed (too many copies), inactivated, or lost altogether. Sometimes, pieces of chromosomes become switched, or transposed, so that a gene ends up in a location where it is permanently and inappropriately turned on or off.

In addition to studying chromosomes or genes, genetic testing in a broader sense includes biochemical tests for the presence or absence of key proteins that signal aberrant genes.

**Understanding Gene Testing**
*What are the uses of genetic testing?*

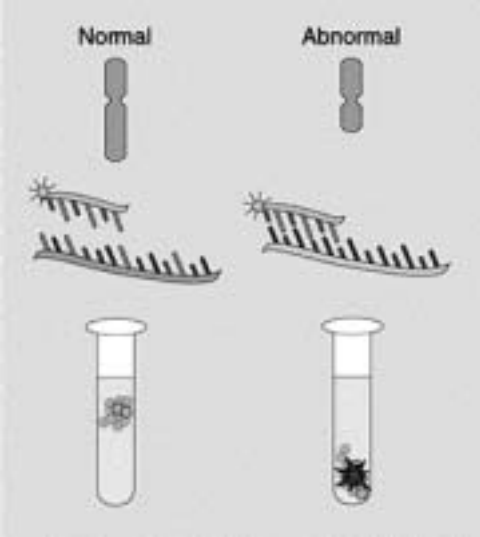
Genetic tests can be used to look for possible predisposition to disease as well as to confirm a suspected mutation in an individual or family.

The most widespread type of genetic testing is newborn screening. Each year in the United States, four million newborn infants have blood samples tested for abnormal or missing gene products. Some tests look for abnormal arrangements of the chemical bases in the gene itself, while other tests detect inborn errors of metabolism (for example, phenylketonuria) by verifying the absence of a protein that the cell needs to function normally.

Carrier testing can be used to help couples to learn if they carry – and thus risk passing to their children – a recessive allele for inherited disorders such as cystic fibrosis, sickle-cell anemia, or Tay-Sachs disease (a lethal disorder of lipid metabolism). Genetic tests – biochemical, chromosomal, and DNA-based – also are widely available for the prenatal diagnosis of conditions such as Down syndrome.

In clinical research programs, doctors make use of genetic tests to identify telltale DNA changes in cancer or precancer cells. Such tests can be helpful in several areas: early detection (familial adenomatous polyposis genes prompt close surveillance for colon cancer); diagnosis (different types of leukemia can be distinguished); prognosis (the product of a mutated p53 tumor-suppressor gene flags cancers that are likely to grow aggressively); and treatment (antibodies block a gene product that promotes the growth of breast cancer).

Much of the current excitement in gene testing, however, centers on predictive gene testing: tests that identify people who are at risk of getting a disease, before any symptoms appear. Tests are already available in research programs for some two dozen such diseases, and as more disease genes are discovered, more gene tests can be expected.




Different types of genetic tests are used to hunt for abnormalities in whole chromosomes, in short stretches of DNA within or near genes, and in the protein products of genes.

**Understanding Gene Testing**

*What are the limitations of gene testing?*

First, current gene tests cannot provide a satisfactory answer for everyone who seems to be at risk for inherited breast or colon cancer. In some families, multiple cases may reflect shared environmental exposures rather than inherited susceptibility. Even when an inherited gene is to blame, it is not necessarily the test gene; the BRCA1 gene mutation, for example, is found in only about half of the families with hereditary breast cancer.

Second, despite major advances in DNA technology, identifying mutations remains a great challenge. Many of the genes of greatest interest to researchers are enormous, containing many thousands of bases. Mutations can occur anywhere, and searching through long stretches of DNA is difficult.

In addition, a single gene can have numerous mutations, not all of them equally influential. The cystic fibrosis gene, for instance, can display any one of more than 300 different mutations, which cause varying degrees of disease; some seem to cause no symptoms at all. Thus, a positive test does not guarantee that disease is imminent, while a negative test - since it evaluates only the more common mutations - cannot completely rule it out.

Furthermore, predictive tests deal in probabilities, not certainties. One person with a given gene, even one that is dominant like the hereditary breast cancer gene, may develop disease, while another person remains healthy, and no one yet knows why. A gene may respond to the commands of other genes or be switched on by an environmental factor such as sunlight.

Perhaps the most important limitation of gene testing is that test information often is not matched by state-of-the-art diagnostics and therapies. Many diseases and many types of cancer still lack optimal screening procedures; it is often not possible to detect an early cancer even in an individual with a known predisposition.

In inherited breast cancer, frequent screening with mammography offers the best chance of early detection, but falls short of prevention. Moreover, mammography is least effective in the glandular breasts of young women, the very ones at greatest risk from an inherited susceptibility. For the moment, the best assurance of prevention may lie in drastic and costly surgery to remove the breasts - but even a total mastectomy can leave some breast cells behind. As for the ovarian cancer that threatens high-risk families, available screening measures often cannot discover disease in time. Here, too, women in high-risk families often opt for prophylactic surgery to remove the ovaries. To date, however, neither type of prophylactic surgery has been proven to prevent completely the occurrence of cancer.

Scientists are actively studying interventions aimed at the prevention of cancer. For example, ongoing clinical trials are evaluating the use of tamoxifen, an anticancer drug, as a breast cancer preventive. However, such approaches are still in the realm of research.

**Understanding Gene Testing**

*What are the risks of gene testing?*

The physical risks of the gene test itself - usually no more than giving a blood sample - are minimal. Any potential risks have more to do with the way the results of the test might change a person's life.

Psychological impact. First, there are the emotions aroused by learning that one is - or is not - likely to develop a serious disease. Many people in disease families have already seen close relatives fall victim to the disorder. The news that they do indeed carry the disease gene can elicit depression, even despair.

Few studies to date have looked directly at the outcome of gene testing for cancer. One study found that, after 3 to 6 weeks, the women identified as gene carriers experienced persistent worries, depression, confusion, and sleep disturbance. Even half of the noncarriers reported that they continued to worry about their risk status.

*A gene test confirming the risk of a serious disease can trigger profound psychological consequences.*

Family relations. Unlike other medical tests, gene tests reveal information not only about ourselves but about our relatives, and the decision to have a gene test, as well as the test results, can reverberate throughout the family. If a baby tests positive for sickle-cell trait, for example, it follows that one of his or her parents is a carrier. It is also possible for gene tests to inadvertently disclose family secrets involving paternity or adoption.

Emotions elicited by test results can produce a shift in family dynamics. Someone identified as carrying the gene may feel anger, while one who has escaped may be overwhelmed by guilt for avoiding a disease that afflicts a close relative.

Family issues are especially prominent in research programs where genetic linkage tests depend on testing many members of the same family. Some family members may not want to participate in the study or know their genetic risks. People considering gene tests may want to find out how their relatives would feel about knowing whether or not they have a disease gene or allowing the information to be given to others.

Someone who elects to have a gene test needs to consider whether or not to share the test results with other members of the family. Do they want to know? Who should be told – spouse, children,

parents, fiance´? Should someone in a high-risk family be tested before she or he marries? What will a positive test mean to one's relationships? If one chooses not to learn the results of the family's gene testing, can such a request be respected? How?

*The question and issues raised by gene testing can challenge family and other personal relationships.*

**Medical choices.** Someone who tests positive for a cancer susceptibility gene may opt for preventive or therapeutic measures that have serious long-term implications and are potentially dangerous or of unproven value. In the first family to be tested for a BRCA1 mutation, for instance, some women chose surgery to remove their breasts - and ovaries, too, after childbearing was completed. Other families told the genetic counselor that they were not interested in even discussing surgery.


*Finding ways to ensure the confidentiality of gene test results is a major concern.*

**Privacy.** Our genes hold an encyclopedia of information about us and, indirectly, about our relatives. Who should be privy to that information? Will a predisposition for cancer, for instance, remain secret - or could the information slip out? The concern is that test results might someday be used against a person. Some people have been denied health insurance, some have lost jobs or promotions, and some have been turned down for adoptions because of their gene status.

Small research studies have conscientiously established safeguards to keep DNA results under wraps. Assurances of confidentiality may be more difficult to come by when larger numbers of people have access to the results. Clinical test results are normally included in a person's medical records. Even if gene testing information could be kept out of the medical record, a person's need for more frequent medical checkups, for example, could provide a tip-off to susceptibility. Might a genetic flaw constitute a "preexisting condition" that would be excluded from insurance coverage?

**Understanding Gene Testing**

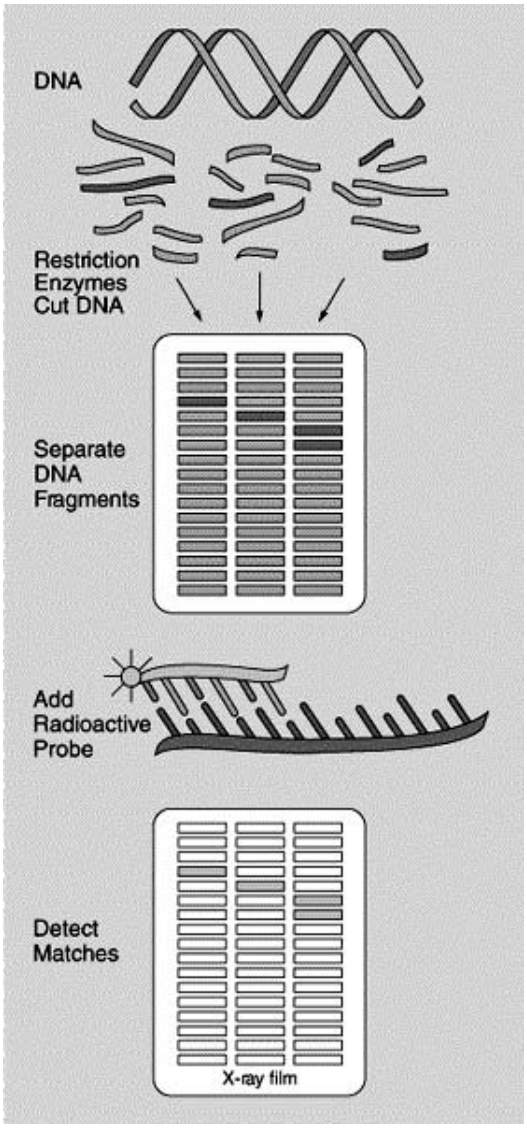
*How do scientists develop predictive gene tests?*

Scientists looking for a disease gene typically have begun by studying DNA samples from members of "disease families," in which numerous relatives, over several generations, have developed the same illness such as colon cancer. Researchers look for genetic markers – easily identifiable segments of DNA – that are consistently inherited by persons with the disease but are not found in relatives who are disease-free. Then, they painstakingly narrow down the target DNA area, pull out candidate genes, and look for specific mutations.

Before a specific gene is located, linked genetic markers can be used to test members of the family under study. However, to test wider populations, it is necessary to find the gene itself. Because the DNA highway is so vast, this can be enormously difficult. In the case of Huntington's disease, it took 10 years to advance from linkage markers to the gene.

Once a disease gene has been cloned (copied to get enough to study in detail) and identified, scientists can construct DNA probes – lengths of single-stranded DNA that match parts of the known gene. (This is possible because, in double-stranded DNA, adenine in one strand always pairs with thymine in the other, and guanine pairs with cytosine.) The single-stranded probe then seeks and binds to complementary bases in the gene. When the probe has been tagged with a radioactive atom, the area of DNA it binds to - the gene – lights up. The fact that some diseases exhibit multiple mutations within the same gene adds to the complexity of gene testing.

Functional gene tests, which detect protein rather than DNA, can demonstrate not only that a mutated gene is present but also that it is actively making an abnormal protein or no protein at all.




*To find a target gene mutation in a sample of DNA, scientists use a DNA probe – a length of single-stranded DNA that matches part of the gene and is linked to a radioactive atom. The single-stranded probe seeks and binds to the gene. Radioactive signals from the probe are then made visible on x-ray film, showing where the probe and gene matched*