

Review Article

Genomic Medicine

ALAN E. GUTTMACHER, M.D.,
AND FRANCIS S. COLLINS, M.D., PH.D., *Editors*

GENETIC TESTING

WYLIE BURKE, M.D., PH.D.

GENETIC testing can provide dramatic clinical benefits. A child known to have multiple endocrine neoplasia type 2 (MEN-2) can be spared medullary carcinoma by undergoing prophylactic thyroidectomy (Fig. 1),¹ and an adult with hereditary hemochromatosis can be spared cirrhosis by the early initiation of phlebotomy treatment.² Genetic testing can also provide diagnostic and prognostic information that aids in difficult clinical decision making. For example, a test for a deletion in the dystrophin gene, the cause of Duchenne's muscular dystrophy, can be used to identify women who are carriers of this condition (Fig. 2).³ A carrier may avoid having an affected child by avoiding pregnancy or by undergoing prenatal testing for Duchenne's muscular dystrophy, with possible pregnancy termination if the fetus is found to be affected.

As these examples illustrate, most available genetic tests address questions related to rare or uncommon diseases. Even hemochromatosis, often described as a common genetic disease, has a prevalence of 0.5 percent or less.⁴ However, the scope of genetic testing is expanding to include tests that assess the genetic risk of common diseases such as cancer and cardiovascular disease.^{5,6}

DEFINITION OF GENETIC TESTING

A genetic test is "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes."⁷ This definition reflects the broad range of techniques that can be used in the testing process. Genetic tests also have diverse purposes, including the di-

From the Department of Medical History and Ethics, University of Washington, Seattle. Address reprint requests to Dr. Burke at the Department of Medical History and Ethics, Box 357120, University of Washington, 1959 NE Pacific, Rm. A204, Seattle, WA 98195, or at wburke@u.washington.edu.

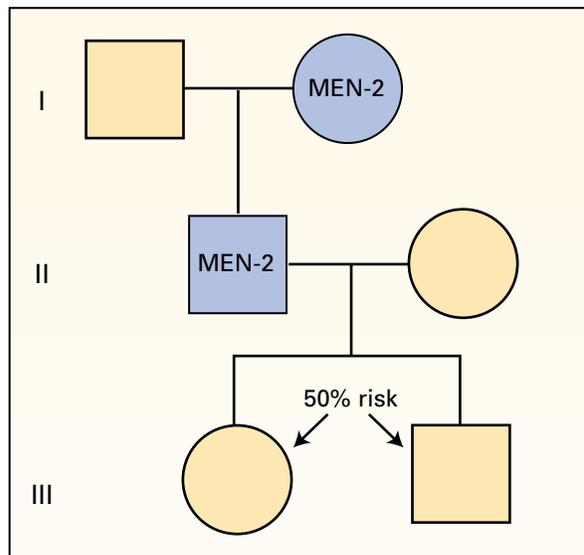


Figure 1. Autosomal Dominant Inheritance.

Children (indicated by the arrows) whose parent is affected by multiple endocrine neoplasia type 2 (MEN-2) have a 50 percent chance of inheriting the condition. Testing can identify the disease in such persons before clinical complications occur. Prophylactic thyroidectomy can be offered to those at risk, to prevent medullary thyroid carcinoma. Squares denote male family members, and circles female family members.

agnosis of genetic disease in newborns, children, and adults; the identification of future health risks; the prediction of drug responses; and the assessment of risks to future children. Examples of currently available genetic tests are given in Tables 1 and 2,⁸⁻¹¹ and a comprehensive and continually updated listing of available tests can be found at the GeneTests-GeneClinics Web site (<http://www.geneclinics.org>).⁸

GENETIC DIAGNOSIS

Genetic testing is often the best way to confirm a diagnosis in a patient with signs or symptoms suggestive of a genetic disease. The technique chosen depends on both the clinical question and the predictive value of the available tests. For a young patient with medullary cancer of the thyroid, for example, the identification of a mutation in the *RET* oncogene confirms that the cancer is a manifestation of MEN2, which accounts for approximately one quarter of cases of medullary thyroid cancer. The *RET*-mutation test can identify 85 to 95 percent of affected relatives of patients with medullary carcinoma.¹²⁻¹⁴

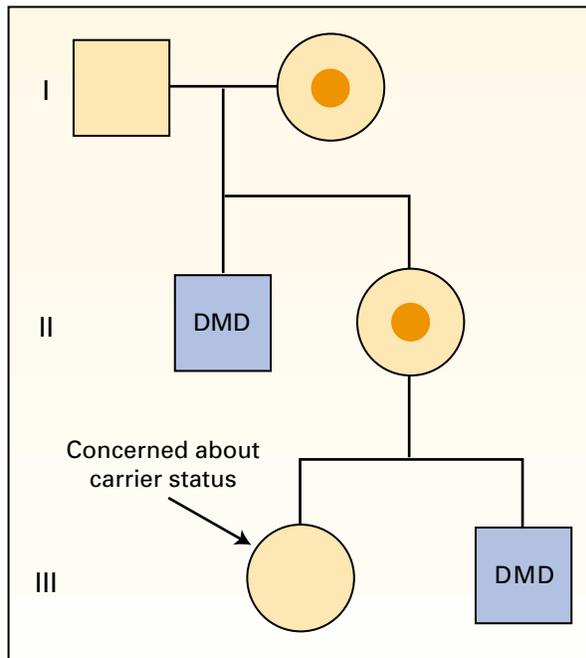


Figure 2. X-Linked Recessive Inheritance.

A woman (indicated by the arrow) wants to know whether she carries the gene for Duchenne's muscular dystrophy (DMD), because her uncle and her brother were both affected (solid symbols), and her mother and grandmother are known to be carriers (symbols with a solid center). She has a 50 percent chance of inheriting the carrier status from her mother. Genetic testing can be used to determine her carrier status if her affected brother has a positive test result. Squares denote male family members, and circles female family members.

Testing for dystrophin gene deletions with the use of DNA-based technology is now the preferred diagnostic test for Duchenne's muscular dystrophy when clinical signs and symptoms suggest the diagnosis. A positive test confirms the diagnosis. A muscle biopsy is needed if the DNA-based test is negative. A negative test occurs in about 30 percent of patients with Duchenne's muscular dystrophy because some mutations in the dystrophin gene are not detected by current DNA testing.¹⁵

This level of genetic complexity is common and is termed "allelic heterogeneity," meaning that there are multiple different mutations (or alleles) in the same gene, all of which may lead to disease. For example, hundreds of different disease-causing mutations have been found in the cystic fibrosis gene¹⁶ and the *BRCA1* and *BRCA2* genes associated with susceptibility to breast and ovarian cancer.¹⁷

In contrast, the most common form of sickle cell anemia, a disease occurring in 1 in 700 blacks in the United States, is caused by a single specific mutation in

the β -globin gene, resulting in a modified hemoglobin, termed hemoglobin S (HbS).¹⁸ Both hematologic and DNA-based tests are available. Diagnostic testing can be done reliably by hemoglobin electrophoresis, but the DNA-based test for the HbS mutation is an important additional option because it makes prenatal diagnosis possible (Fig. 3).¹⁹

Cytogenetic tests are used to diagnose chromosomal disorders, in which chromosomes or chromosomal segments are duplicated, deleted, or translocated to different chromosomes. These tests make it possible to identify the chromosomal basis of conditions such as Down's syndrome, which are caused by the presence of an extra chromosome, the lack of a chromosomal segment, or rearrangement of the chromosomes.^{20,21} One cytogenetic technique, fluorescence in situ hybridization, identifies specific chromosomal regions through the use of fluorescent DNA probes and thus can pinpoint small chromosomal duplications and deletions missed by previous methods.^{22,23} For example, the 22q11 deletion syndrome, a genetic condition caused by small deletions of chromosome 22 (Fig. 4), is characterized by a variety of learning disabilities, palatal abnormalities, and congenital heart disease.²⁴ Using fluorescence in situ hybridization, it has been possible to show that six previously described clinical syndromes, each with an overlapping cluster of physical and cognitive deficits, all represent manifestations of the 22q11 deletion syndrome.²⁴

FAMILIAL RISK

A genetic diagnosis often indicates that other family members are at risk for the same condition. Genetic testing can help in evaluating this risk. For example, when the causative mutation of a genetic condition is known, presymptomatic diagnosis of family members is often possible and may offer an important opportunity for disease prevention. Thus, after a person is given a diagnosis of MEN2 and the causative *RET* mutation is identified, testing of all first-degree relatives is recommended (Fig. 1) so that prophylactic thyroidectomy can be offered to those who inherited the mutation.^{25,26} A small number of other inherited cancer syndromes, such as familial adenomatous polyposis, offer a similar opportunity.²⁷

The identification of risk does not necessarily lead to treatment options, however. Genetic testing for Huntington's disease, an autosomal dominant condition that causes progressive motor and cognitive dysfunction starting in midlife, allows people with an affected parent to determine whether they have inherited the causative mutation.²⁸ If the mutation is present, the person's risk of Huntington's disease is virtually 100 percent, given a normal life span. Yet, no effective intervention or preventive treatment is currently available. The choice to be tested is thus highly personal,

TABLE 1. EXAMPLES OF GENETIC TESTS.*

CONDITION AND AVAILABLE TESTS	COMMENT
<p>Multiple endocrine neoplasia type 2 Molecular tests Panel test: DNA-based detection of common <i>RET</i> gene mutations Sequencing: analysis of DNA sequence of specific coding regions of the gene to detect sequence variation</p>	<p>An autosomal dominant condition causing a high lifetime risk of MTC. The disease has 3 subtypes: 2A, associated with onset of MTC in childhood or early adulthood and an increased risk of parathyroid adenoma or hyperplasia; familial medullary thyroid carcinoma associated with a risk of MTC alone, with onset usually in adulthood; and 2B, associated with onset of MTC in early childhood and with characteristic facial features, mucosal neuromas of the lips and tongue, and ganglioneuromatosis of the gastrointestinal tract.</p>
<p>Duchenne's muscular dystrophy Molecular tests: DNA-based detection of deletions or structural inversions in coding regions of the Duchenne's muscular dystrophy gene Biochemical test: measurement of dystrophin protein in muscle tissue by weight (values are 0–3 percent of normal values) or by immunohistochemical techniques (showing complete or nearly complete absence of dystrophin)</p>	<p>An X-linked recessive condition causing progressive skeletal-muscle weakness and cardiomyopathy. Affected children are typically wheelchair-bound by the age of 12 years. Death is usually due to cardiomyopathy or respiratory failure.</p>
<p>Sickle cell anemia Molecular test: DNA-based detection of the HbS mutation Hematologic test: hemoglobin electrophoresis detects HbS</p>	<p>An autosomal recessive condition causing vasoocclusive events, resulting in pain crises, cerebrovascular complications, and splenic and renal dysfunction. Sickle cell anemia results from the HbS/HbS genotype. Related sickle cell disorders are caused by HbS in combination with other β-globin variants, such as HbC.</p>
<p>Cystic fibrosis Molecular tests Panel test: DNA-based detection of common <i>CFTR</i> mutations; core panel recommended by the American College of Obstetrics and Gynecology and the American College of Medical Genetics contains 25 mutations and is estimated to identify 85 percent of carriers in the general North American population Biochemical test: detection of elevated sweat chloride concentration</p>	<p>An autosomal recessive condition causing progressive lung disease. Most affected patients also have pancreatic insufficiency; other common complications include chronic sinusitis, meconium ileus, and male infertility.</p>
<p>Down's syndrome Chromosome test: staining of chromosomes to detect extra copy of chromosome 21</p>	<p>A chromosomal condition causing mental retardation and characteristic facial features. Other complications may include congenital heart disease and childhood leukemia.</p>
<p>22q11 deletion syndrome Chromosome test: fluorescence in situ hybridization to detect small deletions in chromosome 22</p>	<p>A chromosomal microdeletion causing learning difficulties, congenital heart disease, palatal abnormalities, and characteristic facial features.</p>
<p>Iron overload Molecular tests: DNA-based detection of C282Y and H63D mutations in the <i>HFE</i> gene Biochemical test: measurement of transferrin saturation (serum iron \div TIBC \times 100): if elevated (>60 for men, >50 for women), serum ferritin measured; if elevated (>300 $\mu\text{g/liter}$ for men, >200 $\mu\text{g/liter}$ for women), iron status assessed by liver biopsy or serial phlebotomy</p>	<p>A condition causing excess iron accumulation, resulting in deposition of iron in body tissues. Complications include cirrhosis, primary liver cancer, cardiomyopathy, diabetes, joint pain, and impotence. Most primary iron overload in the United States is due to mutations in the <i>HFE</i> gene, but other genetic disorders of iron overload have also been described.</p>
<p>Venous thromboembolism Molecular test for factor V Leiden: DNA-based detection of the factor V Leiden mutation Biochemical test for factor V Leiden: measurement of activated protein C resistance</p>	<p>The most common genetic risk factor is factor V Leiden, a mutation in the factor V gene. Other genetic contributors include the prothrombin variant 20210A, antithrombin III deficiency, protein S deficiency, and protein C deficiency.</p>
<p>Breast and ovarian cancer Molecular tests Panel test: DNA-based detection of 2 <i>BRCA1</i> mutations and 1 <i>BRCA2</i> mutation common in Ashkenazi Jewish populations Sequencing: analysis of DNA sequence of coding regions and adjacent segments of <i>BRCA1</i> and <i>BRCA2</i> to detect sequence variation</p>	<p>Mutations in the <i>BRCA1</i> and <i>BRCA2</i> genes are associated with an increased risk of breast and ovarian cancer.</p>

*Additional information about these conditions and available genetic tests can be found at <http://www.geneclinics.org>,⁸ <http://www.cdc.gov/genomics/hugenet/reviews.htm>,⁹ http://www.cancer.gov/cancer_information/pdq,¹⁰ and <http://www.ncbi.nlm.nih.gov/omim/>.¹¹ MTC denotes medullary carcinoma of the thyroid, HbS hemoglobin S, HbC hemoglobin C, and TIBC total iron-binding capacity.

TABLE 2. EXAMPLES OF MOLECULAR GENETIC TESTS.*

CONDITION	GENES	REPORTED USES OF TESTING
Neurologic		
Spinocerebellar ataxias	<i>SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, DRPLA</i>	Diagnostic, predictive
Early-onset familial Alzheimer's disease	<i>PSEN1, PSEN2</i>	Diagnostic, predictive
Canavan's disease	<i>ASPA</i>	Diagnostic, prenatal
Nonsyndromic inherited congenital hearing loss (without other medical complications)	<i>GJB2</i>	Diagnostic, prenatal
Fragile X syndrome	<i>FMR1</i>	Diagnostic, prenatal
Huntington's disease	<i>HD</i>	Diagnostic, predictive, prenatal
Connective tissue		
Ehlers-Danlos syndrome, vascular type	<i>COL3A1</i>	Diagnostic, prenatal
Marfan's syndrome	<i>FBNI</i>	Diagnostic, prenatal
Osteogenesis imperfecta types I-IV	<i>COL1A1, COL1A2</i>	Diagnostic, prenatal
Oncologic		
Familial adenomatous polyposis	<i>APC</i>	Diagnostic, predictive
Hereditary nonpolyposis colorectal cancer	<i>MLH1, MSH2, PMS2, MSH3, MSH6</i>	Diagnostic, predictive
von Hippel-Lindau disease	<i>VHL</i>	Diagnostic, predictive
Li-Fraumeni syndrome	<i>TP53</i>	Diagnostic, predictive
Hematologic		
β -thalassemia	β -globin (<i>HbB</i>)	Carrier detection, prenatal diagnosis
Hemophilia A	<i>F8C</i>	Prognostic, carrier detection, prenatal
Hemophilia B	<i>F9C</i>	Carrier detection, prenatal
Renal		
Nephrogenic diabetes insipidus	<i>AVPR2, AQP2</i>	Diagnostic, carrier detection, prenatal
Polycystic kidney disease (autosomal dominant and autosomal recessive)	<i>PKD1, PKD2, PKHD1</i>	Predictive, prenatal
Multisystem		
Achondroplasia	<i>FGFR3</i>	Prenatal
Alpha ₁ -antitrypsin deficiency†	<i>AAT</i>	Diagnostic, predictive
Cystinosis	<i>CTNS</i>	Carrier detection, prenatal
Galactosemia	<i>GALT</i>	Newborn screening, carrier detection, prenatal‡
Neurofibromatosis type 1	<i>NF1</i>	Prenatal
Neurofibromatosis type 2	<i>NF2</i>	Predictive, prenatal

*This table is intended to be illustrative, not exhaustive. Most entries are based on information from GeneTest-GeneClinics at <http://www.geneclinics.org>; this Web site includes a comprehensive list of available molecular genetic tests and further clinical information about these and other genetic conditions.

†Biochemical testing is done to identify the enzyme deficiency.

‡Newborn screening is done by biochemical testing.

and test results have the potential to be stigmatizing or psychologically harmful. For this reason, careful pretest counseling is recommended. A 10-year experience in the United Kingdom suggests that only about 20 percent of those at risk for Huntington's disease pursue such testing.²⁸

In the case of X-linked and autosomal recessive conditions (Fig. 2 and 3), the purpose of genetic testing is often to identify family members who are carriers — that is, persons who are themselves unaffected but who are at risk of having affected children. As with decisions about testing for Huntington's disease, tests to determine carrier status are done primarily for personal, rather than medical, reasons: in this case to facilitate decisions about having children. For women

who are carriers of an X-linked recessive disease, each son has a 50 percent risk of inheriting the disease (Fig. 2). With autosomal recessive diseases, such as sickle cell anemia or cystic fibrosis (Fig. 3), the risk of having an affected child is incurred only if both parents are carriers and is 25 percent for each pregnancy. If carrier status is confirmed, prenatal testing can be offered to provide an opportunity to inform parents about the genetic diagnosis before the birth, so that they can decide what course of action is best for them.

Prenatal diagnosis is also commonly used to diagnose Down's syndrome. This genetic condition is rarely inherited; most cases are due to an error in the formation of ovum or sperm, leading to the inclusion of an extra chromosome 21 at conception.²⁹ As with pre-

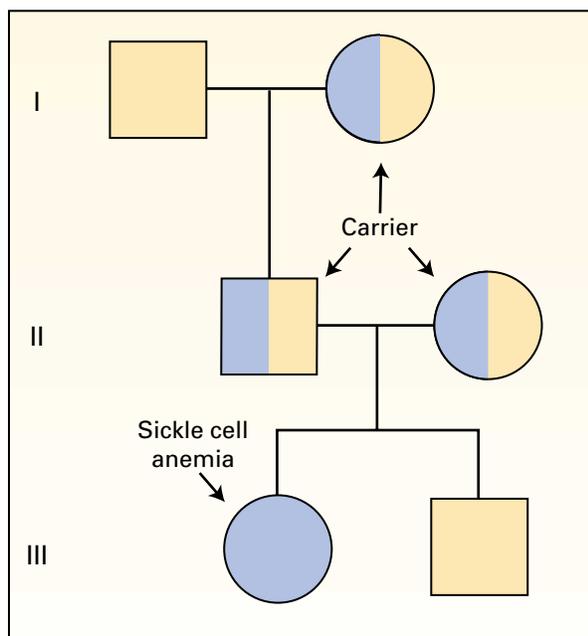


Figure 3. Autosomal Recessive Inheritance.

When an autosomal recessive condition such as sickle cell anemia is diagnosed in a child (indicated by the arrow), the parents are identified as carriers of the sickle cell trait, which is inherited. All children of these parents have a 25 percent chance of being affected. Children who do not have sickle cell anemia have a 67 percent chance of being carriers. Cystic fibrosis is also inherited as an autosomal recessive condition.

natal diagnosis for inherited genetic diseases, this use of genetic testing is focused on reproductive decision making rather than on clinical management of genetic disease.

Genetic testing is also sometimes used to identify family members with mild cases. For example, mild cases of 22q11 deletion syndrome have been documented among parents and siblings of patients with the condition.³⁰ Identifying these affected relatives may explain otherwise unexpected clinical findings, and also provides information about recurrence risks within the family: if a parent is affected, the condition can be passed on to future children.

CLINICAL VALIDITY OF GENETIC TESTS

These different examples help illustrate the importance of a test’s clinical validity, defined as the accuracy with which a test predicts a clinical outcome.⁷ Clinical validity reflects both the sensitivity of the test — the proportion of affected people with a positive test — and the penetrance of the mutations identified by the test. Penetrance refers to the proportion of people with the mutation who will manifest the disease; in the case of genetic diseases like Duchenne’s muscular

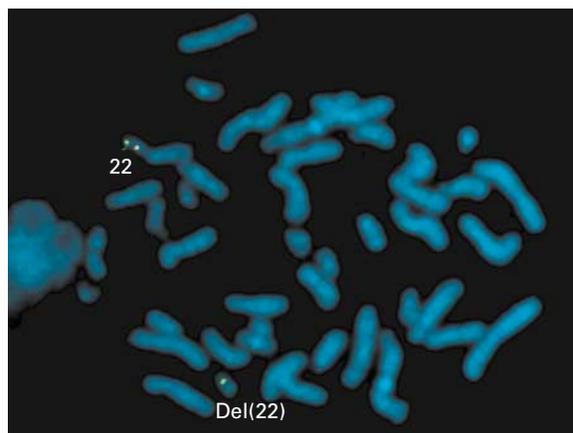


Figure 4. Fluorescence in Situ Hybridization Showing the 22q11 Microdeletion Syndrome.

An orange probe identifies the chromosomal segment that is deleted in the syndrome; thus, the chromosome 22 with the microdeletion — del(22) — lacks this probe. A green probe identifies a different segment of the chromosome and is used as a marker for the two copies of chromosome 22, one of which is normal and thus demonstrates both probes (22). Photomicrograph provided courtesy of Dr. Christine Disteche and Douglas Chapman, University of Washington.

dystrophy, the proportion is virtually 100 percent in those with a normal life span, whereas in the case of hereditary nonpolyposis colon cancer, an inherited colorectal cancer syndrome, about 75 percent are likely to be affected.

Many DNA-based tests have reduced sensitivity because they identify only a subgroup of potentially causative mutations. This limitation is due to the state of scientific knowledge — some causative mutations may not yet be known — and to the properties of clinically available tests. For some conditions, a test for all known mutations would be prohibitively expensive, leading to a pragmatic tradeoff between cost and sensitivity. Just as scientific knowledge and costs change over time, so will the sensitivity and predictive value of various tests.

Reduced sensitivity has important implications for the testing of family members. For example, when a child with Duchenne’s muscular dystrophy is found to have a deletion involving the dystrophin gene, the carrier status of female relatives can be determined by the same test. However, if the affected child does not have an identifiable mutation, the test cannot be used effectively either to determine carrier status or for prenatal diagnosis. An alternative approach — linkage analysis — is possible if two or more family members are affected and available for testing; this approach identifies patterns of DNA markers associated with

the disease in a particular family (Fig. 5). But if the affected child is the only known member of the family with Duchenne's muscular dystrophy, linkage cannot be established, and this approach will not work.

When a genetic test has high sensitivity, people can be tested for carrier status without reference to the

test results of an affected family member. This is the case for sickle cell anemia, which is caused by a specific mutation in the β -globin gene (Fig. 3).¹⁸ In contrast, testing for cystic fibrosis can identify many (but not all) carriers in the general population; currently available tests identify the most common mutations and in the process usually identify 85 percent of carriers in the U.S. population.^{16,31} (The use of genetic testing in population screening is discussed in another article in this series.)

Most well-defined genetic diseases are caused by mutations with a high rate of penetrance and, as a result, have a high positive predictive value — that is, the likelihood of disease is high when the test is positive. This observation may contribute to the perception that current genetic tests are always highly predictive. However, even when mutations are highly penetrant, the negative predictive value of a test — the likelihood that disease is absent if the test is negative — can be low, if the test fails to identify all causative mutations.

GENETIC TESTING TO IMPROVE PREVENTIVE CARE

Genetic tests can also be used to determine genetic contributions to the risk of common diseases, in order to guide preventive care. Testing for *BRCA1* and *BRCA2* mutations provides an opportunity to identify people who may benefit from tailored screening and prevention protocols that are based on their genetic susceptibility to breast and ovarian cancer.³²⁻³⁴ Estimates of the lifetime risk of breast cancer associated with these mutations range from 26 to 85 percent; the risk of ovarian cancer is also elevated but to a lesser extent, and risk estimates also vary.³⁵⁻⁴¹

In conditions with a low rate of penetrance, more evidence is needed to establish the efficacy of interventions to reduce risk.^{42,43} In the case of MEN-2, the evidence favoring prophylactic thyroidectomy derives from the observation of a low rate of medullary thyroid cancer among patients who had the surgery.^{25,26} The power of such studies derives from historical data demonstrating a lifetime risk of cancer of close to 100 percent in patients with untreated MEN2, with an associated high rate of premature mortality.¹ When a genetic test predicts an increased risk rather than a certainty of future disease, the efficacy of interventions to reduce risk is more difficult to measure,⁴² particularly when the level of risk is uncertain, as is the case with *BRCA1* and *BRCA2*. If the risk is initially overestimated — a common bias when mutations conferring risk are found in families selected for high risk — the efficacy of an intervention may be greatly overestimated in the absence of controlled observations.³⁸

This issue will take on greater importance as genetic factors conferring smaller risks are identified.^{44,45} Mutations associated with a high risk account for only a

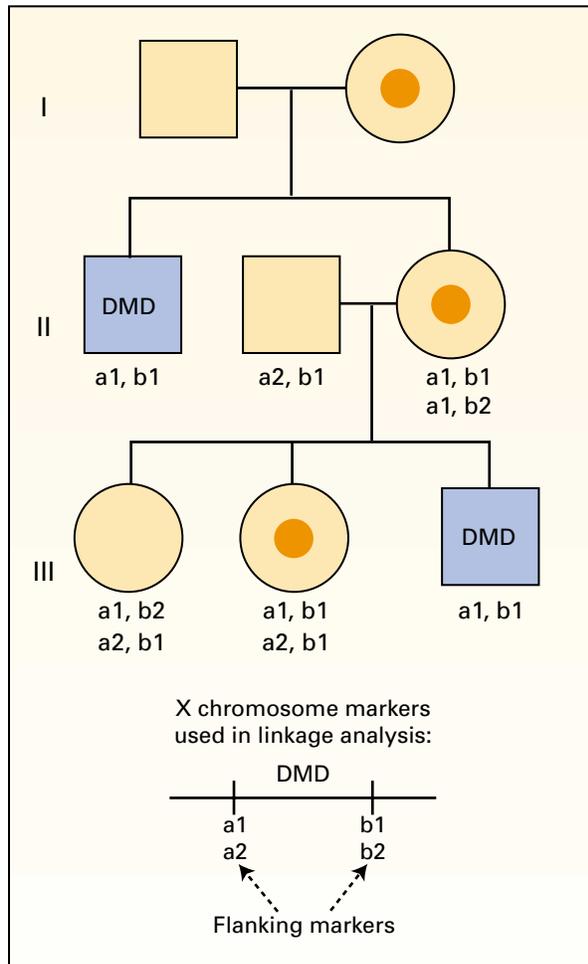


Figure 5. Linkage Analysis to Determine Carrier Status.

When a genetic test fails to identify a mutation in an affected person (solid symbols), linkage analysis can sometimes be used to identify carriers (symbols with a solid center), as shown here for Duchenne's muscular dystrophy (DMD). This analysis takes advantage of variable regions of DNA on either side of the gene (a1, a2, b1, and b2) to identify markers for the chromosome carrying the Duchenne's muscular dystrophy mutation. In this example, markers a1 and b1 identify the X chromosome carrying the mutation. The carrier status of the patient's sisters in generation III can be determined by assessment of these markers. One sister (indicated by the dot) has inherited the X chromosome carrying the Duchenne's muscular dystrophy from her mother, whereas the other has not. Squares denote male family members, and circles female family members.

small percentage of common diseases; mutations in *BRCA1* and *BRCA2* are a rare cause of breast cancer, for example. The largest genetic contribution to health is in the form of common variants that increase or decrease risk to a moderate degree.^{5,46,47} These tests have lower positive and negative predictive values than most currently available genetic tests, but they have potential implications for a larger number of people and are an important byproduct of the Human Genome Project.⁵ Two examples offer insights into the implications of genetic tests of this kind: hemochromatosis and factor V Leiden.

Hemochromatosis, a condition involving excess accumulation of iron, can lead to iron overload, which in turn can result in complications such as cirrhosis, diabetes, cardiomyopathy, and arthritis.⁴ Two mutations in the *HFE* gene, C282Y and H63D, promote excess accumulation of iron. C282Y is the more severe mutation, and the C282Y/C282Y genotype accounts for the majority of clinically penetrant cases.⁴ But current data suggest that clinical disease does not develop in a substantial proportion of people with this genotype.^{48,49} A pooled analysis found that patients with the *HFE* genotypes C282Y/H63D and H63D/H63D are also at increased risk for iron overload,⁵⁰ yet overall, disease is likely to develop in fewer than 1 percent of people with these genotypes. Thus, DNA-based tests for hemochromatosis identify a genetic risk rather than the disease itself.⁵¹ Environmental factors such as diet and exposure to alcohol or other hepatotoxins may modify the clinical outcome in patients with hemochromatosis,⁴ and variations in other genes affecting iron metabolism may also be a factor.⁵² As a result, the clinical condition of iron overload is most reliably diagnosed on the basis of biochemical evidence of excess body iron.^{2,4} Whether it is beneficial to screen asymptomatic people for a genetic risk of iron overload is a matter of debate.^{47,53}

Factor V Leiden offers another example. This factor V gene mutation is relatively common, ranging in prevalence from 1 to 5 percent in different American ethnic groups,⁵⁴ and results in up to an eightfold increased risk of venous thrombosis.^{55,56} Estimates of the annual incidence of venous thrombosis in people who are heterozygous for factor V Leiden range from 0.19 to 0.58 percent,⁵⁷⁻⁵⁹ suggesting a lifetime risk of 12 to 30 percent. However, more than half of the thromboembolic events associated with factor V Leiden occur when other risk factors, such as surgery, use of oral contraceptives, and bed rest, are also present.^{55,57,60} Both gene-gene and gene-environment interactions contribute to the overall risk of venous thrombosis.⁵⁵ Thus, factor V Leiden, like mutations in the *HFE* gene, is a risk factor for disease rather than an indication of the presence of disease.

As is the case for predictive testing for hemochro-

matosis, the clinical usefulness of testing for factor V Leiden is not established. Although a positive test identifies people at increased risk for venous thrombosis, the implications for management are unclear. Interventions such as prophylactic anticoagulation therapy or avoidance of risk factors might be considered, but evidence of the clinical benefit of such interventions is so far lacking.^{61,62}

The issue of specificity of treatment is an important one. New genetic tests to assess the risk of common diseases are likely to have properties similar to those of tests for factor V Leiden. They will identify relatively common genetic traits that interact with other genetic and environmental factors to increase risk. Their clinical usefulness will depend on the availability of specific, effective interventions to reduce risk. In the absence of genotype-specific interventions, the knowledge of a person's genetic susceptibility to a condition could result in worry or job- or insurance-related discrimination without yielding health benefits or could even be harmful to a person's health by reducing motivation to pursue risk-reducing measures.⁶³

INFORMED CONSENT AND GENETIC COUNSELING

Patients are usually given detailed counseling before undergoing genetic testing, to ensure that they make informed decisions about the use of tests with complex personal implications. Genetic counseling is traditionally "nondirective" — that is, counseling provides sufficient information to allow families or individual persons to determine the best course of action for themselves but avoids making testing recommendations.^{64,65} This approach was developed in the context of genetic tests for reproductive decision making and untreatable conditions such as Huntington's disease, in which the value of testing is based on personal preference.

When tests are conducted to improve clinical management, pretest counseling needs differ. A testing recommendation is appropriate, for example, when a test offers an opportunity to prevent disease, as in the case with testing for MEN-2.⁶⁶ Since some tests for genetic risk factors will probably become a routine part of clinical practice, they are likely to be offered without formal pretest counseling. In approaching the question of informed consent to conduct a specific genetic test, however, the potential social and family implications need to be acknowledged, including the potential for discrimination on the basis of genetic-risk status⁷ and the possibility that the predictive value of genetic information may be overestimated.⁶⁷ These considerations suggest that clinicians should err on the side of caution and follow carefully-thought-out informed-consent procedures for genetic testing, unless outcome studies suggest otherwise.

CONCLUSIONS

Genetic testing offers important opportunities for diagnosis and assessment of genetic risk. The sensitivity of tests for rare conditions will continue to improve as additional causative mutations are identified. Genetic tests are available to determine the risk of common diseases, but these often have limited predictive value. Evaluating the clinical usefulness of these tests will require a careful assessment of the risks and benefits of testing; the availability of specific measures to reduce risk in genetically susceptible people will be a major consideration.

One of the difficult challenges in the use of genetic tests is a constantly changing knowledge base. Fortunately, a growing number of Internet sites are available to provide clinicians with up-to-date information (Table 1).^{68,69} Research to evaluate interventions based on genetic risk will assume increasing importance as new tests become available. Because the development of tests to assess risk is likely to outpace the ability to reduce the risk, an ongoing dialogue involving clinicians and policymakers will be needed to develop a consensus about their appropriate clinical use.

Supported in part by a grant (R01-HG02263) from the National Institutes of Health. The contents of this article are solely the responsibility of the author and do not necessarily represent the official views of the National Institutes of Health.

REFERENCES

- Hoff AO, Cote GJ, Gagel RF. Multiple endocrine neoplasias. *Annu Rev Physiol* 2000;62:377-411.
- Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. *Am J Gastroenterol* 1997;92:784-9.
- Abbs S, Bobrow M. Report on the 16th ENMC workshop — carrier diagnosis of Duchenne and Becker muscular dystrophy. *Neuromuscul Disord* 1993;3:241-2.
- Hanson EH, Imperatore G, Burke W. HFE gene and hereditary hemochromatosis: a HuGE review. *Am J Epidemiol* 2001;154:193-206.
- Collins FS. Shattuck Lecture — medical and societal consequences of the Human Genome Project. *N Engl J Med* 1999;341:28-37.
- Roses AD. Pharmacogenetics and the practice of medicine. *Nature* 2000;405:857-65.
- Holtzman NA, Watson MS, eds. Promoting safe and effective genetic testing in the United States: final report of the Task Force on Genetic Testing. Baltimore: Johns Hopkins University Press, 1999.
- GeneTests—GeneClinics home page. Seattle: University of Washington, 2002. (Accessed November 8, 2002, at <http://www.geneclinics.org>.)
- The Human Genome Epidemiology Network: HuGE reviews. Atlanta: Centers for Disease Control and Prevention, 2002. (Accessed October 8, 2002, at <http://www.cdc.gov/genomics/hugenet/reviews.htm>.)
- CancerNet PDQ. Bethesda, Md.: National Cancer Institute, 2002. (Accessed November 8, 2002, at http://www.cancer.gov/cancer_information/pdq.)
- OMIM: online Mendelian inheritance in man. Bethesda, Md.: National Center for Biotechnology Information, 2002. (Accessed October 8, 2002, at <http://www.ncbi.nlm.nih.gov/omim/>.)
- Weisner GL, Snow K. Multiple endocrine neoplasia type 2 [includes: MEN 2A (Sipple syndrome), MEN 2B (mucosal neuroma syndrome), familial medullary thyroid carcinoma (FMTTC)]. Seattle: GeneClinics, 1999. (Accessed November 8, 2002, at <http://www.geneclinics.org/profiles/men2/details.html>.)
- Raue F. German medullary thyroid carcinoma/multiple endocrine neoplasia registry. *Arch Surg* 1998;383:334-6.
- Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 2000;88:1139-48.
- Korf BR, Darras BT, Urion DK. Dystrophinopathies [includes: Duchenne muscular dystrophy (DMD), pseudohypertrophic muscular dystrophy), Becker muscular dystrophy (BMD), and X-linked dilated cardiomyopathy (XLDCM)]. Seattle: GeneClinics, 2000. (Accessed November 8, 2002, at <http://www.geneclinics.org/profiles/dbmd/details.html>.)
- Grody WW. Cystic fibrosis: molecular diagnosis, population screening, and public policy. *Arch Pathol Lab Med* 1999;123:1041-6.
- Brody LC, Biesecker BB. Breast cancer susceptibility genes: BRCA1 and BRCA2. *Medicine (Baltimore)* 1998;77:208-26.
- Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. *Am J Epidemiol* 2000;151:839-45.
- Cao A, Galanello R, Rosatelli MC. Prenatal diagnosis and screening of the haemoglobinopathies. *Baillieres Clin Haematol* 1998;11:215-38.
- Crow JE. Two centuries of genetics: a view from halftime. *Annu Rev Genomics Hum Genet* 2000;1:21-40.
- Capone GT. Down syndrome: advances in molecular biology and the neurosciences. *J Dev Behav Pediatr* 2001;22:40-59.
- Pergament E. New molecular techniques for chromosome analysis. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14:677-90.
- McDonald-McGinn D, Emanuel BS, Zackai EH, Children's Hospital of Philadelphia. 22q11 Deletion syndrome. [Includes: Shprintzen syndrome, DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome (CTAF), Cayler cardiofacial syndrome, Opitz G/BBB]. Seattle: GeneClinics, 1999. (Accessed November 8, 2002, at <http://www.geneclinics.org/profiles/22q11deletion/index.html>.)
- De Decker HP, Lawrenson JB. The 22q11.2 deletion: from diversity to a single gene theory. *Genet Med* 2001;3:2-5.
- Wells SA Jr, Skinner MA. Prophylactic thyroidectomy, based on direct genetic testing, in patients at risk for the multiple endocrine neoplasia type 2 syndromes. *Exp Clin Endocrinol Diabetes* 1998;106:29-34.
- Niccoli-Sire P, Murat A, Baudin E, et al. Early or prophylactic thyroidectomy in MEN 2/FMTC gene carriers: results in 71 thyroidectomized patients. *Eur J Endocrinol* 1999;141:468-74.
- Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, adopted on February 20, 1996. *J Clin Oncol* 1996;14:1730-40.
- Harper PS, Lim C, Craufurd D. Ten years of presymptomatic testing for Huntington's disease: the experience of the UK Huntington's Disease Prediction Consortium. *J Med Genet* 2000;37:567-71.
- Wald NJ, Hackshaw AK. Advances in antenatal screening for Down syndrome. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14:563-80.
- McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! *Genet Med* 2001;3:23-9.
- Tait JF, Gibson RL, Marshall SG, Stern DL, Cheng E, Cutting GR. Cystic fibrosis [CF, Mucoviscidosis: includes: congenital bilateral absence of the vas deferens (CBAVD)]. Seattle: GeneClinics, 2001. (Accessed November 8, 2002, at <http://www.geneclinics.org/profiles/cf/details.html>.)
- Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. *JAMA* 1997;277:997-1003.
- Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999;340:77-84.
- CancerNet. CancerNet PDQ summary on breast/ovarian and colorectal cancer genetics. Bethesda, Md.: National Cancer Institute, 2001. (Accessed November 8, 2002, at <http://cancer.gov/cancerinfo/pdq/genetics>.)
- Struwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997;336:1401-8.
- Thorlacius S, Struwing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. *Lancet* 1998;352:1337-9.
- Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet* 1998;62:676-89.
- Hopper JL, Southey MC, Dite GS, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2: Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* 1999;8:741-7.
- Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* 1999;91:1241-7.
- Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *Br J Cancer* 2000;83:1301-8.
- Satagopan JM, Offit K, Foulkes W, et al. The lifetime risks of breast

- cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* 2001;10:467-73.
42. Welch HG, Burke W. Uncertainties in genetic testing for chronic disease. *JAMA* 1998;280:1525-7.
43. Preventive Services Task Force. Guide to clinical preventive services: report of the U.S. Preventive Services Task Force. 2nd ed. Baltimore: Williams & Wilkins, 1996.
44. Ziv E, Cauley J, Morin PA, Saiz R, Browner WS. Association between the T29→C polymorphism in the transforming growth factor beta1 gene and breast cancer among elderly white women: the Study of Osteoporotic Fractures. *JAMA* 2001;285:2859-63. [Erratum, *JAMA* 2001;286:3081.]
45. Armstrong K. Genetic susceptibility to breast cancer: from the roll of the dice to the hand women were dealt. *JAMA* 2001;285:2907-9.
46. Holtzman NA, Marteau TM. Will genetics revolutionize medicine? *N Engl J Med* 2000;343:141-4.
47. Kaprio J. Science, medicine, and the future: genetic epidemiology. *BMJ* 2000;320:1257-9.
48. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 2002;359:211-8.
49. Asberg A, Hveem K, Thorstensen K, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. *Scand J Gastroenterol* 2001;36:1108-15.
50. Burke W, Imperatore G, McDonnell SM, Baron RC, Khoury MJ. Contribution of different HFE genotypes to iron overload disease: a pooled analysis. *Genet Med* 2000;2:271-7.
51. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J Hepatol* 2000;33:485-504.
52. Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999;341:1986-95. [Erratum, *N Engl J Med* 2000;342:364.]
53. Cogswell ME, McDonnell SM, Khoury MJ, Franks AL, Burke W, Brittenham G. Iron overload, public health, and genetics: evaluating the evidence for hemochromatosis screening. *Ann Intern Med* 1998;129:971-9.
54. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women: implications for venous thromboembolism screening. *JAMA* 1997;277:1305-7.
55. Rosendaal F. Venous thrombosis: a multicausal disease. *Lancet* 1999;353:1167-73.
56. Meyer G, Emmerich J, Helley D, et al. Factors V Leiden and II 20210A in patients with symptomatic pulmonary embolism and deep vein thrombosis. *Am J Med* 2001;110:12-5.
57. Middeldorp S, Meinardi JR, Koopman MM, et al. A prospective study of asymptomatic carriers of the factor V Leiden mutation to determine the incidence of venous thromboembolism. *Ann Intern Med* 2001;135:322-7.
58. Simioni P, Sanson BJ, Prandoni P, et al. Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999;81:198-202.
59. Martinelli I, Bucciarelli P, Margaglione M, De Stefano V, Castaman G, Mannucci PM. The risk of venous thromboembolism in family members with mutations in the genes of factor V or prothrombin or both. *Br J Haematol* 2000;111:1223-9.
60. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Buller HR, Vandembroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995;346:1593-6.
61. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. *Genet Med* 2001;3:139-48.
62. Bauer KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. *Ann Intern Med* 2001;135:367-73.
63. Marteau TM, Lerman C. Genetic risk and behavioural change. *BMJ* 2001;322:1056-9.
64. Genetic counseling. *Am J Hum Genet* 1975;27:240-2.
65. Michie S, Smith JA, Heaversedge J, Read S. Genetic counseling: clinical geneticists' views. *J Genet Couns* 1999;8:275-87.
66. Cummings S. The genetic testing process: how much counseling is needed? *J Clin Oncol* 2000;18:Suppl:60S-64S.
67. Hubbard R, Lewontin RC. Pitfalls of genetic testing. *N Engl J Med* 1996;334:1192-4.
68. Pagon RA, Pinsky L, Beahler CC. Online medical genetics resources: a US perspective. *BMJ* 2001;322:1035-7.
69. Stewart A, Haites N, Rose P. Online medical genetics resources: a UK perspective. *BMJ* 2001;322:1037-9.

Copyright © 2002 Massachusetts Medical Society.

APPLY FOR JOBS ELECTRONICALLY
AT THE NEW NEJM CAREER CENTER

Physicians registered at the new NEJM Career Center can now apply for jobs electronically using their own cover letters and CVs. You can now keep track of your job-application history with a personal account that is created when you register with the Career Center and apply for jobs seen online at our Web site. Visit www.nejmjobs.org for more information.
