

GENETIC TESTING IN PRIMARY CARE

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■ **Abstract** Rapid advances in genetic research are leading to an expanding array of genetic tests. Primary care providers will increasingly be challenged to identify patients whose symptoms, physical findings, or family history indicate the need for genetic testing, and to determine how to use genetic information most effectively to improve disease prevention. In addressing these challenges, practitioners will need to consider the range of different uses of genetic testing, including diagnosis in symptomatic and asymptomatic people, risk assessment, reproductive decision-making, and population screening. They will need a set of core skills and knowledge to evaluate family history and to recognize clinical findings that indicate genetic risk. At the same time, the primary care perspective will contribute to the evaluation of appropriate uses of genetic testing. A partnership between medical genetics and primary care will help to ensure the development of effective policies, educational tools, and practice guidelines for the coming era of genomic health care.

INTRODUCTION

Rapid advances in research are leading to growing knowledge about the genetics of human disease and, thus, to an expanding array of genetic tests (16, 69). Although most genetic services are now provided by genetics professionals in specialty centers, primary care providers will increasingly need to be aware of the clinical implications of genetics. Several medical specialties serve as primary care providers in the United States, including family practitioners, general internists, general pediatricians, obstetrician-gynecologists, and primary care nurse practitioners; together they are responsible for most day-to-day clinical care, including the initial assessment of medical problems, prevention services, and longitudinal care (63). With the clinical integration of genomic information, these providers face two challenges: (a) how to identify patients who are candidates for a genetic work up—patients whose symptoms, physical findings, or family history suggest a genetic cause or risk; and (b) how to use genetic information most effectively to improve disease prevention.

The Spectrum of Genetic Testing

In addressing these challenges, practitioners need to consider the range of different genetic applications in clinical care. Genetic testing has the two general functions of diagnosis and risk assessment, but the context varies widely: genetic testing may be used for diagnosis in symptomatic and asymptomatic people; risk assessment; reproductive decision-making; and population screening. Each use has different implications for primary care.

The increasing focus on the genetics of common diseases is also important. Most genetic diseases are caused by rare gene mutations that disrupt function; for example, cystic fibrosis results from mutations in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene, leading to a defective cellular transport mechanism that causes lung disease, loss of pancreatic enzyme secretion, and other end-organ complications, resulting in premature death (46). However, traditional genetic diseases represent only one end of a continuum of genetic risk, in which a single gene mutation exerts an important effect on clinical outcome (Figure 1). At the other end of the spectrum are diseases affected only minimally by genetics, such as infectious diseases like chicken pox and AIDS. In between are most of diseases seen in primary care, which are caused by a combination of genetic and nongenetic factors.

Countering the popular ideal of genetics as a “blueprint,” primary care providers need to consider genetics in the context of this spectrum. When a genetic disease is present, recognizing it is essential for both the patient and the patient’s family.

Continuum of genetic risk

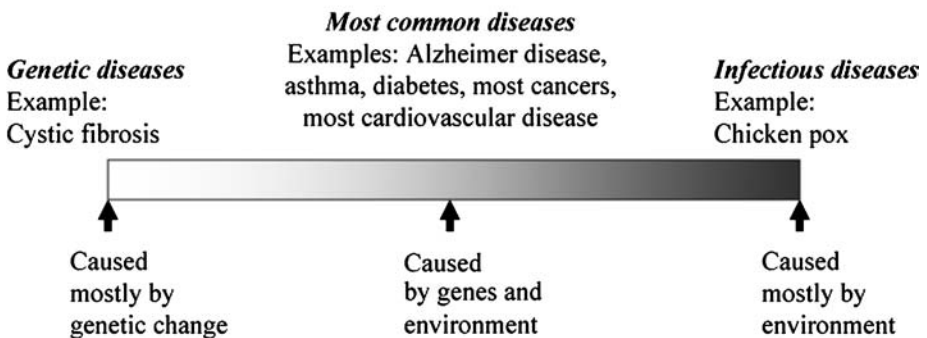


Figure 1 Genetic contribution to disease risk. The figure illustrates the spectrum of genetic contributors to disease risk. At one end are genetic diseases such as cystic fibrosis, in which gene mutations are the primary cause of disease; at the other end are infectious diseases, which are determined primarily by exposure to infectious agents. In between are most diseases, which are caused by a mix of genetic and environmental factors.

In addition, practitioners need to consider the common gene variants that lead to increased disease risk; these genetic risk factors will likely be the subject of intensive research and test development in the near future (17, 32, 35).

Core Skills and Knowledge

Both family history and specific clinical findings can indicate a genetic diagnosis. To use genetics effectively, primary care providers will increasingly need a set of core skills and knowledge to help them identify patients with potential genetic conditions or risks.

Using genetics in clinical practice starts with the collection and evaluation of family history. However, in primary care, the approach to family history differs from the usual practice in medical genetics. The detailed three-generation family history typically obtained by a genetic counselor, often with a review of medical records to confirm the diagnoses of family members, is not feasible in primary care (55). This is due in part to time pressures and limited reimbursement, but also reflects the nature of primary care practice. Most genetic conditions are rare in the primary care patient population; for example, few children with developmental delay have a chromosomal disorder or other genetic cause, and most breast cancer is sporadic not inherited. As a result, family history must be used as a triage tool, with a focus on time-efficiency.

There are several models for this approach. Recommendations for assessing colorectal cancer risk define two risk categories based on family history: individuals with moderately increased risk, who would benefit from early initiation of screening, and individuals whose family history suggests an inherited syndrome for colorectal cancer—hereditary nonpolyposis colon cancer (HNPCC) or familial adenomatous polyposis (FAP)—who would benefit from a genetics referral (77). Similarly, information about history of cardiovascular disease in first-degree relatives is used as to make decisions about the initiation of lipid-lowering therapy in people with hypercholesterolemia (49), and is recommended as a component of a presports evaluation for teenagers (27). There are also models for the referral of women at potentially high risk for breast and ovarian cancer, based on family history (19, 48), although a standard approach has not yet been defined (48).

Triage rules for family history information will likely be most successful when they are focused on a particular health risk and a specific patient group within the primary care population. However, even as rules for the use of family history are developed, additional efforts will be needed to ensure that they are implemented effectively in primary care practice. Although physicians commonly gather family history information through various approaches (13), several studies have documented problems, including gaps in the information obtained, inaccuracies in interpretation, failure to make appropriate genetics referrals or screening recommendations, and lack of confidence in genetics knowledge (30, 37, 58, 60, 65, 66, 67, 75). These observations suggest that additional techniques—such as targeted educational efforts (70), computerized prompts (8), electronic patient decision

tools (55), methods that allow patients to gather family history information in formats useful for the practitioner (78), and formal guidelines within health care systems (48)—will play an important role in ensuring that the risk information provided by family history is appropriately used in primary care practice.

Primary care providers also need to be aware that risk prediction via family history carries inherent uncertainty and is strongly influenced by context. A family history is more informative when the family is large and health information is widely shared among family members. When family history is unobtainable, as when a person is adopted, or a parent died early in life from causes unrelated to genetic risk, the value of family history diminishes. And, because medicine is increasingly successful in disease prevention, family history may “vanish,” because a polyp is removed before colon cancer develops, or lipid-lowering therapy averts a heart attack. These medical interventions constitute family history information, but they are less dramatic and less specific than a disease event. As a result, relatives may be unaware of them. Primary care providers could play an important role in advising patients to share such information and its risk implications with their relatives.

Primary care providers also need to be familiar with clinical presentations that raise the question of a genetic condition. For example, the early diagnosis of cancer or coronary heart disease suggests a possible inherited risk, even when family history is negative. Sometimes further exploration reveals a family history that did not emerge in initial questioning, such as early disease in second- or third-degree relatives, but as noted above, family history may sometimes be noninformative.

Similarly, genetic risk is suggested by the spontaneous occurrence of diseases normally associated with nongenetic risk factors, such as venous thromboembolism occurring in the absence of a precipitating cause (54). Some physical findings suggest genetic risk, such as café au lait spots as an indicator of neurofibromatosis (24) and tendon xanthomas as an indicator of familial hypercholesterolemia (75). Genetic causes are also part of the differential diagnosis of some common symptoms. For example, fatigue and joint pain are symptoms found in the early stages of hereditary hemochromatosis (HHC) (53). Because fatigue and joint pain occur frequently in the primary care population and have other common causes—such as depression, sleep disturbance, and anemia as causes of fatigue, and arthritis and overuse syndromes as causes of joint pain—HHC would not generally be considered in an initial work up of these complaints. However, HHC becomes an important consideration when symptoms are persistent and no other cause can be found, and the primary care provider’s knowledge of this possibility is crucial if the diagnosis is to be made (12).

Genetic Diagnosis

A growing number of cytogenetic, biochemical, and DNA-based tests can be used to diagnose genetic diseases. As primary care providers identify indicators of genetic conditions, through family history or suggestive clinical findings, these tests can be used to confirm genetic conditions. If the patient is symptomatic, the

testing does not represent a novel approach to practice. As with other diagnostic tools, genetic information is sought to improve patient care, by clarifying the prognosis or guiding management.

However, a new genetic diagnosis is different in one respect: it should routinely trigger a consideration of risk in family members. For example, among children with learning disabilities and a history of a cleft palate repair, some have a specific genetic syndrome, 22q11 deletion syndrome, which can be identified through a form of chromosome testing termed fluorescent in situ hybridization (FISH) (53). The diagnosis provides prognostic information (20). It also has important implications for the family, because genetic testing can sometimes identify mildly affected individuals among parents and siblings of people diagnosed with the condition (43).

Another example is using *RET* mutation testing to identify a genetic cause for medullary thyroid cancer. Approximately one quarter of cases of this type of thyroid cancer are due to Multiple Endocrine Neoplasia Type 2 (MEN 2), a genetic condition caused by mutations in the *RET* gene; the *RET* mutation test can identify 85% to 95% of affected people (73). Testing also provides an opportunity for disease prevention. Children identified by *RET* mutation testing to have MEN 2 can be offered prophylactic thyroidectomy (9).

The primary care provider's role in genetic diagnosis initially focuses on identifying patients for whom a genetic referral is indicated. However, the primary care provider often plays a central role in the ongoing follow-up of patients after a genetic diagnosis is made, and may be pivotal in assisting the patients to notify family members of genetic testing options. These roles speak to the importance of establishing partnerships between genetics and primary care to ensure a smooth transition between care provided by the two specialties.

Assessing a Patient's Genetic Risk

As the *RET* testing example demonstrates, genetic tests can identify people with an increased risk of future disease. A growing number of tests are now available to assess genetic risks for common diseases, including cardiovascular diseases, breast and colorectal cancers, and Alzheimer's disease (17, 24). Some risks identified by genetic testing are high; for example, the lifetime risk of breast cancer for women with BRCA1 mutations is about 65% (4). Others identify only moderately increased risks, such as the risk for venous thromboembolism conferred by prothrombin variant G20210A (PT) and Factor V Leiden (FVL) (54).

Predictive genetic tests are used to guide preventive care. In evaluating their potential value, both the accuracy of the risk prediction and the efficacy of interventions to reduce risk are important considerations (11, 24). One difficulty in using predictive tests is that the level of risk associated with a positive test result is often uncertain. This is because penetrance—the likelihood that disease will occur in people with a particular gene variant—is usually determined through long-term observation, and often is not established at the time a test becomes available.

Current technology often identifies only a subset of causative mutations for high-risk genetic syndromes, such as the breast and ovarian cancer risk associated with BRCA1 and BRCA2 mutations (4), or inherited colorectal cancer syndromes (77). This testing limitation leads to the need to test an affected family member first, even when the ultimate purpose of testing is to assess risk in unaffected family members. A patient with a family history of inherited cancer may be surprised—even dismayed—by the suggestion that a relative with cancer be contacted to determine his or her willingness to initiate the testing process. Yet in the absence of a known mutation in the family, a negative test result in an unaffected person could represent either a true negative (the absence of a cancer-predisposing mutation) or a false negative (the presence of a mutation that is not identifiable by current techniques). This point is not intuitively obvious to many clinicians (26) or to patients.

Uncertainty is also a factor in testing for gene variants associated with moderate disease risks, such as FVL and PT. Both can be accurately measured, and each independently identifies an individual as having an increased risk of venous thromboembolism (54). However, the risk reported for these mutations has varied across studies, and is strongly influenced by other risk factors for venous thromboembolism, both genetic and nongenetic (54, 57). Most thromboembolic events in people with FVL and PT occur when nongenetic risk factors—such as surgery, hormone therapy, and immobilization—are also present (41, 47, 62). FVL and PT are common gene variants, with prevalence in people of European ancestry estimated to be about 5% for FVL and up to 4% for PT (54). Risk is significantly higher when both mutations are present. A pooled analysis of case control studies found that the odds ratio for venous thromboembolism was 4.9 (95% confidence interval 4.1 to 5.9) for FVL, 3.8 (95% confidence interval 3.0 to 4.9) for PT, and 20 (95% confidence interval 11.1 to 36.1) for both (23). Homozygotes for FVL also have a substantially increased risk (54).

Although a positive test for FVL or PT identifies increased risk, the appropriate measures to reduce risk are uncertain. The significant bleeding complications associated with long-term anticoagulation (31) argue against routinely using this therapy in individuals who have not yet had a venous thromboembolic event. Recent studies suggest that after a venous thrombosis occurs, the recurrence risk is not higher in people with FVL or PT than in other patients, arguing against any difference in follow-up treatment (21, 56). Avoiding risk factors such as oral contraceptives and hormone replacement therapy might be considered, but the benefits are small relative to the cost of routine screening for gene variants (18).

These observations illustrate the importance of assessing outcomes to determine the appropriate clinical use of genetic risk information. For FVL and PT, testing may be most useful when evaluating unusual patients with presentations suggesting very high risk—for example, young patients with spontaneous blood clots, who may carry more than one thrombophilic factor. The higher risk in such patients arguably suggests they would benefit from long-term anticoagulation, despite its risks. After such patients are identified, additional family-based screening could be considered, to identify family members who might benefit from avoiding nongenetic risk factors for venous thromboembolism.

New genetic tests to assess risk for common disease risks will likely have properties similar to FVL and PT. They will identify relatively common gene variants that interact with other genetic and environmental factors to increase risk. If the risk associated with the gene variant is initially overestimated—a common bias when variants are identified in families selected for clinical disease (7)—the efficacy of interventions to reduce risk may be greatly overestimated if they are not assessed in appropriately controlled studies (71). Yet the clinical value of testing will depend on interventions that are both effective and sufficiently safe to merit use in reducing risk. Otherwise, knowledge about genetic susceptibility would create a potential stigma without compensatory health benefit, and might even produce harm by reducing the motivation to pursue risk-reducing measures (40). These concerns indicate the need to carefully evaluate the health outcomes of testing and associated interventions before tests enter mainstream clinical practice.

Pharmacogenetic Testing

Pharmacogenetic tests represent a special category of predictive genetic tests that will likely play an important role in the clinical practice of the future. These are tests for gene variants, usually in drug-metabolizing enzymes, that predict a person's response to a drug or class of drugs. Because they will allow personalized drug prescribing, they offer a potential means to reduce adverse reactions and increase the efficacy of drug treatment (72).

The enzyme thiopurinomethyltransferase (TPMT) is an example. A variant in the TPMT gene greatly increases the risk of life-threatening reactions to mercaptopurine, a drug used in to treat acute childhood leukemia (45, 72). Approximately 1 in 300 children is homozygous for the variant, and 5% to 10% of the population are heterozygous; genetic testing of children being treated for acute leukemia makes it possible to reduce exposure to mercaptopurines in the small number of children at risk.

The number of other pharmacogenetic tests offering similar potential benefits is not yet known. Benefits will likely be specific to the disease condition and treatment under consideration. As with other predictive tests, the value of pharmacogenetic tests will be based on the accuracy with which they predict drug responses and the degree to which management can be improved based on the test results. The availability of safe alternative drug therapy, or evidence for an improved outcome with a modified drug dose, will also be key factors in determining the value of pharmacogenomic testing.

The drug clozapine illustrates both the promise and the challenge of pharmacogenetics. Clozapine came into use in the early 1990s as a treatment for schizophrenic patients who failed to respond to other medications (42). A treatment response occurs in 30% to 70% of patients; in addition, serious side effects occur in some patients, including leukopenia. In this context, a pharmacogenetic test to identify potential responders or predict risk of adverse reactions could provide a substantial benefit to clinicians and patients.

Several studies have identified polymorphisms associated with clozapine response, including variants of genes coding for neurotransmitter receptors and other functions associated with clozapine activity (42). These data point to an important complexity of pharmacogenetics, the contribution of many different genes to drug response. As a result, pharmacogenetic testing may be most effective when it assesses multiple gene variants. In one report, a panel of 6 polymorphisms (out of 19 studied) predicted a positive therapeutic response to clozapine with a sensitivity of 95% and a specificity of 38% (6). This result is promising, but replication is needed before testing can be considered in clinical practice. False positive results could occur as a result of multiple measurements; in addition, many confounders are possible in addressing this type of research question, including differences in the patients selected for treatment, ambiguity in the clinical endpoints used, or lack of comparability of cases and controls (42). Pharmacogenetics will likely represent an important clinical tool in the future, but tests will require careful prospective evaluation to ensure that they provide a health outcome benefit.

Reproductive Decision-Making

For some genetic diseases, carrier testing and prenatal diagnosis can be used to assess the risk of having a child with the condition. When testing indicates a fetus is affected with a genetic condition, it sometimes results in the choice to terminate a pregnancy. This genetic testing opportunity has been important for some clinical conditions: for example, the birth of children with Tay-Sachs disease and beta-thalassemia has been reduced significantly as a result of carrier testing and prenatal diagnosis (14, 34).

The use of genetic testing for reproductive decision-making contrasts to most other medical tests, and has implications for the nature of the counseling accompanying test use. Most prenatal tests, for example screening for Rh status, are used to facilitate pregnancy management and improve pregnancy outcomes. Genetic testing for reproductive decision-making is offered for a different, fundamentally personal reason; the decision to forego pregnancy, or to terminate a pregnancy when the fetus is affected with a genetic disease, must be based on a couple's values and preferences. This perspective accounts for the strong emphasis on "nondirective counseling" in medical genetics; that is, on a counseling approach that provides sufficient information and support to allow families to determine the best course of action for themselves (3).

Most carrier testing and prenatal diagnosis involves rare genetic disorders and will likely remain within the domain of medical genetics. However, some genetic tests related to reproductive decision-making have already entered primary care practice. Prenatal chromosomal evaluation, to test for Down syndrome in the fetus, is routinely offered to pregnant women aged 35 or over, or when a serology screen indicates an increased risk of Down syndrome (1). Recently, the routine offer of cystic fibrosis carrier testing in prenatal care has been recommended (29). As a result, both family practitioners and obstetricians must be prepared to provide appropriate counseling for this kind of testing, emphasizing, in particular, the elective nature of these tests and the choices associated with them.

Carrier testing is ideally done prior to pregnancy (29) to offer prospective parents additional choices when they are at risk to have a child with a genetic disease. These include avoiding pregnancy or, in some cases, using assisted reproduction and genetic testing prior to the implantation of the embryo, to assure the selection of embryos without the genetic condition (74). Primary care providers, who provide routine, longitudinal care, may be uniquely placed to encourage carrier testing prior to pregnancy.

Population Screening

Virtually all children in the United States are tested for phenylketonuria (PKU) in the newborn period, and most state newborn screening programs test for other genetic disorders as well. The goal of PKU screening is to enable the early initiation of a phenylalanine-poor diet in children with PKU, to prevent mental retardation. New DNA-based tests and tandem mass spectrometry, a technology that allows efficient screening for a large array of biochemical disorders, are expanding newborn screening (68). This new technological capacity has generated policy discussions concerning which tests should be added to newborn screening panels. Most of the 20 to 30 conditions identified by tandem mass spectrometry are not currently treatable. Differences of opinion exist concerning the appropriateness of reporting newborn screening test results on conditions for which treatment is unavailable.

There are similar policy discussions about genetic screening in adults. There are no established programs for genetic screening beyond those tests offered as a part of prenatal care, such as cystic fibrosis carrier screening, but some have been suggested. For example, there is ongoing debate about universal screening for hereditary hemochromatosis (10, 22, 43), and some experts recommend using population-based family history assessment, through health education classes in high schools, to find people with familial hypercholesterolemia (76). As new tests become available, discussion about adult genetic screening will likely increase.

Limitations in Genetic Information

The publicity surrounding the sequencing of the human genome has led to high expectations of clinical benefit. A rapidly growing biotechnology industry plans to develop, market, and profit from genetic tests. As with other new medical products, direct-to-consumer marketing is occurring (29).

Clinicians need to be prepared to address patients' questions and requests for genetic services, some of which may be based on false hopes. For example, a survey of primary care patients indicated that 58% of women would accept a test for BRCA1/2 mutations if offered (5), although the low prevalence of BRCA1 and BRCA2 mutations suggests that few would receive informative results from such testing.

Overly optimistic expectations about genetics are due in part to the way in which genetics is presented in popular media, where the predictive power of genetic information is routinely overestimated, and testing possibilities that are no more than research ideas are often presented as imminently available (36). Dealing

effectively with this phenomenon requires strategies for keeping track of a rapidly expanding knowledge base. In addition to skills in the critical evaluation of genetic information, clinicians need to be able to find, assess, and use authoritative sources of current information. These include a growing number of Internet sites (51, 64).

Addressing Policy Issues: The Need for Partnership

The ethical and social implications of genetic information are diverse. They include the competing claims of confidentiality and family risk, the acceptability of abortion as a means to prevent the birth of a child with genetic disease, risks of stigmatization and discrimination (38, 39), and questions about justice in access to new, expensive technologies such as assisted reproduction. These issues are essential when considering genetic information, and indicate the need to evaluate genetic tests with attention to both social and medical outcomes (32, 33).

Another issue of particular significance to genetic testing is the issue of duty to warn: physicians' potential obligation to disclose genetic risk to family members after making a genetic diagnosis (15, 61). This question is not resolved, but two legal cases have addressed it. A New Jersey case, in which a daughter with familial adenomatous polyposis (FAP) sued the estate of her father's doctor (the doctor and father both being deceased), raises the claim that a doctor has a duty to warn relatives directly concerning genetic risk (59). A Florida case suggests that the duty may be discharged if the doctor counsels the patient to inform relatives (50). A recent statement by the American Society of Clinical Oncology also argues that in the case of inherited cancer risk, a physician's duty is discharged by counseling the patient about the familial risk, after which the obligation to inform family members falls to the patient (2).

As more tests to assess genetic risk become available, the debate on this issue will likely continue. In this and in other policy questions related to genetic testing, including appropriate thresholds for using predictive testing and population screening, primary care providers will provide a useful perspective based on the needs of an unselected patient population and the logistic realities of primary care delivery systems. Conversely, primary care providers will benefit greatly from the participation of medical geneticists in developing effective educational tools and practice guidelines, to ensure the appropriate use of genetic information in primary care practice. In the era of genomic health care, a partnership between medical genetics and primary care will be an important element of good practice.

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ERRATA

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