GENETIC TESTING
A Resource from the American College of Preventive Medicine

A Clinical Reference
The following Clinical Reference provides evidence to support the Genetic Testing Time Tool.

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1. INTRODUCTION

Human genomics, the study of structure, function, and interactions of all genes in the human genome, promises to improve the diagnosis, treatment, and prevention of disease. The proliferation of genetic tests has been greatly accelerated by the Human Genome Project over the last decade. [1]

- It is anticipated that genomics will bring to physicians a powerful means to discover hereditary elements that interact with environmental factors leading to disease.
- However, the expected transformation toward genomics-based medicine will occur in steps as new tests are proven and integrated into practice.
- It will require efforts by many scientists and physicians to begin now to sort out the vast amounts of information in the human genome and translate it into meaningful applications for clinical practice.

Meanwhile, practicing physicians and health professionals need to be trained in the principles, applications, and the limitations of genomics and genomic medicine. [2]

Over 1,500 genetic tests are now available clinically, with nearly 300 more available on a research basis only. The number of genetic tests is predicted to increase by 25% annually. [3] There is a boom in the development of genetic tests using the scanning technology from the Genome Project, but questions remain regarding the validity and usefulness of these newer tests.

- Genetic testing holds immense promise for diagnosis and treatment. Medical professionals today, however, feel more skepticism than promise and for good reason.
- Many of the genetic tests offered today have little or no evidence of clinically proven value. Moreover, the regulatory infrastructure needed to apply due diligence on the utility and validity of these tests is largely nonfunctional or nonexistent. [4]

DEFINITIONS

Genetic Testing
The most current definition for “genetic testing” comes from the DHHS Secretary's Advisory Committee for Genetics, Health and Society, in an oversight report dated April, 2008: [5]

- “A genetic or genomic test involves an analysis of human chromosomes, DNA, RNA, genes, and/or gene products (e.g., enzymes and other types of proteins), which is predominately used to detect heritable or somatic mutations, genotypes, or phenotypes related to disease and health. The purpose of genetic tests includes predicting risk of disease, screening newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. Excluded from the definition are tests conducted exclusively for forensic and identity purposes as well as tests conducted purely for research. Also excluded are tests that are used primarily for other purposes but that may contribute to diagnosing a genetic disease or disorder (e.g., blood smears, certain serum chemistries). For example, cholesterol screening in the general population is not considered a genetic test, but it may reveal a genetic disorder such as an inherited form of hypercholesterolemia.”

Genotype: The genetic constitution of the individual; the characterization of the genes. [6]

Phenotype: The observable properties of an individual that are the product of interactions between the genotype and the environment. [6]

Nucleotides: The monomeric units from which DNA or RNA polymers are constructed. They consist of a purine or pyrimidine base, a pentose sugar, and a phosphate group. [6]

Oligonucleotide: A relatively short single-stranded nucleic-acid chain usually consisting of 2 to 20 nucleotides that is synthesized to match a region where a mutation is known to occur, and then used as a probe. [6]
**Single nucleotide polymorphism (SNP):** A single nucleotide variation in a genetic sequence that occurs at appreciable frequency in the population. [6]

**Penetrance:** The probability of developing the disease in those who have the mutation. [6]

**Analytic validity:** A test’s ability to accurately and reliably measure the genotype of interest, and includes measures of analytic sensitivity and specificity, assay robustness, and quality control. [6]

**Clinical validity:** The ability of the test to accurately and reliably identify or predict the intermediate or final outcomes of interest; usually reported as clinical sensitivity and specificity. [6]

**Clinical utility:** The balance of benefits and harms associated with the use of a genetic test in practice, including improvement in measureable clinical outcomes and usefulness/added value in clinical management and decision-making compared with not using the test. [6]

**Personalized medicine:** A rapidly advancing field of healthcare that is informed by each person's unique clinical, genetic (DNA-based), genomic (whole genome or its products), and environmental information. [7]

- The goals are to take advantage of a molecular understanding of disease to optimize preventive healthcare strategies and drug therapies while people are still well or at the earliest stages of disease.
- Because these factors are different for every person, the nature of disease, its onset, its course, and how it might respond to drug or other interventions are as individual as the people who have them.
- For personalized medicine to be used by healthcare providers and their patients, these findings must be translated into precision diagnostic tests and targeted therapies.

**Genomic medicine:** The use of genomic information and its derivatives (RNA, proteins, and metabolites) to guide medical decision making. It is an essential component of personalized medicine. [8]
2. GENETIC TESTING TODAY

Genetic tests look for variations in a person's genes or changes in proteins coded for by specific genes. Abnormal results could mean an inherited disorder, or an increased risk for a disease. [1]

Gene tests analyze DNA taken from a person's blood, body fluids or tissues.
- Some tests use probes -- short strings of DNA with base sequences complementary to those of an altered gene. Probes look for their complements within a person's genome, and if found, bind to it, identifying the variation. [8]

Genetic tests can be ordered by a primary care doctor, specialist, medical geneticist, or a genetic counselor with MD oversight. [9]
- Patients need to understand the pros and cons of genetic testing, its' benefits and risks, how the information will affect treatment decisions.

Acquiring a sample for most tests is simple and low risk-- most require only a sample of blood, hair, or skin. There is higher risk for prenatal testing which requires a sample from the amniotic fluid or chorionic villus during pregnancy. [9]
- The sample is sent to a laboratory for detection of specific variations in chromosomes, DNA, or proteins, depending on the suspected disorder.
- The laboratory reports the test results in writing to a person's doctor or genetic counselor.

DNA microarrays have many thousands of DNA oligonucleotides to detect SNPs. [9]
- Clinical Gene chips contain only the specific DNA arrays for known diseases or syndromes.
- Many different chips are available, varying in the specific DNA for genotyping.
- The technology allows a genetic laboratory to do 400 to 1000 single genetic tests, rapidly, on a small blood sample.

Development of Genetic Testing
Genetic testing for Mendelian disorders such as cystic fibrosis, Huntington's disease, familial breast cancer, and phenylketonuria, among others, was widely available prior to the genomic era. The genetic basis for complex disease remains unclear. [10]

Association Studies
Association studies look for an increased frequency of a particular genotype at a candidate gene locus in cases compared with controls. In these studies, the candidate genes must be known a priori and are therefore limited by understanding of the genes that contribute to a particular disease.
- Association studies have been abundant in the literature. For coronary artery disease alone, association of 96 polymorphisms in 75 genes has been reported. [11]

Genetic association studies have been limited by their lack of reproducibility. Even though the contribution of these types of association studies remains uncertain, it has been suggested that common genetic variants may contribute to common diseases, supporting the role for continued association studies. [12]
- Although appealing, the candidate gene approach has been fraught with design issues, including strict adherence to the definition of the phenotypes, adequate sample size, issues of multiple testing, and lack of replication. [13]

Single-nucleotide polymorphisms (SNPs)
SNPs (pronounced "snips") are the most common type of genetic variation among people. [14]
- They contribute to variations in physical characteristics, as well as less obvious traits such as personality, behavior and disease susceptibility.

Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA. [14]
• SNPs occur normally throughout a person’s DNA, on average, about every 300 nucleotides, which means there are roughly 10 million SNPs in the human genome.
• They can act as biological markers, helping scientists locate genes that are associated with a disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a role in disease by affecting the gene’s function.
• Most SNPs have no effect on health or development. Some, however, have proven to be very important in human health.
• They can be used to track the inheritance of disease genes within families.
• Researchers have found SNPs that may help predict an individual’s susceptibility to environmental factors such as toxins, and risk of developing particular diseases.

SNPs can also influence responses to pharmacotherapy and whether drugs will produce adverse reactions. The development of new drugs can be made far cheaper and more rapid by selecting participants in drug trials based on their genetically determined response to drugs. [15]
• Studies are ongoing to identify SNPs associated with complex diseases such as heart disease, diabetes, and cancer. [14]

Technology
Recent advances in molecular technologies have resulted in the ability to screen hundreds of thousands of SNPs and tens of thousands of gene expression profiles. While these data have the potential to inform investigations into disease etiologies and thereby advance medicine, the question of how to adequately control both false positive and false negative rates remains. [16]
• About 12 million true SNPs have been identified to date. However, most have not yet been associated with disease susceptibility or drug response. [15]

Genome Wide Association Studies (GWAS)
Genome-wide association studies are a relatively new way for scientists to identify genes involved in human disease. This method searches the genome for single nucleotide polymorphisms (SNPs) in any gene that occur more frequently in people with a particular disease than in people without the disease. [17,18]
• Each study can look at hundreds or thousands of SNPs at the same time. Researchers scan the data to pinpoint genes that may contribute to a person’s risk of developing a certain disease.
• Because GWA studies examine SNPs across the genome, they represent a promising way to study complex, common diseases in which many genetic variations contribute to a person’s risk.
• This approach has already identified SNPs related to several complex conditions including diabetes, heart abnormalities, Parkinson disease, and Crohn’s disease.
• The hope is that future genome-wide association studies will identify more SNPs associated with chronic diseases, as well as variations that affect a person’s response to certain drugs and influence interactions between a person’s genes and the environment.

Many common diseases, including diabetes mellitus, osteoporosis, and cardiovascular disease, have strong genetic influences but the interactions are complex. [19]
• The genotype insufficiently predicts the phenotype because of the powerful effects of other modifying genes, environmental influences, and lifestyle factors.
• The underlying genetic factors are being investigated in the GWAS, with many new (often unexpected) markers identified; in many instances their functional significance is unknown.
3. TYPES OF TESTS

Clinically applicable genetic tests may be used for: [20]

- Newborn screening – to identify individuals with an increased chance of having a specific genetic disorder so that treatment can be started as soon as possible.
- Diagnostic testing - to confirm or rule out a known or suspected genetic disorder in a symptomatic individual of any age.
- Carrier testing - to identify individuals who have a gene mutation for a disorder inherited in an autosomal recessive or X-linked recessive manner.
- Prenatal testing - during a pregnancy to assess the health status of a fetus.
- Preimplantation testing - on early embryos resulting from in vitro fertilization in order to decrease the chance of a particular genetic condition occurring in the fetus.
- Predictive testing – to evaluate risk in asymptomatic individuals with a family history of a genetic disorder

Newborn Screening
Newborn screening programs are usually legally mandated and vary from state to state. [21]

- Performed routinely at birth, unless specifically refused by the parents in writing.
- Not designed to be diagnostic, but to identify individuals who may be candidates for further diagnostic tests.
- Many parents do not realize that newborn screening has been done (or which tests were included), even if they signed a consent form when their child was born.
- Education is necessary with positive screening results in order to avoid misunderstandings, anxiety and discrimination.

In 2005, a federal advisory committee recommended that the number of disorders in state newborn screening programs be expanded from 9 to 29. [22]

Diagnostic Testing [20]

- DNA testing may yield diagnostic information at a lower cost and with less risk than other procedures.
- Confirming a diagnosis may alter medical management for the individual.
- May have reproductive or psychosocial implications for other family members.
- Establishing a diagnosis may require more than one type of genetic test.
- DNA testing may not always be the best way to establish a clinical diagnosis.

Carrier Testing [20]

- Carriers usually do not have symptoms themselves related to the gene mutation.
- Offered to individuals who have family members with a genetic condition, family members of an identified carrier, and individuals in ethnic or racial groups known to have a higher carrier rate for a particular condition.
- Identifying carriers allows reproductive choices.
- Genetic counseling and education should accompany carrier testing because of the potential for personal and social concerns.
- Molecular genetic testing of an affected family member may be required to determine the disease-causing mutation(s) present in the family.
- In some situations, DNA testing may not be the primary way of determining carrier status.
- Carrier testing can improve risk assessment for members of racial and ethnic groups that are more likely to be carriers for certain genetic conditions.

Prenatal Testing
Offered when there is an increased risk of having a child with a genetic condition due to maternal age, family history, ethnicity, or suggestive multiple marker screen or fetal ultrasound examination. [20]
• Routine prenatal diagnostic test procedures are amniocentesis and chorionic villus sampling (CVS). More specialized procedures include placental biopsy, periumbilical blood sampling (PUBS), and fetoscopy with fetal skin biopsy.
• A laboratory that performs the disease-specific test of interest must be identified before any prenatal diagnostic test procedure is offered.
• All prenatal diagnostic test procedures have an associated risk to the fetus and the pregnancy; therefore, informed consent is required, most often in conjunction with genetic counseling.
• In most cases, before prenatal diagnosis using molecular genetic testing can be offered, specific gene mutation(s) must be identified in an affected relative or carrier parent(s).
• Prenatal testing for adult-onset conditions is controversial. Individuals seeking prenatal diagnosis for these conditions should be referred to a professional trained in genetic counseling for a complete discussion of the issues.

Preimplantation Testing (Preimplantation Genetic Diagnosis, or PGD)
Generally offered to couples with a high chance of having a child with a serious disorder. Preimplantation testing provides an alternative to prenatal diagnosis and termination of affected pregnancies. [20]
• Only performed at a few centers and available for a limited number of disorders, but testing options are beginning to expand as more IVF and infertility clinics offering PGD.
• Not possible in some cases due to difficulty in obtaining eggs or early embryos and problems with DNA analysis procedures; also the entire process and procedure used to harvest eggs may not be agreeable to some women.
• Due to possible errors in preimplantation diagnosis, traditional prenatal diagnostic methods are recommended to monitor these pregnancies.
• Cost is very high and usually not covered by insurance.

Predictive Testing
Two types: presymptomatic (eventual development of symptoms is certain when the gene mutation is present, e.g., Huntington disease) and predispositional (eventual development of symptoms is likely but not certain when the gene mutation is present, e.g., breast cancer). [20]
• MEDICALLY INDICATED if early diagnosis allows interventions which reduce morbidity or mortality.
• Even in the absence of medical indications, predictive testing can influence life planning decisions.
• Careful patient assessment, counseling, and follow-up are important due to psychological ramifications.
• Many laboratories will not proceed with predictive testing without proof of informed consent and genetic counseling.
• Identification of the specific gene mutation in an affected relative or establishment of linkage within the family should precede predictive testing.
• Predictive testing of asymptomatic children at risk for adult-onset disorders is strongly discouraged when no medical intervention is available.

Pharmacogenomic Testing
This is another form of testing that is sure to become more common in the future. It involves the study of how genes affect a person’s response to drugs -- combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses tailored to a person’s genetic makeup. [23]
• Many drugs currently available are “one size fits all,” but they don’t work the same way for everyone.
• It is difficult to predict who will benefit from a medication, who will not respond, and who will experience adverse reactions.
• Adverse drug reactions are a significant cause of hospitalizations and deaths in the U.S.
• Researchers are learning how gene variations affect the response to medications. Genetic differences may be able to predict whether a medication will be effective or cause adverse reactions.
Within the past decade several pharmacogenetic tests have emerged to aid clinicians in predicting efficacy or toxicity for some drugs. But, knowledge gaps still impede widespread use in the clinical setting. [24]

- A major gap is that we often do not know the genetic variants responsible for inter-individual differences in drug metabolism or drug response. [25]

**Examples:**

Genetic technology has led to some very important therapeutic innovations, including the use of imatinib mesylate (Gleevec) in BCR-ABL chronic myeloid leukemia and of trastuzumab (Herceptin) in Her2-positive breast cancer, but the much anticipated explosion of new effective treatments has been more modest than expected. [26,27]

- The analysis of thiopurine S-methyltransferase genotypes enables the prediction of toxicity in patients to be treated with either 6-mercaptopurine or azathioprine.
- The uridine 5'-diphosphoglucuronosyl-transferase 1A1 genotype may predict irinotecan toxicity.
- There is a large body of information concerning cytochrome P450 (CYP) polymorphisms and their relationship with drug toxicity and response; however, currently, there is limited use of CYP genotypes to individualize treatments.
- It is well recognized that the CYP2C9 genotype, when combined with the genotype for vitamin K epoxide reductase complex subunit 1, is predictive of dose requirement for oral anticoagulants, a fact that is likely to have clinical utility.
- There is also potential to individualize treatments with certain drugs on the basis of CYP2D6, CYP2C19 and CYP3A5 genotypes.
- There is increasing information on the relationship between response to beta2-adrenoceptor agonists and the genotype for the beta2-adrenoceptor gene.

**SSRI response**

Treatment resistance and intolerance are common with SSRI treatment. [28]

- Some polymorphisms have been associated with the SSRI response.
- But, as yet no randomized trials have tested the efficacy of genetic tests to improve outcomes in those with treatment resistance or treatment intolerance to SSRIs.
- A randomized trial comparing the response with standard psychiatric care and psychiatric care tailored as a result of genetic test results should be completed before the implementation of these tests can be considered.

**Warfarin dosing**

Initiation of warfarin dosing is associated with highly variable responses between individuals. [29]

- Variants of two genes, CYP2C9 and VKORC1, account for 30–50% of the variability; thus, many believe that testing these genes will aid in warfarin dosing recommendations.
- There is strong evidence to support the association between these genetic variants and the therapeutic dose of warfarin.
- However, there is insufficient evidence, at this time, to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naive patients.
4. PROMISE OF PERSONALIZED MEDICINE

Personalized medicine uses the patient's genetic composition to tailor strategies for patient-specific disease detection, treatment, or prevention. [30]

It promises to use molecular markers to signal the risk of disease or its presence before clinical signs and symptoms appear. [31]

- Such a strategy can delay disease onset or minimize symptom severity.
- The molecular foundations that enable personalized medicine include detection of variation in nucleotide sequences of genes and in characteristic patterns of gene expression, proteins and metabolites.
- Genetic and molecular patterns are correlated with disease manifestations, drug responses, treatment prognosis, or prediction of predisposition to future disease states. However, the uncertainties associated with personalized medicine are considerable, including economic, ethical, legal, and societal questions.
- Although much of the promise of personalized medicine remains unproven to date, its foundations appear solid and evidence pointing to its growing importance in healthcare is accumulating rapidly.

Already having an impact
DNA-based risk assessment for common complex disease, molecular signatures for cancer diagnosis and prognosis, and genome-guided therapy and dose selection are important examples for how genome information is already enabling more personalized health care along the continuum from health to disease. [8]

It is also hoped that genetic testing will lead to: [32]

- More innovative ways to diagnose disease and screen for health risks and early symptoms, to be predictive, preventive, and personalized.
- More direction for complex decisions, such as annual mammogram for women in their 40s or PSA testing for any man. With genetic indications of increased risk, the decision to have earlier or more frequent testing is clearer.
- More efficient pharmacotherapy based on the genome
- Much of drug prescribing is trial and error. It wastes resources, under-treats some patients, over-treats others, and causes a lot of side effects in others.
- For example, Vioxx may be an outstanding drug for better than 95% of patients, but for a few it's a terrible drug; these cases reflect a small percentage of patients who carry a gene mutation that leads to the adverse effect.

Slow but steady progress
The expected transformation toward genomics-based medicine will occur gradually; each new test must be proven, and as proven effective will be incorporated into practice. Currently there are hundreds of tests in the pipeline; some will be found to be useful; many will not. [2]

- It will require efforts of many scientists and physicians to sort out the vast amounts of information in the human genome and translate it into meaningful applications in clinical practice.

The ongoing discoveries being made about our genome cause us to question reviews declaring that "personalized medicine is almost here" or that "individualized drug therapy will soon be a reality." [33]

- Numerous reasons exist to show that an "unequivocal genotype" or even an "unequivocal phenotype" is virtually impossible to achieve in current limited-size studies of human populations.
- This problem (of insufficiently stringent criteria) leads to a decrease in statistical power and, consequently, equivocal interpretation of most genotype-phenotype association studies.

The full application of genomic and personalized medicine in health care will require dramatic changes in regulatory and reimbursement policies as well as legislative protections for privacy for system-wide adoption. [8]
There are challenges from both a scientific and a policy perspective; however, they will be confronted and solved with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence based.
5. LIMITATIONS OF GENETIC TESTING

For most diseases, many pieces of the genetic puzzle remain to be discovered, along with how those pieces interact with lifestyle and environmental factors. That means today's tests may falsely reassure people with undiscovered risk factors and needlessly alarm those with undiscovered protective factors. [1]

An important limitation is the lack of a sufficient evidence-based rationale for an association between the genotype and the phenotype. [34]

- Genetic screening strategies should be based on good evidence-based rationales.

Genetic cancer screening has been limited to high-risk individuals with a strong hereditary predisposition to cancer. [35]

- With the cloning of the human genome, it has become apparent that genetic anomalies are not limited to high-risk individuals; more than 10 million genetic variants exist.
- The vast majority of these genetic variants have no functional significance.
- Current efforts are focused on identification of which impact cancer development and/or progression.

Genetic testing for susceptibility to common diseases based on a combination of genetic markers may be needed because the effect size associated with each genetic marker is small. [36]

- For given relative risk values and genotype frequency, the discriminative accuracy increases with increasing heritability but declines with increasing prevalence of the disease.
- For a given value of population-attributable fraction, the discriminative accuracy increases with increasing relative risks, but declines with increasing genotype frequency.
- On the basis of population-attributable fraction and estimates of heritability of disease, the number of risk genotypes required to have a reasonable clinical discriminative accuracy is much higher than the genome profiles available at present. Simply put, we do not have enough data yet.

Common diseases such as type 2 diabetes and coronary heart disease result from a complex interplay of genetic and environmental factors. [37]

- Recent developments in genomics research have boosted progress in the discovery of susceptibility genes and fueled expectations about opportunities of genetic profiling for personalizing medicine.
- Personalized medicine requires a test that fairly accurately predicts disease risk, particularly when interventions are invasive, expensive or have major side effects.
- Recent studies on the prediction of common diseases based on multiple genetic variants alone or in addition to traditional disease risk factors showed limited predictive value so far, but all have investigated only a limited number of susceptibility variants.

New gene discoveries from genome-wide association studies will certainly further improve the prediction of common diseases, but it is another question if this improvement will enable personalized medicine. [37]

- New gene discoveries may not evidently improve the prediction of common diseases to a degree that will change the management of individuals at increased risk.
- Substantial improvements may only be expected if we understand the complete causal mechanisms.
- Genomics research will contribute to this understanding, but it is likely that the intricacies of complex diseases may ultimately limit the opportunities for accurate prediction of disease in asymptomatic individuals since unraveling the complete causal pathways may not be possible.

Although single gene analyses may help elucidate underlying mechanistic pathways, they do not take into account all of the variation in the human genome. [38]

- Correspondingly, advances in genomics, through microarrays, have facilitated characterization of these broader downstream elements.
Genome-wide association studies have been limited by the use of thousands of markers when actually hundreds of thousands are required, and by the use of hundreds of individuals when thousands are required.

- Replication of positive findings in independent populations is essential.
- Several thousand significant single nucleotide polymorphisms and 130 clusters associated with CAD have been identified. They may account for as much as half of the risk for CAD. [39]
- The complexity of genes involved in chronic conditions is overwhelming; genes are often merely an indicator of an environmental factor.

Technological progress has improved the detection rate in patients with familial hypercholesterolemia.

- More than 1000 different molecular causes of familial hypercholesterolemia are documented, and although more than 90% of these clearly cause familial hypercholesterolemia, the remainder require careful interpretation; the relative importance of these is genetic causes remains to be determined. [40]

There are high expectations about the capabilities of pharmacogenetics to tailor psychotropic treatment and "personalize" treatment. [41]

- While a large number of associations, with generally small effect size, have been discovered, a genetic test with widespread use and adoption is still missing.
- A more realistic picture, recognizing the important contribution of clinical and environmental factors toward overall clinical outcome has emerged.
- In this emerging view, genetic findings, if considered individually, may have limited clinical applications.

Prospective cohort studies are costly and time consuming but are necessary to show the clinical utility of genetic testing; they are the best means for understanding how genes interact with environmental risk factors to cause disease. [42]
6. EVIDENCE-BASED RECOMMENDATIONS

There are two major sources of evidence-based recommendations for genetic testing in the U.S.:

- USPSTF, U.S. Preventive Services Task Force
- EGAPP, Evaluation of the Genomic Applications in Practice & Prevention from the Centers for Disease Control.

EGAPP was launched to establish a systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology as they are translated from research into clinical practice. [43]

**USPSTF Recommendations:**

1. **BRCA1 and 2 testing for hereditary breast and ovarian cancer.** [44]
   - Recommend evaluation of family history as first step.
   - For women whose family history of breast and/or ovarian cancer indicates an increased risk of having the BRCA1 or 2 mutation:
     - Recommendation is for counseling, not testing itself -- counseling by a trained professional to assist decisions about testing and follow-up clinical procedures.
     - The woman's decision to be tested should be based on her values and balancing of benefits and harms.
   - Recommend against referral for counseling for women without a high-risk family history.
   - About 2% of adult women (approx 1.8 million) in the general population have a positive family history and could benefit from medical consultation and referral for counseling.
   - Women without a high risk family history pattern have a low probability of having a deleterious mutation in BRCA1 or BRCA2 genes.
   - In a woman who has a clinically important BRCA mutation, the probability of developing breast or ovarian cancer by age 70 years is estimated to be 35% to 84% for breast cancer and 10% to 50% for ovarian cancer.
   - Risk may be reduced by 85% or more with surgery. From a population or public health perspective, thousands of cancers could be prevented, even though the mutation is rare. There are challenges for a clinical practice in implementing this recommendation.

2. **Hemochromatosis** [45]
   - USPSTF recommended against routine screening for hereditary hemochromatosis in asymptomatic individuals, concluding that the potential harms outweigh the potential benefits, given the large numbers of people with a high-risk genotype who would not develop the disease.
   - Genotypic predisposition does not accurately predict future risk for disease manifestation.
   - Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments. There is poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals.

3. **Fecal DNA testing for colorectal cancer screening.** [46]
   - Evidence was insufficient to recommend the test; the balance of benefits and harms could not be determined.
   - Information on harms from fecal DNA testing is limited at this time. Popular misunderstandings could occur about genetic profiling and insurability, but these are without basis because fecal DNA testing relies on the detection of de novo or somatic mutation in the mucosal lining of the bowel and is not related to hereditary (germ-line) mutations. Despite this distinction, general acceptability may limit the use of this test. [47]
   - Has potential as a highly specific test, and it could reduce harms associated with follow-up of false-positive test results.
   - Fecal DNA tests are evolving, and no test is widely used; currently is likely to have a high monetary cost per test.
EGAPP Recommendations:

1. **CYP450 testing for the treatment of depression** [48]
   - The Cytochrome P450 (CYP450) family of enzymes is a major subset of all drug-metabolizing enzymes. In theory, CYP450 genotype could guide SSRI choice or dose to those most compatible with the patient’s metabolizer status. Thus, utilizing the test before treatment to individualize SSRI choice and dose could enhance the response to the drug. EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment for nonpsychotic depression until further clinical trials are completed.
   - CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment.
   - No evidence that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making.

2. **Lynch Syndrome** [49]
   - Lynch syndrome is a hereditary predisposition to colorectal cancer (CRC) and certain other malignancies (e.g., endometrial and gastric cancer) as a result of a germline mismatch repair (MMR) gene mutation.
   - Genetic testing to detect Lynch syndrome in newly diagnosed patients is proposed as a strategy to reduce CRC morbidity and mortality in their relatives, who could be offered counseling and testing, and if they tested positive, colonoscopy.
   - Over 140,000 individuals are diagnosed with colorectal cancer each year and about 4,000 have Lynch syndrome. About half of first-degree relatives of these patients are likely to have the mutation, and colonoscopy reduces risk by about 60%, so thousands of cancers could be prevented.
   - The risk of colorectal cancer in individuals with Lynch syndrome was over 50% of lifetime.
   - Recommended offering counseling and genetic testing for Lynch syndrome to patients newly diagnosed with colorectal cancer to reduce morbidity and mortality in the relatives, not in the patients. There is evidence of potential benefits to the patient’s relatives.

3. **UGT1A1 genotyping in patients with metastatic colorectal cancer** [50]
   - About 15% of cases (22,500) of colorectal cancer may be candidates for irinotecan therapy (they have distant CRC). The adverse effects of this therapy can be extensive, particularly severe neutropenia and diarrhea. These effects may vary with the UGT1A1 genotype.
   - Hence, it has been suggested that knowing the UGT1A1 genotype may allow adjusting the dose to achieve the optimal balance between benefits and adverse effects.
   - The EGAPP Working Group found that evidence is insufficient to recommend for or against the routine use of UGT1A1 genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan, with the intent of modifying the dose as a way to avoid adverse drug reactions (severe neutropenia).

4. **Tumor gene expression profiles for women with early-stage breast cancer** [51]
   - The measurement of gene expression in breast tumor tissue is proposed as a way to estimate the risk of distant disease recurrence in order to provide additional information beyond current clinicopathological risk stratification.
   - EGAPP found insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer -- uncertain if the benefits outweigh the potential harms of using these tests and then modifying treatments based on the test results.

**SUMMARY**

1. Two tests for which widespread use is recommended:
   - Counseling for BRCA1 and BRCA2 genetic testing in women who have a high risk of having those mutations based on their family history [44], and
   - Lynch syndrome testing for patients newly diagnosed with colorectal cancer in order to benefit the relatives of those patients. [49]
2. Another test for which use is *not* recommended:
   - Genetic testing for hemochromatosis in the general population [45]

3. A test for which use is discouraged:
   - CYP450 testing in patients with depression for making decisions about the use of selective serotonin reuptake inhibitors for treatment. [48]

4. Three tests for which evidence is insufficient to make a recommendation:
   - Colorectal cancer screening with fecal DNA in the general population [46]
   - Breast cancer gene expression profiling among women newly diagnosed with early-stage breast cancer to make treatment decisions [51] and
   - UGT1A1 testing for colorectal cancer patients, that is, patients with metastatic disease, again for making treatment decisions. [50]

**Evidence Reports:**
CDC-funded evidence-based reports that guide genomic testing and diagnostic strategies include: [52]
- Depression, CYP450 Testing for Adults Treated with SSRIs: [http://www.ahrq.gov/clinic/tp/cyp450tp.htm](http://www.ahrq.gov/clinic/tp/cyp450tp.htm)
- UGT1A1 Genotyping in Patients with Metastatic Colorectal Cancer Treated with Irinotecan: [http://www.egappreviews.org/workingrp/topics_colorectal.htm](http://www.egappreviews.org/workingrp/topics_colorectal.htm)

**Genetic Testing for Alzheimer’s Disease:**
Alzheimer’s is the object of intense genetic research. Researchers have identified four variants of genes associated with the disease.
- Three — located on chromosomes 21, 14, and 1 — are linked to the early-onset forms of the disease that begins to appear in the early 40s to mid-50s.
- If someone has one of these gene mutations, he or she will at some point develop the disease. These incidents of Alzheimer’s are very rare, however, accounting for only about 1% of all cases.

The fourth gene, APOE-e4 on chromosome 19, is linked to a greater risk of developing late-onset Alzheimer’s, the more common form of the disease.
- Genetic testing for APOE-e4 is controversial and should only be undertaken after discussing the benefits and risks with a physician or genetic counselor.
- APOE-e4 increases the risk of developing Alzheimer’s, but is neither necessary (people without APOE-e4 develop the disease) nor sufficient (not all people with APOE-e4 develop Alzheimer’s).

Genetic testing for Alzheimer’s is not recommended at this time, but, if performed, should be done with pre- and post-test counseling, which includes a full discussion of the implication of the test and all information necessary to make an informed decision. [http://www.alz.org/national/documents/topicsheet_genetictesting.pdf](http://www.alz.org/national/documents/topicsheet_genetictesting.pdf)
7. PROS AND CONS OF GENETIC TESTING

PROS [1,53]
People in families at high risk for a genetic disease have to live with uncertainty about their future and their children's future.

- A genetic test can provide a sense of relief if it is negative for the altered gene.
- It may reduce the need for, or at least the intensity of, check-ups, screening and preventive therapy.
- Even if the test is positive, there are potential benefits, such as earlier disease detection, more targeted surveillance, and more effective prevention strategies such as motivating a person to make behavioral changes to lower their chance of disease.
- Either way it reduces uncertainty, which helps people to make informed choices about their future.

Pharmacogenetic testing can help to identify the best medicine or dose of a medicine; can help reduce adverse effects. [1]

The physical risks associated with most genetic tests are very small, particularly if only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek) is required.

- Saliva-based DNA testing, which is even less invasive, is now being performed in both research and clinical settings.

CONS
Prenatal testing carries a small but real risk of losing the pregnancy (miscarriage) because it requires a sample of amniotic fluid or tissue from around the fetus. [54]

Many of the risks associated with genetic testing involve emotional, social, or financial consequences of the test results. [54]

- People may feel angry, depressed, anxious, or guilty about their results.
- It may create tension within a family because the results can reveal information about other family members in addition to the person who is tested; it may put pressure on them to be tested.

A serious issue in genetic testing is the "worried well" – those who believe their genetic predisposition places them at higher risk than they really are. [55]

- For example, people who are heterozygous for ApoE4 have an increased risk of developing Alzheimer's disease, but 50% to 75% of people carrying this allele never get Alzheimer's, and no current treatment can slow the disease. But many such people worry excessively about developing the disease.

The possibility of genetic discrimination in employment or insurance is also a concern, even though there are laws to prevent these practices. [54]

- In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law preventing discrimination against people based on their genetic information. This legislation bars health insurance companies and employers from discriminating against individuals on the basis of their genetic information. [101]

Genetic tests can only provide limited information about an inherited condition; they cannot determine if or when a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. [54]

- Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.
OTHER ISSUES

Impact of knowing positive carrier status
The impact of carrier status on risk perspectives is not well understood.
- A systematic review showed that, for affective outcomes, most studies reported negative effects, but they were short-lived. [56]
- For behavioral outcomes, an increase in screening behavior was found in carriers, but the change in behaviors was less than expected.
- Perceived risk decreased over time; there was generally no difference between carriers and noncarriers 12 months after genetic testing.

Overall, predispositional genetic testing has been shown to have no significant impact on psychological outcomes or changes in perceived risk, and little effect on behavior. [56]
- Better patient education strategies are required; there are no negative psychological effects of knowing more.

Stigmatization regarding mental disorders
An optimistic view is that information on the genetic risk for mental disorders will reduce blame and social stigma in individuals living with mental disorder. [57]
- A pessimistic view is that genetic testing will stigmatize those at risk of mental disorders.

Ethical issues
Individuals have a moral obligation to communicate genetic information to their family members. Genetic health professionals should encourage individuals to communicate this information to their family members, and genetic health professionals should support individuals throughout the communication process. [58]

Health care professionals have a duty to inform patients about the potential genetic risks to their relatives. [58a]
- Then, depending on the circumstances, the health care professional may have a privilege to warn at risk relatives where: the harm is serious, imminent and likely; prevention or treatment is available; and where a health care professional in like circumstances would disclose. Seriousness defies exact definition and must be determined on an ad hoc basis.

Concerns about testing
The integration of pharmacogenetic testing into routine care depends upon both patient and physician acceptance of the tests. [59]
- A German study found that most patients (96%) and half of physicians (52%) appreciated the availability of pharmacogenetic tests for a disease such as asthma.
- But a third of patients worried about potential unfavorable test results (35%) and violation of privacy (36%).
- Physician concerns were mainly related to the possibility that patients might feel pressure to be tested (72%) or to be disadvantaged by health insurance (61%).
8. ROLE OF PRIMARY CARE

Primary care physicians represent the front line of screening for inherited disease risks. [60]
- Family physicians are increasingly involved in delivering genetic services. [61]

Health care professionals should augment their current practice by:
- obtaining a multigenerational genetic family history for each patient,
- assessing all patients for potentially heritable conditions,
- providing referrals to genetic health professionals as needed,
- offering genetic testing when indicated, and
- considering an individual's genetic makeup in the selection of medications and treatments for that person.

Clinicians should be able to identify patients who are candidates for genetic testing. [62]
- When identified, patients should be offered counseling and follow-up, with referral as appropriate, to ensure delivery of care consistent with current standards.
- When patients experience barriers to needed health care, clinicians should advocate for their needs. Clinicians must ensure the autonomy and informed decision-making of all patients.
- Clinicians must also provide emotional support and accurate information about disease risks and risk reduction measures, including uncertainties.

Clinicians need to learn how to read and interpret the results of genetic tests, and to understand when to refer patients to specialists and ask for second opinions and reinterpretation of genetic information. [63]

All health care professionals ought to be prepared to address the complex personal, cultural, theological, ethical, legal, and social issues associated with genetic testing and other genetic issues commonly encountered in clinical practice. [63a]
- Family physicians must be prepared to explore their patients' decisions for or against genetic testing, their motivation for testing and the potential psychosocial effect of both deciding to undergo or forgo genetic testing for cancer-related genes. Also important are deciding whether patients qualify for the tests; coping with the waiting period before testing can be done; and discussing positive, negative, and inconclusive outcomes of testing. [63b]

A qualitative study using focus groups examined family physicians’ experiences in dealing with genetic susceptibility to cancer. Participants anticipated an expanding role for family practices in risk assessment, gate-keeping, and ordering genetic tests. They were concerned about the complexity of genetic testing, the lack of evidence regarding management, and the implications for families. [63c]

Patient Needs

Patient interest in genetic testing for susceptibility to both heart disease and cancer is high. [63d]
- A nationally representative survey in the UK found that 2 out of 3 people were interested in being tested for genetic susceptibility to these two diseases.

When patients want to make informed decisions about genetic testing, they require genetic knowledge, and they prefer to get this information from their primary care doctor. [64]
- Most patients, especially older and lower educated, feel they have a poor understanding of genetics.
- Attitudes towards genetics were rather positive, especially among younger and higher educated patients. Higher levels of genetic knowledge were associated with a more favorable attitude towards genetics.

Patients need more direct support in making sense of genetic information. [65]
- Information about genetic susceptibilities was difficult to make sense of, as it related to ambiguous risks for participants and family members, complicated and unfamiliar terminology and multiple genes and preventive strategies.
When helping a patient evaluate a genetic test the health care provider must assure: [66]
- Understanding of the purpose and appropriateness of the test
- Accuracy and clinical significance of results
- Reliability of the laboratory

**Need to allay fears of discrimination**
Though the US passed the Genetic Information Non-Discrimination Act, many questions remain of how individuals confronting genetic disease view and experience possible discrimination. Discrimination can be implicit, indirect and subtle, rather than explicit, direct and overt; and be hard to prove. Patients may be treated "differently" and unfairly, raising questions of how to define "discrimination", and "appropriate accommodation". [66a]

A survey of patients showed that they were often unclear and wary about legislation. Fears and experiences of discrimination can shape testing, treatment, and disclosure. Discrimination can be subjective, and take various forms. [66a]
- Providers need to be aware of, and prepared to address, subtle and indirect discrimination; ambiguities, confusion and potential limitations concerning current legislation; and needs for education about these laws. Policies are needed to prevent discrimination in life, long-term care, and disability insurance, not covered by GINA.
9. CHALLENGES FOR CLINICIANS

Genetic testing is expanding rapidly to become part of mainstream medicine. While genetic tests bring with them the promise of improved diagnosis and treatment for patients, they also raise several policy challenges, including the lack of a coherent oversight system to ensure the quality of tests and testing laboratories, the rise of direct-to-consumer genetic testing, and the dearth of professional guidelines to assist the transition of genetic tests from research to medical practice. [67]

Increasing use of genetic testing requires providers to be knowledgeable regarding ethical, policy, and practice issues in order to minimize risk for harm, protect the rights of individuals and families, and consider societal context in the management of genetic test results. [67a]

- Primary care providers are not sufficiently prepared to meet the growing genetic consultation needs of the adult population. [67b]
- Even genetics professionals may also be ill-suited for this challenge, since geneticists and genetic counselors have traditionally had greater experience in pediatric and prenatal settings.

Hereditary cancer risk assessment, counseling, and testing are becoming ever more complex as the understanding of the genetic components of disease grows. [68]

- The demand for highly trained professionals with expertise in this field, such as genetic counselors, is also growing.
- The challenge is in identifying patients appropriate for genetic assessment and counseling.

Patients have varying reactions to test results – some understand them, others ignore them; it is complex information. [55]

- Primary care providers must be able to handle these situations; address misperceptions, provide good information at a level the individual patient can understand, or get them to someone who will counsel them.

The need to communicate genetic information
The implications for primary care include the need to understand and communicate the current limitations of genetic testing, especially the direct to consumer versions. [69]

- Emphasizing the caution needed in the premature introduction of over-the-counter testing without a sound evidence base.

Physicians must become as facile in interpreting this type of predictive information as they are with other types of medical data, while recognizing the unique ethical, legal, and social implications of genetic testing. [69a]

- Decision-making needs to include the analytic performance of genetic tests, their validity in predicting health outcomes, and the utility of the genetic information in improving health and preventing disease.

A qualitative study found that inconsistent and informal communication of test results -- for example by phone -- leads to confusion. [65]

- Patients did not necessarily overestimate their risk, but some were uncertain about whether they were taking the right preventive actions and/or whether their children were at risk.
- Information about genetic susceptibilities was difficult to make sense of, as it related to ambiguous risks for participants and family members, complicated and unfamiliar terminology and multiple genes and preventive strategies.
- Patients need more direct support in making sense of genetic information, if this information is to bring the anticipated health benefits, and not fuel health inequalities or create ethical problems.
- Clinicians need guidance to help them introduce genetic tests, communicate their results and explain their implications.
Dealing with patients who are getting online information
The Internet has changed the way medical practitioners communicate and educate themselves and their patients. The Internet has provided enormous opportunity, but it has also led to complexity and uncertainty. [69b]

- Patients are increasingly drawn to online resources for medical information. Physicians often get angry or irritated when patients seek and retrieve information on their own. Attempts to mediate patients' online activities can stress the patient/physician relationship. This could lead to misunderstandings, miscommunications, and fray an already fragile trust.

Nearly 2 out of 3 patients who use the internet would consider ordering a genetic test online and believe that their physician has a professional obligation to help them interpret the results of genetic tests they do on their own. Physicians should be prepared for patient demands for information and counsel on the basis of these results. [69c]
10. PRACTICE PATTERNS

A survey of primary care physicians’ experience ordering and referring patients for genetic testing in 2002 found that 60% of primary care physicians have ordered a genetic test and 74% have referred a patient for genetic testing. [70]

- Approximately 62% have referred a patient for genetic testing to a genetics center/counselor or to a specialist, and 17% to a clinical trial.
- Minority-serving physicians were significantly less likely to have ever ordered a genetic test for breast cancer, colorectal cancer, or Huntington disease, or to have ever referred a patient for genetic testing relative to those serving fewer minorities.

About half of physicians in a nationally representative random sample had ordered or referred a patient for BRCA1/2 testing in the past year. [70a]

- Another national survey showed that two out of three (68.2%) of those who did order BRCA1/2 testing during 2004 to 2005 usually or always provided some counseling before testing. [74]
- Counseling was more complete when assisted by a genetic counselor or nurse geneticist.

A 2006 survey of family physicians examined attitudes and practices related to the use of genetics when a patient who requested BRCA1/2 genetic testing was not appropriate for referral based on U.S. Preventive Services Task Force guidelines. [70b]

- Only 8% correctly did not refer to genetic services; 92% referred for genetic services, with 50% referring for genetic counseling. 65% believed that if they refused to refer for genetic services it would harm their relationship with the patient.

A survey of physicians from a large health care delivery system showed that physicians who were more confident in interpreting and explaining factor V Leiden (FVL) genetic testing results ordered the test more often. [70c]

- Frequent-FVL physicians were more confident in interpreting and explaining FVL test results.

Use of genetic testing is higher among racial majority versus minority patients for reasons that remain unclear.

- A survey of family physicians of the Massachusetts Practice Based Research Network to assess whether their attitudes about cancer-predictive genetic testing related to the race of their patients showed that those whose practices had higher proportions of White patients were more likely to strongly endorse the value of screening for inherited cancer risk (ORadj 3.18, 95% CI 1.05, 9.66). [60]
- These findings suggest that clinical attention to genetic screening, at least for cancer risk, is greater in practices serving fewer racial minority patients.

A population-based survey of African-Americans showed that 9 out of 10 would definitely/probably take a genetic test for colon cancer, although only fewer than half knew much about genetic testing. [70d]

The trend in use and discussion of genetic testing is promising, but more data is needed.

- More primary care physicians in 2001 were discussing the subject of genetic screening with their patients and more physicians were referring their patients for genetic evaluations and testing for cancer risk, compared with 1996. [71]
11. BARRIERS TO ENHANCING PRACTICE

Cost of testing
Cost of genetic testing was the most frequently cited barrier to genetic testing for cancer risk. [71]

Poor knowledge of genetics
PCPs’ baseline genetic knowledge was self-rated as uniformly poor. Confidence was highest in eliciting family history and providing psychosocial support and lowest in discussing risks/benefits of genetic testing and in counseling. [61]
- Role-play with clinicians has been shown to be an effective practice for raising awareness of the process and content of genetic counseling.

Clinically relevant genetics knowledge is essential for appropriate assessment and management of inherited cancer risk, and for effective communication with patients. A national physician survey assessed knowledge of predictive genetic testing for breast/ovarian and hereditary non-polyposis colorectal cancer (HNPCC) syndromes. [72]
- Results showed limited physician knowledge about key cancer genetics concepts, more so in general and family practitioners than specialists.

Lack of awareness of tests
Awareness of genetic testing for breast/ovarian cancer was high (91%) but less for colorectal cancer (60%). [73]
- Use of referral genetics counseling services was associated with confidence in knowledge of referral criteria and core competencies in genetics, and awareness of the program and where to refer.
- Use of genetics referral services is associated with increased knowledge of services, and confidence in skills.

Poor relationship between primary care and genetics services
Communication between primary care physicians who treat adults and genetics specialists is suboptimal and the identification and referral of adult patients for genetic services need improvement. [67]

Primary care physicians are less comfortable with identifying patients for referral (p < 0.001) and with discussing genetics (p < 0.002) than specialists. [76]
- The largest barriers to referral were lack of program awareness and limited knowledge regarding patient eligibility, improved insurance coverage, and antidiscrimination legislation.
- Physician-targeted marketing and education may improve the referral process.

Lack of guidelines
Published guidelines that address how to deliver genetic services to adult patients are unavailable for many genetic conditions. [67]

Uncertainty of genetic testing issues
A national survey of physicians from 8 specialties about attitudes toward genetic testing showed that US physicians have great uncertainty about issues surrounding genetic testing for cancer susceptibility. [77]
- 89% reported a need for physician guidelines, 81% thought that patients with positive genetic test results are at risk for insurance discrimination, and more than 53% thought that it was difficult to ensure the confidentiality of test results.
- Almost 25% indicated that genetic tests for cancer susceptibility have too many inaccurate or ambiguous results; nearly 75% thought that clear guidelines are not available for managing patients with positive test results.
- Only 29% overall reported feeling qualified to provide genetic counseling to their patients.
- Only 40% of PCPs considered themselves qualified to recommend genetic testing to their patients (vs. 84% of oncologists).
Fear of Discrimination
A survey of physicians and nurses in California showed that 96% viewed genetic testing as beneficial for their patients, but 75% believed fear of genetic discrimination would cause patients to decline testing. [78]

- Over 60% were not aware of federal or California laws prohibiting health insurance discrimination.
- A positive attitude toward genetic testing was the strongest predictor of referral (odds ratio: 3.55 [95% confidence interval: 2.24-5.63], P < 0.001).
- The higher the belief in genetic discrimination, the less likely a participant was to refer (odds ratio: 0.72 [95% confidence interval: 0.518-0.991], P < 0.05), whereas more knowledge of genetic discrimination law was associated with comfort recommending (odds ratio: 1.18 [95% confidence interval: 1.11-1.25], P < 0.001) and actual referral (odds ratio: 3.55 [95% confidence interval: 2.24-5.63], P < 0.001).

Low rates of family history screening
Evidence has shown low and inconsistent rates of family history screening among generalist physicians. Many family physicians lack confidence in their ability to screen patients for a family history of cancer despite recognizing its importance to their practice. [79]

- A survey of all active members (691) of the Massachusetts Academy of Family Physicians, found that, although 87% believed screening to be important, less than two thirds believed they were effective in screening.
12. CLINICIAN RESOURCES

Greater use of referral services is associated with increased knowledge of services, and confidence in skills. Need more timely services as well as education about hereditary cancers and susceptibility testing. [73]

Training and resources
Clinicians need guidance to help them introduce genetic tests, communicate their results and explain their implications. [65]

PCPs are interested in learning more about who should receive genetic testing and what tests are available. Training in counseling and risk communication is desired, as are ‘just-in-time’ resources to guide clinical decisions. [80]

- PCPs are eager to learn about genetic medicine. Educational efforts should build on PCPs’ prior knowledge base, highlight the clinical relevance of genetic medicine to primary care practice, and emphasize ‘red flags’: cues to alert PCPs to a potential genetic contribution.

Shared decision-making has been advocated, and 75% preferred this approach with their patients. Physicians who preferred their patients to play an active role in decision-making were more likely to report encouraging patients to look for information, and to report having enough time to discuss decisions in visits. [81]

In October 2007, the Society of Gastroenterology Nurses and Associates joined the American Nurses Association and 48 other nursing organizations endorsing the document Essential Nursing Competencies and Curricula Guidelines for Genetics and Genomics. [82]

The science of genetics will impact every aspect of health care, from primary care to specialized care. [83]

- Nurses are on the front line and will be expected to recognize patterns of disease that may indicate a possible genetic link, educate the family about the implications of a potential genetic susceptibility and refer the family for counseling.
- To accomplish this, each nurse should have a minimum basic knowledge of genetics, and formal education for those who educate and counsel.

Practice Guidelines
Given the complexity and limitations of genetic testing for risk of breast and ovarian cancer, the development and broad dissemination of clinical guidelines and education of physicians are needed. [84]

A survey of a stratified random sample of 1,251 physicians from 8 specialties found that nearly 9 out of 10 want guidelines. [77]

- Nearly 3 out of 4 thought that clear guidelines are not available for managing patients with positive test results.

Communication Training
Clinicians need guidance to help them introduce genetic tests, communicate their results and explain their implications. [65]
13. DIRECT TO CONSUMER GENETIC TESTING

Traditionally, genetic tests have been available only through healthcare providers who order the appropriate test from a laboratory, collect and send the samples, and interpret the test results. [85]

Findings from the genome wide association (GWA) studies have been used to calculate an individual's risk for a number of common diseases. This has led to a growing number of genetic tests marketed directly to consumers (DTC) over the Internet or print media, including nutrigenomic tests and associated products and services. They are also known as at-home, or over the counter, genetic testing. [85]

- This shifts the control of genetic testing from the clinical domain and medical professionals into the hands of consumers.
- No longer is genetic testing being carried out solely for medical reasons, by specialists in clinical genetics. Testing is now being used to empower consumers and can be used “to shed new light on your distant ancestors, your close family and most of all, yourself” (23andMe).

Companies are already selling ‘lifestyle-genetic’ tests and related lifestyle advice. [85]

- A test kit is mailed to the consumer instead of being ordered through a doctor’s office.
- It involves collecting a DNA sample at home, often by swabbing the inside of the cheek, and mailing the sample back to the laboratory. In some cases, a blood draw is required.
- Consumers are usually notified of the results by mail or over the telephone.
- In some cases, a genetic counselor or other healthcare provider is available to explain the results and answer questions.
- Cost ranges from several hundred to more than a thousand dollars.

Some groups have condemned companies for selling genetic tests in advance of scientific support. Others are concerned that the tests may not motivate lifestyle improvements, instead causing distress in people receiving adverse test results and complacency in those receiving reassuring results. [85]

Pros
Direct-to-consumer genetic testing may promote awareness of genetic diseases, and allow consumers to take a more proactive role in their health care. [85]

Cons
At-home genetic tests have significant risks and limitations for consumers, including: [85]

- Being misled by unproven or invalid tests.
- Making important decisions about treatment or prevention based on inaccurate, incomplete, or misunderstood information about their health.
- An invasion of genetic privacy if their genetic information is used in an unauthorized way.
- Overemphasizing a single piece of information about health—other genetic and environmental factors, lifestyle choices, and family medical history may be more important.

A GAO report evaluating claims made for direct to consumer genetic tests found that the tests may: [86]

- mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information, e.g., “you may be at increased risk for developing heart disease” -- could relate to anyone
- needlessly alarm consumers into thinking that they have an illness or that they need to buy a costly supplement to prevent an illness
- suggested “personalized” supplements were substantially the same as typical vitamins and antioxidants found in any grocery store for a fraction of the price
- falsely assure consumers that they are healthy when this may not be the case
- recommendations were promised to be based on a unique genetic profile, but instead provided only common sense recommendations.
Issues of concern include the limited knowledge of patients and health care providers of the available genetic tests, difficulty in interpretation of test results, lack of federal oversight of companies offering genetic testing, and issues of privacy and confidentiality. [86]

- Until all of these considerations are addressed, direct or home genetic testing should be discouraged because of the potential harm of a misinterpreted or inaccurate result.

The implications of test results are usually inadequately addressed. [87]

- To allow consumers to make informed decisions about DTC tests, more comprehensive disclosure of information about genetic tests is needed to improve transparency about current evidence on the strengths and limitations of gene-disease associations to allow consumers to make informed decisions about DTC tests.

Lack of Oversight
There is currently no regulatory oversight of genetic test utility, despite consensus in the Public Health Genomics community that clinical utility (including psychological and behavioral impact) of all emerging genetic tests should be evaluated before being introduced for individual use. [88]

- Clearly, empirical data in this area is much needed, to inform understanding of the potential utility of these tests, and of whether stricter regulation of commercial exploitation is needed.

Direct-to-consumer testing challenges many assumptions that underlie genetic testing practices while at the same time exposing the deficiencies in the current regulatory frameworks. [89]

The Challenge
Direct-to-consumer genetic testing is an unavoidable consequence of our ability to cheaply and accurately measure gene structure. The risk associated with DTC testing is the loss of control over how and when this information is disclosed to individuals, but it is difficult to prevent the wide availability and access the public now has to these tests. [90]

- Therefore, the key challenge is to set up social, educational, and technical means to support individuals who have access to their genome.

ACMG Statement on Direct-to-Consumer Genetic Testing, April 7, 2008
The American College of Medical Genetics believes that the following should be considered minimum requirements for any genetic testing protocol:

1. A knowledgeable professional should be involved in the process of ordering and interpreting a genetic test. Genetic testing is highly technical and complex. A genetics expert such as a certified medical geneticist or genetic counselor can help the consumer determine whether a genetic test should be performed and how to interpret test results in light of personal and family history. A number of risks can be reduced if a genetics professional is involved in genetic testing. These risks include lack of informed consent, inappropriate testing, misinterpretation of results, testing that is inaccurate or not clinically valid, lack of follow-up care, misinformation, and other adverse consequences.

2. The consumer should be fully informed about what the test can and cannot say about his or her health. Many DTC genetic tests do not give a definitive answer, but rather only a probability of developing a disease. Such information needs to be communicated to the consumer in the appropriate context and in an understandable fashion that is linguistically and culturally appropriate.

3. The scientific evidence on which a test is based should be clearly stated. Test providers should provide easy-to-understand information with primary references documenting the scientific data on which a specific test is based.

4. The clinical testing laboratory must be accredited by CLIA, the State and/or other applicable accrediting agencies. The accreditation process ensures that laboratories adhere to strict standards and guidelines for clinical testing. Test result reports to consumers should indicate the specifics of the lab’s accreditation.
5. **Privacy concerns must be addressed.** Prior to testing, the consumer should be informed regarding who will have access to test results, what security is in place to protect these results, what will happen to the DNA sample once testing is complete and how to access a complaint procedure to report breaches of privacy. Also, the issues of possible employment and insurance discrimination and the potential impact on other family members should be discussed prior to obtaining genetic testing.

http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=/CM/ContentDisplay.cfm&ContentID=2975


1. Are consumer-friendly informational materials available? Were they developed or reviewed by healthcare professionals with expertise in genetics (e.g. trained genetic counselors)? Are they suitable for individuals seeking and receiving direct-to-consumer testing services?
2. Is information disclosed to potential consumers regarding test purpose, potential limitations, validity and accuracy, using language that is written for consumers?
3. Will results be given in a manner understandable to the average consumer, with a clear explanation of their clinical implications, if any, and including resources providing appropriate follow-up?
4. Are patients encouraged to share their medically relevant genetic test results with their healthcare providers and family members who may also be at risk?
5. Are consumer referrals to healthcare professionals with expertise in genetics available, either on staff or independent of the commercial entity, both before and after testing to assure appropriate medical follow up, including psychological counseling as needed?
6. Is there a process for obtaining and documenting informed consent in a manner consistent with accepted medical practices as well as state and local regulations?
7. What safeguards are in place to protect consumer/patient privacy?
8. Has the company implemented policies that adhere to testing guidelines and position statements of professional organizations, including the National Society of Genetic Counselors, the American College of Medical Genetics, American Society of Human Genetics and others? These may include relevant guidelines for genetic testing of minors or other potentially vulnerable populations.
9. Are the genetic tests performed by appropriately credentialed laboratories (e.g. CLIA certified)?

**NSGC Position Statement:** [http://www.nsgc.org/about/position.cfm#DTC](http://www.nsgc.org/about/position.cfm#DTC)

**Test Validity and Utility**

Before undergoing any genetic test, it is important to be sure that the test is valid and useful.
- A genetic test is valid if it provides an accurate result.
- Two measures of accuracy are analytical validity and clinical validity.
- Analytical validity refers to how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent?
- Clinical validity refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.

Another measure of the quality of a genetic test is its usefulness, or clinical utility.
- Clinical utility refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.


**Laboratory Quality**

All laboratories that perform health-related testing, including genetic testing, are subject to federal regulatory standards called the Clinical Laboratory Improvement Amendments (CLIA) or even stricter state requirements.
• CLIA standards cover how tests are performed, the qualifications of laboratory personnel, and quality control and testing procedures for each laboratory.
• CLIA standards are designed to ensure the analytical validity of genetic tests.
• They do not address the clinical validity or clinical utility of genetic tests.
• The FDA requires information about clinical validity for some genetic tests.
• No one regulates clinical utility; it is left to consumers, health providers, and health insurance companies.

Some labs that develop DTC genetic tests are not CLIA-certified, so it can be difficult to tell whether the tests are valid.

http://ghr.nlm.nih.gov/handbook/testing/validtest

Interpreting Results
The results of genetic tests are not always straightforward, making them challenging to interpret and explain.

• It is important for patients to ask questions about the potential meaning of test results both before and after the test is performed.
• Healthcare professionals use the medical history, family history, and the type of genetic test to interpret the results.

A positive test result means that a change in a particular gene, chromosome, or protein of interest was found.

• May confirm a diagnosis, indicate that a person is a carrier, identify an increased risk of developing a disease (such as cancer), or suggest a need for further testing.
• May also have implications for blood relatives.
• A positive result usually cannot establish the exact risk of developing a disorder, or predict the course or severity of a condition.

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration.

• This can indicate that a person is not affected by a particular disorder, is not a carrier, or does not have an increased risk of developing a certain disease.
• It is possible, however, that the test missed a defective gene because many tests cannot detect all genetic changes that can cause a particular disorder.
• Further testing may be required to confirm a negative result.
• In some cases, a negative result might not give any useful information.

http://ghr.nlm.nih.gov/handbook/testing/interpretingresults
14. COMMUNICATING WITH PATIENTS

The decision to have genetic testing is unlike any other in primary care. Whereas genetic testing for diagnostic purposes is often medically indicated, for example to evaluate a child with multiple malformations and/or developmental disabilities, genetic screening for disease predisposition is usually an elective decision that is both personal and complex. [93]

People have many different reasons for being tested or not being tested. [93]

• For many, it is important to know whether a disease can be prevented if a gene alteration causing a disease is found. For example, those who have inherited mutations associated with familial cancer syndromes have options such as screening or early treatment. Pharmacogenetic testing may also find the best medicine or dose of a medicine for a certain person.

• In other cases, there is no treatment. There are no preventive steps or cures for Huntington Disease. But test results might help a person make life decisions, such as career choice, family planning or insurance coverage.

Primary care providers must also develop skills in basic genetic counseling. Successful communication requires the use of plain language delivered at an appropriate level of literacy for each patient. [94]

Ethical and clinical guidelines and policies have been developed to address the communication of genetic information to families. [95]

• The following ideals were common in their guidelines: (1) individuals have a moral obligation to communicate genetic information to their family members; (2) individuals should be encouraged to communicate the information to their family members; and (3) individuals should be supported throughout the communication process.

Most physicians have positive attitudes toward patient participation in medical decision-making. [96]

• Many see their role as an expert who educates the patient but retains control over the decision-making process; others take a more collaborative approach, encouraging patients to assume decisional priority.

• With genetic counseling, physicians often introduce the concepts, but usually a genetic counselor will provide more specific information about the pros and cons of the test, as well as the social and emotional aspects of testing. [93]

Some considerations in communicating with patients about the psychosocial and health impacts of testing include: [97]

• Individuals have very different understandings of genetic risk information that frame their testing perceptions and behavioral responses.

• Motivations to undergo testing are complex; decision aids may be helpful, but are lacking.

• Findings on psychological and behavioral impacts of genetic testing vary markedly, with some evidence of minimal or positive effects and other evidence indicating negative consequences that may be undetectable using common measures of general well being.

• Research demonstrates wide-ranging influences of testing on family dynamics, and use of genetic testing with children is of increasing concern.

• More research is needed to determine how to structure health communications and counseling to motivate informed use, promote positive responses, and optimize behavior change. Given the ramifications of genetic information for families, personalized genomics will demand a shift toward a family-based healthcare model.

Family Dynamics

Managing family dynamics is also important. [94]

• Patient and family members may have different perceptions of risk and attitudes toward genetic testing.
• Information for one person often has medical consequences for other related individuals, and healthcare providers must successfully navigate this delicate arena to improve outcomes for everyone involved.
• Asking the patient who to involve in these discussions is an important part of navigating the emotional terrain.

Risk Information
Communicating genetic-risk information is fraught with difficulties, and there are no universally accepted guidelines for clinical practice. [98]
• The Heuristic-Systematic Model (HSM) of information processing is a useful perspective from which to view genetic-risk communication.

Family communication about genetic risk is a deliberative process, in which: sense is made of personal risk; the vulnerability and receptivity of the family member is assessed; decisions are made about what will be conveyed; and the right time to disclose is selected. [99]
• The communication strategy varies within families as well as between families.
• Inherent in these processes are conflicting senses of responsibility: to provide potentially valuable information and to prevent harm that may arise from this knowledge.

Risk probabilities are often difficult for patients to understand. [100]
• For example, a genetic report may state that a person's risk of developing a disease or condition is 5 times higher than average, but it fails to mention that the average risk is < 0.01%. The result is not so alarming when put in perspective of actual risk, and when all of the individual variables associated with the disease or condition are considered.

Misperceptions
Many misperceptions exist about genomics. Some think genetic susceptibility “equals” health destiny. Genetics may occasionally be the direct cause of disease (e.g., Huntington's disease), but it is the combination of predisposing genetics and environmental factors that causes most common conditions, such as diabetes mellitus, asthma, and heart disease. [100]
• Patient misperceptions often occur as a result of consumer advertising.
• As direct-to-consumer genetic tests become more ubiquitous, clinicians must understand and be able to explain to patients which test results are clinically relevant and which are merely unsubstantiated claims.
• Understanding misperceptions helps clinicians provide accurate information to patients.

Address discrimination concerns:
In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law preventing discrimination against people based on their genetic information. This legislation bars health insurance companies and employers from discriminating against individuals on the basis of their genetic information. [101]
Genetic evaluation and counseling for genetic testing is best provided by genetics professionals who have specialized degrees and experience in medical genetics and counseling. Genetics professionals include geneticists, genetic counselors and genetics nurses. Genetics professionals:

- Discuss the medical, social and ethical decisions surrounding genetic testing
- Provide support and information to help a person make a decision about testing
- Interpret the results of genetic tests and medical data
- Explain possible treatments or preventive measures [1]

**Recommendations**

When to refer for genetic counseling:

- The Professional Practice and Guidelines Committee of the American College of Medical Genetics (ACMG) has generated lists of common reasons for referral for genetics professionals and other healthcare providers. [91]
- The lists are divided into pediatric, prenatal, and adult indications.

Other practice guidelines for specific issues are provided by the ACMG at: [link]

**Consultation with a Genetics Professional** [92]

Genetics professionals include medical geneticists (doctors who specialize in genetics) and genetic counselors (certified healthcare workers with experience in medical genetics and counseling).

- A clinical geneticist is a physician who specializes in genetic disorders and conditions. Clinical geneticists work in academic, hospital, group and private practice settings. [103]
- PhD medical geneticists are geneticists with expertise in genetic risk assessment, the interpretation of genetic test results and the communication of genetic information to patients, families and other health care workers. [103]
- Nurses, psychologists, and social workers trained in genetics can also provide genetic consultations.

The role of the genetic counselor or nurse is similar to that of a nurse practitioner. [102]

- Patients may be seen independently by a genetic counselor or nurse, but in cases where a diagnosis needs to be established, a medical geneticist must be directly involved.

**Genetic Counselor**

A genetic counselor is a health care professional with specialized graduate degrees and experience in the areas of medical genetics and counseling. Genetic counselors enter the field from a variety of disciplines, including biology, genetics, nursing, psychology, public health and social work. [103]

- Genetic counselors work as members of a health care team, providing information and supportive counseling to patients and families affected by or at risk for genetic conditions.
- Genetic counselors work with patients, families, physicians and laboratories to identify genetic risks, investigate problems, interpret and communicate information about genetic disorders, analyze inheritance patterns and risks of recurrence and review available options with patients and families.

Search for a clinical geneticist in local area: [link]

Search for a genetic counselor in local area: [link]

Reasons for referral to a genetic counselor, medical geneticist, or other genetics professional include: [102]
- A personal or family history of a genetic condition, birth defect, chromosomal disorder, or hereditary cancer.
- Two or more pregnancy losses (miscarriages), a stillbirth, or a baby who died.
- A child with a known inherited disorder, a birth defect, mental retardation, or developmental delay.
- A woman who is pregnant or plans to become pregnant at or after age 35. (Some chromosomal disorders occur more frequently in children born to older women.)
- Abnormal test results that suggest a genetic or chromosomal condition.
- An increased risk of developing or passing on a particular genetic disorder on the basis of ethnic background.
- People related by blood (for example, cousins) who plan to have children together. (A child whose parents are related may be at an increased risk of inheriting certain genetic disorders.)

Sample Preconception/Prenatal Assessment Tool

Sample Pediatric Assessment Tool

Sample Adolescent/Adult Assessment Tool

Genetic Counseling
Genetic counseling is an important part of the decision-making process for genetic testing. It may be helpful even if testing is not available for a specific condition to enhance understanding of the condition and the genetic link. [92]

During counseling, a genetics professional will:
- Interpret and communicate complex medical information.
- Help each person make informed, independent decisions about their health care and reproductive options.
- Respect each person’s individual beliefs, traditions, and feelings.

A genetics professional will NOT:
- Tell a person which decision to make.
- Advise a couple not to have children.
- Recommend that a woman continue or end a pregnancy.
- Tell someone whether to undergo testing for a genetic disorder.
16. ORDERING GENETIC TESTS

Genetic tests may be ordered by a medical geneticist or genetic counselor as part of a genetic consultation, or they may be ordered by a primary or specialty care provider. [104]
Considerations when ordering a genetic test include:
- Choosing a Laboratory
- Pretest Counseling and Informed Consent
- Sample Logistics and Supporting Documentation
- Test Result Interpretation and Follow-up

CHOOSING A LABORATORY [105]
GeneTests was created to simplify the search for genetic testing laboratories, which may be difficult to locate. For many diseases, there may be only one laboratory providing genetic testing. U.S. patents have been issued covering diagnostic testing for some genetic disorders. A given laboratory may or may not be the exclusive licensee to such a patent.

If there is a choice of laboratories, the following factors should be considered:

Laboratory Personnel
Genetics laboratory personnel have two major roles: processing patient samples (technologists), and interfacing with referring clinicians regarding their patients (clinical consultants). Lab personnel, who are usually certified in their specialty, may include lab directors, supervisors, technologists, and genetic counselors.

The test offered by the laboratory must match the specific clinical need
- Some diseases are caused by mutations in more than one gene. It is important to be sure that the lab selected is testing the appropriate gene(s).
- Different kinds of DNA tests are available. The laboratory selected should offer what is most appropriate for a specific clinical situation. For instance:
  - A specific gene mutation (e.g., if the familial mutation has been identified)
  - A panel of mutations (e.g., the Ashkenazi Jewish BRCA1 panel of 3 mutations)
  - The complete gene sequence

Direct contact with the laboratory is needed to assess the laboratory's experience and qualifications
- Does the laboratory have CLIA certification? Any other certification?
- Is the laboratory associated with a reputable company or university?
- Is the laboratory director board-certified?
- Is the laboratory's work published in the medical literature?
- What is the laboratory's experience with the specific test being ordered?

Ease of Communication
- What professionals are on staff to help assess the appropriateness of testing, determine the best testing paradigm for the family, and interpret test results?
- Does the laboratory have information on tests offered and logistics of sample collection and shipping easily available by phone, fax, or Internet?
- What information is contained in the test result report (e.g., raw data, interpretation, references, sensitivity and specificity information)?

Geographical Location
- Some states have restrictions on insurance coverage or, as is the case in New York, additional regulatory restrictions.
- Samples shipped outside of the U.S. must go through Customs, which requires that hazard identification and a statement of value accompany the sample. Language barriers and time zones can also be an issue.
**Turn-Around Time: Sample receipt to test result**

- Clinical laboratories generally have similar turn-around times for tests performed using the same methodology.
- A shorter turn-around time is advantageous only when it can be determined that quality control and thoroughness are not compromised.
- Test results for pregnancy management (prenatal diagnosis) are considered urgent due to restrictions on options late in pregnancy. Pregnancy dating should be included with all prenatal samples.
- The laboratory should be notified in advance of any sample that is "stat" (rush), as the sample processing may be different.

**Cost: May vary from less than $100 to more than $2000**

- Test methodology. Low complexity tests (e.g., single gene mutation) are less expensive than high complexity tests (e.g., full gene sequencing)
- Laboratory testing strategy. Some labs test for a large number of mutations all at once; other labs test in stepwise fashion, beginning with the most common mutations.
- Number of individuals tested. Several family members may need to be tested to obtain a meaningful test result.
- Contractual agreements. Hospitals, insurers, and laboratories negotiate contracts to set the price of testing and amount of reimbursement.
- Specimen handling. Some cell types require culturing or other special handling before testing.
- Additional services. Genetic consultation or counseling is usually recommended and sometimes required before genetic testing is performed. These fees should be considered in the total cost.

**PRETEST COUNSELING AND INFORMED CONSENT** [106]

If genetic testing is clinically available and useful for a particular patient, the patient needs to understand why it is being offered and its implications for medical management and psychosocial well-being. If a competent patient (or parent/guardian) agrees to the proposed genetic test after full disclosure, this constitutes informed consent. Informed consent may be verbal or written. Some laboratories require written documentation of informed consent.

Pretest counseling includes:

- Assessing the patient's risk perception, expectations and support systems.
- Explaining the implications of testing vs. not testing for medical management and reproductive options.
- Describing the methods used to obtain specimens and associated risks.
- Reviewing test accuracy (sensitivity and specificity).
- Estimating the chance that the test will be positive based on available information (e.g., family history, clinical symptoms).
- Discussing any out-of-pocket costs to the patient.
- Establishing a plan for conveying test results. Depending on the circumstances, results may be given:
  - in person
  - by phone, with or without a follow-up appointment
  - by mail (negative results only)
  - only when positive (e.g., newborn screening)
  - Results should be revealed only to the individual tested, or his/her parent or guardian, unless explicit permission has been granted to share results.
- Addressing potential discrimination concerns. Describe protections offered by the Genetic Information Nondiscrimination Act (i.e., discrimination from health insurers and employers, but not disability, life or long-term care insurance). [101]
Additional issues relevant in some testing situations:

- Need to clarify biological relationships (parentage, zygosity) for linkage studies.
- Potential discrimination in employment, insurability or educational opportunities, especially in predictive testing. (Some states have laws in place prohibiting genetic discrimination).
- Results from research testing are not generally available for patient care.

SAMPLE LOGISTICS AND SUPPORTING DOCUMENTATION [107]

Contact the lab directly to ask the following questions:

What are the sample requirements?
- Are samples from other family members needed?
- What specimen type is needed?
- Does the specimen need to be cultured before shipping?
- What is the requested amount of specimen? Will less be accepted in hard-to-draw situations?
- What information should be included on the label?

What supporting documentation is needed?
- Does the lab have a specific requisition form?
- What clinical history should be included?
- Are medical records or test results on family members needed?
- Is family history needed for test interpretation? A pedigree is an efficient way to show family relationships. See Sample Pedigree for Laboratory Documentation.
- Is ethnicity relevant to test interpretation?
- If crossing international borders, are hazard labels and customs paperwork included?

How should the sample be transported?
- What is the correct delivery address?
- When is delivery accepted?
- Should the sample be frozen, refrigerated or at room temperature during shipping?
- Is there a courier to the lab, or is taxicab, mail or overnight shipping required?

TEST RESULT INTERPRETATION AND FOLLOW-UP [108]

Test results are provided in writing by the laboratory to the referring clinician. The details of the lab report vary by lab, but may include:

- Raw data
- Clinical interpretation of test result
- Sensitivity and specificity information
- References

See Sample Lab Report.

The clinician explains the meaning of the test result to the patient and to other family members as needed. Test results and follow-up should be documented in the medical record and a copy made available to the patient. For many conditions, educational materials may be available from patient support organizations.
For Positive Test Results

<table>
<thead>
<tr>
<th>If the test purpose was...</th>
<th>The interpretation is...</th>
<th>And follow-up includes genetic counseling 1 and...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic testing</strong></td>
<td>Clinical diagnosis is confirmed</td>
<td>Medical management and treatment</td>
</tr>
<tr>
<td><strong>Predictive testing</strong></td>
<td>The likelihood of showing disease symptoms is increased</td>
<td>Counseling for life planning; Medical management if available</td>
</tr>
<tr>
<td><strong>Carrier testing</strong></td>
<td>The patient is a carrier</td>
<td>Testing offered to partner and family members as indicated; Prenatal testing offered if indicated</td>
</tr>
<tr>
<td><strong>Prenatal testing</strong></td>
<td>A fetus is diagnosed with a specific condition</td>
<td>Pregnancy treatment/management or termination</td>
</tr>
<tr>
<td><strong>Newborn screening</strong></td>
<td>Disease in a newborn is suggested; Carrier status in a newborn may be identified.</td>
<td>Confirmatory testing; if positive, medical management and treatment Carrier testing offered to parents</td>
</tr>
</tbody>
</table>

1. Genetic Counseling includes discussion of expected course of the disorder; possible interventions; underlying cause; risks to family members; reproductive options; support.

For Negative Test Results

<table>
<thead>
<tr>
<th>If the test purpose was...</th>
<th>The interpretation is...</th>
<th>And follow-up may include...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic testing</strong></td>
<td>Clinical symptoms are unexplained</td>
<td>Further testing and/or follow-up genetic consultation</td>
</tr>
<tr>
<td><strong>Predictive testing</strong></td>
<td>The likelihood of showing symptoms is decreased</td>
<td>Counseling for survivor guilt and long-range life planning; No high-risk surveillance needed</td>
</tr>
<tr>
<td><strong>Carrier testing</strong></td>
<td>High likelihood that the individual is not a carrier; Low risk of having a child affected with the condition in question</td>
<td>Testing offered to other family members if indicated</td>
</tr>
<tr>
<td><strong>Prenatal testing</strong></td>
<td>If fetus was symptomatic (e.g., by ultrasound findings), clinical symptoms remain unexplained and may need further investigation. If fetus was not symptomatic, the chance of the condition tested for is very small.</td>
<td>If fetus was symptomatic, further testing and/or pregnancy management If fetus was not symptomatic, no follow-up</td>
</tr>
<tr>
<td><strong>Newborn screening</strong></td>
<td>The newborn is not expected to have the condition tested for</td>
<td>No follow-up</td>
</tr>
</tbody>
</table>

17. REIMBURSEMENT

Many genetic tests, procedures and clinical geneticist visits (genetic services) are covered by health insurance, however, some are not, and coverage varies between insurance companies. [109]

- Coverage may depend on whether your clinical geneticist, or laboratory in the case of a genetic test, is an approved provider for your insurance company. Insurance coverage of genetic services is changing continuously as increasing numbers of genetic services are being covered by insurers.

A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage. [109]

- Some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person’s health insurance coverage.
- Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state’s privacy protection laws before they ask their insurance company to cover the costs.

Your doctor may be able to tell you whether your genetic tests, procedures, or visits to a clinical geneticist (genetic services) will be covered by your health insurance. [103]

- Sometimes, it will be necessary to call the insurance company to confirm. It may also be necessary to call your insurance company before a visit to a clinical geneticist to get pre-approval, and at the time of your appointment to get pre-approval for any recommended tests or procedures.
- To get the best information from your insurance company about what genetic services will be covered, it might help to have a list of the CPT codes that your doctor will be billing. Your doctor may also be required to provide the insurance company with documentation of medical necessity. [103]

CPT Codes for Genetic Counseling

The AMA CPT Editorial Board and CMS recently introduced a new CPT code (96040) to cover genetic counseling (GC) visits provided by counselors only. [103a]

- Previously, GC-related consultations were billed as Evaluation & Management (E&M) visits that necessitated presence of a physician to qualify for payment from most third-party payers.

Other coding information for genetic services is available at:

18. ROLE OF FAMILY HISTORY

Health care professionals have long used family history as a risk assessment tool.
- In the era of the Human Genome Project, systematically collecting and using family history data in counseling patients about lifestyle choices is an important step in personalizing health care. [110]
- Provides information about heritable risks as well as shared factors that contribute to the risk for common diseases, such as diabetes, stroke, cancer, and heart disease. [111]
- Also used to determine who might benefit from genetic testing and to interpret the results of genetic tests.

Effectiveness of Family History Compared to Genetic Testing
For some polygenic disorders (i.e., multiple genes involved) current genetic testing is usually no better than simple family history at predicting risk. [112]
- Some complex disorders, such as hereditary cancer syndromes, are associated with single genes whose expression is modified by the environment, so need to be differentiated from polygenic disorders.
- Also, there are other exceptions, such as some forms of cardiovascular disease, and early-onset Alzheimer’s disease that are related to a few variants.

On the flip side, sometimes genetic testing for complex disorders such as cancer, even single-gene types, can be misleading in families with strong family histories. Sometimes there might be an underlying genetic predisposition in a family, but it goes undetected by current genetic testing, only because the mutation(s) has not yet been scientifically recognized or a test to detect it has not yet been developed.

Interest in genetics has led to the reemergence of the detailed family history. [113]
- The decision to pursue genetic testing should be guided by risk estimates determined by family history.
- Genetic testing should supplement family history, not supplant it. [114]

Familial clustering of a disease is a direct indicator of genetic risk, if environmental factors can be excluded. If familial clustering is lacking, the likelihood of a genetic influence is small. [115]
- Disease correlation between spouses suggests environmental sharing and a higher correlation between siblings and particularly twins shows heritable effects.
- Data suggest high heritabilities for chronic obstructive pulmonary disease, asthma, noninfective enteritis and colitis, cerebral palsy and endocrine and metabolic diseases.
- In the era of genome scans, family history data should be involved in the assessment of the validity of genome scans.

Sensitivity and predictive value
For most conditions for which data are available, sensitivities and positive predictive values are low (typically < 25% for sensitivity and < 10% for predictive value). [111]
- Exceptions are atopic diseases, mood disorders, major depression and cancer, in which sensitivities are closer to 50% or more and predictive values are in the 25% to 50% range.
- Sensitivities for various types of cancer range from 33% to 95%.
- Specificities tend to be very high (typical range, 90% to 98%).
- Atopic conditions and mental illnesses are exceptions; specificities are lower -- 50% to 75%.
- Not surprisingly, cross-sectional data generated higher sensitivities than longitudinal data.
- However, family history, as currently measured in isolation, is neither a sensitive nor a highly predictive measure of common disease.
When Does Family History Matter the Most?

Family is most relevant with diseases associated with single gene mutations, such as hereditary breast and ovarian cancer (BRCA1 or BRCA2 mutations) and hereditary nonpolyposis colorectal cancer. [111]

Family members affected:

It is most significant when first-degree relatives who share 50% of their genes are affected. [116]

- For CHD, family history in a sibling increases risk more than a parent. [117]
- Family history is somewhat less important for second-degree relatives (grandparents, grandchildren, aunts, uncles, nieces, nephews, half-siblings), who share 25% of their genes.
- Third-degree relatives (first cousins) share 12.5% of their genes.

Family history is particularly significant if a condition occurs: [110]

- at an earlier age than usual in a family member (e.g., colon cancer in a parent prior to age 50),
- in more than 1 close relative,
- in an atypical gender (e.g., breast cancer in a grandfather or father), or
- several related conditions occur within a family (e.g., breast and ovarian cancer).

Limitations of Family History Information

Accuracy of family history information is always somewhat questionable. [118-120]

- Sudden deaths sometimes are often incorrectly attributed to heart disease, and cause of death on death certificates is often not accurate.
- Life threatening or life ending conditions (heart attack, stroke, cancer, etc) are more likely to be known than are chronic conditions that are more subtly life threatening (hypertension, diabetes, dyslipidemia). [110]

The quality of self-reported family history data varies considerably. [110]

- History for first-degree relatives is more reliable than for second-or third-degree relatives.
- Recent past is more accurate than more distant past.
- Families who are geographically and emotionally closer have more accurate information than dispersed or alienated families.
- Adopted individuals often know little about their family medical history, but may be able to find out more.

Little is known about how the setting of taking a family history affects accuracy. The method of collection could be important (e.g., a paper checklist completed before a clinic visit, an interactive computer tool, or in-person interview with a clinician). [111]

- People more accurately report the absence of disease than the presence of disease in family members. Little evidence exists for many conditions, as well as for relatives other than first-degree relatives.
- Little is known about the harm that could result from misinterpretation of family history information, i.e., the frequency of unnecessary tests and procedures or how often clinicians inappropriately reassure and neglect to promote beneficial measures in the presence of an otherwise high risk for preventable disease.

Factors Discourage Obtaining and Using a Family History

The time spent by clinicians and the lack of tools and technology to analyze and interpret the data obtained inhibit clinicians from routinely taking a family history. [111]

- Clinicians may not be adequately compensated for the time required to obtain and interpret family history.
- Despite these barriers, almost half of clinicians report collecting and using a family history in their practice.
Perceptions of Risk
The psychological risks for a family history intervention seem low or nonexistent. [111]

Patients’ knowledge of family history does not always translate into a realistic sense of vulnerability to getting a condition that runs in the family. [110]

- Individuals may underestimate or overestimate their own personal risk.
- Many people with a family history of early heart disease (before age 55 in men, before age 65 in women) do not believe that they will get heart disease themselves, even if they have multiple other risk factors for CHD.
- They may rationalize their denial by citing differences between them and the family members who got heart disease (“My father smoked; I quit smoking several years ago”).
- While nearly a third of women do not understand that a family history of premenopausal breast cancer increases their risk for breast cancer, many women with a family history of breast cancer overestimate their risk for developing breast cancer.

Impact of Knowing Risk
Knowledge of family history does not always produce desirable health behaviors, even in those who understand their increased risk. [110]

- Many continue to smoke cigarettes despite having a parent or sibling die from tobacco-related causes such as lung cancer. Such irrational behavior often is defended with fatalism or resignation (“You’ve got to die from something,” “I’d rather die smoking than live without smoking”).
- Family history of a condition such as breast cancer sometimes generates avoidance behavior -- fear serving as an obstacle to self-care practices (regular breast self-examination) or to obtaining recommended screening tests (mammography) and thus lead to lost opportunities for early disease detection.

Gathering Family History Information
Eliciting and recording family history information can be problematic, even with an electronic medical record (EMR). [121,122]

- Text-based family history that is recorded haphazardly, with no consistent format, is difficult to review and use in subsequent patient interactions.
- Significant family history data added to patients’ problem lists serve as a reminder of potential genetic risk, however, primary care clinicians infrequently add family history to problem lists, and historically, they have not made good use of the family history information they elicit.

The genogram (an expanded version of the genetic pedigree) is a useful graphic method for recording, displaying, and retrieving family history data. [123]

- A self-administered genogram can be created by the patient at home or in the waiting room prior to the clinical visit, assisted by a medical assistant or nurse. [124]
- Templates can be downloaded. [125]
- Some providers prefer to do the genogram themselves with new patients; sends strong message about the importance of family history and the value of family-oriented care. [126]

What to Ask About Family History
A thorough family history should also include family lifestyle patterns including: [110]

- dietary habits and cultural food preferences,
- exercise habits and weight status,
- tobacco abuse (cigarettes, cigars, pipe, oral tobacco, and snuff),
- alcohol and drug use and abuse,
- stress coping skills and emotional support,
- anger impulse control, conflict, and abuse (verbal, physical, sexual).
Family History Tools
Several family history tools may be quickly and easily utilized by primary care providers and patients:

- **American Medical Association**: Family History Tools: Website with tools including "Prenatal Genetic Screening Questionnaire," "Pediatric Clinical Genetics Questionnaire," and "Adult Family History Form" [127]
- **Centers for Disease Control and Prevention**: Website with family history tools and resources [128]
- **US Surgeon General's Family History Initiative: "My Family Health Portrait"**: Web-based tool for patients to organize family history and to share with healthcare providers and family members. [129]
- The National Office of Public Health Genomics online genetic pedigree program for public use. [130]
19. RESOURCES

General Information:
- CDC Office of Genomics and Disease Prevention: http://www.cdc.gov/genomics/
- The Genetic Alliance: http://www.geneticalliance.org/
- National Human Genome Research Institute: http://www.genome.gov
- The Collaboration, Education and Genetic Test Translation (CETT) Program: http://www.cettprogram.org

Information for Health Care Providers:
- Genetics and your practice: http://www.marchofdimes.com/gyponline/index.bm2

Information about Discrimination:
- http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf

Information On Tests And Labs:

Position Statements:
- National Society of Genetics Counselors: http://www.nsgc.org/about/position.cfm#DTC

Direct to Consumer Testing:
- FDA Facts for consumers: http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm
- National Society of Genetic Counselors Position Statement: http://www.nsgc.org/about/position.cfm#DTC
- ACMG Statement on DTC Testing: http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=/CM/ContentDisplay.cfm&ContentID=2975

Genetic Test Evidence Reports:
- http://www.ahrq.gov/browse/gentestbr.htm

Pharmacogenomics Information:
About Genetic Consultations:
- National Genome Research Institute: [Frequently Asked Questions About Genetic Counseling](#).
- [Overview of genetic counseling](#) is available from the Wellcome Trust.
- GeneTests: [additional information about genetic consultations](#).

Finding a Genetics Professional:
- The National Society of Genetic Counselors directory of genetic counselors in the US, by location, name, area of practice/specialization, and/or ZIP Code: [http://www.nsgc.org/resourcelink.cfm](http://www.nsgc.org/resourcelink.cfm)
- The National Cancer Institute directory of professionals who provide services related to cancer genetics. Search by type of cancer or syndrome, location, and/or provider name: [http://www.cancer.gov/search/genetics_services/](http://www.cancer.gov/search/genetics_services/)

Assessment:
- National Newborn Screening and Genetics Resource Center: [http://genes-r-us.uthscsa.edu/](http://genes-r-us.uthscsa.edu/)

Family History Tools:
- CDC Family history tools and resources: [http://www.cdc.gov/genomics/famhistory/index.htm](http://www.cdc.gov/genomics/famhistory/index.htm)

Specific Disease Information:
- Genetics and Rare Diseases Information Center: [http://rarediseases.info.nih.gov/GARD](http://rarediseases.info.nih.gov/GARD)
- Genetics and Rare Conditions: [http://www.kumc.edu/gec/support/](http://www.kumc.edu/gec/support/)

Interpreting Genetic Study Evidence:
A 3-part series in JAMA, January 2009
- Attia J, Ioannidis JPA, Thakkinstian A, et al. How to use an article about genetic association: C: what are the results and will they help me in caring for my patients. JAMA. 2009;301:304-308. [Abstract](#)
For Patients:

- Genetic Testing: What it means for your health and your family's health: [http://www.genome.gov/Pages/Health/PatientsPublicInfo/GeneticTestingFactSheet.pdf](http://www.genome.gov/Pages/Health/PatientsPublicInfo/GeneticTestingFactSheet.pdf)
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