GENETIC TESTING
A Resource from the American College of Preventive Medicine

A Time Tool for Clinicians
ACPM's Time Tools provide an executive summary of the most up-to-date information on delivering preventive services to patients in the context of a clinical visit. Information presented is based on evidence presented in peer-reviewed journals. Please refer to the Genetic Testing Clinical Reference for more information.

GENETIC TESTING
Progress in the Promise of More Personalized Medicine

Genetic testing for single-gene disorders and familial cancer syndromes is an accepted and valuable part of clinical care. But, the completion of the Human Genome Project ushered in a new era of genetic testing. The technology that enabled the mapping of the 25,000 genes of the human genome now allows the scanning of these genes for variants. Large scale genome wide association studies (called GWAS) have proliferated in the last five years. They compare genes of people with and without a specific disease to identify variants that occur more frequently in those with the disease. These variants become the target of new genetic tests for the disease. There are currently about 1500 such tests available, with more being developed all the time.

The Promise – Care That is More Predictive, Preventive, and Personalized
The promise of personalized medicine has not yet been realized, but it is real – earlier diagnosis, individualized screening and prevention strategies, more effective treatment, better targeting of pharmacotherapy with fewer adverse effects, and more direction in complex decisions, such as mammograms for women in their 40s or PSA testing for men. Progress will occur in steps as the clinical utility of new tests is proven.

But, private companies are taking advantage of the increasingly affordable technology and lack of oversight to offer genetic screening directly to consumers without a medical referral. Their promise – tailored risk assessment and personalized nutrition and lifestyle recommendations. Demand is on the rise. The “business” of genetic testing is booming.

More Questions than Answers
Are these test results reliable? Are they valid? Do they improve outcomes? Are we holding genetic tests to the same standard of evidence as other tests? The GWAS provide only weak evidence of an association. Prospective studies are needed to test these associations. For most tests, there is currently little evidence of predictive value or clinical utility. It does not mean the tests are not valid, only that the studies have not been done.
Gene function is far more complex than gene structure. In this sense, the Genome Project has resulted in more questions than answers. Nearly every disease has a genetic component, but it is usually not well understood and typically involves multiple genes interacting with each other and with environmental factors. In the process, genes may be turned on or turned off. For most diseases, we don’t know all of the genes involved, how they interact or what turns them on or off. The field of epigenetics (factors that influence gene expression) is the new frontier.

Genetic testing has also become more complex. Current technologies can test for hundreds of thousands of variants simultaneously. This technology vastly exceeds our current ability to interpret the results. Finally, the regulatory infrastructure to evaluate genetic tests is largely nonfunctional or nonexistent. Only tests that are sold to laboratories as “kits” are regulated by the FDA (only about 1% of available tests). State laws are inadequate and inconsistent. At this point the market largely determines what tests are available to consumers.

The Challenge for Primary Care Clinicians
Genetic testing has traditionally been the domain of Medical Genetics specialists and carrier screening programs where medical professionals direct the testing. But, increasingly, specialists in other areas, particularly oncology and cardiovascular medicine, are using specific genetic tests to guide diagnosis and therapy. Primary care physicians will be asked about these tests because they will play an increasingly important role in specialist clinical practice and because patients will be seeking them from direct to consumer companies as individual tests, sets of tests, or as part of a larger screening.

Primary care providers (PCPs) must be ready to inform patients about the pros and cons of genetic tests, or at least refer them to a genetic counselor. The informed choice process with genetic testing is more complex – differentiating susceptibility from inevitability, addressing social, ethical and family issues that are not part of traditional diagnostic or screening tests.

Obstacles and Strategies
Several barriers exist for PCPs in managing patient interest in genetic tests, including:

a. **Lack of training in genetics**: Many PCPs lack confidence in their ability to discuss genetic testing with patients.
   • Strategies: Establish associations with experts, attend trainings, take advantage of educational opportunities, such as the online resources from the NIH Human Genome Research Institute.

b. **Keeping up with developments in genetic testing**: The increasing number of tests, the volume of research, and the difficulties in interpreting results are overwhelming.
   • Strategies: Use the NIH funded website, www.genetests.org , to provide up to date information about genetic tests and diseases, as well as testing labs and counselors.

c. **Changing reimbursement**: There are now CPT codes for genetic counseling, but coverage of tests and counseling varies.
   • Strategies: More genetics services are being covered when ordered by a clinician, but patients may need to contact their insurers to find out what services are currently covered.

d. **Lack of referral network for counseling**: Due to reimbursement issues, many genetics professionals remain in academia.
   • Strategies: Use online resources to locate genetics clinics, clinical geneticists and genetic counselors in your area.
Educating Patients about Genetic Testing
People have many different reasons for being tested. A clinical geneticist or genetic counselor is usually best equipped to discuss the pros and cons of a genetic test, along with the social and emotional aspects of testing. Individuals may not anticipate all of the issues involved.

But there are a few key issues that primary care clinicians can and should go through with patients in the initial discussion of genetic testing:

- Genetic testing is rapidly expanding, with hundreds of tests in the pipeline. The value of each new test needs to be proven. Some will be valid; many will not.
- Genetic information about disease risk is in a state of flux. As we learn more about the relationship between genetic variants and certain diseases, risk estimates might change.
- Current genome scans only allow us to correlate genetic variants with disease. Further research is needed to understand how these variants affect the disease process.
- The impact of genetic information on individual attitudes and behaviors is not well understood, but it is something you have to consider. If your gene test said your risk is high, would you do anything differently? If it said your risk is low, would that change anything?

If a Patient is Considering a Direct to Consumer (DTC) Test
PCPs have a responsibility to inform patients of the limitations of direct to consumer tests if a patient is considering one. Some questions to discuss:

- What test are you considering? Where did you hear about the test?
- What is your purpose for having this test? What are your expectations?
- What is the testing company promising?
- Do they provide the scientific evidence that supports the test?
- How much will it cost? What type of counseling is provided?
- How will your privacy be protected?

These tests are not regulated. For most, the company that developed the test provides only documentation of analytical validity. There is seldom any evidence of clinical value.

- Genome-based health and disease risk predictions and nutritional and supplement recommendations may sound good, but this type of test is years away.
- A recent government report found that such tests are misleading and possibly even harmful because their claims cannot be scientifically proven.
- Patients should be cautioned that such tests may be costly and their results misleading or medically meaningless.

Considering a Genetic Test in Primary Care
The following applies to tests for disease risk or pharmacogenetics that a primary care doctor will be most likely to see in primary care.

1. **Identify the condition (indication) of interest**
   - Assess the individual’s risk and the role of genetics in the condition.

2. **Assess family history**
3. Genetic testing should supplement it, not supplant it
   • To make the assessment more efficient use the downloadable form from the AMA.

4. Identify reason(s) for test
   • Will it help resolve the patient’s uncertainty/anxiety about the disease? Will it clarify disease risk? Will it assist with prevention or treatment plans, life decisions, etc?
   • Will it lead to a more definitive diagnosis or assist in the treatment or prevention plan?

5. Discuss briefly the validity and clinical utility of the test
   • Address details of the specific test – history of the test, evidence supporting it, recommendations that may be made based on test results.

6. Determine the patient’s interest in being tested
   • Discuss the patient’s values, preferences, and plans

7. Address misperceptions
   • Expectation that risk will be clearly established – genes are only part of the picture, and, in some cases, a relatively minor part (except single gene diseases)
   • Belief that a positive test means the disease is inevitable – explain the concept of “penetrance”—that not all disease mutations are always expressed. Different genetic diseases have different levels of penetrance, some low, some very high.
   • Fears of discrimination and privacy concerns – the Genetic Information Non-Discrimination Act (GINA), passed in 2008 protects the patient.

8. Review the general pros and cons of genetic testing
   Pros:  a. Negative result can provide relief.
          b. Positive result can motivate preventive actions.
          c. Either result reduces uncertainty and enables more informed decisions.
          d. Positive result may help identify disease risk in family members, who can then pursue testing and treatment as indicated
   Cons:  a. Possibility of an incorrect result or improper interpretation, as with any lab test.
          b. Positive result may cause anxiety or depression, or guilt or anger, especially if little can be done to prevent or treat the condition; make loved ones depressed or anxious too
          c. Positive result may cause undue stress for family members.
          d. Sometimes a genetic test will reveal a novel genetic variant that has unknown clinical significance, leading to uncertainty about how to manage this information.
          e. Negative result may cause undervaluing of other risks, false sense of immunity.
          f. Cost; may have to pay for counseling too; retesting if uncertain.

9. Emphasize getting genetic counseling
   • Understand the science behind the test – what it can really tell you.
   • Complete informed consent prior to testing.
   • Reduce chance of inappropriate test; assure credentials of testing lab.
   • Understand protections of privacy, employment and insurance discrimination.
   • Proper interpretation of results.
10. Develop a plan for testing
   • If the patient is undecided about testing: Obtain more information or refer for counseling
   • If the patient decides to proceed with testing: 1) Pre-test counseling, 2) Order test, 3) Interpret results, 4) Post-test counseling
   • If the patient decides against testing: Offer a preventive plan – screening, lifestyle, medical therapy

11. Arrange the next step
   • Follow-up visit – additional information, decision support, prevention plan
   • Referral for counseling – genetics clinic, medical geneticist or genetic counselor

Final Thoughts
The remarkable achievements of the Human Genome Project promise great opportunities for disease prediction, treatment, and prevention. Marker sets will have greater predictive value. Disease risks will be better defined. Subgroups will be identified for more or less intensive screening and treatment. Pharmaceutical therapy will be individualized, with serious adverse effects reduced. Genetic testing and counseling will play an increasingly important role in medical practice in the coming years.

But, for now, the rules haven’t changed. The availability of tests still far exceeds the evidence to allow us to accurately interpret and apply the results. It is vital to insist on good data before embracing good ideas. When prospective data shows that a genetic test really does improve patient outcomes, it will be embraced. A good family history and targeted, evidence-based genetic testing remain the foundation for assessing inherited risks. At this point, the best use of genetic risk information remains to motivate a greater commitment to pursue a healthy lifestyle and preventive practices that have been proven to improve outcomes.

For other information and useful links, visit the American College of Preventive Medicine website at www.acpm.org.