

The National Society of Genetic Counselors'

Genetic Testing Resource

what you need to know and how a Genetic Counselor can help



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1) Introduction

Genetic testing is diverse and complex. Understanding how tests work is critical to appropriate utilization.¹ This document addresses:

- 1) Key issues in genetic testing
- 2) Testing categories and their differences
- 3) Healthcare professionals' roles in counseling, test selection, utilization, and coverage recommendations
- 4) Expertise of genetic counselors.

Although genetic counselors are not involved in ordering every genetic test, in many situations they can provide expertise and support to patients, providers and payers. This document provides an overview of the critical issues around genetic testing and the role that genetic counselors have in the genetic testing process.

2) Types of DNA Tested

Most genetic tests analyze the germline genetic sequence (genetic variants present in *all* body cells—from conception). However, some tests examine the individual genetic material or genome of somatic tissue (non-reproductive cells), such as cells from a cancerous tumor. Somatic tests can uncover underlying variants that may be present in all or some of the body's cells—and may indicate that additional germline genetic testing is appropriate. This document will primarily focus on germline genetic testing.

3) Types of Technology and their Uses

Over the years, scientists have developed different ways to analyze the structure of human chromosomes and the DNA sequence. Currently, no single technology or test type can evaluate for every possible genetic variation. Different test types use various technologies that assess the structure and sequence of human DNA. Figure 1 highlights common tests and the different questions these tests seek to answer.

¹ Appendix A includes links to NSGC's positions on topics related to genetic testing that this document does not address.

A selection of

Genetic Test Types

and the questions they seek to answer



Karyotype - How many chromosomes are there? Any regions visibly missing or extra or rearranged?

FISH analysis - Are there smaller regions missing or extra in a certain area?

Chromosomal microarray - Are there extra or missing sections of any of the chromosomes?

Single gene sequencing - What is the sequence of a particular gene in question?

Panel testing - What is the sequence of a set group of genes?

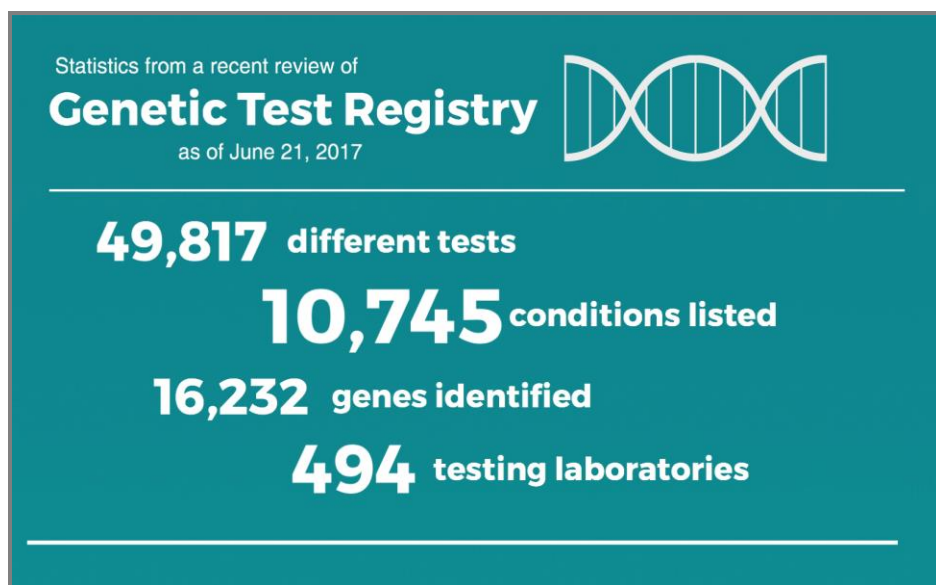
Exome analysis - What is the sequence of the coding region (all genes) for this individual?

Genome analysis - What is the sequence of all DNA for this individual?

Epigenetic analysis - How does the structure of DNA molecules affect the way certain genes are expressed?

4) Genetic Test Complexity

Genetic testing is complicated, but invaluable in medical diagnoses and determining treatments for many diseases and conditions. There are different ways to test for a certain conditions, and the number of testing options continues to grow. The Genetic Test Registry shows just how many testing options currently exist:



In a 2015 speech on the Precision Medicine Initiative, former President Barack Obama described precision medicine as a method for “delivering the right treatments, at the right time, every time to the right person.”² To keep with the rapid pace of genetic-testing innovation, providers ordering genetic tests must think critically about the right test for the right person, at the right time, to ensure appropriate utilization and maximum benefit.

Identifying the *right* family member to test is critical to accurate and efficient diagnosis. Testing a family member who has already developed a disease, for example, is ideal to determine whether a genetic variant is hereditary. If not possible, it is important to identify the *next*-best person to test. Testing the wrong person can waste time and resources.

Determining the *right* time to pursue testing is also critical. Test results can affect the medical, psychological, and social functioning of an individual and family. For example, benefits and risks of testing a child for an adult-onset condition should be carefully weighed to preserve the child’s autonomy and right to an open future. In some cases, it may be advantageous to proceed with testing during childhood, while other times, testing should be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of the information.



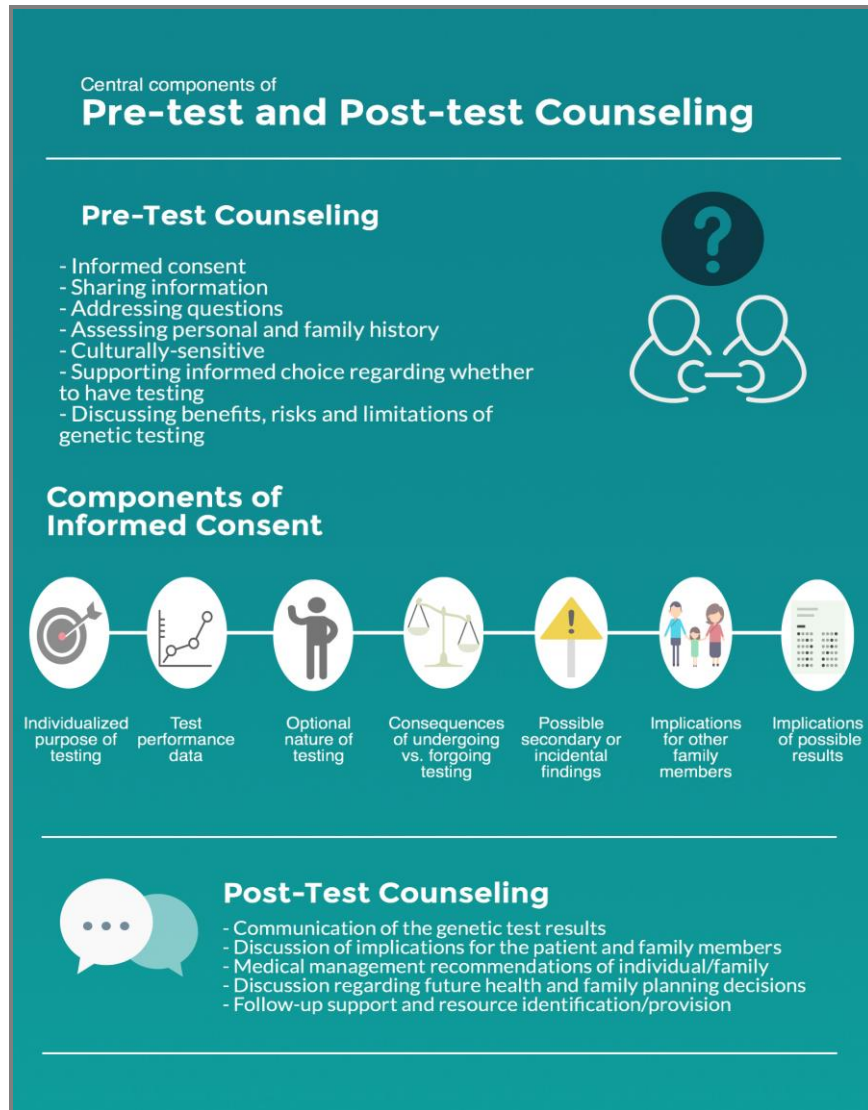
It is crucial to identify the right genetic test to order, at the right time, for the right person.

When several available tests appear similar, the *right* genetic test may not be immediately obvious. Prenatal genetic testing for carrier conditions such as cystic fibrosis is an example. Many tests can identify cystic fibrosis carriers, but the effectiveness of each test depends on each specific case. In some situations, testing only one specific variant known in a family is sufficient. In other cases, testing the entire cystic fibrosis gene is necessary.

It is critical that healthcare providers have the skills to navigate information to ensure informed decision-making regarding genetic test-selection. Making sense of genetic tests and selecting the most appropriate test is a skill that requires a broad genetics knowledge base and an understanding of the relevant genetic tests available.

5) Genetic Counseling

An important component of genetic testing is pre- and post-test genetic counseling. Genetic counseling helps patients and families understand their testing options and the potential impact of test results. This twofold process includes pre- and post-test counseling.



The extent and delivery method of genetic counseling, and whether it includes pre- and post-test counseling, may vary depending on the setting and type of test. For certain tests, it is critical to consult a genetics specialist, such as a genetic counselor or medical geneticist, before *and* after ordering a test. For example, when pursuing whole exome sequencing, both pre- and post-test genetic counseling are necessary to help the individual:

- understand options and make informed selections as to the type of additional results he/she wishes to receive (e.g. medically actionable incidental findings and carrier status)
- understand the results related to the primary indication for testing and other selected results
- understand the implications of results for medical management and impact on relatives.

Service delivery models for pre- and post-test genetic counseling vary depending on the nature of the test and the indication for testing. With the increasing demand for genetic services, many genetics experts use telephone counseling for individuals who cannot obtain an in-person counseling appointment due to time constraints or lack of available practitioners in the region.

a) Pre-Test Genetic Counseling

Pre-test genetic counseling informs patients/families about the benefits, risks, and limitations of undergoing genetic testing before ordering a test. Pre-test counseling should review the patient's personal and family history, discuss the test's benefits and limitations, and explain and obtain informed consent. The informed-consent process considers the individual's/family's beliefs, knowledge base, and values to help patients decide whether to pursue testing and which test to undergo. In some cases, delaying or declining testing may be the best choice.

Inadequate pre-test counseling can adversely affect the patient's understanding of the genetic testing process, as well as the accuracy of the test ordered. Several aspects of pre-test counseling are below.

i) Family Health History

Identifying and properly assessing genetic risk factors helps individuals and families understand the degree of concern for a genetic condition. Collecting a patient's family health history benefits the risk-assessment process. Genetic counselors use a comprehensive three-generation family history to help guide decisions on testing options to help interpret test results and to identify at-risk relatives who may need to undergo testing or develop treatment/monitoring plans. Sometimes, an asymptomatic patient may need an affected relative to undergo genetic testing before being tested.

Key components to the

Family Health History

- Health status of all first and second degree relatives
- Health status of third degree relatives, when relevant
- For these genetic relatives and patient:
 - Current age or age at death
 - Sex at birth
 - Medical conditions with ages of onset
- Maternal and paternal ethnicity
- Consanguinity
- The date the family health history was obtained
- Review of relatives' genetic test results and other pertinent medical records when possible



Collecting and assessing family history helps providers determine the appropriate genetic test to order. For example, the test ordered to diagnose Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome associated with birth defects and an increased risk for tumors, depends on family history.

Because 40 percent of BWS is due to changes in the *CDKN1C* gene, a skilled provider may first order a test of the *CDKN1C* gene if the family history assessment found relatives with BWS symptoms. If no family history indication exists, a skilled provider would order a different genetic test because methylation abnormalities cause most family history-negative BWS cases.

Family history also helps identify at-risk family members who can benefit from genetic counseling. In the inherited cardiac disease, hypertrophic cardiomyopathy (HCM), the walls of the heart thicken to cause fainting, reduced exercise capacity, and possibly sudden death. If a skilled genetics provider found a genetic cause through a family-history assessment, he/she would offer targeted testing for first-degree relatives for the identified genetic variant.

This allows family members who carry the genetic variant to benefit from routine screening and treatment for HCM. In this case, genetic testing can result in significant healthcare cost savings, as the targeted genetic test can cost \$200-\$400, whereas an echocardiogram costs at least \$3,000.^{2,3} Known as the cascade

² <http://www.uhhospitals.org/rainbow/patients-and-visitors/billing-insurance-and-medical-records/patient-pricing-information>

³ <https://www.invitae.com>

effect, family-history assessments and genetic testing, when appropriate, can lead to targeted screening, early detection, and possible disease-prevention in family members of an individual.

It is important to note that genetic testing complements, but does not *replace*, personal- and family-history assessments. Both provide valuable information, especially when used together. While genetic testing can confirm a clinical diagnosis and provide targeted testing for at-risk relatives, family history and clinical evaluation can be more important than genetic test results.

Marfan syndrome, a connective-tissue disorder that can cause ocular, skeletal, and cardiovascular problems, is an example. An individual who meets criteria for Marfan syndrome may undergo *FBNI* gene sequencing (a Marfan-associated gene) and receive negative results. Despite negative results, the patient would still be diagnosed with Marfan syndrome based on clinical findings (often called a “clinical diagnosis”).

Another example of the value of family history is Alzheimer disease risk-assessment. Some tests, including options for direct-consumer purchase, screen for a common genetic variant in the *APOE* gene that increases an individual’s chances of developing Alzheimer disease. Environmental factors and other genes not tested may also contribute to the disease’s development.

It is possible for an individual to develop Alzheimer disease *without* having the common variant in *APOE*, and many individuals with the variant will never develop the condition. Because of this limitation of genetic testing for Alzheimer disease, family history is a vital component to assess an individual’s risk. This may not be clear to an individual who tests for Alzheimer disease outside of the healthcare setting or who does not review his/her results with a genetic counselor or other genetics professional.

The National Society of Genetic Counselors’ (NSGC) Family Health History position statement (NSGC 2016) provides more information about family health history and cascade testing.

ii) **Test/Lab Selection**

The genetic testing market is highly competitive and rapidly expanding. Most genetic tests are laboratory-developed tests (LDTs) that the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) oversee. Not all tests on the market are conducted in CLIA/CAP facilities, including some direct-to-consumer genetic tests.

In addition to state and local regulations, most genetic laboratories follow professional guidelines, such as the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for interpreting sequence variants, to ensure consistent genetic test results.


As genetic testing advances and expands, selecting the appropriate genetic test and laboratory becomes even more critical. Providers usually make testing recommendations for individuals after a genetic evaluation that assesses medical and family history and physical exam—when appropriate. These recommendations should reflect the medical indications, as well as patient/family preferences.

The variability among laboratories offering clinical genetic testing, and among tests offered within a laboratory, makes pre-test counseling/comprehensive genetic evaluations valuable. Here are relevant questions a provider should ask a laboratory when selecting a test.

Factors to consider when

Selecting a Genetic Test

- Which test is being run?
- Which technology is used?
- How are results analyzed?
- What tissue/sample type is tested?
- Is confirmatory analysis offered?
- What is the detection rate for the condition(s) in question?
- Which CPT (billing) codes are utilized?
- Are additional services offered (e.g., prior authorization, DNA banking, reanalysis, familial testing)?
- Are laboratory professionals available for consultation?
- What is the pricing structure?
- What is the turn-around time for results?
- What is the laboratory's experience with this test?
- Does the company participate in data sharing?



"Genetic tests come in many shapes and sizes."

Because of the complexity of genetic testing and the connections made between genetic variants and disease, test-result interpretations today may differ from future interpretations due to the available data. A healthcare provider has the duty to inform patients that more information may be available about a genetic variant in the future that could change a test's interpretation.

iii) **The Utility and Validity of a Genetic Test**

In an ideal world, a genetic test would provide an accurate result every time and would yield results that would be useful to every individual. However, every test has limitations. A particular test may properly detect a genetic variant that a test usually detects—but not every time. A test may not detect every genetic variant that leads to a particular genetic disease, which causes a “false negative” result. A test that is a perfect fit for one individual may have little or no use for another individual. A provider should consider these variations by determining a test's clinical validity, analytical validity, and clinical utility.

The infographic is a teal-colored box with a white circle containing a lowercase 'i' icon. The title is 'Questions to ask about a GENETIC TEST before it is ordered'. Below the title, there are three questions in a list:

- Accuracy?* Does the testing technology give the same answer every time?
- Medical Value?* Is there strong evidence to link the test results with a given disease or risk factor?
- Usefulness?* Are there accepted healthcare changes to make based on the result and will results impact life decisions?

Analytical validity focuses on the *laboratory science* of a test. Can a test consistently and reliably do what the laboratory/company promises? Do laboratory procedures ensure test-result accuracy? The standards set forth by CLIA regulate analytical validity of genetic tests.

Clinical validity assesses a test result's *medical implications* and how they pertain to a particular disease or risk factor. Is the evidence strong enough to connect an identified variant to a certain feature or disease? Rather than asking if the laboratory correctly reported the “positive” result (analytic validity), clinical validity focuses on a test's value in the context of the patient's health.

Clinical utility focuses on ordering and applying a test's result in a clinical setting. Just because a test exists does not mean everyone should undergo the test or that everyone will equally benefit from the test. This is true for all types of medical tests—not just clinical genetic testing.

Testing variants in the *HFE* gene is an example of a genetic test's limited clinical utility. This gene is connected to hemochromatosis, a common iron-overload disorder. However, widespread population testing shows that testing the *HFE* gene *by itself* has little benefit in the absence of iron-overload symptoms or a family history of the condition. Some groups such as ACMG state that *HFE* testing is indicated only if a family history of hereditary hemochromatosis exists or an individual receives positive test results indicating high iron.⁴

Assessing analytic validity, clinical validity, and clinical utility is not a simple task. Relying on marketing and information on company websites is rarely sufficient for making informed clinical decisions about test selection and interpretation. The ordering healthcare provider may be misguided when attempting to assess a test's utility and validity—not necessarily because of false information, but because of the lack of critical information available to properly assess a test. The consumer genetic testing market also makes this difficult for consumers, as the inherent weaknesses of many genetic tests are often not readily available.

[Genetics Home Reference](#)⁵ provides information on analytic validity, clinical validity, and clinical utility for those who want to learn more about these topics.

iv) **Navigating Payer Coverage**

Insurance coverage for testing can often influence test uptake, availability, and selection. Coverage may depend on the indication, type of test ordered, and testing laboratory (in or out of network). Payers often require preauthorization for certain tests to assess medical necessity and plan coverage. Insurance companies may request clinical information and evidence for the necessity of specific genetic tests from the healthcare provider.

⁴ <http://www.choosingwisely.org/patient-resources/making-smart-decisions-about-genetic-testing/>

⁵ <https://ghr.nlm.nih.gov/primer/testing/validtest>; accessed 8/31/17

Some payers also require genetic counseling before covering a test for specific genetic conditions. Testing coverage varies among payers and among individual-coverage policies. Even after coverage is confirmed, determining the test's cost to a patient/family can be difficult to quantify due to negotiated rates, co-pays, co-insurances, out-of-pocket maximums, and deductibles.

While coverage policies differ, many payers cover genetic testing if a test meets certain criteria. Payers base these criteria on published literature, evidence-based assessments, and professional organization clinical practice guidelines. With the increasing number of genetic tests, and the associated costs for both patient and payer, healthcare providers have a responsibility to both the patient and the healthcare system to use evidence-based practices when ordering a genetic test.

The cost of testing to the patient is only one part of the financial ramifications of testing. The costs of the tests to payers, as well as the downstream effects of any change in medical management, are also important to consider. Testing is often not medically necessary if a test result would not alter medical management or improve outcomes. On the other hand, genetic testing can make a dramatic difference in screening recommendations, management, and outcome, such as the case of predictive testing for certain hereditary cancer syndromes.

For example, Lynch syndrome is a hereditary cancer syndrome that greatly increases the risk for colorectal, endometrial, and other cancers. Women with Lynch syndrome are at increased risk for both uterine and ovarian cancers. While screening for uterine cancer is somewhat effective, there is no effective ovarian cancer screening to date.

The current recommendations are to discuss the availability of a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) to remove the uterus, ovaries, and fallopian tubes with patients.⁶ At-risk family members who test negative for the familial mutation do not need uterine or ovarian cancer screening—or TAH/BSO. Those who do test negative for the familial mutation do not need screening that is more aggressive and can follow general population screening recommendations, despite the family history.

⁶ https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Providers have a responsibility to both the patient and the healthcare system to assure test ordering practices are evidence-based.

As genetic testing options expand, they continue to outpace researchers' abilities to publish data supporting testing, especially for complex tests such as multi-gene panels. Some payers classify such tests as experimental or investigational because of the lack of published literature supporting the benefits of the tests. This can create access barriers to some of the most cost-effective and relevant genetic tests. Payers cyclically review tests and may not be able to immediately respond to new data. As a result, they may instead cover genetic tests that are costlier and less relevant to a given clinical situation.

In these situations, genetic counselors are critical in the decision-making process. Genetic counselors use existing literature to identify genes that have either recognized guidelines supporting testing or have enough published data to support medical-management changes associated with an identified pathogenic mutation. The final section of this document will explore the training, expertise, and value of genetic counselors.

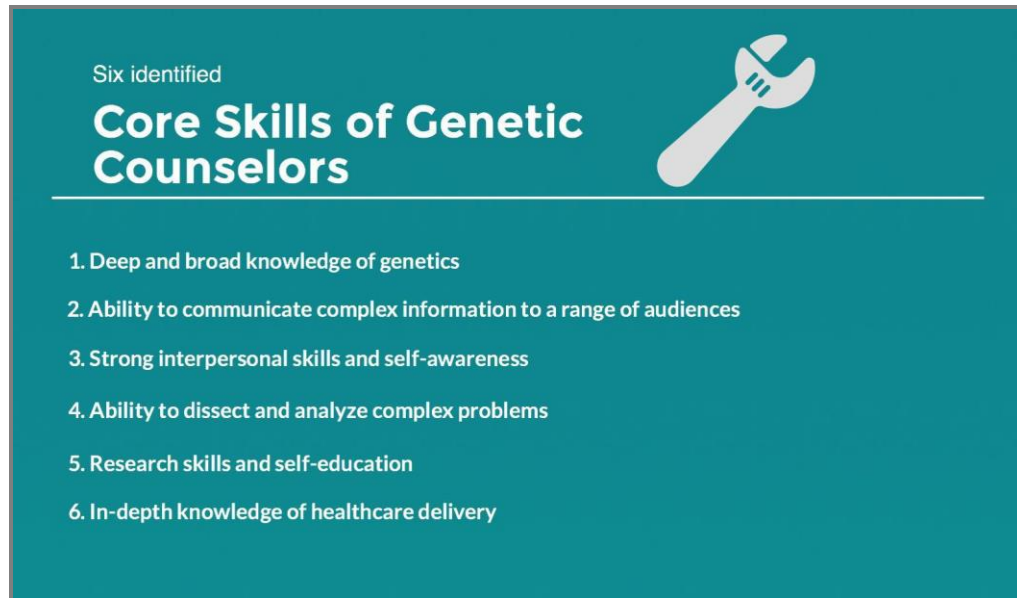
b) Post-Test Genetic Counseling

Post-test genetic counseling helps patients understand test results and how these results may affect their families' healthcare decisions. The post-test counseling session explains test results and implications, provides supportive resources, and discusses potential treatment options and referrals to specialists for a personalized medical-management plan. Supportive resources may include books, websites, support groups, patient-advocacy groups, clinical and research trials, follow-up steps, and referrals to other specialists.

6) Genetic Counselor Expertise and Value


The technical complexities of genetic testing, the time needed for pre- and post-test counseling, and the psychosocial components of counseling make genetic counselors critical. Genetic counselors complete two-year accredited masters-level genetic counseling graduate programs that focus on specialized genetics/genomics training, counseling training, and supervised clinical placements.

The genetic counselor certifying body, the American Board of Genetic Counseling (ABGC), sets forth competencies that include analyzing and interpreting genetic information that provides the basis for differential diagnosis, risk assessment, and genetic testing (ABGC Practice-Based Competencies, n.d.). A 2008-2009 NSGC survey to evaluate genetic counselors' core and additional professional skills identified six key skill areas for genetic counselors.



Six identified

Core Skills of Genetic Counselors



1. Deep and broad knowledge of genetics
2. Ability to communicate complex information to a range of audiences
3. Strong interpersonal skills and self-awareness
4. Ability to dissect and analyze complex problems
5. Research skills and self-education
6. In-depth knowledge of healthcare delivery

While many healthcare providers learn about genetics as part of their training program, genetic counselors must pass a certification examination and then maintain certification by obtaining continuing education and re-certifying every five years (Recertification, n.d.). Many states with licensure laws require more stringent continuing education standards.

This ongoing education keeps genetic counselors up to date in a rapidly advancing field and ensures they have the expertise to identify the appropriate test for a given clinical situation. One study found that when genetic counselors assessed genetic test orders at a commercial laboratory prior to performing testing, they changed 26 percent of the orders, which saved referring institutions an average of \$48,000 per month (Miller et al. 2013).

Genetic counselors' expertise goes beyond cost-savings to include an individual's personalized care. Communicating the meaning of a test result to the individual and discussing the subsequent actions an individual can take based on test results increases the chance of an improved clinical outcome. Studies show that pre- and post-test genetic counseling can increase the individual's compliance with the recommended medical-management plan (Rutherford et al., 2014).

7) Conclusion

The genetic testing market shows no signs of slowing. Results from genetic tests will become integral to medical decision-making and will continue to extend to all areas of healthcare. The knowledge to choose an appropriate laboratory and the right test for the right person requires an advanced skill-set that includes a broad understanding of components such as the tested DNA, the value of family-history review, and the utility or validity of a genetic test.

The genetic counseling process is vital to identifying the most appropriate family member to test, selecting the most appropriate genetic test, and recommending the best course of action. Proficient and comprehensive genetic evaluations help reduce unnecessary and incorrect testing and optimize efficiency. The provision of appropriate genetic testing as well as accurate interpretation is imperative to avoid unnecessary or harmful medical procedures.

Appropriate risk assessment, testing, and results interpretation allows for anticipatory guidance and/or medical-management recommendations that help optimize the health of individuals. Genetic counselors are valuable members of any genetic testing scenario and are often crucial members of programs created to translate genetic testing into clinical use.

Appendix A: Links to Current NSGC Positions Statements on Various Topics in Genetic Testing

- [Prenatal Cell-Free DNA Screening](#)
- [Direct Access to Genetic Testing](#)
- [Prenatal Testing For Adult-Onset Conditions](#)
- [Genetic Testing and Adoption](#)
- [Incidental Findings in Genetic Testing](#)
- [Genetic Testing of Minors for Adult-Onset Conditions](#)
- [Regulation of Genetic Testing](#)

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