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Genetic Tests:Clinical Validity and Clinical Utility

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Abstract

When evaluating the appropriate use of new genetic tests, clinicians and health care policymakers must consider the accuracy with which a test identifies a patient's clinical status (clinical validity) and the risks and benefits resulting from test use (clinical utility). Genetic tests in current use vary in accuracy and potential to improve health outcomes, and these test properties may be influenced by testing technology and the clinical setting in which the test is used. This unit defines clinical validity and clinical utility, provides examples, and considers the implications of these test properties for clinical practice.

Keywords

clinical validity; clinical utility; predictive value; penetrance Subject Group: Genetics and Genomics; Clinical Molecular Genetics; Cancer Genetics

Introduction

The sequencing of the human genome has initiated an era of gene discovery, leading to a growing understanding of the genetic determinants of disease. This research forms the basis for an increasing array of genetic tests that are now available for use in health care. Clinicians and health care policymakers face the task of determining appropriate test use. Three categories of test performance need to be considered in this evaluation process: analytic validity, clinical validity, and clinical utility (Holtzman and Watson, 1999).

Analytic validity refers to the accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal deletion, or biochemical indicator, is identified in a given laboratory test. Most genetic characteristics of clinical interest can be tested by a variety of protocols. Technical issues arising in the evaluation of analytic validity include the specific technical requirements of the assay chosen, its reliability, the degree to which reliability varies from laboratory to laboratory, and the complexity of test interpretation

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INTERNET RESOURCES

http://www.cms.hhs.gov/clia/

Clinical Laboratory Improvement Amendments (CLIA) Home Page.

http://www.genetests.org

GeneTests Web site with link to online journal GeneReviews, containing the following articles:

Shohat, M. and Halpern, G.J. 2012. Familial Mediterranean fever.

Moline and Eng C. 2005. Multiple endocrine neoplasia type 2.

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(Burke et al., 2002). A genetic test will not be considered suitable for clinical use unless it meets acceptable standards for analytic validity, as defined by professional standards and federal regulation (CLIA Home Page; http://www.cms.hhs.gov/clia). Other units (see, e.g., *units 8.2 & 9.2*) in this manual provide detailed information about the procedures used to measure the analytic validity of different genetic tests.

In considering test use, the clinician must also consider clinical validity and clinical utility (Holtzman and Watson, 1999). These test properties refer to the accuracy with which a test identifies a patient's clinical status (clinical validity) and the risks and benefits resulting from test use (clinical utility). Genetic tests vary in their accuracy and potential to contribute to improved health outcomes. In addition, clinical validity and utility may be influenced by testing technology and the clinical setting in which the test is used. In particular, recent developments in sequencing technology, including tests using targeted gene sequencing, whole exome and whole genome analysis, raise new challenges in the evaluation of clinical validity and clinical utility. This unit reviews the implications of these test properties for clinical practice.

Clinical Validity

The term clinical validity was proposed by the NIH-DOE Task Force on Genetic Testing to describe the accuracy with which a genetic test identifies a particular clinical condition (Holtzman and Watson, 1999). It is described in terms of sensitivity, specificity, positive predictive value, and negative predictive value (Table 9.15.1).

Diagnostic Testing

When a test is used diagnostically, clinical validity measures the accuracy with which the test identifies a person with the clinical condition in question. For example, a test for mutations in the *RET* gene based on either targeted mutation analysis or sequence analysis of select exons can detects disease-causing mutations in 95% to 98% of persons with multiple endocrine neoplasia type 2 (MEN2), an autosomal dominant condition conferring a high risk of medullary thyroid carcinoma and associated endocrine abnormalities (see Internet Resources for 2013 article by Moline and Eng in *GeneReviews*). From this observation, the sensitivity of the test can be defined as 95% to 98%. Specificity is assumed to approach 100%, based on the high penetrance observed in MEN2 families—i.e., the high likelihood that the disease will occur in an individual with the disease-related genotype. [Penetrance for specific disease manifestations and age of onset vary in different subtypes of the disease, but is high for all subtypes, as reviewed by Moline and Eng (2013).] As with all diagnostic tests, the measurement of test sensitivity and specificity requires a definitive alternate method for diagnosis, commonly referred to as the "gold standard," to which the genetic test can be compared. For many genetic diseases, including MEN2, definitive diagnosis is based on a constellation of medical and pedigree data (Fig. 9.15.1).

The positive and negative predictive values of the test are important measures of clinical validity (Table 9.15.1). These measures allow the clinician to determine how reliably the test can confirm or refute a suspected diagnosis. When both penetrance and test sensitivity are high, as with MEN2, positive and negative predictive value is generally also high. However,

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the positive predictive value is strongly influenced by the prevalence of disease in the population tested. The very small error rates occurring with optimal laboratory performance can result in a low positive predictive value when testing is done among individuals with a low likelihood of disease (Table 9.15.2).

Many genetic tests have lower sensitivity than the *RET* mutation test. Limitations in sensitivity usually occur because only a subset of causative mutations are identified by the test. Sensitivity may sometimes be influenced by ethnicity. For example, a test for mutations in the *FMF* gene has an estimated sensitivity ranging from 70% to 95% for detecting individuals with Familial Mediterranean Fever (FMF; see Internet Resources for 2012 article by Shohat and Halpern in *GeneReviews*). When this test is done in an individual with clinical symptoms suggestive of FMF, the positive predictive value of the test is very high, similar to MEN2 testing. The negative predictive value of the test may be limited; thus, a positive test result can confirm a diagnosis of FMF in a patient with a history and examination findings suggestive of the disease. If the patient is from an ethnic group for which test sensitivity is limited, a negative test leaves a substantial residual risk of FMF (Table 9.15.3).

Sequencing methods can enhance diagnostic sensitivity. Gene sequencing, for example, can identify more variants than methods designed to assay known mutations, such as a targeted mutation analysis. Targeted gene sequencing, utilizing next generation sequencing to evaluate multiple genes related to a particular diagnostic question, can detect much more variation than sequencing of a single gene. Finally, a whole exome or whole genome analysis dramatically expands the information provided by generating detailed information about hundreds or thousands of genes, including genes unrelated to the diagnostic question. There are limitations to next generation sequencing, however. This approach may produce false positive and false negative findings as well as many findings that are difficult to interpret or of uncertain clinical significance [see also Unit 9.22]. Many variants identified by sequencing may be difficult to classify as either normal variation or pathogenic, particularly novel or rare variants, making the clinical validity of the test difficult to evaluate. This difficulty is compounded by the need to clarify the phenotype for which testing is being done. When the *RET* gene is assessed as a component of a test sequencing multiple genes related to inherited cancer susceptibility, for example, many different cancer-related conditions may be under consideration. In this circumstance, the gold standard for assessing clinical validity may be difficult to define. In addition, whole exome/whole genome tests raise questions about the scope of analysis to be undertaken and the reporting of secondary or incidental findings, as discussed below under Clinical Utility [See also Units 9.22 and 9.23] As a result, the gain in sensitivity from genome sequencing must be weighed against its potential downsides.

Carrier Testing

Tests used diagnostically can also be used to identify carriers for X-linked and autosomal recessive genetic diseases. Sensitivity is the key parameter when carrier testing is done. It is measured by studying individuals who are obligate carriers. Parents of a child with an autosomal recessive disease are considered obligate carriers, because a de novo mutation in

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an affected child is much less likely than inheritance of a mutation from each parent. With X-linked diseases, by contrast, de novo mutations may account for a substantial proportion of affected individuals; the mother can be considered an obligate carrier only if there are additional affected family members, such as an affected brother or more than one affected son. When a test is known to have limited sensitivity, carrier testing is best accomplished by a two-step process, starting with testing of the affected family member. If a specific mutation (or two mutations, for autosomal recessive diseases) is detected, it forms the basis for a highly sensitive test among relatives who are at risk to be carriers. If a specific mutation cannot be identified, other means are needed to identify carriers; in some cases this can be accomplished through linkage analysis (Chapter 1).

The sensitivity of some carrier tests is very high. For example, sickle cell carriers can be identified reliably using either electrophoresis to detect HbS or a DNA-based assay to detect the β-hemoglobin mutation causing HbS (Ashley-Koch et al., 2000). In this case, sensitivity is limited only by errors in test handling and laboratory procedure. More often, carrier tests detect a majority of carriers, but not all. The false-negative rate can vary among different racial/ethnic groups. For example, the 23-mutation panel recommended for population-based cystic fibrosis (CF) carrier screening (Lebo and Grody, 2007) detects 80% of white American carriers, but has a higher sensitivity among people of Northern European descent (90%) and Ashkenazi Jews (97%) and a lower sensitivity among Hispanic-Americans (57%) and African-Americans (69%).

As with diagnostic testing, next-generation sequencing offers an opportunity for expanding the scope of carrier testing (Grody et al, 2013). Tests using this technology can generate information about carrier states in hundreds of autosomal and X-linked recessive conditions, which vary in severity and penetrance. Some conditions for which carrier testing can be done may manifest in adulthood, so that testing has the potential to identify the condition among persons tested for carrier status. As a result, this testing approach poses challenging questions regarding the selection of appropriate conditions to include in the test and the appropriate methods to ensure fully transparent pre-test counseling (Grody et al 2013).

Predictive Testing

Genetic testing can be done in asymptomatic individuals to identify genetic susceptibility to future disease. In this use of genetic testing, clinical validity measures the accuracy with which the test predicts a future clinical outcome. This measure is dependent on the penetrance of the genetic trait being measured and the prevalence of the clinical condition. In the case of MEN2, for example, *RET* mutation testing provides an accurate way to detect affected family members before any clinical symptoms have occurred (Table 9.15.2), because family members have a high a priori risk, the test has high sensitivity, and the mutations detected by the test have high penetrance.

Clinical validity is reduced when penetrance is lower. Testing for the C282Y mutation in the *HFE* gene offers a dramatic example. After gene discovery in 1996, the majority of people with hereditary hemochromatosis were found to be homozygous for C282Y (Hansen et al., 2001). This finding suggested that population screening for the C282Y/C282Y genotype might provide a valuable prevention opportunity: people with a positive test could be treated

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with regular phlebotomy, to prevent the iron overload that causes cirrhosis and other clinical problems in *HFE*-associated hemochromatosis. However, population-based studies now suggest that only a minority of individuals with the C282Y/C282Y genotype develop clinical disease (Asberg et al., 2007; Beutler, 2007; Allen et al., 2008). As a result, the positive predictive value of the genotype is low. The modifying factors that account for differences in outcome among C282Y homozygotes have been difficult to define (Beutler, 2007); however, high alcohol intake, viral hepatitis and polymorphisms in several genes involved in iron transport or metablolism appear to influence the likelihood of clinical symptoms (Gan et al, 2011). Penetrance is consistently lower in women than in men. Based on the finding of low penetrance, the US Preventive Services Task Force recommended against population screening for *HFE*-associated hemochromatosis (US Preventive Services Task Force, 2006), but testing in individuals with suggestive symptoms or a family history of the condition may identify an important opportunity for prevention.

Mutations associated with disease susceptibility are often first defined in “high-risk” families, characterized by multiple affected family members. These studies may overestimate risk compared to studies in large, unbiased populations. For example, hereditary breast-ovarian cancer syndrome (HBOC), due to mutations in the *BRCA1* and *BRCA2* genes, was first identified in families selected for the presence of breast cancer under age 60 or ovarian cancer in four or more family members (Ford et al., 1994). The lifetime risk of breast cancer is estimated to be ~85% in mutation carriers from these high-risk families, but studies using less selected populations have consistently estimated a lower lifetime risk (Begg, 2002). These observations suggest that the families in the initial studies represented the severe end of a spectrum of risk associated with *BRCA1* and *BRCA2* mutations, and that other factors, both genetic and nongenetic, modify the risk associated with these mutations (Burke and Austin, 2002). Subsequent studies indicate both genetic and nongenetic influences on clinical outcome (Shouen and Foulkes, 2011), including an important age cohort effect that suggests modifying social or environmental factors: women with *BRCA* mutations born before 1920 have experienced a lower lifetime risk of cancer than their daughters and granddaughters with the same mutations (Levy-Lahad and Friedman, 2007). Research following the discovery of the *BRCA1* and *BRCA2* genes has demonstrated that the genetics of breast cancer risk is complex: Different *BRCA* mutations may confer different levels of risk; variants in other genes modify the effect of BRCA mutations; and several other genes associated with breast cancer risk have been identified, with gene variants conferring varying degrees of risk (Shouen and Foulkes, 2011).

As both the HBOC and hemochromatosis examples illustrate, the variable clinical consequences associated with a genotype can be due due to a mix of gene-gene and gene-environment interactions. As a result, the clinical validity of many genetic tests may remain imprecise even when all appropriate studies have been completed. Similarly, pharmacogenomic variants—gene variants associated with differences in response to pharmaceutical agents—only partially predict drug response due to other factors that also play a role such as diet, concurrent therapies or clinical status (Nebert et al., 2008), and most gene variants associated with common complex diseases confer modest relative risks (Altshuler and Daly, 2007). As a result, significant methodological challenges arise in

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assessing the different contributors to risk and their interactions (Janssens et al, 2011). In addition to the complexity of gene-gene and gene-environment interactions, many gene variants have pleiotropic clinical effects (Sivakumaran et al, 2011).

As knowledge is gained, genome sequencing may allow for tests that improve the prediction of genetic risk in complex diseases. It may be possible, for example, to develop genomic tests that can identify individuals with *BRCA* or *HFE* mutations who are at increased or decreased risk for particular clinical outcomes, based on the presence of gene variants in other genes with modifying effects. However, in both these conditions, as in complex diseases more generally, environmental factors play a role in clinical outcome, leading to inherent limitations in the use of polygenic screening to assess risk (Khoury et al, 2013).

Measurement of Clinical Validity

Important variables in evaluating evidence about clinical validity include the populations studied, the laboratory assay used, and the clinical endpoints measured (Burke et al., 2002). The definition of the reference standard is also important. For example, when clinical and pedigree findings are used to evaluate test sensitivity and specificity, careful attention must be paid to how these clinical measures are defined, including whether measurement is blinded. The size and selection criteria for the study population have the potential to introduce important biases and limitations, and the age of the population studied is a central consideration, particularly for predictive tests. In the evaluation of low-penetrance mutations, test performance may be difficult to interpret without concurrent measurement of nongenetic factors that contribute to clinical outcomes. Comparability of cases and controls is an important factor when a case-control study design is used.

Clinical Utility

Clinical utility refers to the risks and benefits resulting from genetic test use. The most important considerations in determining clinical utility are: (1) whether the test and any subsequent interventions lead to an improved health outcome among people with a positive test result; and (2) what risks occur as a result of testing. Complete measurement of clinical utility requires evaluation of the medical and social outcomes associated with testing, and subsequent interventions for people with both positive and negative test results. When treatment is unavailable, a genetic test with high clinical validity may be useful to establish a diagnosis or provide prognosis; in this situation, the value of testing is determined by clinical validity.

When treatment is available, the most convincing evidence of clinical benefit comes from randomized controlled trials demonstrating an improved clinical outcome in those who received the treatment, compared to those who did not (Woolf, 2000). However, this standard has been difficult to achieve in medical genetics. For rare, highly penetrant disorders, treatment may appropriately be based on knowledge of disease biology, with benefits assessed by historic controls. An example is the use of prophylactic thyroidectomy in children with MEN2 to prevent medullary thyroid cancer. Evaluation of small cohorts receiving this therapy indicate a definite benefit, with few cases of medullary carcinoma occurring over several years of follow-up among patients who would historically have been

at high risk (Brandi et al., 2002; Skinner et al., 2005). This finding indicates high clinical utility for *RET* mutation testing, because it provides a means to identify individuals who would benefit from preventive surgery. Further, data on the correlation between genotype and age of onset of medullary thyroid cancer can be used to define the optimal timing for prophylactic surgery (Raue and Frank-Raue, 2010).

The MEN2 example illustrates that observational data may provide a sufficient basis for clinical practice despite small study samples and the lack of randomization, blinding, or other controls used to improve the quality of data in clinical trials. When the genetic condition is well understood, the expectation of benefit from a particular treatment may be high enough to make evaluation of testing by a randomized trial ethically unacceptable—for example, early screening colonoscopy in Lynch syndrome (previously termed hereditary nonpolyposis colorectal cancer or HNPCC; Jarvinen et al., 2000; Vasen et al, 2013). Even in the case of drug treatment, a randomized study design may not be required for rare conditions, and the outcomes studied may be limited to intermediate biological measures. For example, replacement therapy for α(1)-antitrypsin (AAT) deficiency was approved on the basis of clinical studies demonstrating that replacement therapy could maintain target serum levels in people with severe deficiency, rather than on the basis of improved clinical outcomes (WHO, 1997). Subsequent clinical outcome data remain limited, although they suggest benefit for patients with severe AAT deficiency (Abboud et al., 2001, Zamora et al., 2008).

Given these considerations, the appropriate management of many genetic diseases—and therefore the clinical utility of the associated genetic tests—may be determined by the collection of high-quality observational data, such as well-designed cohort studies or case series (Wilken, 2001). With this approach, however, uncertainties may remain long after the treatment is introduced, particularly regarding the timing of treatment and the selection of patients most likely to benefit.

Although observational data may provide an acceptable basis for determining the clinical utility of tests for rare, high-risk genetic conditions, this standard is not likely to be acceptable for gene variants associated with common, complex disorders or for pharmacogenomic variants. Determining whether the test has adequate predictive value for clinical use requires comparison with alternatives (Simonds et al, 2013). For example, many genetic tests identify individuals with an increased risk for cardiovascular disease. However, these tests are typically less informative than intermediate measures of risk such as lipid profiles, which capture the effects of both genotype and environmental exposure such as diet and other lifestyle factors (Humphries et al., 2004). Even when a gene variant is established as an independent risk factor, further evaluation is required to determine whether it assists in clinical management (Burke and Psaty, 2007; Simonds et al, 2013). These observations argue for the importance of controlled studies of outcomes when determining the clinical utility of genetic tests for low-penetrance gene variants.

These concerns underscore an important challenge of whole exome and whole genome analysis. These tests provide an efficient means to assess variation in multiple genes. In addition to providing information related to the diagnostic question, however, they can

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provide information for many genes unrelated to the patient's presenting complaints. In this way whole exome and whole genome tests provide an opportunity for opportunistic screening, aimed at identifying genetic risks that were not otherwise suspected. The positive and negative predictive value of such test results cannot be calculated without substantially more population-based data than are currently available. In addition, as more information is provided by a test, more potential outcomes, both positive and negative, must be considered, including those associated with false positive or indeterminate findings. These issues add to the complexity of decision-making about secondary or incidental findings from whole exome and whole genome testing [See also Units 9.22 and 9.23].

Measurement of Clinical Utility

As with clinical validity, important variables in evaluating clinical utility include the size and selection criteria for the study population, the laboratory assay used, the clinical outcomes measured, and (where relevant) the comparability of cases and controls (Burke et al., 2002). The interventions to be studied, anticipated benefits, and current understanding of the disease process determine the acceptability of the study design, including whether a randomized clinical trial is needed to establish clinical utility.

A study that is limited to medical outcomes does not provide complete information about the implications of testing. Factors affecting access to testing and treatment, including the appropriateness of physician referrals, the cost of services, and the acceptability of the recommended treatment to patients, may play a crucial role in the medical outcomes of testing. The potential for adverse social consequences of genetic testing is also a consideration. The development of qualitative and quantitative methods to evaluate these outcomes represents an important challenge in the evaluation of the clinical utility of genetic and genomic tests.

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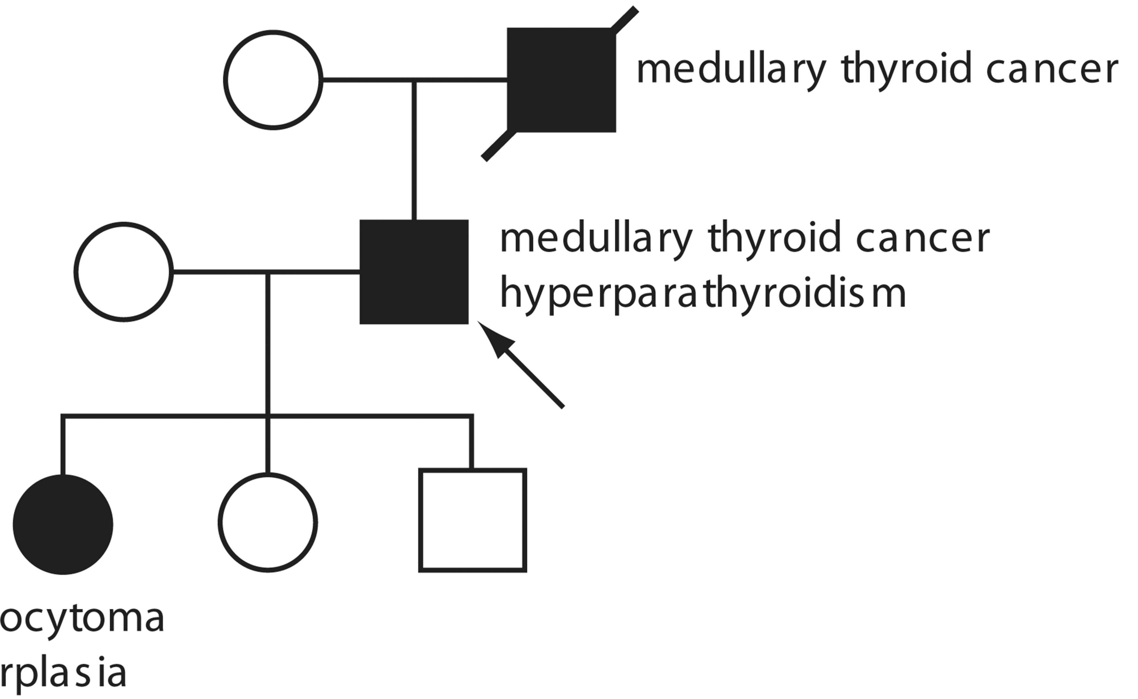

Figure 1.

Family with multiple endocrine neoplasia type 2 (MEN2). A definitive diagnosis of MEN2 can be made in the proband (arrow), on the basis of clinical findings of MEN2 (medullary thyroid cancer and hyperparathyroidism), combined with a family pedigree demonstrating autosomal dominant inheritance of the clinical problems associated with MEN2, including medullary thyroid cancer in the proband's father, and pheochromocytoma and C-cell hyperplasia (a precursor of medullary thyroid cancer) in the proband's daughter.

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Table 9.15.1

Test Properties Measuring Clinical Validity

Test parameter	Definition
Sensitivity	Among people with a specific condition, the proportion who have a positive test result
Specificity	Among people who do not have the condition, the proportion who have a negative test result
Positive predictive value	Among people with a positive test result, the proportion who have the condition
Negative predictive value	Among people with a negative test result, the proportion who do not have the condition

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Table 9.15.2

Genetic Testing for MEN2

	General population	Individuals with medullary thyroid carcinoma	History of affected 1st-degree relative, not tested	History of affected 1st-degree relative with identified mutation
Risk for MEN2 in tested individual	1/30,000	1/5	1/2	1/2
Test sensitivity	98%	98%	98%	99.9%[a]
Test specificity	99.9%[a]	99.9%[a]	99.9%[a]	99.9%[a]
Positive predictive value	3.3%	99.6%	99.9%	99.9%
Negative predictive value	99.9%	99.5%	98.1%	99.9%

[a]It is assumed that sensitivity and specificity of tests do not reach 100%, even for highly accurate tests, due to minor limitations in analytic validity and errors in laboratory procedure. For this example, test specificity is assumed to be 99.9%, and when a 1st-degree relative is tested for a known familial mutation, sensitivity is assumed to be 99.9%.

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Table 9.15.3

Example: Predictive Value of Test for Familial Mediterranean Fever (FMF) in Hypothetical Scenario of High Clinical Suspicion and Limited Test Sensitivity[a]

Results of testing[b]	
Positive predictive value of test	99.9%
Negative predictive value of test	37%
Residual likelihood of FMF if test is negative	63%

[a]Scenario: Symptoms suggestive of FMF are noted in a patient of Arab ethnicity with a negative family history of FMF. Prior to testing, an experienced clinician estimates a 90% chance that the patient has FMF; that is, that 90 out of 100 individuals with the patient's clinical presentation will have the disorder. Sensitivity of testing in a person of Arab ethnicity is estimated to be 70% (see Internet Resources for 2012 article by Shohat and Halpern in *GeneReviews*).

[b]Assuming test specificity of 99.9%.