Methods Guide for Medical Test reviews

Paper 11

Genetic Tests as Predictive Indicators

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AHRQ Publication No. xx-EHCxxx-EF
<Month Year>

Effectiveness and Comparative Effectiveness Reviews, systematic reviews of existing research on the effectiveness, comparative effectiveness, and comparative harms of different medical tests, are intended to provide relevant evidence to inform real-world health care decisions for patients, providers, and policymakers. In an effort to improve the transparency, consistency, and scientific rigor of the work of the Effective Health Care (EHC) Program, through a collaborative effort within the Evidence-based Practice Center Program, have developed a Methods Guide for Medical Test Reviews. We intend that these documents will serve as a resource for our EPCs as well as for other investigators interested in conducting systematic reviews on medical tests.

This Medical Test Methods guide is intended to be a practical guide for those who prepare and use systematic reviews on medical tests. This document complements the EPC Methods Guide on Comparative Effectiveness Reviews (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318), which focuses on methods to assess the effectiveness of treatments and interventions. The guidance here applies the same principles for assessing treatments to the issues and challenges in assessing medical tests and highlights particular areas where the inherently different qualities of medical tests necessitate a different or variation of the approach to systematic review compared to a review on treatments. We provide guidance in stepwise fashion for those conducting a systematic review.

The *Medical Test Methods Guide* is a living document, and will be updated as further empirical evidence develops and our understanding of better methods improves. Comments and suggestions on the *Medical Test Methods Guide* and the Effective Health Care Program can be made at www.effectivehealthcare.ahrq.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Paper 11. Genetic Tests as Predictive Indicators

The general principles for evaluating genetic tests are similar to those for interpreting other prognostic or predictive tests, but there are differences in how the principles need to be applied and in the degree to which certain issues are relevant, particularly when considering genetic test results that provide predictive rather than diagnostic information. This paper is not intended to provide comprehensive guidance on evaluating all genetic tests. Rather, it focuses on issues that have been of particular concern to analysts and stakeholders and on areas that are of particular relevance for the evaluation of studies of genetic tests. In this paper, we reflect on genetic tests used to (1) determine risk or susceptibility in asymptomatic individuals (to identify individuals at risk for future health conditions, e.g., BRCA1 and BRCA2 for breast and ovarian cancer); (2) reveal prognostic information to guide clinical management and treatment in those with a condition (e.g., Oncotype Dx® for breast cancer recurrence); or (3) predict response to treatments or environmental factors including diet (nutrigenomics), drugs (pharmacogenomics, e.g., CYP2C9 and VKORC1 tests to inform warfarin dosing), infectious agents, chemicals, physical agents, and behavioral factors. We do not address genetic tests used for diagnostic purposes.

Clinicians, geneticists, analysts, policymakers, and other stakeholders may have varying definitions of what is considered a "genetic test." We have chosen to use a broad definition in agreement with that of the Centers for Disease Control and Prevention (CDC)-sponsored Evaluation of Genomic Applications in Practice and Prevention (EGAPP) and the Secretary's Advisory Committee on Genetics, Health, and Society,[1] namely: "A genetic test involves the analysis of chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), genes, or gene products (e.g., enzymes and other proteins) to detect heritable or somatic variations related to disease or health. Whether a laboratory method is considered a genetic test also depends on the intended use, claim, or purpose of a test."[1] The same technologies are used for diagnostic and predictive genetic tests; it is the intended use of the test result that determines whether it is a diagnostic or predictive test.

In this paper, we discuss common challenges and principles for addressing those challenges related to (1) developing the topic and structuring a genetic test review (context and scoping), and (2) performing the review. We do not attempt to reiterate the challenges and principles described in earlier sections of this *Medical Test Methods Guide*, but focus instead on issues of particular relevance for evaluating studies of genetic tests.

Common Challenges

Genetic tests are different from other medical tests in their relationship to the outcomes measured. Reviewers need to take into account the penetrance of the disease, which is related to time lag to outcomes, variable expressivity, and pleiotropy. These particular aspects of genetic tests result in specific actions at various stages of planning and performing the review.

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Penetrance

Evaluations of predictive genetic tests should always consider penetrance, defined as "the proportion of people with a particular genetic change who exhibit signs and symptoms of a disorder."[2] Penetrance is a key factor in determining the future risk of developing disease and assessing the overall clinical utility of predictive genetic tests. Sufficient data to determine precise estimates of penetrance are sometimes lacking.[3-4] This can be due to the lack of reliable prevalence data or a lack of long-term outcomes data. In such cases, determining the overall clinical utility of a genetic test is difficult. In some cases, modeling with sensitivity analyses can be helpful to develop estimates.[3]

Time Lag

The time lag between genetic testing and clinically important events should be assessed in critical appraisal of studies of such tests. Whether the duration of studies and followup is sufficient to characterize the relationship between a positive test and clinical outcomes is an important consideration. In addition, it should be determined whether or not subjects have reached the age beyond which clinical expression would be likely.

Variable Expressivity

Variable expressivity refers to the range of severity of the signs and symptoms that can occur in different people with the same condition.[2] For example, the features of hemochromatosis vary widely. Some individuals have mild symptoms, while others experience life-threatening complications such as liver failure. The degree of expressivity should be considered in the evaluation of genetic tests.

Pleiotropy

Pleiotropy occurs when a single gene influences multiple phenotypic traits. For example, the genetic mutation causing Marfan syndrome results in cardiovascular, skeletal, and ophthalmologic abnormalities. Similarly, BRCA mutations can increase the risk of a number of cancers, including breast, ovarian, prostate, and melanoma. Of note, penetrance, variable expressivity, and pleiotropy are terms generally used to describe autosomal dominant, single gene disorders.

Other Common Challenges

Another common challenge in evaluating predictive genetic tests is that direct evidence for the impact of the test results on health outcomes is often lacking. The evidence base may often be too limited in scope to evaluate the clinical utility of the test. In addition, it is often difficult to find published information on various aspects of genetic tests. Most notably, there may be insufficient published data related to the analytic validity of some genetic tests.

Genetic tests also have a number of technical issues that are particularly relevant to assessing their analytic validity. These technical issues may differ according to the type of genetic test and may influence the interpretation of a genetic test result.

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Common challenges arise when attempting to use genetic tests to determine susceptibility or risk in asymptomatic individuals. The utility of such tests may depend on the ability of individuals (e.g., patients or health care providers) to report and identify certain clinical factors.

Finally, statistical issues must be taken into account when evaluating studies of genetic tests. For example, genetic test results are often derived from analytically complex studies that have undergone a very large number of statistical tests.

Principles for Addressing the Challenges

Principle 1: Use an Organizing Framework Appropriate for Genetic Tests

Organizing frameworks for approaching the evaluation of genetic tests have been developed by the United States Preventive Services Task Force (USPSTF), the CDC, and EGAPP.[1,5-6] The model endorsed by the EGAPP initiative[1] was based on a previous Task Force report[7] and developed through a CDC-sponsored project, which piloted an evidence evaluation framework that applied the following three criteria: (1) Analytic validity (technical accuracy and reliability), (2) clinical validity (ability to detect or predict an outcome, disorder, or phenotype), and (3) clinical utility (whether use of the test to direct clinical management improves patient outcomes). A fourth criterion was added: (4) ethical, legal, and social implications.[5] The ACCE model (Analytic validity, Clinical validity, Clinical utility, and Ethical, legal and social implications) includes a series of 44 questions that are useful for analysts in defining the scope of a review, as well as for critically appraising studies of genetic tests (Table 11-1). The initial seven questions help to guide an understanding of the disorder, the setting, and the type of testing. A detailed description of the methods of the EGAPP Working Group is published elsewhere.[1]

Table 11-1. ACCE model questions for reviews of genetic tests[5]

Element	Questions
Disorder/setting	1. What is the specific clinical disorder to be studied? 2. What are the clinical findings defining this disorder? 3. What is the clinical setting in which the test is to be performed? 4. What DNA test(s) are associated with this disorder? 5. Are preliminary screening questions employed? 6. Is it a stand-alone test or is it one of a series of tests? 7. If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)?
Analytic validity	8. Is the test qualitative or quantitative? 9. How often is the test positive when a mutation is present? 10. How often is the test negative when a mutation is not present? 11. Is an internal quality control program defined and externally monitored? 12. Have repeated measurements been made on specimens? 13. What is the within- and between-laboratory precision? 14. If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner? 15. What range of patient specimens have been tested?

Element	Questions
	16. How often does the test fail to give a usable result? 17. How similar are results obtained in multiple laboratories using the same, or different technology?
Clinical validity	18. How often is the test positive when the disorder is present? 19. How often is the test negative when a disorder is not present? 20. Are there methods to resolve clinical false positive results in a timely manner? 21. What is the prevalence of the disorder in this setting? 22. Has the test been adequately validated on all populations to which it may be offered? 23. What are the positive and negative predictive values? 24. What are the genotype/phenotype relationships? 25. What are the genetic, environmental or other modifiers?
Clinical utility	26. What is the natural history of the disorder? 27. What is the impact of a positive (or negative) test on patient care? 28. If applicable, are medical tests available? 29. Is there an effective remedy, acceptable action, or other measurable benefit? 30. Is there general access to that remedy or action? 31. Is the test being offered to a socially vulnerable population? 32. What quality assurance measures are in place? 33. What are the results of pilot trials? 34. What health risks can be identified for follow-up testing and/or intervention? 35. What are the financial costs associated with testing? 36. What are the economic benefits associated with actions resulting from testing? 37. What facilities/personnel are available or easily put in place? 38. What educational materials have been developed and validated and which of these are available? 39. Are there informed consent requirements? 40. What methods exist for long term monitoring? 41. What guidelines have been developed for evaluating program performance?
Ethical, legal, and social implications	42. What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues? 43. Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements? 44. What safeguards have been described and are these safeguards in place and effective?

Abbreviations: ACCE = Analytic validity, Clinical validity, Clinical utility, and Ethical, legal and social implications; DNA = deoxyribonucleic acid.

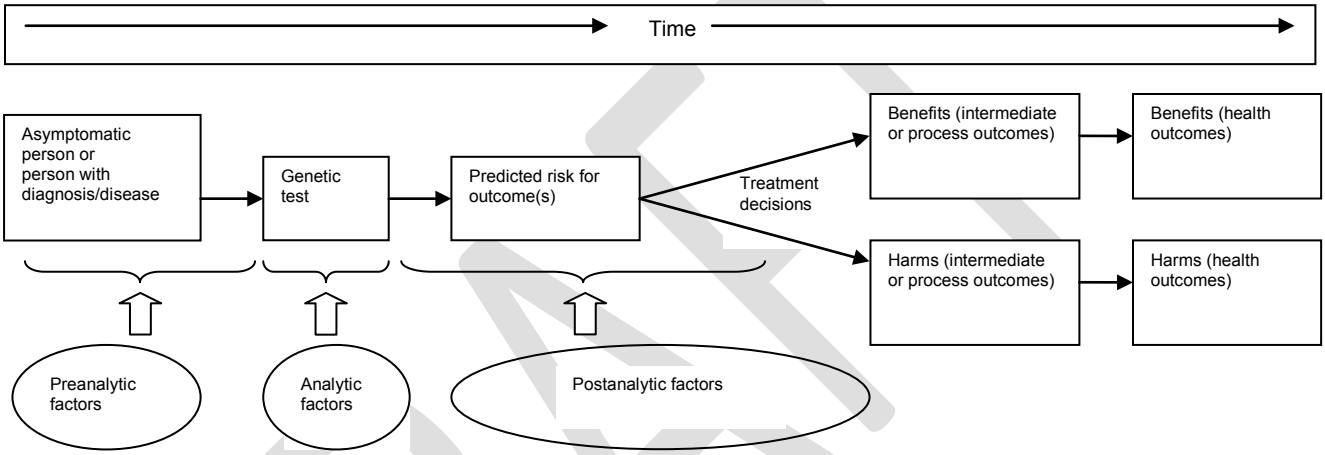
Principle 2: Analytic Frameworks Should Reflect Predictive Nature of Genetic Tests and Incorporate Appropriate Outcomes

It is important to have a clear definition of the clinical scenario and analytic framework when evaluating any test, including a predictive genetic test. Prior to performing a review, analysts should develop clearly defined key questions and understand the needs of decisionmakers and the context in which the tests are used. They should consider whether this is a test used for determining future risk of disease in asymptomatic individuals, establishing prognostic information that will influence treatment decisions, or predicting response to treatments (either effectiveness or harms)—or used for some other purpose. The PICOTS typology (Patient

population, Intervention, Comparator, Outcomes, Timing, Setting) should be clearly described as it will inform the development of the analytic framework and vice versa.

In constructing an analytic framework for evaluating a genetic test, it may be useful for analysts to consider preanalytic, analytic, and postanalytic factors particularly applicable to genetic tests (described later in this paper), as well as the key outcomes of interest. Analytic frameworks should incorporate the factors and outcomes of greatest interest to decisionmakers. Figure 11-1 illustrates a generic analytic framework for evaluating predictive genetic tests. This framework can be modified as necessary for a variety of situations.

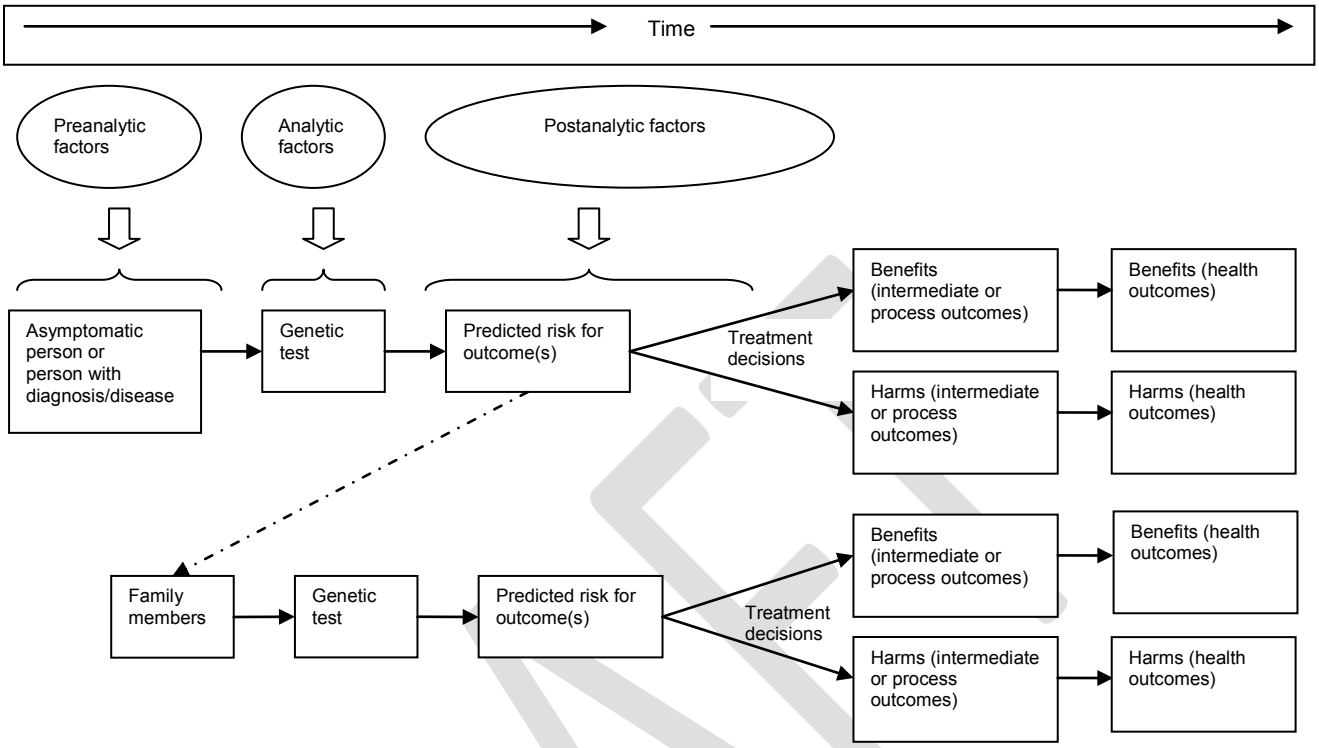
Figure 11-1. Generic analytic framework for evaluating predictive genetic tests



In addition to effects on family members, psychological distress and possible stigmatization or discrimination are potential harms that may result from predictive genetic tests, particularly those test results that predict probability of disease occurring with a high likelihood, especially if no proven preventive or ameliorative measures are available. For these potential harms, analysts should take into account whether the testing is for inherited or acquired genetic mutations/variations since these factors influence the potential for harms. In addition, whether the condition related to the test is multifactorial or follows classic Mendelian inheritance will affect the potential for these harms.

Depending on the context, the impact of genetic testing on family members may be important. One approach to including family members in the analytic framework is illustrated in Figure 11-2.

Figure 11-2. Generic analytic framework for evaluating predictive genetic tests when the impact on family members is important



Principle 3: Search Databases Appropriate for Genetic Tests

The Human Genome Epidemiology Network (HuGE Net) Web site can provide a helpful supplement to searches, as it includes many meta-analyses of genetic association studies as well as a source called the HuGE Navigator that can identify all types of available studies related to a genetic test.[8]

When assessing the gray literature, U.S. Food and Drug Administration (FDA)-approved test package inserts contain data summaries of the analytic validity data that were instrumental in gaining FDA clearance for marketing or approval. Package inserts are available on the FDA and manufacturer Web sites. Laboratory-developed tests do not require FDA clearance, and there is no requirement for publicly available data on analytic validity. When there are no published data on analytic validity of a genetic test, the external proficiency testing program carried out jointly by the American College of Medical Genetics (ACMG) and the College of American Pathologists (CAP) can be useful in establishing the degree of laboratory-to-laboratory variability, as well as some sense of reproducibility.[9-11]

An AHRQ "horizon scan" found two databases—the LexisNexis® database (www.lexisnexis.com) and Cambridge Healthtech Institute (CHI) (www.healthtech.com/)—that had high utility in identifying genetic tests in development for clinical cancer care. A number of others had low-to-moderate utility, and some were not useful.[12]

Principle 4: Consult With Experts To Determine Which Technical Issues Are Important To Address in Assessing Genetic Tests

There are a number of technical issues related to analytic validity that can influence the interpretation of a genetic test result, including preanalytic, analytic, and postanalytic factors.[13-14] In general, preanalytic steps are those involved in obtaining, fixing or preserving, and storing samples prior to staining and analysis. Preanalytic factors relevant to predictive genetic tests may also include a person's age, sex, ethnicity/race or ancestry, parental history of consanguinity, and family health history. Important analytic variables include the type of assay chosen and its reliability, types of samples, the specific analyte investigated (e.g., specification of which alleles, genes, or biochemical analytes were evaluated), specific genotyping methods, timing of sample analysis, and complexity of performing the assay. Postanalytic variables relate to the complexity of interpreting the test result, variability from laboratory to laboratory, and quality control.[13-14] Comparative effectiveness review teams should include or consult with molecular pathologists, geneticists, or others familiar with the issues related to the genetic tests being evaluated to determine which of these technical issues are pertinent for a given review. Table 11-2 summarizes some of the preanalytic, analytic, and postanalytic questions that should be addressed.

Table 11-2. Questions for assessing preanalytic, analytic, and postanalytic factors for evaluating predictive genetic tests*

Element	Questions
Preanalytic	What patient characteristics are relevant to the analytic validity of the test (e.g., age, sex, ethnicity, race, ancestry, parental history of consanguinity, family health history)? What types of samples were used? How were samples obtained? How were samples handled and stored prior to analysis?
Analytic	What type of assay was used? What is the reliability of the assay? What specific analyte was investigated (e.g., specification of which alleles, genes, or biochemical analytes were evaluated)? For DNA-based tests, what is the definition of the genotype investigated? Did the study test for all potentially relevant alleles? For DNA-based tests, what genotyping methods were used? When were samples analyzed (compared to when they were collected)? Was the timing of analysis equal for both study groups (if applicable)? How often does the test give a usable result (what is the "call rate")?
Postanalytic	How are the test results interpreted and applied? How complex is interpretation and application? What quality control measures were used? Were repeated measurements made on specimens? How reproducible is the test over time? How reproducible is the test when repeated in the same patient multiple times? How reproducible is the test from laboratory to laboratory?

*Adapted from Burke et al., 2002[13] and Little et al., 2002.[14]

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Principle 5: Distinguish Between Functional Assays and DNA-based Assays To Determine Important Technical Issues

Some studies may utilize DNA-based assays whereas others may utilize functional assays with different sensitivity and specificity. Functional assays may have the advantage of showing the functional significance of an underlying genetic polymorphism and, thus, may provide more important information. However, they may be affected by a number of factors and do not necessarily reflect the polymorphism alone. Unmeasured environmental factors, other genetic polymorphisms, and various disease states may influence the results of functional assays. In addition, functional assays that measure enzyme activity are taken at a single point in time. Depending on the enzyme and polymorphism being evaluated, the variation in enzyme activity over time should be considered in critical appraisal. Contrasting results between studies using DNA-based molecular methods and those using phenotypic assays have been reported.[14-16]

For DNA-based tests, a variety of sample sources are available (e.g., blood, cheek swab, hair) that should hypothetically result in identical genotype results.[14,17-21] However, DNA may be more difficult to obtain and purify from some tissues than from blood, particularly if the tissues have been fixed in paraffin versus fresh samples (DNA extraction from formalin-fixed tissue is difficult, but sometimes possible).[14] Some studies utilize different sources of DNA for cases and controls, introducing potential measurement bias from differences in the ease of technique and test accuracy. Extraction of DNA from tumors in oncology studies may raise additional issues that influence analytic validity, including the quantity of tissue, admixture of normal and cancerous tissue, amount of necrosis, timing of collection, and storage technique (e.g., fresh frozen, paraffin, formalin).[14]

When evaluating DNA-based molecular tests, the complexity of the test method, laboratory-to-laboratory variability, and quality control should all be assessed. A number of methods are available for genotyping single nucleotide polymorphisms that vary in complexity and potential for polymorphism misclassification.[14,22-24] Considering laboratory reporting of internal controls and repetitive experiments can be useful in assessment of overall analytic validity. The method of interpreting test results may influence complexity as well. For example, some tests require visual inspection of electrophoresis gels. Inter-observer variability should be considered for such tests.[14,25]

Principle 6: Case-control Studies Should Be Carefully Evaluated for Potential Selection Bias

In critical appraisal of any case-control study, it is important to determine whether cases and controls were selected from the same source population. In the case of genetic studies, the geographic location of the population does not suffice. Rather, having cases and controls matched for ethnicity/race or ancestry is important since the frequencies of DNA polymorphisms vary from population to population (i.e., population stratification). It has been noted that many case-control studies of gene-disease associations have selected controls from a population that does not represent the population from which the cases arose.[14-15,26-28] In general, only nested case-control studies could have low enough potential for selection bias to provide reliable information.

Principle 7: Determine Added Value of Genetic Test Over Existing Risk Models

For some scenarios, a number of clinical factors associated with risk assessment or susceptibility may already be well characterized. In such cases, comparative effectiveness reviews should determine the added value of using genetic testing along with known factors compared with using the known factors alone. For example, age, sex, smoking, hypertension, diabetes, and cholesterol are all well-established risk factors for cardiovascular disease. Risk stratification of individuals to determine cholesterol-lowering targets (to a low-density lipoprotein of 160, 130, or 100) is based on these factors.[29] Assessment of newly identified polymorphisms—such as those described on chromosome 9p21[30]—that may confer increased risk of cardiovascular disease and have potential implications for medical interventions should be evaluated in the context of these known risk factors. In this scenario, investigators should determine the added value of testing for polymorphisms of chromosome 9p21 in addition to known clinical risk factors compared with using clinical factors alone.

Principle 8: Studies of Genetic Tests Have Particular Statistical Issues

Hardy-Weinberg equilibrium. Most allele distributions follow a usual distribution, known as Hardy-Weinberg equilibrium (HWE). Genetic association studies should generally report whether the frequencies of the alleles being evaluated follow HWE. There are a number of reasons that distributions may deviate from HWE, including new mutations, selection, migration, genetic drift, and inbreeding.[31] In addition, when numerous polymorphisms are tested for associations with diseases or outcomes, as in many genome-wide association studies, many of them (5 percent) will deviate from HWE based on chance alone (related to multiple testing).[32] Although it is not specific and possibly not sensitive, deviation from HWE may be a clue to bias and genotyping error.[32] Analysts should consider whether studies have tested for and reported HWE. A more detailed discussion of this topic as it relates to genetic association studies has been published elsewhere.[31-32]

Sample size calculations. When assessing the internal validity of studies of genetic tests, it is important to assess whether sample size calculations appropriately accounted for the number of variant alleles and the prevalence of variants in the population of interest. This is particularly relevant for pharmacogenomic studies evaluating the functional relevance of genetic polymorphisms.[33] Such studies often enroll an insufficient number of subjects to account for the number of variant alleles and the prevalence of variants in the population.[33]

Genetic association studies. Genetic test results are sometimes derived from analytically complex studies that have undergone a very large number of statistical tests. These may be in the form of genome-wide association studies searching for associations between a huge number of genetic polymorphisms and health conditions. Such association studies may launch further understanding of the importance of genetics in relation to a variety of health conditions but should generally be considered hypothesis generating rather than hypothesis testing or confirming cause-effect relationships.[14] Close scrutiny should be applied to ensure that the evidence for the association has been validated in multiple studies to minimize both potential confounding and potential publication bias issues. In addition, it should be noted whether

appropriate adjustments for multiple comparisons were used. Many recommend using a P value of less than 5 x 10^{-8} for the threshold of significance in large genome-wide studies.[32,34-35]

When a genetic mutation associated with increased risk is present, evaluating potential causality can be difficult as many other factors may influence associations. These include environmental exposures, behaviors, and other genes. Many genetic variants identified that are thought to influence susceptibility to diseases are associated with low relative and absolute risk.[14,36] Thus, exclusion of non-causal explanations for associations and consideration of potential confounders are central to critical appraisal of such associations. It may also be important to explore biologic plausibility (e.g., from *in vitro* studies) to help support or oppose theories of causation.[14]

Overlapping data sets. Identifying studies for comparative effectiveness reviews may sometimes result in publications regarding prevalence of genetic variants that arose from overlapping data sets.[14] For example, genome-wide association studies or other large collaborative efforts, such as the International Warfarin Pharmacogenomics Consortium, may pool samples of patients that were previously included in other published studies.[2] To the degree possible, investigators should identify overlapping data sets and avoid double-counting. It may be useful to organize evidence tables by study time period and geographic area to identify potential overlapping data sets.[14]

Illustrations

Since the completion of the Human Genome Project, the Hap Map project, and related works, there have been a great number of publications describing the clinical validity of genetic test results (e.g., gene-disease associations), but many fewer studies of the clinical utility of genetic test results. A review of genetic testing for cytochrome P450 polymorphisms in adults with depression treated with selective serotonin reuptake inhibitors (SSRIs) developed an analytic framework and five corresponding key questions which, taken together, provide an example of a well-defined predictive genetic test scenario that explores a potential chain of evidence relating to intermediate outcomes (Figure 11-3).[37] The authors found no prospective studies of the use of genotyping to guide treatment that measured clinical outcomes. They constructed a chain of questions to assess whether sufficient indirect evidence could answer the overarching question by evaluating the links between genotype and metabolism of SSRIs (phenotype), metabolism and SSRI efficacy, and metabolism and adverse drug reactions to SSRIs.

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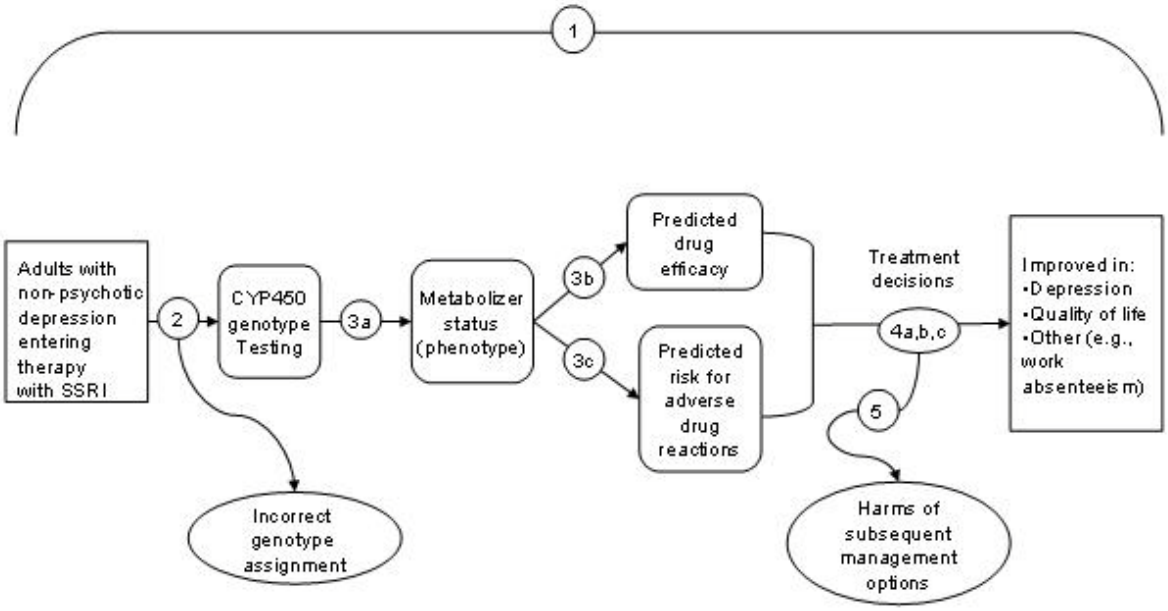
Figure 11-3. Analytic framework for evidence gathering on CYP450 genotyping test for SSRI treatment of depression.[37] Numbers refer to the key questions addressed.



Abbreviation: SSRI = selective serotonin reuptake inhibitor.

An EPC report on HER2 testing to manage patients with breast cancer and other solid tumors provides a detailed assessment of challenges in conducting a definitive evaluation of preanalytic, analytic, and postanalytic factors when there is substantial heterogeneity or lack of available information related to the methods of testing.[38]The authors noted that it had been only very recently that many aspects of HER2 assays were standardized, and that the effects of widely varying testing methods could not be isolated. Thus, they approached this challenge by providing a narrative review for their first key question (KQ1. What is the evidence on concordance and discrepancy rates for methods [e.g., FISH, IHC, etc.] used to analyze HER2 status in breast tumor tissue?).

Additional considerations arise when evaluating genetic test results used to determine susceptibility or risk in asymptomatic individuals. The utility of such tests may depend on the ability of patients and providers to report and identify certain clinical factors. For example, tests for BRCA mutations may be used to predict the risk for breast and ovarian cancer in high-risk women (i.e., those with a family history suggesting increased risk).[3,39] However, because we do not know all of the genes that contribute to hereditary breast and ovarian cancer and because analytic methods to detect mutations in the known genes are not perfect, population-based testing for hereditary susceptibility to breast and ovarian cancer is currently not an appropriate strategy. Rather, family history-based testing is the paradigm that is recommended to guide the use of BRCA testing for hereditary susceptibility to breast and ovarian cancer.[3] Ideally, following this paradigm, genetic testing should begin in an affected family member suspected of having a hereditary susceptibility (due to an early age at onset, multifocal disease, or their position in the pedigree). If a deleterious mutation is identified, then testing of at-risk family members for this familial mutation will be highly informative; if the mutation is identified in family members, the

cancer risk can be better defined and risk-appropriate interventions can be recommended. If a familial mutation is not found, then testing of at-risk relatives is not generally recommended. However, often an affected family member is not available for genetic testing. In these cases, testing of an at-risk relative first is an option, although interpreting results of such testing can be complex, particularly when a pathogenic mutation is not found or when a variant of uncertain significance is identified. In these instances, it is imperative that the test result interpretation and overall cancer risk assessment are considered within the context of an individual's personal and family history risk factors.

Thus, family history is a genetic/genomics tool that is used to (1) identify people with possible inherited disease susceptibilities, (2) guide genetic testing strategies, (3) help interpret genetic test results, and (4) assess disease risk. The ability of providers to accurately determine a family history that confers increased risk is a key prerequisite to the utility of BRCA mutation and other predictive genetic testing. Sensitivity and specificity of self-reported family history are important in determining overall usefulness of predictive genetic testing.[3]

Summary

Key points are:

- The general principles that apply in evaluating genetic tests are similar to those for other prognostic or predictive tests, but there are differences in how the principles need to be applied or the degree to which certain issues are relevant.
- It is important to have a clear definition of the clinical scenario and an analytic framework when evaluating *any* test, including predictive genetic tests.
- Organizing frameworks, such as the ACCE model, and analytic frameworks are useful constructs for approaching the evaluation of genetic tests.
- In constructing an analytic framework for evaluating a genetic test, analysts should consider preanalytic, analytic, and postanalytic factors; such factors are useful when evaluating analytic validity.
- Predictive genetic tests are characterized by a delayed time between testing and clinically important events.
- It may be difficult to find published information on the analytic validity of some genetic tests. Web sites (FDA or diagnostic companies) and gray literature may be important sources.
- In situations where clinical factors associated with risk are well characterized, comparative effectiveness reviews should assess the added value of using genetic testing along with known factors compared with using the known factors alone.
- Analysts should consider whether studies have tested for and reported Hardy-Weinberg equilibrium.
- For genome-wide association studies, reviewers should determine whether the association has been validated in multiple studies to minimize both potential confounding and publication bias. In addition, it should be noted whether appropriate adjustments for multiple comparisons were used.

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