Defining purpose: a key step in genetic test evaluation

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The introduction of new genetic tests, like other medical innovations, can be conceptualized as a three-step process. Tests are proposed for use based on research findings and clinical reasoning; an evaluation occurs; and judgments are made about clinical use and reimbursement (Fig. 1). The evaluation may be informal, as when a clinician determines whether a new test will be helpful in a particular patient encounter, or formal, as when a practice guideline panel utilizes a defined methodology to assess a test or a health care funder utilizes a set of criteria to determine test coverage.

Although genetic tests are often described in terms of technology, a full evaluation requires that the test be considered as a clinical process in which the laboratory assay, or other testing procedure, is done to acquire information about a particular health condition, in a defined population, for a specific clinical purpose.[1] Genetic tests have a wide range of health care applications. They are used to confirm the presence of a genetic condition, identify reproductive risks, and select preventive therapy. Testing occurs in newborn screening programs and in primary, specialty, and prenatal care, and may be initiated on the basis of clinical symptoms, family history, or population demographics. Genetic tests also utilize a range of technologies, and vary considerably in their predictive value. This diversity poses a challenge for the evaluation process.

Several groups have considered methods for genetic test evaluation,[2–5] and model programs for systematic evaluation have been established in the United States (Evaluation of Genomic Applications in Practice and Prevention[6]) and the UK (the UK Genetic Testing Network[7]). To date, however, the evaluation process has not fully addressed the clinical diversity of genetic tests. The Evaluation of Genomic Applications in Practice and Prevention project has focused on genetic tests related to common disorders and drug therapy, whereas the United Kingdom Genetic Testing Network has primarily addressed tests for single gene disorders.

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Disclosure: The authors declare no conflict of interest.

Submitted for publication April 25, 2007.

Accepted for publication July 6, 2007.

DOI: 10.1097/GIM.0b013e318156e45b

An effort by the Secretary's Advisory Committee on Genetic Testing to categorize genetic tests into those requiring higher versus lower levels of scrutiny was not successful.[8]

To address the challenge of genetic test diversity, we propose an outcome-orientated taxonomy for defining test purpose. A focus on health outcomes allows the definition of a small and informative set of purposes for genetic testing, despite the range of technologies and clinical settings in which testing occurs. Defining test purpose in turn clarifies the benefits to be expected from the testing process, and provides guidance to clinicians and policy makers concerning the evidence needed to support test use. Defining test purpose, therefore, is an important first step in genetic test evaluation.

Essential differences in genetic test purpose

From the perspective of clinical outcomes, genetic tests have one or more of the following three purposes:

1. Reduction in morbidity or mortality of the person tested
2. Provision of information relevant to the health of the person tested
3. Assistance in reproductive decision-making

Family-based genetic testing is often recommended after a genetic diagnosis is made, and could be construed as an additional purpose for testing. For example, female relatives are offered testing after a *BRCA* mutation has been detected in the family, to identify affected relatives who might benefit from preventive measures. Testing may also be offered to family members after certain genetic diagnoses, such as Duchenne muscular dystrophy, to assist reproductive decision-making. As these examples illustrate, family-based detection does not represent an independent reason of genetic testing, but rather enables achievement of one of the essential testing purposes.

Different considerations arise in evaluating tests for each of the three purposes (Table 1). For tests intended to reduce morbidity or mortality, an effective intervention is needed, ideally supported by controlled studies demonstrating an improved health outcome in test-positive individuals who receive the intervention. For tests in which information is the endpoint—for example, tests done to provide a diagnosis or prognosis for conditions lacking effective treatment—evidence is needed concerning the predictive value of test results and the value of the results to patients and health care providers. When the information is used in reproductive decision-making, there is an additional focus on societal norms related to the use of services such as selective abortion and preimplantation genetic diagnosis (PGD).

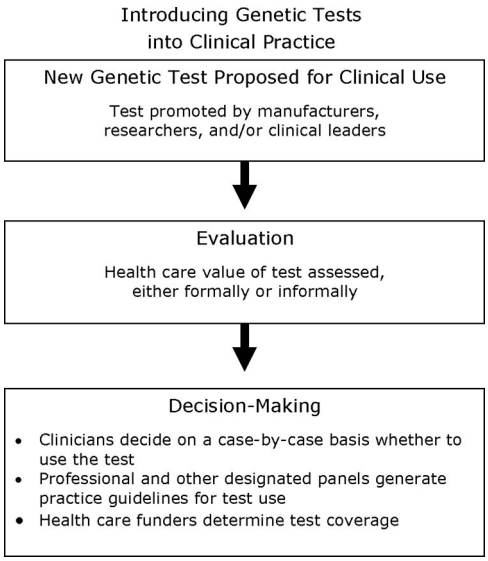

Fig. 1. Genetic tests, like other medical innovations, are introduced into health care in a three-step process.

Testing to reduce morbidity or mortality

Reducing morbidity and mortality is the central task of health care; any genetic test that is proposed for this purpose has an a priori claim to be considered for clinical use. Cogent examples of tests in current use include newborn screening for phenylketonuria (PKU), to identify infants who will benefit from a phenylalanine-restricted diet to prevent mental retardation[9]; *RET* mutation testing, to identify persons with multiple endocrine neoplasia type 2 (MEN 2) who will benefit from prophylactic thyroidectomy to prevent cancer and monitoring for pheochromocytoma and hyperparathyroidism[10]; and family-based testing after a mutation associated with hereditary nonpolyposis colon cancer (HNPCC) has been identified in a patient with cancer, to identify family members who will benefit from early and aggressive colon cancer screening.[11]

As the examples demonstrate, reducing morbidity or mortality requires an effective intervention for those with a positive test result. Therefore, when a genetic test is proposed for the purpose of reducing morbidity or mortality, two questions must be answered: (1) Is there an effective and acceptable intervention? and (2) Does the use of the genetic test in a specified population enable health care providers to determine the appropriate use of the intervention?

The answer to these questions is clearly yes for PKU, MEN 2, and HNPCC. The unique diet required by children with PKU prevents mental retardation, and the testing protocol allows accurate identification of children at risk. Although the interventions are less specific for MEN 2 and HNPCC, the genetic test result provides the information needed for appropriate use of these interventions. In HNPCC, for example, the primary intervention is colonoscopy, which is widely used in the general population for colon cancer screening. For people with HNPCC, however, screening is initiated at a much earlier age (20–21 years vs. 50 years) and is repeated more frequently (1–2 years vs. 10 years), based on data that document a high colon cancer risk, early onset of colon cancer and a short polyp dwell time,[11] and reduced mortality with this colonosocopy screening protocol.[12]

These examples represent genetic conditions with high penetrance, resulting in a high positive predictive value for the test. Genetic tests with lower predictive value may also be used to reduce morbidity and mortality. For example, it is estimated that only 20%–25% of infants who screen positive for medium chain acyl-CoA dehydrogenase deficiency (MCADD) would suffer serious disability or premature death if untreated, but

Table 1
Purpose as a guide to test evaluation

	Reduce morbidity and mortality	Provide information relevant to the health of the person tested	Assist reproductive decision-making
Unique components of evaluation	Define: Intervention(s) to be offered to test positive individuals Health outcomes to be improved by intervention	Define: Relevance of information to health care or quality of life, in absence of definitive treatment	Define: Reproductive actions that can be taken as a result of test information
	Determine: Efficacy of intervention(s) for achieving desired outcomes Costs and risks of intervention(s)	Determine: Value of information to patients and clinicians, in absence of definitive treatment	Determine: Patient preferences regarding use of genetic tests and associated reproductive actions Relevant laws, regulatory processes and societal norms
Shared components of evaluation	Define: Population to be tested Disorder for which testing is done Laboratory assay or other technology to be used		
	Determine: Reliability of assay Sensitivity, specificity and positive and negative predictive value of test for disorder in question Acceptability of testing process to patients and clinicians		

simple dietary measures that are safe for all individuals with MCADD can prevent these adverse outcomes.[13] Pharmacogenetic tests with limited predictive value may also have clinical utility. Observational data suggest that certain variants of the *CYP2C9* and *VKORC1* genes account for 10% and 35%, respectively of the individual variation in response to the anticoagulant warfarin.[14] A test for these variants will identify individuals who require lower doses of warfarin or are at increased risk for bleeding complications,[14,15] and has the potential to improve the safety of warfarin therapy.

What evidence is needed to evaluate genetic tests used to reduce morbidity and mortality? The most definitive assessment of the test and associated interventions is a randomized clinical trial. Under some conditions, this kind of evidence may not be considered necessary to establish the value of a genetic test. An example is the use of prophylactic thyroidectomy for individuals with *RET* mutations, an intervention that was instituted based on observational data and historical controls.[10] In this case, several factors provided justification for testing: family studies indicated high penetrance of *RET* mutations, the primary intervention for test-positive individuals (thyroidectomy) was sufficiently well characterized to define safe use, and pathophysiological reasoning suggested substantial benefit.

For most genetic tests, however, and in particular for those assessing pharmacogenetic and common disease susceptibilities, a more stringent evaluation is needed. For example, the effectiveness of *CYP2C9* and *VKORC1* testing before warfarin therapy is difficult to ascertain without studies comparing outcomes of genetic testing protocols to the accepted practice of cautious warfarin dosing. A rigorous assessment is particularly important when the risk is moderate and the intervention is already in common use. For example, several gene variants identify people with moderately increased risk for cardiovascular diseases or diabetes.[16–19] Preventive care for such individuals includes counseling regarding diet, avoidance of smoking, and exercise—all measures recommended for the public at large. Although people with increased risk may derive greater benefit, a genetic test result is not necessary to select a prevention program that will reduce morbidity or mortality, in contrast to the PKU, MEN 2, and HNPCC examples. Therefore, before the test can be considered for clinical use, a careful evaluation of the outcomes of testing is needed: does the test, in fact, achieve its purpose of reducing risk, either by motivating increased compliance with lifestyle changes, or serving as a cost-effective means to identify candidates for resource-intensive case management? The evaluation also needs to consider potential harms of testing, such as stigma or psychological distress for people with positive results or false reassurance for those with negative results.

Health information as the primary endpoint of testing

Although most health care is focused on reducing morbidity and mortality, genetic tests are frequently used in circumstances where definitive treatment is lacking. For example, a diagnosis of Duchenne muscular dystrophy provides meaningful prognostic information, but treatment is supportive, with a limited effect on the natural history of the disorder.[20] Similarly, vision loss in the retinal dystrophies cannot be prevented or delayed, but a diagnosis can provide important information that may inform personal decisions such as educational or career plans.[21] In these instances, genetic testing and subsequent interventions do not reduce impairment significantly, and appropriate care could have been provided based on medical signs and symptoms. However, the genetic diagnosis resolves uncertainty, and by defining expectations and allowing planning, may reduce the psychological or social burden of the genetic disorder.

In considering tests for this purpose, the greatest difficulty lies in the subjective nature of the benefits. Generally, the most persuasive examples involve tests that are highly predictive for well-defined and serious health problems, like Duchenne muscular dystrophy and retinal dystrophy. However, many tests may be perceived as beneficial by some, even when they are not endorsed by experts. For example, three expert panels have recommended against the use of ApoE genotyping to predict Alzheimer disease risk, on the grounds of poor predictive value and lack of preventive treatment,[22–24] but some individuals value this information.[25] Therefore, when the purpose of a genetic test is primarily to provide health information, three questions arise: (1) Is the health condition or risk important? (2) Does the genetic test provide reliable information? and (3) How should a health care system decide whether or not to include the test as a covered health care service?

In some cases, health care efficiencies justify the test. An accurate prognosis may allow more focused care. In addition, after a genetic diagnosis has been made, a negative test result in an at-risk family member removes the need for follow-up or concern related to the genetic risk. Identification of a genetic diagnosis may also simplify care by ruling out other considerations. For example, a diagnosis of Gilbert disease explains episodic elevations of bilirubin and allows the patient to avoid work-up for more worrisome hepatic disorders.[26]

However, the benefits of genetic information are often focused on personal and social concerns. In an interview study, parents of disabled children diagnosed with specific genetic conditions identified several benefits of the diagnosis, including relief of parental guilt, resolution of uncertainty, a clearer understanding of the child's future needs, the potential to contact others in the same situation for mutual support, and in some cases help justifying social and medical services.[27] A genetic diagnosis can explain a rare, unexpected or painful event—such as a child who is disabled and blind, or a fatal cancer in a young adult—and both clinicians and families often welcome such explanations.

The evaluation of genetic tests in this context raises questions of values and perspective. A test might be perceived to be of limited value from a population perspective, yet might produce important benefits for a patient or health care provider, by reducing uncertainty about the patient's health status. Descriptive and qualitative studies can help to evaluate these benefits by documenting the experience of tested individuals and

their families. Ultimately, however, health care systems need to consider the appropriate deliberative processes for determining which tests to offer. In systems based on equity and accountability, coverage decisions should seek a fair distribution of benefits, based on clearly stated rationales that takes into account the perspectives of different stakeholders.[28]

Testing to assist reproductive decision-making

When genetic tests are used to inform reproductive decision-making, they raise broader questions about test use. This category includes tests to identify carriers for autosomal and X-linked recessive disorders, prenatal tests to screen for or diagnose genetic disorders in the fetus, and genetic tests used in assisted reproduction to determine whether an embryo has a genotype associated with disease.

Carrier and prenatal testing are offered to families after the diagnosis of a child with a severe genetic disorder, such as Duchenne muscular dystrophy. Usually, testing is offered to provide the choice of termination in future pregnancies. Some families wish to pursue prenatal diagnosis to prepare for the birth of a child with a genetic disorder. In addition, certain carrier and prenatal tests are offered routinely to pregnant women, such as prenatal tests to identify an increased risk of trisomy 21[29] and carrier testing among populations with an increased prevalence of certain autosomal recessive diseases, such Tay-Sach disease in Ashkenazi Jewish populations[30] and β-thalassemia in Mediterranean communities.[31]

When a genetic test is proposed to assist reproductive decision-making, the key questions include both test performance and the social implications of testing: (1) Does the genetic test provide reliable information about a health condition in a future child? (2) What technologies or interventions are available to reduce the likelihood of having a child with a genetic disorder? and (3) What uses of testing and technology are consistent with the laws and values of the society?

The acceptability of prenatal diagnosis and selective pregnancy termination varies widely among societies, and also among individuals within a given society. In recognition of the role of personal values in reproductive decision-making, carrier and prenatal genetic testing are generally offered in the context of counseling services and education to support individual choice.[32] Whether current practice adequately supports reproductive autonomy has been a matter of concern: some critics suggest that the routine offer of prenatal testing may subtly direct choice[33] or devalue the lives of disabled persons.[34] These debates underscore the societal interest in assuring the appropriate use of reproductive genetic testing.

The option of PGD adds further complexity. PGD involves testing embryos created through in vitro fertilization, to avoid implantation of embryos with genetic disease.[35] For some couples, selection of an embryo for its genetic characteristics is morally preferable to selective pregnancy termination. The threshold for test use appears to be more permissive for PGD than for selective abortion; for example, PGD has been offered to avoid births of children with genetic susceptibility to adult-onset cancers and for sex selection.[36,37]

With a growing number of tests potentially available for use in reproductive decision-making, policy makers need robust procedures for developing consensus on the tests and reproductive technologies to be offered within a health care system. Practice standards for prenatal genetic testing are currently determined by professional consensus, whereas PGD is subject to statutory regulation in most developed countries (although not in the United States). This oversight signals an increasing level of societal concern as the scope of reproductive technology increases.

Diagnostic and predictive genetic tests

Certain terms are commonly employed to capture the clinical goals of genetic testing. A genetic test is termed *diagnostic* if it is used to identify the cause of a health problem, and *predictive* if it provides information about a future health risk. Among predictive genetic tests, a distinction is often made between presymptomatic and susceptibility tests: in this distinction, the test for Huntington disease is considered presymptomatic because it identifies a genotype with high penetrance and thus predicts a certainty or near certainty of future disease.[38] A susceptibility test, by contrast, identifies only an increased probability of future disease. The level of risk varies: a person with an HNPCC-associated mutation has about an 80% lifetime risk of developing colon cancer,[11] whereas a person with factor V Leiden has a 10%–20% lifetime risk of developing a venous thrombosis.[39]

These terms provide information about genetic test purpose but they are less precise than the outcome-oriented set of purposes we propose here. In fact, terms like diagnostic and predictive do not get to the heart of why a particular genetic test is undertaken. A test result, whether for diagnosis or prediction, could be used for any of the essential test purposes: to reduce morbidity or mortality, provide health information about the person tested, or assist in reproductive decision-making (Table 2).

Screening refers to predictive testing done on the entire population, or in some subset of the population in which risk might be increased. Populations to be tested are usually defined demographically, as in newborn screening. The test is not initiated by a patient seeking advice to alleviate anxiety or to solve a problem, but by the health care system or the state, based on a determination of the groups who might benefit from the information provided by screening. Genetic screening is used both to reduce morbidity and mortality, as in newborn screening, and to aid reproductive decision-making, as in carrier screening.

Multiple purposes

For many genetic tests, the purpose is straightforward. Tests related to cancer susceptibility are done to reduce cancer-related morbidity and mortality, through screening or other risk-reducing measures. Pharmacogenetic tests are also done to reduce morbidity and mortality, by preventing adverse drug reactions and allowing the selection of drug therapies that maximize benefit. Categorizing these tests according to purpose helps to clarify the evaluation process: in each of these examples, evidence is needed for the effectiveness of the spe-

Table 2
Use of genetic diagnostic, predictive, and screening tests to achieve different test purposes

Test purpose	Diagnostic	Predictive tests		Screening
		Presymptomatic	Susceptibility	
Reduce morbidity/mortality	Testing for acute intermittent porphyria	*RET* mutation testing to identify MEN 2 in unaffected family member	Testing for known *MSH2* mutation in unaffected family member	Newborn screening for phenylketonuria
Provide information relevant to health of person tested (in absence of definitive treatment)[a]	Testing for retinitis pigementosa	Testing for Huntington disease	Testing for APOE genotypes associated with Alzheimer disease	[a]
Assist reproductive decision-making[b]	Prenatal cytogenetic testing to detect trisomy 21 Prenatal molecular testing to detect Huntington disease		[b]	Tay-Sach carrier testing

[a]Accepted guidelines for screening programs argue against screening when medical interventions are not available.[40]
[b]Diagnostic and presymptomatic tests are not distinguishable when testing is prenatal. Cancer susceptibility testing has been reported with preimplantation genetic testing,[36] but current norms argue against the use of selective abortion to prevent birth of children with genetic susceptibilities.

cific changes in clinical management that are based on test results.

The process of specifying purpose may have added value for tests with multiple clinical purposes. A test for Huntington disease can be used to provide health information in the person tested or for reproductive decision-making; a test for cystic fibrosis can direct clinical management or identify a carrier. Each purpose represents a separate potential claim for clinical utility. In considering the use of a given genetic test, policy makers need to identify all the potential purposes and ensure an appropriate evaluation of each.

This process is particularly important when the test purpose is not immediately apparent. Two hypothetical examples illustrate this point (Table 3). The first is a test to identify susceptibility to age-related macular degeneration, a possibility based on current research.[41,42] The test might be done to reduce incidence or morbidity of the condition. However, justification of testing for this purpose would require preventive or genetically tailored treatments that do not currently exist (Table 3). In the absence of such interventions, the test could be contemplated as a source of information; patients might value such information about future risk to vision. For this purpose, the focus of evaluation would be on patient preferences and quality of life associated with testing.

The second example is a hypothetical test for a panel of mutations associated with mental retardation. The test could be done in a child with developmental delay, for prognosis and to avoid unnecessary work-up; it could also be considered as a test for prenatal diagnosis (Table 3). Given current norms for the use of prenatal tests, a higher predictive value would likely be required for prenatal use than for testing in a symptomatic child.

Priority-setting

A consideration of test purpose can also assist health care funders in setting priorities for coverage of services. In general, tests that reduce morbidity and mortality are likely to be accorded a higher priority for funding than tests for which information is the primary endpoint. For example, the hypothetical test to identify risk for age-related macular degeneration (Table 3) is likely to be accorded a higher priority if prevention measures are available than if the test is done primarily to provide information. Other considerations arise in priority setting, including the value of the test to patients and health care providers. A test that results in a modest reduction in morbidity may be given less priority than a test that identifies a severe untreatable disease, particularly if the disease has previously been difficult to diagnose.

Efficiency and cost are also important considerations: to what extent does the use of the test improve outcomes or reduce costs compared with what is achievable by the current standard of care? The answer may differ depending on how the genetic test is integrated into health care, that is, as a replacement for an existing risk assessment, as a triage test used to select patients for an existing test or treatment pathway, or as an added test. In the latter case the relevant factor will be the marginal added benefit over the marginal added cost.[43] Efficiency measures, such as number needed to test to prevent one adverse outcome,[44] and cost-effectiveness analyses[45] also provide important information for the priority-setting process.

Priorities may differ according to perspective. For example, a test for polymorphisms in the hypothetical gene *BALD1* might identify individuals with a high likelihood of developing male pattern baldness, who could benefit from topical minoxidil therapy. From a health systems perspective, this test is likely to be accorded a low priority for funding when compared with a test to predict Huntington disease, even though the latter is untreatable. Treatment of baldness would likely be viewed as cosmetic therapy, with a poor claim on health care funding, whereas Huntington disease is a condition of serious medical consequence. However, consumers might prioritize these services differently, arguing that the test for *BALD1* mutations (and associated minoxidil therapy) could provide a tangible

Table 3
Use of test purpose to guide initial evaluation process

Example 1: Test for gene variants associated with age-related macular degeneration
Purpose A: To reduce morbidity and mortality of age-related macular degeneration
Evidence needed
Predictive value of test in population to be tested
Interventions for test positive individuals resulting in reduced incidence or severity of macular degeneration
Evidence that negative tests results do not reduce compliance with recommended routine eye examinations or prevention measures (e.g., smoking cessation)
Purpose B: To provide individuals with salient health information for purposes of psychological preparation or reassurance
Evidence needed
Predictive value of test in population to be tested
Interest in information provided by test among patients and clinicians
Improved quality of life associated with test results
Evidence that negative tests results do not reduce compliance with recommended routine eye examinations or prevention measures (e.g., smoking cessation)
Example 2: Test for genotype associated with moderate mental retardation
Purpose A: To provide prognostic information for a child with developmental delay
Evidence needed
Predictive value of test in population to be tested
Interest in information provided by test among patients and clinicians
Improved quality of life associated with test results
Evidence that negative tests results do not result in false reassurance
Purpose B: To provide information for reproductive decision-making
Evidence needed
Predictive value of test in population to be tested
Evidence that the use of the test for selective abortion or embryo selection is consistent with societal norms for reproductive genetics

benefit to many individuals at a relatively low cost, whereas Huntington disease is a rare disease and presymptomatic diagnosis of unclear benefit.

CONCLUSIONS

Genetic tests are used in a variety of clinical settings, and incorporate a wide range of measurements. However, all genetic tests are done for one or more of three essential purposes: to reduce morbidity and mortality, provide important information about the health of the person tested in the absence of definitive treatment, or assist reproductive decision-making.

Defining test purpose is necessary to determine the benefits expected from testing, and is a logical first step in evaluating the clinical utility of a test. Arguably, a test should be shown to achieve its intended purpose before it is considered for clinical use. If the test is done to reduce morbidity or mortality, evidence is needed for improved health outcomes after testing and the associated interventions, compared with current care. Judgments about the benefits of tests that provide health information or assist in reproductive decision-making may be more subjective, and require deliberation about the appropriate uses of genetic information in the delivery of health care.

Defining a test as diagnostic or predictive, or appropriate for a screening program, helps to determine the populations to be tested and the clinical circumstances under which testing will occur. However, these terms provide insufficient information to define intended benefit of testing. By contrast, a statement of test purpose informs policy makers about the goals of the testing process, providing the necessary context for the evaluation process and subsequent priority setting.

ACKNOWLEDGMENTS

Supported in part by a UK National Health Service International Fellowship and by the Center for Genomics and Healthcare Equality (NIH Grant P50HG003374). This work was based in part on a report submitted to the United Kingdom Genetic Testing Network entitled, "Moving Beyond ACCE: An Expanded Framework for Genetic Test Evaluation by Wylie Burke and Ron Zimmern" (September 2007).

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