Managed Care in the Genomics Era: Assessing the Cost Effectiveness of Genetic Tests

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Background: Despite the fact that the Human Genome Project was completed only recently, genetic tests already have entered the marketplace, some with few or no long-term data to support their use. Managed care organizations will face reimbursement decisions for genetic tests on a growing scale, and they should have a framework in place to evaluate the clinical and economic outcomes of this new class of diagnostics.

Objective: To develop a set of criteria that could assist decision makers in evaluating the cost effectiveness of genetic testing.

Methods: A literature review was conducted of marketed genetic tests and criteria used to evaluate the clinical and economic benefits of genetic testing. Criteria were developed and pilot-tested on currently available genetic tests in colon cancer, periodontitis, acute lymphoblastic leukemia, and anticoagulation.

Results: A robust cost-effectiveness analysis requires data demonstrating (1) genotype-phenotype association; (2) genetic variant prevalence; (3) clinical outcome severity and incidence; (4) interventions for the variant group; and (5) sensitivity, specificity, and timing of the assay result. In addition, calculating the number of patients who need to be screened based on the above factors is useful for evaluating genetic tests.

Conclusions: When evaluating a genetic test for reimbursement, these criteria can help to: (1) quantify the potential clinical benefit and economic savings ; (2) assess the robustness of a cost-effectiveness analysis; and (3) clarify areas where data are deficient. These criteria should be used to inform the decision-making process in the context of ethical, legal, and social issues related to genetic testing.

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With the completion of the Human Genome Project, researchers are seeking ways to translate genetic information into clinical applications. Understanding how genes relate to human diseases and drug therapies will require further extensive research. However, some genetic tests already have entered the marketplace, with few or no long-term clinical data to support their use. Managed care organizations (MCO's) will face reimbursement decisions for genetic tests on a growing scale. Therefore, it is imperative that MCOs have a framework in place to evaluate the clinical and economic benefits of this new class of diagnostics.

The application of gene sequencing technology to human health falls under 2 broad categories: disease risk and pharmacogenomics (**Figure**). The field of disease-risk testing seeks to understand the genetic basis of disease processes, thereby creating opportunities to develop genetic tests and new therapeutics that will identify individuals predisposed toward certain diseases, and to identify markers for risk of future disease, thereby enabling the use of preventive interventions. The field of pharmacogenomics seeks to understand how genetic diversity can explain variation in drug response observed in patient populations. The ultimate goal of pharmacogenomics is to tailor drug therapy to appropriate subpopulations, thereby minimizing the risk of adverse effects and increasing effectiveness.[1] Both disease-risk and pharmacogenomic genetic tests currently available include tests for hereditary colon cancer, periodontitis, and breast cancer; and examples of pharmacogenomic applications include testing for warfarin and 6-mercaptopurine slow metabolizers.

To make informed decisions regarding reimbursement for any drug or diagnostic, managed care medical and pharmacy directors need evidence of clinical efficacy and economic value.[2] Many MCOs use a drug formulary to guide appropriate drug utilization. When clinical outcomes are the primary consideration, the formulary can be an effective management tool with good acceptance by the provider community.[3] Formulary commit-

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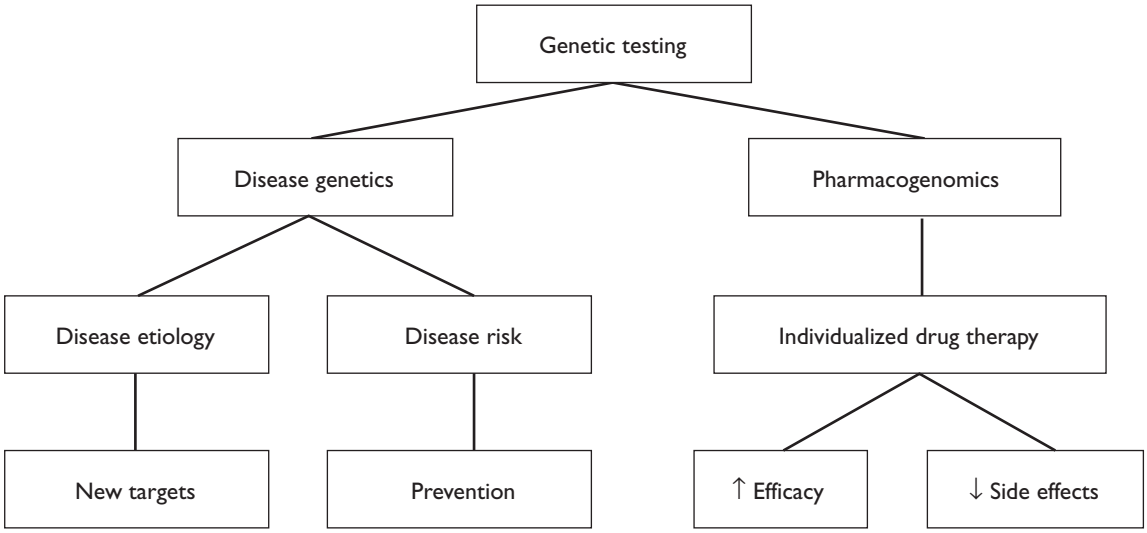
Figure. Categories of Genetic Testing



Note that "prevention" refers to medical care interventions or lifestyle changes designed to lower a patient's risk of disease.

tees utilize cost-effectiveness information to quantify the incremental improvement in clinical and economic benefits that a new treatment provides compared with the standard of care. Use of cost-effectiveness studies has increased in the past decade in an effort to contain healthcare costs and deliver the greatest healthcare value. The United States Panel on Cost Effectiveness in Health and Medicine has provided general recommendations for performing such studies.[4,5] Similar recommendations are in place in other countries,[6,7] and the Academy of Managed Care Pharmacy has recently adopted guidelines for submitting dossiers with clinical and economic data in the US managed care market.[2,3] The challenge for decision makers will be to ensure that there is sufficient evidence of clinical and economic benefit for genomic technologies.

Requirements for reimbursement of genetic tests should be no less stringent than those governing the reimbursement of pharmaceuticals and other diagnostics. This is particularly true because genetic tests can be expensive, and misinterpreting their results could lead to unwarranted medical care, exposing the patient to unnecessary risk and the MCO to additional costs. In this article, we propose a set of criteria that can assist decision makers in evaluating the cost effectiveness of genetic testing.

Previously, we defined a cost-effectiveness framework to help evaluate pharmacogenomic-based technologies.[8] The purpose of the current article is to expand this framework to include disease-risk genetic testing.

METHODS

We conducted a review of published articles that presented criteria for evaluating disease-risk genetic tests.[9,10] To provide a framework for the development of the current criteria, we supplemented this body of literature with our previous analysis of pharmacogenomic testing. We developed a draft set of criteria based on these studies and evaluated their comprehensiveness by applying them to genetic tests that shared the following characteristics: (1) a body of literature had established an association between a genetic variant and a clinical outcome; (2) there was a proposed intervention to reduce risk in the genetic variant groups; and (3) reimbursement was being sought from payers. A final set of criteria was developed based on this evaluation.

RESULTS

Five genetic tests matched our criteria for review: hereditary nonpolyposis colorectal cancer for colon cancer, interleukin-1 (IL-1) for periodontal disease, BRrCA1/2 for breast cancer, CYP2C9 for warfarin therapy, and thiopurine *S*-methyltransferase for 6-mercaptopurine therapy (**Table 1**). We identified 5 key criteria for evaluating the cost effectiveness of genetic tests based on the above examples: genotype–phenotype association, genetic variant prevalence, clinical outcome characteristics, inter-

Table 1. Examples of Marketed Genetic Tests and Their Potential for Sound Economic Evaluation

Gene	Target Population	Gene-Clinical Outcome Association	Prevalence of Genetic Variants	Clinical Outcome	Improvement Over Current Practicee	Test Availability and Approximate Cost
Pathogenomics						
Mismatch repair genes (MMR)	Patients with family history of colon cancer	Established through prospective cohort studies	1.0%-5.0% of all colorectal cancers in Caucasian populations*	Prediction of risk for colon cancer (HNPCC)†	Improvement over standard flexible sigmoidoscopy screening	Available from multiple testing facilities: cost includes patient counselling $1300-$3600
Interleukin-1 (IL-1)	Patients with mild periodontitis	Established through a case-control and retrospective cohort study	25%-35% in Caucasian populations‡	Prediction of risk for severe periodontitis§	May increase compliance with regular dental therapy and oral hygiene	Interleukin Genetics, Inc $200
BRCA1	Women from families with both breast and ovarian cancer, or at least 4 cases of breast cancer (any age)	Established through case-control studies	3.3% in Caucasian women with breast cancer‖	Prediction of risk for breast cancer	More frequent clinical screening by physical breast examination	Myriad Genetic Laboratories, Inc $2760
Pharmacogenomics						
CYP2C9	Patients receiving warfarin	Retrospective cohort studies	25%-35% in Caucasian populations¶	Avoidance of major bleeding events#	May allow for more accurate dosing in slow-metabolizing patients	Genelex $135
Thiopurine *S*-methyl-transferase (TPMT)	Children receiving 6-mercaptopurine for treatment of acute lympho-blastic leukemia	Established through retrospective and prospective cohort studies	0.3%-1.0% in Caucasian populations**	Reduced hematopoietic toxicity**	Improvement over empirical methods of dose adjustment	DNA Sciences, Inc $395

*Ponz de Leon 1996.[11]
†Ramsey et al 2001.[12]
‡Kornman et al 1997.[13]
§Greenstein and Hart, 2002.[14]
‖Newman et al 1998.[15]
¶Sullivan-Klose et al 1996.[16]
#Higashi et al 2002.[17]
**Krynetski and Evans 1999.[18]

vention for patients with the variant genotype, and assay characteristics (**Table 2**).

Genotype–Phenotype Association

The genetic test should be supported by a body of literature that establishes an association between the variant gene and a clinically relevant outcome (phenotype).[19] The genotype-phenotype association can be expressed as a relative risk (RR) or an odds ratio. For example, patients with a certain variant gene might have a 50% higher lifetime risk of developing cancer; the RR of cancer for that mutation is thus 1.5. The strength of the association between genotype and phenotype also is measured by the positive predictive value (PPV) and can be calculated based on the RR, incidence of disease, and prevalence of the variant genotype.[9] For a variant

genotype with an RR of 1.5, a disease incidence of 5% (0.05), and a variant genotype prevalence of 30%, the PPV would be:

$$[1.5(0.05) \times 100] \div [0.30(1.5 - 1) + 1] = 6.5\%.$$

Therefore, there is a 6.5% probability that the disease will develop in a person with a positive test result (the PPV). The PPV is approximately equal to the penetrance of the disease.[9]

Ideally, the genotype–phenotype association should be established through a prospective study design, where the genetic sample is obtained at study onset. A prospective study design minimizes the effect of selection bias, especially if the variant gene is associated with survival or the likelihood of seeking treatment. However, most evaluations of genetic markers to date have relied on retrospective cohort or case-control study designs because of the practical constraints of evaluating associations between rare genetic markers or rare phenotypic events. Such studies should be carefully evaluated for selection bias. For example, how many patients were not included in the cohort because they were lost to follow-up?

The association between genotype and phenotype can be complicated by environmental interactions. For example, having the IL-1 composite genotype may be a risk factor for periodontitis (RR = 2.7, prevalence = 30%), but smoking also is a risk factor.[13] Furthermore, the interaction of smoking and the IL-1 genotype may modify the risk of periodontitis, so that patients who have the IL-1 genotype *and* smoke will have a substantially higher risk (RR = 7.7)[20] A proper economic analysis accounts for high-risk subpopulations that bear both the genetic variant and an environmental risk factor by demonstrating: (1) the risk associated with the environmental factor; (2) the prevalence of the environmental factor in the genetic variant group, and (3) any interaction effect between the environmental factor and the gene variant.

Genetic Variant Prevalence

The cost effectiveness of genetic testing is highly dependent upon the prevalence of the target genetic variation. For example, if the frequency of a variant genotype is 0.5%, then only 1 patient with that variant allele would be detected for every 200 patients tested, on average. Thus, testing for variant genotypes that occur infrequently will be cost effective only in instances when the clinical and economic benefits of identifying patients with variant alleles are significant.[8] Mismatch repair genes (MLH1 and MSH2) are risk indicators for a hereditary form of colon cancer,[21,22] but are implicated in less than 5% of the colorectal cancer burden.[11,23] Similarly, the BRCA1 mutation, a risk factor for breast cancer, may have a prevalence of less than 3% in US women diagnosed with this disease.[15] An MCO must therefore scrutinize the value of genetic testing in the context of the total burden of disease.

The prevalence of the genetic variant may be dependent on the racial and ethnic make-up of the population, and an evidence-based analysis should include citations detailing prevalence estimates in different populations. For example, P-450 gene CYP2C9, which metabolizes warfarin, contains two 2 polymorphisms

Table 2. Criteria for Assessing the Cost Effectiveness of Genetic Tests

Factors	Characteristics Favoring Sound Economic Evaluation
Genotype–phenotype association	Strong association between gene variant and clinically relevant outcomes.
Genetic variant prevalence	Variant allele prevalence is high enough to warrant testing. Prevalence in racial subgroups is specified.
Clinical outcome characteristics	Genetic testing results in improved clinical outcome measured as a significant impact on quality of life, mortality, or expensive medical care costs. The severity and incidence of the outcome are specified.
Intervention for the variant group	The incremental use of genetic testing (vs standard care) provides a significant reduction in the overall event rate as measured by the attributable risk reduction.
Assay characteristics	A rapid, reliable, and relatively inexpensive assay is available. Sensitivity, specificity, and all costs associated with the assay have been identified.

(2C9*2 and *3) that have been well characterized in Caucasians; however, the 2C9*2 allele has not been found in Asians,[16,24,25,27] and the prevalence of both alleles are is considerably lower in Africans.[16,26] Cost-effectiveness models should reflect the racial distribution of the MCO's patient population.

Clinical Outcome Characteristics

The severity of the clinical outcome (phenotype) for which the genotype is a risk factor should be considered. The outcomes of tooth loss, major bleeding, and hematopoietic mortality carry widely disparate cost consequences, yet reimbursement in the range of $135 to $395 is sought for genetic testing for all these conditions (Table 1). Drugs that have a narrow therapeutic index, cause severe or expensive adverse side effects, and have significant interpatient variability are more likely to be associated with a severe outcome and, thus, are better candidates for pharmacogenomic testing.[8,28]

The incidence of the phenotype also is critical and should be specified in the population to be tested. The true measure of a test's performance is its ability to reduce the overall event rate as measured by the attributable risk reduction. For example, if the baseline rate is very low (eg, 1 in 100 000), even a gene that confers a 10-fold greater risk would imply an event rate of 1 in 10 000 for patients who test positive. It would be difficult for any testing scenario to achieve cost offsets by reducing an event rate that is already considered rare.

Intervention for Patients With the Variant Genotype

A clinician should be able to recommend a proven-effective intervention for a patient who tests positive. For example, with disease-risk tests, prophylactic therapy (pharmacologic intervention, surgical intervention, or lifestyle modifications) could be shown to prevent or delay disease onset. If the RR reduction that can be achieved by an intervention is known, this can be multiplied by the attributable risk inferred by the genotype to estimate an attributable risk reduction (ARR) and number needed to treat (NNT). For example, if the baseline risk of disease (phenotype) is 1 in 1000 with the normal gene, and the variant gene confers a 10-fold higher risk, then the absolute risk in patients who test positive is 1 in 100. If an intervention can reduce this risk by 50%, then the ARR is $0.50 \times 0.01 = 0.005$, or 0.5%. This means that 200 positive patients ($1 \div 0.005$) would have to be treated to prevent 1 event. Furthermore, assuming a variant gene prevalence of 10%, detecting 200 positive patients would require screening 2000 patients ($200 \div 0.10$). This last calculation assumes that the test is 100% sensitive (eg, every patient who tests positive has the variant gene).

The incremental clinical and economic benefits of genetic testing also depend on current practices for monitoring drug response and predicting disease risk. Plasma drug levels often are often used to monitor toxic drugs such as 6-mercaptopurine, whereas surrogate markers such as blood pressure for hypertension, lipid levels for hypercholesteremia, and blood glucose for diabetes are used to measure drug response for chronic diseases. If inexpensive and validated means of monitoring drug response exist, pharmacogenomics may offer little incremental benefit. However, commonly used surrogate markers such as forced expiratory volume in 1 second for asthma and blood pressure for hypertension may not be well correlated with clinical and economic outcomes.[29,30]

The incremental benefits of using disease-risk tests to detect genetic risk for a disease may become complex because one genotype can be implicated in the risk for several diseases. Mutation carriers of the mismatch repair genes (required for repair of DNA damage) are at high risk for developing colorectal cancer at an early age (median age at diagnosis is 45 years), but they also have increased risk of developing several extracolonic neoplasms, such as endometrial, small bowel, gastric, renal pelvis, ureter, and ovarian cancer.[11,23] The IL-1 genotype is a risk factor for periodontitis, but polymorphisms of the IL-1 alpha and IL-1 beta alleles also have been implicated in the disease pathways of rheumatoid arthritis,[31] polyarthritis,[32] coronary artery disease,[33] and inflammatory bowel disease.[34] Although models do not have to account for all disease implications of a specific genotype, providers should be aware that genetic testing could carry unforeseen benefits (or consequences).

Assay Characteristics

The accuracy of the assay (ie, its sensitivity and specificity) should be specified for any genetic test. Although test accuracy often is high, any claims about test accuracy should be validated against the gold standard of direct sequencing. As gene chips, automated gene sequencers, and bioinformatics software improve,[35,36] genetic tests will become cheaper. However, the cost of a genetic testing strategy may include induced costs such as additional clinic visits, genetic counseling, and further diagnostics. These costs should be included in the analysis, and will in part be a function of patients' willingness to participate in interventional strategies.

For pharmacogenomic tests, the ability to obtain a rapid assay result may be a key driver of the cost-effectiveness analysis. This is particularly true when initiation

of drug therapy can result in an immediate adverse event if dosing (or choice of drug) is incorrect. In the case of warfarin dosing, the first 3 months after initiation of drug therapy are considered the highest risk period for bleeding adverse events.[37] Therefore, a genetic test to identify a slow metabolizer should provide results before the first dose is administered, if the purpose of the test is to reduce the risk of overcoagulation during therapy initiation.

All models should distinguish between the test's ability to detect a genetic variation (diagnostic performance) and its ability to predict disease or risk of adverse events (PPV). The latter ability is related to the strength of the association between the genetic variation and the disease or drug outcome.

Indirect Costs Associated With Genetic Testing

Genetic testing may introduce a variety of indirect costs to the payer, patient, and possibly the patient's family. Potential indirect costs to the payer include counselling or therapy costs subsequent to a positive result. Changes in functional, emotional, or social status may result from knowing one's genetic predisposition toward severe and debilitating diseases such as Alzheimer's or Huntington's disease. Emotional responses before and after genetic testing have been characterized in patients at risk for Alzheimer's disease, Huntington's disease, and breast cancer.[38-40] Documented responses are described below.

Anxiety. Anticipation of test results, unknown risk status for the disease, and positive confirmation of a genetic risk may all may elicit a response of anxiety. This response may be characterized by hypervigilance, intrusive thoughts, sleep disturbances, confusion, and persistent worry about the future.[39,40]

Depression. Patients, relatives, and spouses alike may become depressed if results of a genetic test are positive.[39] One study demonstrated that 71% of women age 45 years and under who were found to have a BRCA1 mutation reported feeling depressed 6 weeks after testing.[40,41]

Guilt. An observed side effect of genetic testing in BRCA1 studies has been guilt.[41,42] Patients who test positive may feel guilty about transmitting deleterious genes to their offspring or burdening a spouse with the emotional and financial task of caregiving. Patients who test negative may have a form of "survivor guilt" because they did not receive the deleterious genes, whereas other family members did.[41,42]

These potential adverse effects of genetic testing on patient quality of life and payer costs will vary based on the gravity of the disease in question. However, they should be explicitly identified and incorporated into the economic analyses.

Demand For Genetic Testing

Economic models may not be able to account for several variables that are important predictors of the demand for genetic testing. Previous studies among patients susceptible to genetic diseases yielded 6 key variables.[41,43,44]

- Baseline levels of knowledge
- Baseline perceptions of the benefits
- Limitations and perceived risks of genetic testing
- Depression (mood disturbance) and functional health status
- Education
- Health insurance status.

These variables will affect the demand for genetic testing among the population under care at an MCO. The test-related cost of medical care will be a function of the available interventions and the likelihood that patients testing positive will seek medical treatment. The effect of demand should be considered when estimating the budgetary impact of providing reimbursement for the test.

EXAMPLE: WARFARIN AND CYP2C9 GENOTYPING

Cost-savings or cost effectiveness can be assessed when the genetic test is supported by sufficient data demonstrating: (1) an association between the variant group and an elevated risk of an event occurring; (2) prevalence of variant gene in the treated population; (3) rate of the clinical event in the treated population; (4) an intervention that can reduce the event rate in the variant group; and (5) a sensitive and specific test with rapid results.

As an example, let us assume 100 patients are treated for 1 year with the anticoagulant warfarin. Patients treated with this drug are at risk for major bleeding events requiring hospitalization. Applying the criteria yields the following information: (1) Patients with a variant CYP2C9 gene (the variant group) have a 2.34 times higher risk of bleeding compared with patients without the variant gene (the normal group); (2) Thirty percent of patients have a variant CYP2C9 gene; (3) The rate of bleeding events is 8% per year; (4) The intervention for the variant group may include a lower initial dose and increased surveillance for bleeding risk factors, but the potential decrease in risk is not known; (5) A test is currently available that can provide accurate information about a patient's genotype status before warfarin therapy is initiated.

The variables can be described as:

$Rate_{AE}$ = 0.08 (overall bleeding rate)
RR_{Var} = 2.34 (genotype-phenotype association)
$Prev_{Var}$ = 0.30 (variant genotype prevalence)
$Prev_{Norm}$ = 0.70 (normal genotype prevalence).

Given these data, we can estimate the adverse event rates for both the normal and the variant groups using the following equation:

$$Rate_{AE(Norm)} = \frac{}{(RR_{Var})(Prev_{Var}) + Prev_{Norm}} = 0.057$$

$$Rate_{AE(Var)} = (RR_{Var})(Rate_{AE(Norm)}) = 0.133,$$

which gives the following adverse event rates:

$Rate_{AE}$ in normal group = 5.7 %

$Rate_{AE}$ in variant group = 13.3 %.

If we assume that the adverse event rate in the variant group could be, at best, reduced to the adverse event rate in the normal group, then the ARR that could be achieved is 13.3% – 5.7% = 7.6 %. The NNT is then:

NNT = 1 ÷ 0.076 = 13.

Thus, 13 patients with the variant genotype must be "treated" (ie, lower starting dose, increased surveillance) to prevent 1 adverse bleeding event over a 1-year time period. A number needed to screen (NNS) also can also be derived. The number of patients that would need to be screened to prevent 1 bleeding event can be calculated by dividing the NNT by the prevalence of the variant genotype:

NNS =NNT ÷ ($Prev_{Variant}$) = 13 ÷ 0.3 = 44.

If we assume the cost of the genetic test is $135 (Table 1), the total screening cost required to prevent 1 adverse event is:

$135 × 44 = $5940.

A formal cost-effectiveness analysis would be required to determine whether genetic testing (and additional costs of counseling and increased surveillance) could produce cost-effective reductions in morbidity and mortality for this patient population. However, the approach described above is a straightforward method to roughly estimate the cost effectiveness of a testing strategy. For example, the cost of testing of $5900 might be compared with the cost of the event that is being avoided, in this case major bleeding requiring hospitalization.

DISCUSSION AND CONCLUSIONS

Disease-risk and pharmacogenomic tests have enormous potential to provide a low-cost, rapid, and reliable way to screen populations for disease risk and drug response. However, these tests also will require solid clinical, epidemiologic, and economic data to support their use in a safe, effective, and cost-effective manner.

Although some genetic tests may make a rapid journey from bench to bedside, the ultimate destination for this diagnostic class will be decided by the healthcare marketplace. As genetic tests become more ubiquitous, decision makers should have the tools in place to respond with an appropriate level of reimbursement. The criteria described in this paper should help decision makers (1) quantify the clinical benefit and economic savings that can be achieved, (2) assess the robustness of a cost-effectiveness analysis, and (3) clarify areas where data are deficient when evaluating a genetic test for reimbursement.

There are important issues not addressed by these criteria. The benefits of disease-risk testing are intertwined with ethical and psychological dilemmas not only for the patient, but for their first-degree relatives as well. Furthermore, the genetic marker is fixed and unchanging throughout the lifetime of the individual. These issues can be captured in part by measurement of the quality-of-life dimensions discussed above, but the ramifications for health and life insurance, employment, and advance disability planning are not yet determined and are beyond the scope of this paper.

In conclusion, manufacturers of genetic tests should provide detailed clinical and economic information, (including data from published and unpublished studies), and outcomes modeling, similar to the submission of evidence for drug formularies. The value of genetic testing can be difficult to gauge because of the complex issues involved, but conducting and reporting cost-effectiveness analyses according to practical guidelines can help ensure that these tests are being used in a safe, beneficial, and cost-effective manner.

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