

Genetic Testing and Pharmacogenomics: Issues for Determining the Impact to Healthcare Delivery and Costs

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Objectives: To determine the potential impact of genetic testing and pharmacogenomics on healthcare delivery and costs.

Study Design: Literature review.

Methods: We examined 3 examples: (1) BRCA1/2 testing for breast cancer risk, (2) HER2/neu overexpression testing to guide drug treatment in women with breast cancer, and (3) CYP2C9 testing before the use of the anticoagulant warfarin. We discussed each genetic testing example from the perspective of the patient, provider, insurer, industry, government, and society.

Results: The expanded use of genetic information offers many potential clinical benefits, but also many economic challenges. One of those challenges will be managing the impact of genetic testing on healthcare delivery and costs.

Conclusions: Systematic, evidence-based technology assessments and economic evaluations will have to be used to guide the incorporation of genomics into clinical practice. More research also will be needed to assess patient preferences and willingness to pay for genomic technologies; how providers can assess and use genomic technologies; and how the industry, insurers, and government can best balance the relevant costs and benefits.

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Many have asserted that the wealth of knowledge offered by the human genome portends a time of rapid change in medicine.¹ However, genomic technologies will influence not only health outcomes but also the delivery and cost of healthcare; and in this era of increasing concern about healthcare costs, it will be impossible to consider the implications of genomic medicine without also considering the economic implications.²⁻⁵ Harold Varmus, MD, former director of the National Institutes of Health, noted in an editorial in *The New England Journal of Medicine* that a key question is: "How much will the expanded use of genetic information further escalate the cost of healthcare, and who will pay for it?"⁴ Although many studies have addressed issues related to the privacy and fair use of genetic information,² there has been surprisingly little discussion of the implications of genetic testing and pharmacogenomics for healthcare delivery and costs.⁶⁻⁹ Ultimately,

these issues will substantially influence how patients and providers adopt and utilize genomic technologies.

This paper reviews the current literature to assess the potential impact of genetic testing and pharmacogenomics on healthcare delivery and costs. Our objectives are: (1) to provide an overview of the key issues from the perspectives of patients, providers, insurers, industry, government, and society; (2) to discuss examples from the empirical literature; and (3) to point out areas for future research. In particular, we highlight how key considerations are evolving as genetic testing is being developed for common conditions and drug-prescribing decisions, instead of being used only to predict future risk of disease in small, relatively high-risk populations.

The **Figure** illustrates 2 applications of genomics: (1) the use of genetic testing to predict disease risk and (2) the use of genetic information to guide drug development and prescribing ("pharmacogenetics/pharmacogenomics"). This review examines both of these applications (also called "genetic testing" or "genomic medicine" for brevity), but it does not examine the use of genomics to develop gene-based therapies.

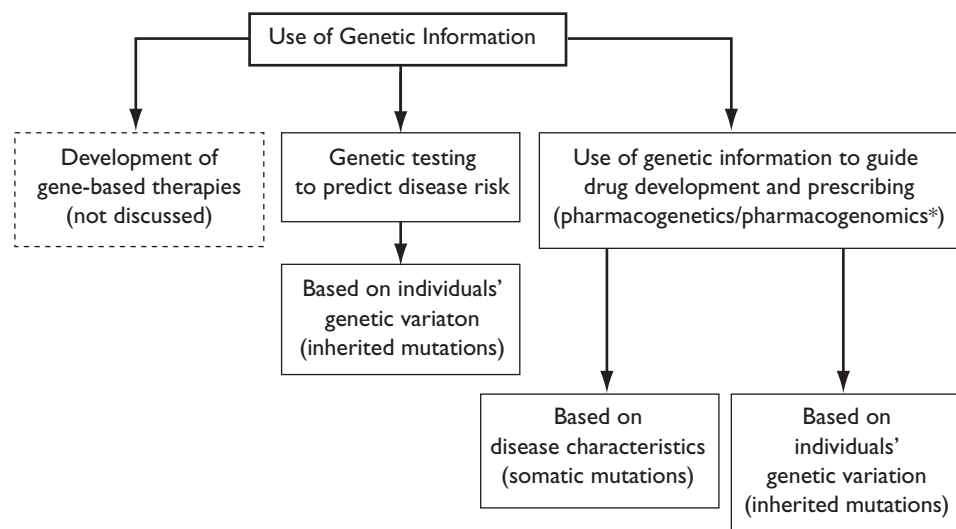
The majority of growth in genetic testing today involves finding tests that aid in diagnosing diseases, predicting future disease risk, or predicting drug response.^{3,10-14} The number of genetic tests that are expected to move from the research setting to market will require providers without specialty training in genetics to become "practitioners of genomic medi-

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Figure. Primary Applications of the Use of Genetic Information



*Note: We use the terms pharmacogenetics and pharmacogenomics interchangeably.

ciné.”^{3,7} For example, Roche announced the launch of a genetic test to predict how individuals will react to a “large range of drugs.”¹⁵ Therefore, the translation of basic science findings in genomics into clinical practice must become a major priority.^{16,17}

It is critical that we begin now to understand the impact of genetic testing—both positive and negative—on healthcare delivery and costs, even though these new technologies have generally not been widely adopted in healthcare systems. With concerns over rising healthcare costs, the impact of genetic testing on healthcare delivery and costs will need to be considered in assessing its potential added value before such technologies are disseminated. Analyses can inform future decision making and highlight the circumstances under which genetic testing strategies could prove to be either a poor or a good use of scarce healthcare resources.

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STAKEHOLDER PERSPECTIVES

Below we examine the conflicts and challenges to the relevant US stakeholders in implementing genetic testing. We provide illustrations throughout using 3 types of genetic testing that offer interesting contrasts and comparisons:

1. Genetic testing for the purpose of predicting future disease risk based on an inherited mutation in an individual (ie, germline mutation). We use the

example of testing for BRCA1/2 mutations, which are associated with a higher risk of breast and ovarian cancer. It has been estimated that 5% to 10% of breast cancers have an inherited component (including BRCA mutations as well as others), and that approximately 60% to 80% of women with BRCA mutations will develop breast cancer.¹⁸ BRCA testing (BRACAnalysis[®] test) is relatively expensive (>\$2000 for counseling and testing¹⁹), and the primary available interventions require surgery (prophylactic removal of the breasts and/or ovaries).

2. Genetic testing for the purpose of *prescribing drug therapy based on genetic variation of the disease* such as acquired mutations in tumors (ie, somatic mutation). We use the example of testing for overexpression of HER2/neu oncogenes, which are genetic alterations in specific cell types that determine prognosis and the potential for response to drug therapy, specifically trastuzumab (Herceptin[®], Genentech, South San Francisco, Calif) in the case of breast cancer. It has been estimated that 25% to 30% of breast cancer cases exhibit overexpression of HER2/neu,²⁰ and women who are treated with Herceptin have demonstrated a 25% improved median survival time.²¹ The test for HER2/neu is relatively inexpensive, but an annual course of Herceptin therapy has been estimated to cost \$27 000 to \$81 000.²²
3. Genetic testing for the purpose of *prescribing drug therapy based on genetic variation of the individual* such as variant alleles in drug-metabolizing enzymes. We use the example of testing for variation in CYP2C9 before the use of the anticoagulant warfarin, which requires careful dosing and patient follow-up because of bleeding risk and significant interpatient variability in drug response. Approximately 20% to 30% of Caucasian patients receiving long-term warfarin therapy have at least 1 variant allele, which has been shown to be associated with an increased risk of overanticoagulation and bleeding events.²³⁻²⁵ A genetic test for warfarin is not yet in routine clinical use, but because warfarin is prescribed to more than 1 million patients in the

United States annually, the potential cost impact is large. **Table 1** summarizes these examples and stakeholder perspectives, which are discussed in detail below.

Patients

Patients are the ultimate consumers of healthcare technology, and many are aware of or interested in genetic testing. According to a nationally representative survey, 41% of individuals in the United States have heard that genetic tests can determine whether a person is at greater risk of developing cancer,²⁶ and 79% of respondents in a population-based survey stated that they would take a genetic test to predict whether they will develop Alzheimer’s disease.²⁷

Will patients actually agree to genetic testing or individualized drug therapies based on genetics? Most of the patient preference research to date has been conducted within research settings, focusing on testing for rare, high-penetrance mutations such as BRCA1/2. These studies have generally shown that uptake of genetic testing is much less than interest in testing because of concerns about cost, lack of effective treatment options for those testing positive, privacy and discrimination concerns, limited predictive value, and negative impact on quality of life.²⁸

Will patients pay out-of-pocket or higher prices for genetic testing or individualized drug therapies? There is little evidence on this issue. One poll found that two thirds of respondents said they would pay extra for a “genetically customized drug that you knew would work for you.”²⁹ Anecdotal evidence suggests that patients often pay out-of-pocket for genetic testing for risk susceptibility because of concerns about confidentiality or lack of coverage by insurance companies, although this is unlikely to be the case for testing for drug therapies.

One indication that demand for genetic technologies could soon affect clinical practice is the increase in direct-to-consumer advertising of genetic testing.³⁰⁻³² For example, Genelex advertises testing for 3 important drug-metabolizing enzymes (CYP2D6, CYP2C19, and CYP2C9) at \$250 per test or \$650 for all 3 tests (<http://www.healthanddna.com>, accessed July 31, 2003); and Myriad Genetics advertises testing for inherited cancer risk including BRCA1/2 (<http://www.myriad.com>, accessed July 31, 2003). As with other tests,³³ there is widespread debate over the wisdom of marketing tests directly to consumers.^{30,34}

Overall, the clinical and economic impact of genetic testing will be larger if direct-to-consumer advertising and insurance coverage cause patients to embrace genetic testing for common diseases and for individual

Table 1. Summary of Key Stakeholder Perspectives for 3 Uses of Genetic Testing

Stakeholder(s)	Uses of Genetic Testing		
	Predict Disease Risk	Target Drug Therapies Based on Genetic Variation of Disease	Target Drug Therapies Based on Genetic Variation of Patient
Patients	Patient interest, but uncertainty about whether patients will use the tests	High patient demand	Patient interest, but whether patients will use the tests is unknown
Providers	Challenging implementation issues	Implementation is relatively more straightforward	Unknown, but implementation challenges are likely to vary
Industry	Mixed interest for pharmaceutical firms Potentially greater interest for diagnostics-only firms	High interest for pharmaceutical firms and diagnostic firms	Mixed interest for pharmaceutical firms High interest for diagnostic firms
Insurers	Mixed coverage	High coverage	Unknown, but likely to be covered
Government	More concerns about regulatory and societal issues	Fewer concerns about regulatory and societal issues	Some concerns about regulatory and societal issues
Society	Unknown costs and benefits	Unknown costs and benefits	Unknown costs and benefits

targeting of drug therapies. Research can help us understand these preferences,³⁵ particularly in situations where the information reveals modest increases in risk for common diseases or adverse drug effects. Ultimately, if consumers come to consider genetic tests in the same way they perceive, for example, a cholesterol screening test, demand for these tests will be driven less by concern about the risks of their use than by their perceived benefits and costs. The examples of BRCA1/2 and HER2/neu testing illustrate how patient demand is likely to differ for genetic testing to predict risk versus drug prescribing. In a nationally representative survey of the US adult population, only 1% reported having had any genetic test for cancer risk.²⁶ For example, 1 study found that only one quarter of high-risk women actually pursued BRCA testing after counseling.³⁶ In contrast, there was strong patient demand and advocacy for access to Herceptin and for fast Food and Drug Administration (FDA) approval of the therapy and testing.³⁷ Thus, it appears likely that there will be strong patient demand for genetic testing when it is directly related to key treatment decisions.

Providers

Providers face complex questions regarding the costs, benefits, and risks of genetic-testing technologies (see Suther and Goodson³⁸ for a review). First, they face the challenge of keeping abreast of what tests are available; their accuracy, predictive validity, and cost; and which patients are most appropriate for testing. Second, they must consider whether the test offers true advantages over the current standard of care. For example, there has been debate about whether genetic tests are superior to ferritin screening for detecting individuals at risk for adverse effects of hemochromatosis because of the low penetrance of the relevant mutations.³⁹ A third issue is how the test might change patient management. As noted above, many genetic tests are available to identify risks for diseases for which there is no treatment. Given the rising costs of healthcare, health insurers may limit patients' and providers' interest in getting this information because of the need to limit the use of tests with uncertain clinical benefit.⁴⁰ Fourth, clinicians must decide the appropriate level of counseling and informed consent for genetic tests—and who will provide and pay for it. Most providers are not trained to provide genetic counseling,⁴¹ and insurers may not reimburse for counseling outside of genetics-specialist settings. Finally, some genetic variants may be quite uncommon in certain racial or ethnic groups.⁴² Clinicians will face the difficult task of balancing the arguments against testing in populations where prevalence of the variant is quite low against the practical and ethical issues of identifying

individuals from these populations and informing them that testing is not indicated.

These challenges are likely to differ for genetic testing to predict risk of disease versus genetic testing to guide drug prescribing. Genetic testing to predict high disease risk in currently healthy persons (eg, BRCA testing) often requires providers to have extensive knowledge of genetic counseling. A nationally representative survey found that, although 31% of physicians had ordered or provided cancer susceptibility tests in the past 12 months (including, but not limited to, testing for BRCA), the majority of these physicians (87%) had referred these patients elsewhere rather than providing the testing themselves and 50% of physicians overall felt unqualified to recommend cancer susceptibility testing.⁴³ In contrast, testing for specific drug targets (eg, HER2/neu testing) involves clinical decisions that are part of treating a person with a medical condition. However, future use of genetic testing to target drugs based on individuals' genetic variation may be more complex, for example, when determining the appropriate use of genetic testing for drugs with complex metabolic pathways.

Industry

The availability of genetic tests and targeted drug therapies will depend on the economic incentives for pharmaceutical, diagnostic, and genomics companies to develop and market them. From the pharmaceutical-industry perspective, genomic technologies offer an interesting contrast in opportunities for drug development versus threats to market share.

On the one hand, there are economic incentives for industry to develop genomic-based drug therapies. Genomics will likely provide a multitude of new drug targets, enable the development of drugs that avoid problematic genetic variants in drug-metabolizing enzymes, and increase the development of preventive interventions for patients identified as being at higher risk for future disease (eg, use of cyclooxygenase-2 inhibitors to reduce risk of familial colon cancer⁴⁴). Furthermore, if pharmacogenomics leads to drug therapies with greater efficacy and safety, these therapies are likely to have a higher price that reflects this added value. Genetic profiling of patients enrolled in Phase I and II clinical trials may allow for smaller Phase III clinical trials that have a greater chance of success, resulting in decreased development time and cost, and shorter FDA approval times. Additionally, genomics offers the opportunity to rescue drugs that have not been approved because of side effects or lack of efficacy by targeting them to patients with specific genetic profiles.^{7,45,46}

There also are economic disincentives for the pharmaceutical industry to develop genomic-based drug therapies. Of most concern, targeted drugs may lead to decreased market share and fewer blockbuster drugs. For example, genetic testing may help us decide which patients will not respond well to specific types of anti-hypertensives, cholesterol-lowering medications, or antidepressants.^{47,48} If the relevant mutations are prevalent, large numbers of patients may be steered toward specific drugs. It also is not clear whether the current market structure will provide the necessary incentives for the development of drugs targeted toward patients with rare genetic variants, such as many racial minority populations.^{45,46,49} However, even a “niche” drug, if used as a presymptomatic preventive measure for those at increased genetic risk, may prove profitable.¹⁰

A major shift as a result of the availability of genetic information is that drug/diagnostic combinations are becoming more important; thus, the diagnostics industry will play a critical role in the implementation of genetics.⁵⁰ (We thank an anonymous reviewer for this point.) The shift toward combination products also portends greater integration of the diagnostics and pharmaceutical industries, which have historically operated and been regulated relatively independently.^{51,52}

In contrast to the mixed incentives for pharmaceutical firms, the diagnostics industry has a potentially clearer incentive to use genetic information.⁵³ Genetic information is likely to increase the market for diagnostics, as genetic tests will be required for risk prediction and to stratify patients regardless of whether they receive a drug or intervention.^{54,55} Indeed, it has been suggested that diagnostic firms may profit sooner from genomics than pharmaceutical firms.⁵⁴ Still, the availability of tests will depend on reimbursement rates, which to date have varied.^{55,56} Moreover, the regulatory climate as it relates to the diagnostic industry is uncertain. The regulation of diagnostics has historically been less comprehensive than the regulation of drugs, but the use of genetic information may require changes in the prevailing regulatory framework.⁵⁷

Herceptin and the associated tests offer an illustration of the issues for both the pharmaceutical and diagnostics industries. Herceptin, which is considered to be a major success story for the biotech industry, illustrates the promise of finding novel therapies for certain genetic variations in a disease state. Herceptin also illustrates the potential for diagnostic firms, as 2 available tests are listed on the label, thus conferring a monopoly to those firms.⁵⁸

Insurers

Health insurers play a large role in defining patient

and provider access to new medical technologies through their coverage policies and clinical guidelines.^{59,60}

Limited data suggest many genetic tests are not covered or coverage policies have not been determined. For example, 84% of insurers reported having never made a decision to cover BRCA testing, 12% had received an inquiry and decided not to cover testing, and 4% had made a decision to cover the test.⁵⁹ Another survey found that half of plans had no coverage policy for prophylactic mastectomy or oophorectomy following BRCA 1/2 testing, and an additional one quarter of plans did not cover such surgery.⁶¹

Genetic tests can be expensive; for example, BRCA1/2 full sequencing costs \$2975 (http://www.myriadtests.com/doc/Myriad_Patient_Auth_Form.pdf. Accessed June 15, 2004), and the downstream costs that follow from testing can be much more costly than the test itself (eg, prophylactic surgery). In addition, although the cost of genetic testing is expected to continue to drop, health insurers may face large outlays if initial testing results in extensive testing of family members. Because most genetic tests will become available well in advance of evidence that using these tests will favorably affect patient outcomes, insurers will face the dilemma of whether to bear the economic burden of testing while waiting for definitive studies to be conducted.⁴⁵ Although cost is only 1 factor in determining coverage policies, insurers have reported concerns that the costs of covering genetic testing will be too high.⁵⁹ Furthermore, many patients change plans frequently; thus, individual health plans are unlikely to realize the full benefits of preventive interventions.

Another determinant of the impact of genetic testing will be clinical guidelines. For example, many managed care organizations use drug formularies to guide drug utilization.⁶² However, targeting drugs based on genetic test results will increase the complexity of formularies and require that formularies consider relative trade-offs. Payers also will have to determine whether to require genetic testing before initiating certain drug therapies.⁶³ From the insurer perspective, testing for risk prediction versus drug prescribing provides a study in contrasts. Insurance companies have not universally covered testing for risk prediction (eg, BRCA testing); in contrast, because HER2/neu testing and appropriate treatment now are considered the standard of care, insurers cover both testing and Herceptin. It remains to be seen whether insurers will cover broader genetic testing. Testing for relatively rare, highly penetrant gene mutations is expensive on an individual level but modest on a health plan level. In contrast, testing for more common mutations and for targeting drug therapies is relatively less expensive on an individual basis, but will

apply to a much larger population; thus, the total costs may be substantial, although these costs may be balanced by improvements in health and savings in other medical costs. Therefore, it will be critical that insurers have the cost and outcome data necessary to evaluate genomic technologies.⁵⁹

Government

Government and regulatory agencies have a role in determining (1) the safety and efficacy of genomic technologies; (2) reimbursement policies for public health insurance programs; and (3) relevant laws, regulations, and guidelines.^{64,65} The FDA will face a number of issues regarding the approval of genetic tests, including to what extent genetic data may be required in the drug approval process, whether there will be further review of previously approved drugs as relevant genetic data become available, whether testing may be required before drug therapy is initiated or after initiation, the comarketing and labeling of tests and drugs, and patent protection for drugs developed for small, genetically defined populations through the Orphan Drug Act.^{9,66-69} A long-standing issue that will gain prominence as more genetic tests are developed is the current status of regulatory review of genetic tests. Although the FDA oversees the safety and efficacy of new drugs and diagnostics in the United States, most genetic tests are not regulated by the FDA because they are considered "clinical services" rather than marketed kits.^{57,70} Laboratory testing is regulated under the Clinical Laboratory Improvement Amendments (CLIA); however, CLIA does not examine clinical validity or utility (<http://www.cms.hhs.gov/clia>).^{51,71}

Reimbursement policies are determined for public insurance enrollees through the Centers for Medicare & Medicaid Services. The government also has a role in

developing guidelines for population screening⁵ and in protecting individuals from discrimination based on genetics for purposes of health insurance.⁷²

Overall, any changes in the regulatory structure relevant to genetic tests will be key events in the future of genomic medicine. Government may have a role in encouraging private and increasing public investment in genomic technologies if current levels are not socially optimal.⁴⁵ This is particularly true because commercial testing has advanced rapidly in the United States, causing concerns about the effects on accessibility, price, and quality.^{73,74} Because of this commercialization, industry and economic incentives will play a relatively larger role in determining the overall impact of genomic technologies unless there is government intervention.⁷³

BRCA testing in particular illustrates the controversies over the commercialization of genetic testing and thus where the government may play an important role. The patenting of human genes has been very controversial, and the case of BRCA has been no exception. The patent for the BRCAAnalysis[®] test is held by Myriad Genetics, which has been criticized for monopolizing the BRCA test by requiring that full sequencing testing be done only at its laboratory and by pricing the test higher than if were more readily available. The concern is that these restrictions will reduce access and discourage further research.⁷⁵

Societal

The perspectives discussed above ultimately contribute to an overall societal perspective. From this perspective, the goal is to maximize the benefits from genetic testing while minimizing the risks and costs for all stakeholders. Two formal, systematic approaches to weighing the costs, benefits, and risks of genetic testing are cost-effectiveness and cost-benefit analysis.

However, in a systematic review of the literature, we found that there are currently few economic analyses of genetic testing, particularly for drug therapies, and that the studies cover a limited number of genetic mutations and diseases (ie, the majority of analyses of genetic testing for risk prediction are concerned with prenatal screening such

Table 2. Factors Influencing Cost-Effectiveness of Genetic Testing

- Prevalence of the genetic mutation and the disease in the population.
- Severity and cost of the disease or outcome the test is designed to predict or diagnose.
- Strength of the association between the genetic mutation and clinical outcomes (penetrance).
- Availability of effective interventions that can be implemented on the basis of genetic information and that provide a reduction in the relevant event rate compared with standard care.
- Whether testing is for prediction of future risk or for immediate diagnostic or prescribing decisions.
- Cost, turnaround time, and accuracy of the test and whether the results provide information for a single condition or multiple conditions.
- The cost of counseling (if relevant).
- The potential downstream and indirect costs and benefits such as the extent to which family members are tested, the potential ramifications of loss of privacy if genetic results are disclosed, etc.

as that for cystic fibrosis; K. A. Phillips, S. L. Van Bebber, J. Sakowski, unpublished data, 2004).

Although the lack of cost-effectiveness evaluations of genetic testing undoubtedly reflects the currently limited use of these technologies, it is important to systematically evaluate their likely costs and benefits *before* they are widely implemented. We have identified key factors that are likely to determine the cost-effectiveness of genetic testing, and they provide a research agenda for future analyses (Table 2; see also references 10 and 76).

Surprisingly, there has been only 1 published, comprehensive cost-effectiveness analysis of testing for BRCA. This analysis found that screening high-risk women (Ashkenazi Jews) for BRCA1/2 is relatively cost-effective only if all women who test positive undergo prophylactic surgery.⁷⁷ We found only 1 cost-effectiveness analysis of testing for HER2/neu and treatment with Herceptin.⁷⁸ Yet in other countries that require cost-effectiveness analyses for new pharmaceuticals (eg, Australia, the United Kingdom), Herceptin was not immediately covered because of the high cost of the drug therapy and the limited impact on survival (therapy has been estimated to increase median survival times from 20 to 25 months²¹).⁷⁹

CONCLUSION

The expanded use of genetic information offers many potential clinical benefits but also many economic challenges. One of those challenges will be managing the impact of genetic testing on healthcare delivery and costs. Thus, systematic, evidence-based technology assessments and economic evaluations will have to be used to guide the incorporation of genomics into clinical practice. Future research also will be needed to assess patient preferences and willingness to pay for genomic technologies; how providers can assess and use genomic technologies; and how the industry, insurers, and government can best balance the relevant costs and benefits.

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