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Economic Evaluation of Pharmacogenetic Tests

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Abstract

Ever since the sequencing of the human genome was completed, prediction of treatment response in terms of genetic variation has been seen as an important and achievable goal. Pharmacogenetics is the study of how genetic differences affect variation in response to medication. One potential goal of pharmacogenetics is to be able to deliver “personalized medicine” by making management decisions that optimize patient health outcomes based on a patient's genetic makeup.

Pharmacogenetic tests have the potential to (i) predict intended response, the goal outcome of the medication; (ii) predict unintended response to the medication, such as adverse events; (iii) titrate medication dose; and (iv) inform the development of novel therapeutics.

As genetic tests draw closer to clinical use, it is crucial to make projections of the cost-effectiveness of these tests so that their potential for widespread use can be critically evaluated and so that they can be developed in ways that optimize their usefulness. Scientists and clinical policymakers need information on how such tests can best be formulated and applied. For example, how can the tests be formulated to maximize test performance characteristics? What are the potential benefits of using a test to identify nonresponders vs. the risks of mistakenly withholding these medications from a patient who may be misclassified by the test? Should the tests be offered routinely or in a stepwise approach to medication treatment? Should they be offered to all patients with a disease or only to high-risk subgroups, and how should those subgroups be defined? What will be the costs of such tests?

Several important factors are assessed in a pharmacoeconomic evaluation. These include:

1. Cost of the pharmacogenetic test

With rapid advances in genetic technology, costs of genetic testing have decreased in recent years. This decrease in cost has led to a proliferation of research in the area and will also contribute to the likelihood that pharmacogenetic tests will be affordable. Costs include the charges directly related to a pharmacogenetic test, but the true costs include a broader range,

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CONFLICT OF INTEREST

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such as costs related to obtaining samples and the time and resources needed to counsel patients on the test results. In addition, costs related to downstream changes in treatment due to testing need to be accounted for. If a pharmacogenetic test prevents hospitalizations, then the cost savings of such prevented hospitalizations need to be accounted for.

2. Cost of the medication

The cost of the medication is closely related to the cost-effectiveness of the medication. An expensive medication is less likely to be cost-effective unless the associated test is highly accurate, the medication has significant benefit, and few alternative treatments are available.

3. Test performance

Performance of a test is evaluated through sensitivity, specificity, positive and negative predictive value, and the area under the receiver operating curve. For a pharmacogenetic test to be adopted, high positive predictive value is important. If a test has low sensitivity for predicting response to a medication, the test may not be favorable economically, because many patients who will not respond and should discontinue a medication may not be identified. High specificity is particularly important. For example, erlotinib (Tarceva) inhibits activation of the epidermal growth factor receptor, a protein kinase that is involved in many cell processes and is overexpressed on the surfaces of cells such as those involved in nonsmall cell lung cancer. The sensitivity of the test for the epidermal growth factor receptor mutation is only 32%, yet the specificity is 87%. Erlotinib costs \$40,000/year and has the potential for significant side effects, including interstitial lung disease. Nevertheless, erlotinib is used for select patients because of its high specificity.

4. The disease burden

Tests involving common diseases will have higher costs than those involving rare diseases, assuming the cost per test is the same. If a high proportion of patients test positive, thereby benefiting from the test, it is more likely to be cost-effective.

5. Benefits of testing compared to empiric treatment

The benefits of testing strategies include (i) identification of nonresponders or patients who require higher doses of medication, who would never be clinically detected under the status quo; (ii) earlier identification of nonresponders who would eventually be clinically detected under the status quo but may develop toxicities despite their nonresponse; and (iii) identification of candidates for novel therapies that are not available without the test.

Pharmacogenetic tests can predict response to medications and help researchers develop novel drugs. In this article, we briefly review two of the pharmacogenetic tests that have received attention in the literature. First, we review human epidermal growth factor receptor-2 (HER2) testing and trastuzumab, a monoclonal antibody that was specifically developed to target the HER2 receptor. The second review deals with CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1) testing for warfarin. The cytochrome P450 2C9 is responsible for the phase I metabolism of warfarin. Two common polymorphisms of the

CYP2C9 gene, *CYP2C9*2* and *CYP2C9*3*, are associated with warfarin dose requirements and the risk of hemorrhage. Warfarin causes anticoagulation by inhibiting the VKORC.

EXAMPLE 1: HER2 TESTING FOR TRASTUZUMAB

One example of pharmacogenetic testing is testing for the HER2 (*HER-2*, *c-erb-B2*, or *neu*) gene. Trastuzumab (Herceptin) is a humanized monoclonal antibody that causes cell death by targeting the receptor HER2, expressed on the cell surface. Trastuzumab therapy targets tumors that overexpress the HER2 protein, and genetic testing helps identify overexpression of HER2. In patients with HER2+ metastatic cancer, the addition of trastuzumab has been demonstrated to improve response rate, time to progression, overall survival, and quality of life.^{1,2} Trastuzumab is also efficacious as a single agent in first-line treatment of HER2+ metastatic breast cancer. Furthermore, trastuzumab reduces the risk of recurrence and mortality in patients with early-stage breast cancer. Multiple studies have examined the cost-effectiveness of HER2 testing, but the results of the studies are mixed. In the next section, we review six components for evaluating the cost-effectiveness of HER2 testing.

1. Cost of the pharmacogenetic test

Testing for HER2 status is complex because there are two common methods of testing: immunohistochemistry, which detects overexpression of HER2 protein, and fluorescence *in situ* hybridization, which detects amplification of the HER2 gene. Immunohistochemistry is easier to perform and less expensive, at one-fourth the cost of fluorescence *in situ* hybridization, but studies suggest that fluorescence *in situ* hybridization has better reliability and validity.^{3,4}

2. Cost of the medication

One study estimated that the cost of treating patients with HER2+ breast cancer would increase by ~\$1 billion for trastuzumab treatment alone.⁵ In addition to the high monetary cost for the recommended 12 months of therapy (~\$50,000/person based on the average sales price), trastuzumab has potential adverse events when given in combination with chemotherapy, particularly anthracycline-based chemotherapy.⁵ The most serious adverse event is cardiotoxicity, with significant decline of left ventricular ejection fraction observed in 10% of patients and symptomatic heart failure in 1–4%.⁶ Therefore, treatment with trastuzumab requires serial testing with echocardiography or radionuclide ventriculography to monitor for cardiotoxicity.

3. Test performance

HER2 testing needs to have high predictive value to ensure that patients who can benefit from trastuzumab test positive and patients who will not benefit do not suffer adverse effects, such as cardiotoxicity. Nevertheless, significant variation in HER2-testing practices exists. The lack of a standardized single method for immunohistochemistry detection of HER2 antigens in breast cancer tissue has caused a decrease in the accuracy of the test; the panel concluded that 20% of HER2 testing at the time was inaccurate. The panel made recommendations to standardize testing procedures with a testing algorithm that includes

both immunohistochemistry and fluorescence *in situ* hybridization; it is therefore possible that the accuracy of HER2 testing will improve.

4. The disease burden

It is estimated that 184,000 new cases of breast cancer will be detected in 2008, and that 40,000 patients with the disease will die.⁷ Of these, at least 18% are HER2+.^{8,9} Previous studies of high-risk breast cancer patients have suggested that 30% of patients are HER2+,¹⁰ but studies that include all patients with a new diagnosis of invasive breast cancer suggest that ~18–20% of patients with breast cancer are HER2+.^{8,9} Because breast cancer is common and a high proportion of patients are HER2+, the number of individuals affected is high, making HER testing potentially economically attractive.

5. Benefits of testing compared to empiric treatment

Currently, HER2 testing identifies candidates for a novel therapy, trastuzumab, that is appropriate to use without the test. Thus, HER2 testing provides an alternative, potentially effective treatment.

EXAMPLE 2: CYP2C9 AND VKORC1 TESTING FOR WARFARIN

Our second example is the pharmacogenetics of warfarin, a coumarin anticoagulant that treats and prevents venous and arterial thromboembolic events. Initiation and maintenance of warfarin therapy are difficult because of wide variation in response and dose requirements of warfarin among individuals. The warfarin dose is monitored and adjusted to maintain each patient's prothrombin time and international normalized ratio (INR) within a narrow therapeutic range such that the risk of thromboembolism is decreased without increasing the risk of hemorrhage. Warfarin is one of the first medications to be relabeled by the US Food and Drug Administration to explain that an individual's genetic makeup could influence response to the drug. Also, pharmacogenetic testing for warfarin was one of the first such tests to receive the agency's approval. Single-nucleotide polymorphisms in the cytochrome P450 (CYP)2C9 system and the gene for VKORC1 are associated with warfarin dose requirements.

A report by AEI-Brooking Joint Center for Regulatory Studies suggested that testing for polymorphisms in the *CYP2C9* and *VKORC1* genes would decrease health care spending in the United States by \$1.1 billion annually with a range of \$100 million to \$2 billion. However, this report was conducted before any published clinical studies had demonstrated that testing for CYP2C9 and VKORC1 improved patient outcomes. Formal cost-effectiveness studies are needed once results from clinical trials are available. In the next section, we review five components for evaluating the cost-effectiveness of CYP2C9 and VKORC1 testing.

1. Cost of the pharmacogenetic test

The cost of testing for CYP2C9 and VKORC1 range from \$250 to \$630, which seems relatively inexpensive.

2. Cost of the medication

Warfarin is a generic medication that is relatively inexpensive. The main “cost” of warfarin is the potential for adverse events such as complications associated with hemorrhage. In 2003 and 2004, anticoagulants ranked first in the number of total mentions of deaths for drugs causing “adverse effects in therapeutic use.”

3. Test performance

Multiple studies have demonstrated that, once INR has been stabilized, *CYP2C9* genotypes are strongly related to warfarin dose; however, studies demonstrating clinical efficacy are still ongoing. The warfarin dose is decreased by 22–76% for patients who have *CYP2C9* polymorphisms compared to those with the wild-type genotype. For *VKORC1*, patients with the BB genotype require a warfarin dose increased by 35% and those with AA genotypes require 32% less warfarin, compared with AB-genotype patients. Nevertheless, few studies have examined the effect of knowing the presence of *VKORC1* or *CYP2C9* polymorphisms during the first few months of initiation of warfarin therapy, when the risk for bleeding complications is greatest. One study found that, in comparison with patients with the non-A/non-A haplotype, patients with the A/A haplotype of *VKORC1* had a significantly lower time to the first INR within the therapeutic range, whereas the *CYP2C9* genotype was not a significant predictor of the time to the first INR within the therapeutic range. Thus, test performance of *CYP2C9* and *VKORC1* is promising, but clinical evaluations are ongoing. In addition, we need to question whether testing for *VKORC1* or *CYP2C9* polymorphisms will allow improvement in the time to therapeutic INR.

4. The disease burden

In the United States, up to 2 million patients/year may begin warfarin therapy and up to 800 patients/year may experience adverse drug events associated with warfarin use. Therefore the number of people who could benefit for *CYP2C9* and *VKORC1* testing is high.

5. Benefits of testing compared to empiric treatment

In this example, the benefits of testing for *CYP2C9* or *VKORC1* when dosing warfarin are compared with the alternative strategy of following prothrombin time and INR without testing. One study in residents of long-term care facilities found that only half of the candidates for warfarin therapy were actually receiving it, and the therapeutic range of the INR was maintained only half of the time. Adverse events associated with warfarin therapy are common, and many are preventable. One of the reasons for underuse of warfarin may be the reluctance to undergo the difficult period of titrating warfarin dosing while increasing the risk of adverse events. One potential benefit of pharmacogenetic testing for warfarin, therefore, is more appropriate initial dosing and a shorter titration period, allowing for improvement in time to therapeutic INR.

In summary, the human genome era brings great anticipation for the potential of predictive medicine. Economic evaluations of pharmacogenetic tests will be critical for these tests to be integrated into routine clinical practice. Economic evaluations will need to incorporate the costs of pharmacogenetic tests, the costs of medications, test performance, the burden of disease, the benefits of testing as compared with empiric treatment, and the availability of

alternative treatments. Quantification of the potential health and economic impact of different strategies is important for decision making by funders, policymakers, drug developers, and clinicians.

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