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An Economic Framework for Evaluating Personalized Medicine

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ABSTRACT

Pharmacogenomics and personalized medicine promise to improve health care for chronically ill patients by increasing drug effectiveness and minimizing side effects of drug therapy. There may also be substantial savings realized by eliminating costs associated with failed treatment. Since these issues are not adequately explored across disease areas, the overall economic impact of personalized medicine remains uncertain. Using asthma as illustration, this paper describes a new framework for analyzing the potential value of using a pharmacogenomic diagnostic test in clinical practice.

Broadly considered, personalized medicine is the use of molecular markers to guide the diagnosis and treatment of disease toward the characteristics of individual patients. It derives from the idea that an apparently indistinct disease seen in a population reflects a group of distinct molecular disorders in individuals, generating inter-patient variability in disease progression and treatment response. [1-3] Individual variation accounts for a wide range of medical and economic consequences, from inefficiencies in drug discovery and development to ineffectiveness of drug treatment to drug-induced morbidity and mortality. Addressing these consequences via personalized medicine could benefit patients, and impact health care providers and payers, and the pharmaceutical industry. [4-6]

The techniques of personalized medicine – including molecular diagnostics, pharmacogenomics, and targeted therapies – provide a direct link between pathogenic molecular mechanisms and clinical symptoms. When appropriate markers are known, diagnostic tests allow precise diagnosis and dosing, prediction of disease progression, prediction of treatment response and prediction of adverse drug reactions for individual patients. Pharmacogenomic markers, probably the most widely discussed molecular markers, would use genomic information to individualize disease diagnosis and treatment. Throughout this paper, we use the term pharmacogenomics to refer broadly to the

relationship between gene variation and drug effect. Though sometimes used interchangeably, pharmacogenetics has been most often used in the research literature in connection with variation in drug metabolizing enzymes. (See Bailey or Evans)

Pharmacogenomics promises safer and more effective drug treatment, biomarkers to guide drug discovery at its earliest stages, and a context for prioritizing future advances in medical treatment on the basis of the relative safety, efficacy, or dosing regimens of existing and potential therapies. [7-10] There may also be substantial savings realized by eliminating costs associated with failed treatment. But pharmacogenomics presents many challenges to our health care, drug development, medical education, regulatory, and social systems. [11] The potential costs are also numerous – more expensive drugs, threats to patient insurability, reduced drug revenue, increased regulatory complexity, reduced physician independence, and threats to personal privacy. Since these issues are not adequately explored across disease areas, the overall economic impact of personalized medicine remains uncertain.

Economic analyses of pharmacogenomics have focused on cost effectiveness and cost benefit. Typically the data for these kinds of analyses in health care come from population-based studies, such as randomized controlled trials or cohort studies. [12] But for most indications, a pharmacogenomic intervention

has not yet been developed, so a population-based study comparing interventions is impossible. University of Washington researchers developed a set of cost-effectiveness criteria for considering specific disease, drug, and genetic test combinations. [13] A cost impact analysis from ATKearney predicted that total revenues for current blockbuster drugs in the cholesterol-lowering and arthritis markets would decline, that pharmacogenomics would reduce potential revenues for drugs that show only reduced side effects but no improved efficacy over existing technology, and that, depending on the indication, overall market size could increase using pharmacogenomics to address currently unmet medical needs. [14]

Currently absent in the debate emerging around pharmacogenomics is a framework for evaluating its benefits that is robust and sensitive to all its potential advantages. A modified cost offset analysis could demonstrate whether pharmacogenomics would prove worthwhile in economic terms. A cost offset is recognized if greater utilization of one aspect of health care, say pharmaceuticals, reduces the use of other types of health care. Although cost offset studies are rarely able to take account explicitly for treatment response, in the United States they have proven of interest to payers to make decisions about coverage. [15, 16] Were it possible through a diagnostic test to identify who would not respond to a given

therapy, the costs of non-response could be eliminated for many patients and reduced for the population as a whole—thereby generating a cost-offset relative to treatment costs in the absence of such a test. Key variables determining this potential cost offset are the sensitivity of the test, cost of the test, effectiveness of personalized treatments, and the relative costs of responders and non-responders.

This paper presents an analytical framework for considering many of the tradeoffs that may arise when a diagnostic test is used to predict drug response. We offer an empirical test of these ideas, using patients with asthma to illustrate the framework. These results could potentially guide future economic evaluation of new diagnostic tests based on advances in pharmacogenomics. Importantly, they may also influence biomarker discovery strategies to ensure consistency between market priorities and the future stream of product introductions.

DATA and METHODS

We used retrospective claims data to define our study population and calculate total health care costs on a per-patient annualized basis. Our data were derived from the MarketScan claims and encounter databases for 1995–2000. MarketScan is the largest set of databases of its kind, containing detailed descriptions of inpatient and outpatient

medical care services for persons who are covered in over 160 large corporate-sponsored healthcare plans (approximately 2.8 million covered lives in 2000). The analytic file contains patients with fee-for-service health plans and those with partially- or fully-capitated plans. Because data on costs were not available for the capitated plans, the value of patients' service utilization under the capitated plan was priced and imputed using average payments per procedure, from the MarketScan FFS inpatient and outpatient claims, further stratified by region and year.

Our framework determines the economic consequences of implementing pharmacogenomics in the clinic using a diagnostic test to predict drug response. Using retrospective claims data for asthma patients, we calculated the cost offset realized by predicting the likelihood of response to an alternative existing treatment using a hypothetical pharmacogenomic test. Because the diagnostic test is hypothetical, the alternative treatment remains undefined. This illustrates that our framework is general and could be applied to other indications where diagnostic tests for personalizing treatment regimens have not been developed.

We employed "risk analysis" as our analytic approach to compare the health care costs of an observed treatment protocol (Base Case) with those in a hypothetical treatment protocol

including a pharmacogenomic test for drug efficacy (Test Case). The difference between the overall costs of the Base Case, where non-responding patients continue to suffer their symptoms despite treatment, and the Test Case, where a pharmacogenomics test helps identify an appropriate treatment, is the cost offset realized as a result of using the test.

Individuals between the ages of 4 and 64 with evidence of asthma were selected from the intersection of the claims, encounter, enrollment, and pharmaceutical data files. We defined evidence of asthma as follows:

- At least two outpatient claims with primary or secondary diagnoses of asthma; or At least one emergency room claim with primary diagnosis of asthma, and a drug transaction for an asthma drug 90 days prior or 7 days following emergency room claim; or At least one inpatient claim with primary diagnosis of asthma; or
- A secondary diagnosis of asthma and a primary diagnosis of respiratory infection in the same claim.

We included only patients with evidence of outpatient prescription drug coverage and evidence of continuous plan enrollment during the pre-study (12 months) and follow-up periods (24 months), a total of 36 months. We followed subjects' resource utilization for twenty-four months after their index

date (the date on which these inclusion criteria are met). We excluded patients with a diagnosis of chronic obstructive pulmonary disease (COPD), or with one or more diagnosis or procedure codes indicating pregnancy or delivery.

In our analysis, total health care costs are actual payments to providers for all health services, including inpatient hospitalizations, outpatient services and filled prescriptions, whether or not directly related to asthma. Thus, our results are relatively insensitive to diagnostic coding mistakes or discrepancies.

The population of Base Case patients was subdivided into responders and non-responders using a binary measure of medication complexity as a proxy for whether the asthmatic responded to treatment over the study period. Asthmatics with a high level of medical complexity were designated Non-responders and were defined as patients with at least three different pharmaceutical prescriptions or with at least one asthma emergency room (ER) visit or hospitalization over the first 12 months of the study period. All other asthmatics were categorized as Responders, or asthmatics with a low level of medical complexity.

We simulated total healthcare costs under a variety of conditions, including test cost, test sensitivity, and the probability of treatment response. We randomly selected patients

without replacement based on the probability of response to treatment parameter (hereafter called "Sample A"). We used a "seed value" to retain the same randomly selected patients across iterations of the simulation. Based on the test sensitivity parameter, we randomly selected Non-responders from Sample A who would become Responders (hereafter called "Sample B"). Then to estimate the cost of being a Responder for each of the selected Non-responders, we randomly selected a Responder patient from the Base Case and assigned that patient's cost to the patient in Sample B. The cost of the test was added to the total healthcare costs for all non-responders in Sample A. We then compared these simulated costs (hereafter called "Test Case" costs) to the Base Case costs. Seven hundred variants of the simulation were run, examining 10 values of test sensitivity, 14 values of test cost, and 5 values of probability of treatment response (i.e., $700=10 \times 14 \times 5$).

The range of test costs we modeled was derived from data provided by the Molecular Diagnostic Testing Unit at a major teaching hospital in Boston. The reported costs, which represented a range of charges for genetic tests that are currently used in the hospital, across all disease categories, varied from \$135 to \$1850. In the simulation, we extended the range to \$100 to \$2100 to account for possible economies of

scale and the potential for more costly technological advances in the future.

The test sensitivity parameter determined the probability that Non-responders from the Base Case would become Responders in the Test Case. In our simulation, we iterated the value of this parameter from 0.1 to 1.0 in 0.1 increments to determine a model for the effect of this parameter on treatment costs using the test. Test specificity was not modeled in our algorithm since it does not impact the transition of Non-responders to Responders, and thus, under our hypothesis, it would not affect the difference in overall health care costs.

The probability of treatment response parameter determined the distribution of Responders and Non-responders in each simulation and was iterated in 0.10 increments beginning with the special case of the observed value of 0.667. We reasoned that the probability of treatment response could be higher than the response rate determined by the medical complexity analysis.

We compared the Base Case and Test Case costs, and used T-tests to evaluate the significance of the differences.

Results

We identified 28,324 asthmatics in the sample. The mean costs for all asthmatics over the study period were \$3,805. Using

medical complexity, we classified 66.7% as Responders and 33.3% as Non-responders, giving the observed 0.667 probability of treatment response. As expected, Non-responders had higher health care costs than Responders, with annualized mean costs of \$5,132 and \$3,140 per patient, respectively. The typical Responder in our sample experienced a 0.6% chance of an asthma-related emergency room visit, and a 0.4% chance of an asthma-related hospitalization during the 24-month study period. On the other hand, the typical Non-responder in our sample had an 8.7% chance of visiting the ER for asthma, and a 5.8% chance of being hospitalized for asthma, during the same period. These estimates are consistent with those from other recent studies of asthma costs using patient claims data. For example, Birnbaum *et al.* found that annual per-capita employer expenditures for asthmatic patients were 2.5 times higher than patients without asthma claims (\$5,385 versus \$2,121, respectively). [17]

Exhibit One shows the simulated mean cost savings for varying levels of test sensitivity, test cost, and treatment effectiveness. These selected results characterize the cost differential (Base Case - Test Case) and how it varies with test sensitivity and test cost and probability of treatment response. With low test costs, low diagnostic test sensitivity between 0.3-0.4 yielded positive cost savings. For diagnostic tests costing more than \$1,050, however, no cost-savings occur

regardless of the sensitivity of the test, or the effectiveness of the treatment. For all probabilities of treatment response examined, the cost savings increases with decreasing test cost and increasing test sensitivity.

Under the most favorable circumstances, with a test sensitivity of 100 percent and \$100 test cost, using the pharmacogenomic test could result in cost savings of \$410 per person per year even if use of the test did not result in any additional gain in treatment effectiveness. It seems likely, however, that the use of a pharmacogenomic test would also result in some additional gains in treatment effectiveness, even in the absence of new therapies, by directing patients to treatments to which they would be more likely to respond. The cost savings associated with incremental improvements in the effectiveness of therapies, when coupled with a diagnostic test, are also shown in Exhibit 1. It is apparent that the sensitivity of the diagnostic test influences the magnitude of potential cost savings more than improvements in the effectiveness of treatments. However, potential cost savings are also sensitive to the cost of the test.

Discussion

More than 30 years ago, Lewis Thomas, in his collection of "Notes of a Biology Watcher" from the *New England Journal of Medicine*, insightfully described the differences between what he called, "halfway technology" and the "genuine technology of medicine." He noted that new therapies based on a solid understanding of the underlying scientific mechanisms would make clinical decisions about treatment much easier. Thomas may well have correctly predicted that the "genuine technology of medicine" would come when new therapies would be based on a full understanding of scientific mechanism. He may not have realized how many new and different kinds of questions would be raised, as a result of the changes in the way treatment selection decisions and future R&D investment decisions are made. Nevertheless, he was writing – at least in part – about pharmacogenomics.

We found that personalizing therapy through the use of a diagnostic test would result in a cost offset from the perspective of payers when the test is sensitive and the cost of performing the test is relatively modest. From a societal perspective, the benefits of personalized medicine are potentially much greater than those demonstrated in this paper. This underestimate of benefits results largely because the analysis of medical costs does not include the indirect benefits that accrue to payers, employers and society when patients make

more rapid recovery from illness and resume productive lives. For example, Weiss *et al.* estimated that direct medical costs comprise approximately 58 percent of the estimated societal costs, with costs resulting from productivity loss accounting for the remaining portion. [18] Other societal costs include those associated with absences from school, quality of life, and caregiver burden [19-22].

The economic benefits that accrue from personalized medicine would be realized as cost offsets from avoided costs of treatment non-response, including unnecessary medication costs and potential adverse reaction treatment costs. In addition to prioritizing the economic viability of diagnostics aimed at multiple personalized medicine approaches such as dosing, side effects, or treatment response, the analytical framework developed here has the potential to guide the target profile of future drug discovery efforts.

Further Considerations The availability of a test for drug responders adds a layer of complexity to a set of similar decisions that are already commonplace. A key policy question will be whether the costs of treatment failure could be offset by the costs of diagnostic testing when a new diagnostic becomes available.

We now extend the results described above by offering a set of illustrative calculations to examine the tradeoffs between diagnostic testing costs and costs arising from the failure of the initial therapy selection. We analyze the following situation: Current practices for many diseases, including asthma, call for patients to be initially treated with a first line therapy. If they fail to respond, alternative therapies are selected until a suitable one is identified. Suppose there is a diagnostic test that can report the likely response of a given patient to alternative existing therapies. In reality, there may be a number of possible therapies from which to choose, and it would actually require layers of testing to narrow the field to the ideal drug. For simplicity, we are considering only one therapeutic alternative and one diagnostic test with 90% sensitivity and 100% specificity for 1000 patients.

Exhibit 2 presents the results of these calculations. Choosing to administer the diagnostic test to newly diagnosed patients at the outset incurs the cost of testing a large population but avoids the cost of non-response to the initial therapy. Testing only patients not responding to the initial therapy after six months would reduce testing costs by limiting the size of the population tested, but would incur greater costs of therapy as a result of treatment failures.

Columns C and D of table 2 present the three-year cumulative (without discounting) costs or cost savings associated with the two alternative strategies – test all early or test a sub-population later? Results of the calculations suggest that, when considering alternate existing therapies of comparable expense, testing all patients early on makes the most sense unless the test is costly or not sensitive.

A dimension of personalized medicine not directly considered in this paper is the pairing of diagnostic testing with novel treatments targeted specifically to individuals whom the tests identify as appropriate candidates. Novel treatments such as biologics, treatments based on recombinant DNA, etc., are increasingly providing treatment options for patients who are unresponsive to conventional therapies, or who have conditions for which no treatment previously existed. Often, however, such novel treatments are very expensive. The results in Exhibit 2 show that testing could even be valuable if the novel therapeutic is significantly more expensive.

Limitations of Analysis Our analysis is subject to the limitations associated with the use of a retrospective, administrative database to infer episodes of illness and medical care. In particular, with respect to medications, we are able to determine that prescriptions were filled, but not whether the

patients actually complied with the regimen. This limitation may be particularly important in the asthma context, in which some of the medications are likely to be prescribed for use on an "as needed" basis.

Policy Implications Sooner, rather than later, new drugs will begin to emerge as a result of the application of pharmacogenomics and other advances in biological sciences. Our increased understanding of the molecular basis of disease will likely yield efficiencies that will ultimately improve the quality of care and lower health-related costs. However, in the process of integrating this new knowledge and its related technologies, there will be substantial value migration in health care that will require new models to assess value and evaluate the true contribution to patient care.

Some of these drugs will prove to be highly effective, or much better tolerated than their predecessors, among certain members of a candidate pool that meet criteria that are identifiable with the help of a molecular marker. A diagnostic test, based on such a marker, will identify the patients who are the promising candidates. A portion of those who would benefit from the new drug may also be successfully managed with existing, less costly treatments. This paradigm suggests the need to carefully consider alternative clinical policies that assess the appropriate timing and evaluate the cost effectiveness of the

diagnostic test. Additionally, as scientific advances promise to bring extraordinary changes to the practice of medicine, it will be critical to ensure that commercial, scientific, technological and clinical incentives be aligned in order to facilitate the stream of innovative new therapies that we anticipate will emerge from medical research, and to maintain reliable access for physicians and for their patients. Our approach provides a new tool for these considerations. Our results suggest that diagnostic tests in the context of personalized medicine would be valuable in a wide range of circumstances.

Acknowledgments:

Exhibit 1

Selected simulation results, illustrating the value of pharmacogenomic testing in asthma treatment

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**Based on N=9,444 non-responding asthmatics

| Test Cost | Probability of Treatment Response | Annualized Cost Savings (\$)* | | | |
|-----------|-----------------------------------|--------------------------------------------------|-----|-----|------|
| | | Per Person at Various Levels of Test Sensitivity | | | |
| | | Test Sensitivity | | | |
| \$100 | | 1.0 | 0.9 | 0.5 | 0.1 |
| | 0.667 (observed) | 410 | 358 | 192 | 6 |
| | 0.70 | 452 | 393 | 198 | 2 |
| | 0.80 | 483 | 468 | 254 | 21 |
| | 0.90 | 588 | 515 | 283 | 48 |
| | 1.0 | 635 | 588 | 320 | 36 |
| \$350 | | | | | |
| | 0.667 (observed) | 326 | 275 | 109 | -77 |
| | 0.70 | 369 | 310 | 115 | -81 |
| | 0.80 | 399 | 384 | 171 | -62 |
| | 0.90 | 505 | 431 | 200 | -35 |
| | 1.0 | 551 | 505 | 237 | -48 |
| \$700 | | | | | |
| | 0.667 (observed) | 210 | 158 | -8 | -194 |
| | 0.70 | 252 | 193 | -2 | -197 |
| | 0.80 | 283 | 268 | 54 | -179 |
| | 0.90 | 388 | 315 | 83 | -152 |
| | 1.0 | 435 | 388 | 120 | -164 |

Exhibit 2

Cost savings (in parentheses) or burdens of using a pharmacogenomic test for drug efficacy in 1000 patients. In Scenario 1, patients not responding to the first-line treatment after six months are tested to determine the drug they are most likely to respond to. In Scenario 2, all patients are tested.

| Test Cost | Prob. Of Treatment Response | Annualized Cost Offset (from Exhibit 1) | A. Scenario 1 - 1 year out | B. Scenario 2 - 1 year out | C. Scenario 1 - 3 years out without discount | D. Scenario 2 - 3 years out without discount |
|-----------|-----------------------------|-----------------------------------------|----------------------------|----------------------------|----------------------------------------------|----------------------------------------------|
| \$100 | 0.7 | \$393 | (\$12,516.67) | \$8300.00 | (\$104,216.67) | (\$175,100.00) |
| | 0.9 | \$515 | (\$43,916.67) | (\$54,500.00) | (\$198,416.67) | (\$363,500.00) |
| \$350 | 0.7 | \$393 | \$70,816.67 | \$258,300.00 | (\$20,883.33) | \$74,900.00 |
| | 0.9 | \$515 | \$39,416.67 | \$195,500.00 | (\$115,083.33) | (\$113,500.00) |
| \$700 | 0.7 | \$393 | \$187,483.33 | \$608,300.00 | \$95,783.33 | \$424,900.00 |
| | 0.9 | \$515 | \$135,333.33 | \$504,000.00 | (\$60,666.67) | \$112,000.00 |

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