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The Value of Pharmacogenomic Information

John A. Graves, Zilu Zhou, Shawn Garbett, and Josh F. Peterson

A key objective of precision medicine is to guide health care decision-making with genetic data to improve patient care—a vision that is fueled by extraordinary advances in the discovery of genomic variation that predicts both disease risk and therapeutic response (Shurin and Nabel 2008). For example, the Food and Drug Administration (FDA) recognizes many interactions between gene variants and drug-related outcomes: currently more than 120 drug labels include references to germline genomic information that can affect prescribing across a wide array of diseases and conditions (FDA 2017). Yet while scientific evidence underlying precision medicine is expanding rapidly, parallel efforts to understand its economic dimensions remain lacking (Fragoulakis et al. 2015; Feero, Wicklund, and Veenstra 2013; Khoury et al. 2008).

Our focus here is on pharmacogenomics (PGx), or the application of genetic testing to guide drug selection and/or dosing. Among potential clini-

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cal uses for human genetics, pharmacogenomics is often cited as integral to the vision of how precision medicine might be immediately applied to routine clinical practice (Collins and Varmus 2015; Shurin and Nabel 2008; Conn 2017; Phillips et al. 2001; Ginsburg 2005). The promise of pharmacogenomics is informed not only by a growing base of scientific discovery on drug-gene associations, but also by technical improvements that have dramatically lowered the cost of genetic tests and increased the capacity of health information systems. For example, in 2001 it cost nearly $100 million to sequence a single human genome (NHGRI 2017); today, it costs roughly $1,000—approximately the cost of three outpatient specialist visits (Machlin and Scott 2015). Likewise, improvements in clinical information systems and interoperability have led to modern electronic health records (EHRs) that can store genotypic data and return actionable drug-gene information through decision aides at the point of prescribing (Gottesman et al. 2013; Pulley et al. 2012; J. F. Peterson et al. 2013; Denny et al. 2012).

Existing research on the value of pharmacogenomics has focused primarily on the short-term cost effectiveness of single-gene tests—an approach that ignores the potential lifetime value of multiplexed genetic testing strategies (Fragoulakis et al. 2015; Berm et al. 2016; Verhoef et al. 2016; Kazi et al. 2014). Compared with single-gene testing, these strategies—which include whole genome sequencing (WGS), whole exome sequencing (WES), and multiplexed genetic panel testing—facilitate the acquisition of wide swaths of genetic information all at once. Thus, a drug-gene pair for which single-gene testing is found to be cost ineffective could potentially improve overall value when integrated within a broader multiplexed testing strategy, since information on that gene can effectively be obtained at little to no marginal acquisition cost via WGS, WES, or panel testing.

Despite these potential advantages, the overall value of pharmacogenomic testing remains uncertain (Phillips and Van Bebber 2005; Fragoulakis et al. 2015). In part, this is because the scientific basis underlying pharmacogenomics is evolving (Zineh, Pacanowski, and Woodcock 2013; Phillips et al. 2001; Ginsburg 2005). In addition, this uncertainty also arises because the cascading impact of multiplexed testing on individual, provider, and payer incentives and behavior, as well as downstream health care spending and outcomes, remain poorly understood (Fragoulakis et al. 2015; Feero, Wicklund, and Veenstra 2013). As a consequence, reimbursement for genetic tests remains uneven and focused almost exclusively on payment for single-gene tests (Frueh 2013). This, in turn, has slowed investment and translation of broader pharmacogenomic testing strategies into clinical practice; currently, only a handful of health systems have implemented discrete pharmacogenomic data into their clinical workflows. These efforts have not been funded via reciprocal payer reimbursement, but rather using internal funds or from external (drug industry and NIH) sources. At the very least, if the economic dimensions underlying pharmacogenomics are not better understood it will

be difficult, if not impossible, to capture the potential value of pharmacogenomics in particular and precision medicine more broadly.

In this study, we couple evidence from a real-world implementation of pharmacogenomics with a discrete event simulation model for multiplexed genomic testing. In doing so, we build on theoretical insights to estimate both the value of pharmacogenomic information (i.e., the dollar-valued opportunity cost of not incorporating genomic information into therapeutic decision-making) and the cost effectiveness of alternative genomic testing approaches. Notably, the scalability and flexibility of our simulation approach affords us the ability to conduct large-scale probabilistic sensitivity analyses (PSA) under which we reestimate our model over a large (varying) parameter space. Coupled with novel methods in metamodeling and value of information (VOI) analysis, this allows us to identify key economic, scientific, and behavioral parameters that can affect decision-making on the optimal genetic-testing strategy. We discuss how these insights can be used to prioritize future research and to inform implementation of genetic testing in ways that maximize its value.

Our primary finding is that relative to a no-testing strategy, multiplexed genetic testing is not cost effective at the lower end of commonly used societal willingness-to-pay thresholds (e.g., $50,000 per quality-adjusted life year [QALY]). However, at slightly higher thresholds ($118,000/QALY or greater) a preemptive multiplexed testing strategy is optimal conditional on the ability of a health system to ensure that pharmacogenomic information is regularly utilized by clinicians. To the extent that physicians are no more likely to utilize genetic-testing information that was obtained upstream as they are to order a new genetic test, then a serial single-gene testing strategy is still preferred, particularly over short (e.g., ten-year) time horizons.

Given widespread churn in both physician patient panels and insurance markets (Graves and Nikpay 2017; Graves and Mishra 2016), as well as behavioral frictions that result in less than 100 percent of physicians ordering or acting upon the results of a genetic test (J. F. Peterson et al. 2016), these findings point to distinct design and financing challenges for pharmacogenomics. For example, the long time horizon over which the value of pharmacogenomic information accrues suggests that individual payers may have diluted incentives to reimburse for multiplexed pharmacogenomic testing, even if the resource cost of testing and storage distribution of genomic information is further streamlined. Indeed, our VOI results reveal that the most important parameters driving whether pharmacogenomic testing is cost effective are not related to the cost of the genetic test itself, but rather (a) the strength of evidence on the risk reduction in severe adverse events associated with a pharmacogenomically guided alternative therapy, (b) the additional social resources it takes to deliver a pharmacogenomic alternative, and (c) the likelihood that physicians procure and/or act upon genetic variants that affect the prescription. We demonstrate that these factors, focused

in particular on certain high-yield drug-gene pairs, are key to understanding how pharmacogenomic precision medicine can be most cost effectively integrated into routine clinical practice.

The remainder of this chapter proceeds as follows. The next section provides basic background information on pharmacogenomics, genomic testing strategies, and evidence on the implications of genetic testing on both individual and physician behavior. We also provide background information on PREDICT, the real-world pharmacogenomics implementation that directly informs our simulation model. We then outline a basic theoretical model of the value of genomic information that builds on prior work on the expected value of individualized care. Following that, we outline the details and assumptions of our discrete event simulation model. We next discuss the translation of the discrete event simulation (DES) model to a coupled time differential delay equation that facilitates probabilistic sensitivity analysis. We provide a brief overview of metamodeling and VOI methods we utilize to identify parameters with the greatest optimal decision leverage in our model, and that can be used to guide future research on pharmacogenomics. A results section follows, and a final section concludes.

3.1 Background

The utility of sequencing patients and return of actionable genetic variation has grown with the rapid pace of discovery within large sequenced cohorts, disease registries, and genomic medicine implementation studies (Green et al. 2016; Gottesman et al. 2013; Weitzel et al. 2016; Carey et al. 2016). The primary applications of germline sequencing are selection and dosing of therapies guided by pharmacogenomics and diagnosis, prognosis, or risk stratification guided by genomic variants informing disease risk.

Of particular relevance for the present study is the list of drug-gene pairs published by the Clinical Pharmacogenomic Implementation Consortium (CPIC). The CPIC provides guidelines for selecting or dosing medications based on pharmacogenomic variants (Relling and Klein 2011; CPIC 2017). The organization also rates the strength and robustness of evidence underlying drug-gene interactions and the clinical utility of use within affected populations. Similarly, the American College of Medical Genetics (ACMG) also publishes a curated list of potentially actionable disease-risk genes found in clinical exome or genome sequencing. These genes have strong associations with hereditary cardiomyopathies, familial cancer syndromes (e.g., Lynch syndrome, breast and ovarian cancer), and arrhythmias, among other conditions (Kalia et al. 2017).

3.1.1 Pharmacogenomic Testing Strategies

The application of pharmacogenomic testing in clinical settings can be considered using two types of strategies. One is reactive **serial testing of**

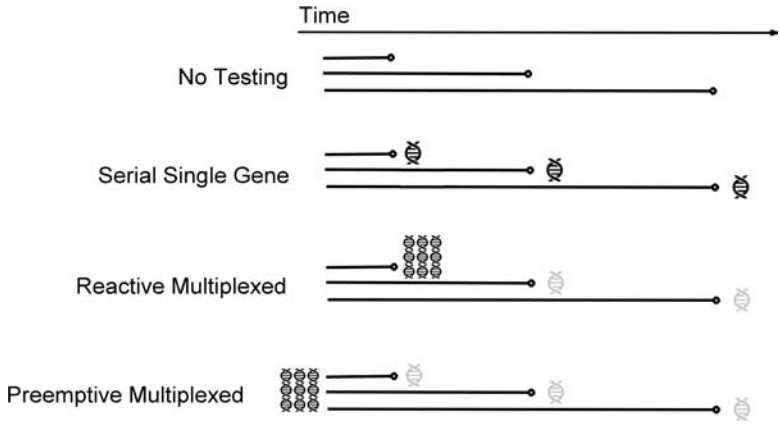

Fig. 3.1 Pharmacogenomic testing strategies

Notes: The figure provides visualizations of the genetic testing strategies considered for a hypothetical patient who experiences three indications for a drug with a pharmacogenomic alternative. Time is represented on the x-axis, while specific opportunities for genetic testing (e.g., a new drug indication) are indicated by the hollow rounded points. Single-gene testing is denoted by the single double helix. Multiplexed testing strategies (e.g., whole genome sequencing, whole exome sequencing, panel testing) are denoted by the cluster of nine double helixes. At a given indication time, the availability of genetic information obtained upstream (e.g., through earlier multiplexed testing) are denoted by a gray-shaded double helix.

single genes. Under this strategy, genotyping for specific variants is undertaken in individual subjects at the point of care, and then acted on when the results become available (typically within a week). By comparison, under a **multiplexed** strategy, dense genotypic information is acquired once using a genetic panel test or through WGS or WES. This information is then stored in advanced EHR systems, allowing genotype-based recommendations to be routinely delivered in the future (Schildcrout et al. 2012). Multiplexed testing could be carried out either *reactively* (i.e., panel-based testing or sequencing is initiated at the first pharmacogenomic drug indication) or *preemptively* (i.e., testing is carried out upstream of any drug indication under the expectation that the information will be stored and available for future use). Figure 3.1 summarizes these drug-testing scenarios.

3.1.2 Reimbursement Policy for Pharmacogenomic Testing Strategies

With the decreasing cost of genotyping and the very high cost of severe adverse events (e.g., warfarin-related intracranial hemorrhage is estimated to cost approximately $40,000; see Ghate et al. [2011]), multiplexed genomic screening may represent a more cost-effective approach to the current clinical standard of single-gene testing. The marginal cost of obtaining additional genomic information in a panel test is small, and is virtually nonexistent in sequencing-based strategies that capture nearly all of an individual's actionable germline genomic information. Meanwhile, advances in clinical

information systems and lessons from real-world implementations have yielded low-cost strategies for the storage and dissemination of genomic testing information through EMRs and decision aides. (Pulley et al. 2012; Delaney et al. 2012; Denny et al. 2012).

Despite these favorable properties, reimbursement of multiplexed and even single-gene testing from major public and private payers remains uneven (Feero, Wicklund, and Veenstra 2013; Khoury et al. 2008; Frueh 2013; Teng et al. 2012; Scott 2011; Cohen 2012; Faulkner et al. 2012). Limited support for reimbursement of PGx reflects the reality that the majority of payers view genetic testing as experimental (Khoury et al. 2008; Grosse 2014; Feero, Wicklund, and Veenstra 2013). Reimbursement challenges are particularly acute for genomic screening because of the pace of innovation and the size of the potential impact. For example, a recent Blues plan coverage policy stated:

> genetic panels are considered investigational because the current scientific evidence is not yet sufficient to establish how test results from panels which include a broad number of genes may be used to direct treatment decisions and improve health outcomes associated with all components of the panels. (BCBS 2013)

This policy was developed because of valid concerns about the generation and return of ancillary information (i.e., "incidental" findings that point to susceptibility of disease risk), as well as concern about the scientific validity of markers that were being included in sequencing panels.

In addition, it is increasingly clear that what happens *downstream* of genetic testing is also a critical determinant of payers' skepticism (Kohane, Hsing, and Kong 2012; Vassy et al. 2017). For example, a 2005 randomized controlled trial of genetic testing for Alzheimer's disease found that individuals who tested positive were 5.76 times more likely to adjust their long-term insurance plans (Zick et al. 2005). In a more recent randomized controlled trial (RCT) of WGS, patients randomized to WGS were twice as likely to be recommended a new clinical action (e.g., a follow-up visit or referral to a specialist) from their primary care physician (Vassy et al. 2017). Moreover, patients receiving WGS had overall six-month spending patterns that were 30 percent higher than the non-WGS arm, mostly due to higher rates of follow-up lab tests and specialty visits (Vassy et al. 2017). These results have fueled concerns over whether genetic testing will exacerbate adverse selection into insurance plans, or might otherwise raise costs in the health care system.

3.1.3 Toward Better Evidence for Pharmacogenomics

There are distinct challenges to understanding whether the additional health benefits from pharmacogenomics are worth the additional costs they induce. For one, given the low incidence of adverse events and the rela-

tive infrequency of risk alleles, few PGx scenarios have support for overall economic or clinical benefit when measuring genetic variants to care for an average risk population. Cumulatively, however, the potential value of pharmacogenomics may be large. For example, a recent retrospective study of 52,942 patients in a Vanderbilt University Medical Center (VUMC) medical home population revealed that over a five-year period, nearly two-thirds were exposed to at least one of fifty-six CPIC drugs (Schildcrout et al. 2012). Within this population, an estimated 383 severe adverse events over five years could have potentially been avoided had pharmacogenomic information been utilized (Schildcrout et al. 2012).

The collection of evidence on the value of pharmacogenomics is difficult, however, because the lifetime benefits of screening for gene variants are exceedingly difficult to estimate experimentally using standard research strategies. Clinical trials and prospective cohorts typically measure short-term benefits or harms of disclosing genetic data to patients and their physicians. The time horizon for assessing clinical and economic differences after personalized screening interventions or even genetically tailored preventive therapy may be exceptionally long, often decades. In addition, the benefits (or harms) will likely vary based on patients' demographics, variant rate, phenotype status, family history of disease, environmental exposures, and other nongenomic risk factors. Many of these factors are rarely, if ever, collected as baseline measures in an RCT if they do not relate directly to the trial design itself.

Designing research studies to explain how clinical benefits may change within all of these key subgroups is not feasible without very large sample sizes and long-term follow-up. Even if feasible, RCT-derived data often does not provide the external validity to implement genetic testing in diverse, uncontrolled clinical practice settings. For these reasons, synthesizing direct and indirect evidence on the costs and benefits of pharmacogenomics testing within a modeling framework offers a way forward for understanding the trade-offs of implementing personalized medicine in practice, and ultimately informing both future research priorities and precision medicine reimbursement policy. That is the goal of this study.

3.1.4 Evidence from Pharmacogenomics Implementations

Direct, real-world evidence for our model is derived from the Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment (PREDICT) program, a clinical quality improvement initiative at VUMC (Pulley et al. 2012). This program has genotyped almost 15,000 patients since 2010 as a part of routine care. Through PREDICT, VUMC established procedures for applying clinically significant gene variants to decisions involving drug selection and dosing. As a distinctive feature of the program, healthy outpatients are prospectively identified (using a prediction model) as candidates for genotyping based on their likelihood of

receiving certain drugs in the future. These patient records are subsequently monitored to assess the impact of genetic variant information on physician decision-making and subsequent utilization and clinical outcomes. VUMC has already implemented five functional algorithms (warfarin dosing, antiplatelet therapy selection, thiopurines (azathioprine and mercaptopurine), tacrolimus, and simvastatin guidance), with more in development. The PREDICT program has served as a prototype for a general understanding of applying multiplexed genomic data in practice (Teutsch et al. 2009; Khoury et al. 2009; Gottesman et al. 2013; Weitzel et al. 2016; Johnson and Weitzel 2016).

We draw upon the PREDICT cohort for several parameters that inform the construction of our model. First, we utilize the PREDICT medical home cohort of 140,166 patients to query the frequency at which they were prescribed the forty-two CPIC Level-A drugs. These drug frequency estimates are then used to classify each drug-gene pair into one pharmacogenomic class, as described in the simulation approach section below. Second, we draw upon internal data on physician responses to genotyping to inform parameters governing physician utilization of genotyping information in our model. These parameters, for example, are set to reflect the observation that only about 50 percent of physicians switched to a pharmacogenomic alternative for antiplatelet therapy in cases where the patient was identified as a poor or intermediate metabolizer of clopidogrel, a CPIC Level-A drug (J. F. Peterson et al. 2016).

3.2 Theory: The Value of Genomic Information

To further motivate our simulation approach, we first outline a framework for how a simulation model might be used to estimate the value of genomic information (VOGI). This framework is based on the model developed by Basu and Meltzer (2007), which draws on Bayesian decision theory and value of information methods (Basu and Meltzer 2007; Claxton et al. 2001; Claxton and Sculpher 2006). Conceptually, the VOGI model provides a framework for estimating the opportunity cost (if any) of failing to incorporate genetic information into therapeutic decision-making.

Suppose that patients are heterogeneous in their characteristics, and in particular they vary in their susceptibility to adverse events based on genomic traits that affect their ability to metabolize drugs. Assume this heterogeneity is captured by model parameters $\boldsymbol{\pi} = \{\pi_1, \ldots, \pi_I\}$, and that for a given drug treatment option α (e.g., a standard therapy and a costlier pharmacogenomic alternative therapy) quality-adjusted life years and costs are captured by $Q(\alpha, \boldsymbol{\pi})$ and $C(\alpha, \boldsymbol{\pi})$, respectively.

We next define the net monetary benefit (NMB) as a summary measure of cost effectiveness. The NMB is a common metric summarizing (in dollar terms) the health benefits and costs of a given strategy (Neumann et al.

2016). In this context, the NMB for alternative drug treatment strategies is captured by

$$\text{NMB}(\alpha, \boldsymbol{\pi}) = \lambda \cdot Q(\alpha, \boldsymbol{\pi}) - C(\alpha, \boldsymbol{\pi}), \tag{1}$$

where λ is the fixed value of the marginal societal willingness to pay for an incremental health improvement (i.e., \$100,000/QALY). Thus, NMB captures the (dollar-valued) overall health benefit of a given drug therapy, net of the costs of administering the therapy.[1] In a baseline (i.e., no testing strategy), physicians are unaware of their patients' genetic variant status and base their prescribing decisions on the distribution of α in the population.

In a standard cost-effectiveness analysis, the strategy that maximizes the NMB across the population would be selected as the "optimal" strategy (Neumann et al. 2016). That is, this strategy yields the largest (dollar-valued) health gain net of its costs for a given willingness to pay and among the strategies under consideration

$$\max_{\alpha} \quad E_{\boldsymbol{\pi}}[\text{NMB}(\alpha, \boldsymbol{\pi})]. \tag{2}$$

Based on population average risk, the optimal strategy under this approach may be to treat all patients with the standard therapy, even though the alternative drug may produce superior net health benefits for a select population of individuals with a genetic variant.

Now suppose that physicians can directly observe and act upon patient heterogeneity in response to the drugs, and that they do so 100 percent of the time. In other words, the physician optimally chooses a drug therapy and maximizes the NMB for each patient. In that case, the average NMB for the population is given by

$$E_{\boldsymbol{\pi}}[\max_{\alpha} \quad \text{NMB}(\alpha, \boldsymbol{\pi})]. \tag{3}$$

We obtain an estimate of the VOGI by taking the difference between equations (3) and (2):

$$\text{VOGI} = E_{\boldsymbol{\pi}}[\max_{\alpha} \quad \text{NMB}(\alpha, \boldsymbol{\pi})] - \max_{\alpha} \quad E_{\boldsymbol{\pi}}[\text{NMB}(\alpha, \boldsymbol{\pi})]. \tag{4}$$

Conceptually, the VOGI provides an estimate of the opportunity cost (in dollar terms) of failing to incorporate genetic information into therapeutic decision-making (Basu and Meltzer 2007). In other words, for a given λ it provides an estimate of the maximum amount society would be willing to pay (per patient) to implement genotype-tailored care. We will return to this conceptualization of VOGI in the results section by fitting our model under two strategies: (a) a no genotyping strategy, and (b) a strategy in which information on patients' genetic variant status is obtained (for free) and acted upon 100 percent of the time, as above. The estimate NMB difference

1. A related concept, the net health benefit (NHB), captures the gain in QALYs net of any (QALY-valued) costs: $\text{NHB}(\alpha, \boldsymbol{\pi}) = Q(\alpha, \boldsymbol{\pi}) - C(\alpha, \boldsymbol{\pi})/\lambda$.

between these two strategies provides an estimate of VOGI in our simulated patient population.

3.3 Simulation Approach

Our estimates of the VOGI and cost effectiveness of alternative genomic testing strategies are drawn from a discrete event simulation (DES) model. Specifically, this model simulates the lifetime trajectories of patients who are at risk of developing an indication for any one of the forty-two CPIC Level-A drugs (i.e., none of the simulated patients are on any of the CPIC Level-A drugs at the initiation of the model).

Discrete event simulation is a modeling methodology designed to incorporate the timing and interdependency of events (Karnon et al. 2012; Caro and Möller 2016; Standfield, Comans, and Scuffham 2014). Though its origins are in industrial engineering and operations research, DES is increasingly used in health technology assessments (Standfield, Comans, and Scuffham 2014; Jacobson, Hall, and Swisher 2006; Stahl 2008). For example, in a DES it is straightforward to allow the probability of some future event to depend on the time spent in a given state (e.g., the probability of a pharmacogenomically related adverse event declines as the amount of time spent on the drug increases). In addition, in cases where pharmacogenomic information informs the initial dosing of a drug (e.g., in the case of warfarin, which has received a great deal of pharmacogenomic attention), DES can readily accommodate the arrival rate of the genomic information. Such dynamics are difficult, if not impossible, to model using more standard Markov approaches (Caro and Möller 2016).

3.3.1 Simple Pharmacogenomic Model Structure

Our DES model tracks a population of forty-year-old females at risk of exposure to an array of up to $K = 42$ CPIC drug indications with potentially actionable pharmacogenomic drug selection and/or dosing opportunities. The choice of forty-year-old females allows us to match secular mortality in our model to observed life expectancy as reported in current US life table data; in principle, any age-gender combination—or even a distribution of ages and genders matching any observed population—could be used.

For a given drug indication k, exposure over time is defined based on an exponential distribution—though, again, any statistical distribution, or even an empirical distribution matched to observed data—could be used. Moreover, for the sake of modeling simplicity we assume that drug exposures are independent events.[2]

2. In an ongoing cardiovascular drug-gene panel model, we relax these assumptions by modeling time-to-drug exposure using a Weibull distribution with copulas that capture the dependence in exposure across different drugs. (See www.rightsim.org for more information.)

Individuals exposed to drug k are at risk of a composite adverse event (e.g., acute myocardial infarction [AMI], bleed, muscle myopathy) that carries a case fatality rate and a permanent utility decrement among survivors. In this simple scenario, we assume that all individuals exposed to the drug indication are prescribed a standard therapy. Each individual is followed until death, and remains at risk of an indication for all K drugs throughout their lifetime. However, once an individual is exposed to a given drug she is no longer at risk of a second exposure to that drug.

Our model also includes a pharmacogenomic alternative therapy that, if administered to individuals with a genetic variant, reduces the risk of the composite adverse event. Our baseline case assumes that 20 percent of the population has the genetic variant and models a relative risk of 0.70 for the composite event under the pharmacogenomic alternative. This value tracks closely with recent evidence on the risk reduction of a composite adverse event from genomically tailored dosing of warfarin (Gage et al. 2017). However, as noted below in our PSA analysis, we test the sensitivity of the model to a wide range of gene prevalence and relative risk values.

For the reference case we also assume the pharmacogenomically guided alternative is costlier than the standard therapy. Because we consider a societal perspective, this cost difference is not a reflection of differences in price. Rather, these costs reflect the reality that identifying patients with a genetic variant and delivering a pharmacogenomic alternative involves an opportunity cost that requires additional resources (e.g., the costs of implementing genetic testing data storage and dissemination of results at the point of service). Likewise, use of a pharmacogenomic alternative may also trigger additional downstream utilization and/or testing. The incidence of these costs on society would also be captured by the higher relative cost of the pharmacogenomic alternative in our model.

Our baseline case assumes that the relative cost of the pharmacogenomic alternative is three times the standard therapy—though, again, we test the sensitivity of this assumption by allowing the relative cost parameter to vary over a large range of values. Notably, this also allows us to consider our results in light of different perspectives. When viewed through the lens of a health care system perspective, for example, costs may also reflect differences in drug acquisition costs due to pricing differences (Garrison et al. 2010; Hay et al. 2010). For instance, during their exclusivity periods the costs of prasugrel and ticagrelor—the pharmacogenomic alternatives to generic clopidogrel—are considerably higher.

Figure 3.2 provides a Petri net representation of the DES model structure for a single-drug scenario k.[3] The figure plots a bipartite network in which the nodes represent events (e.g., initial drug indication, adverse event, secu-

3. A Petri net diagram is a bipartite graph representation of a discrete event dynamic system (J. L. Peterson 1981).

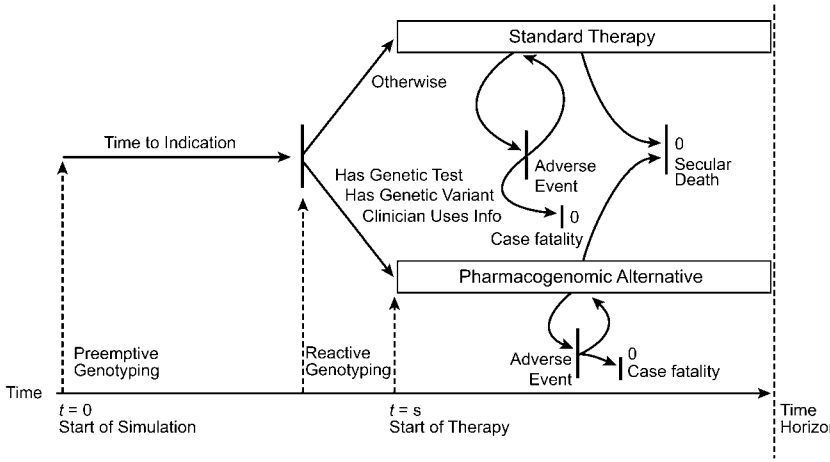

Fig. 3.2 Discrete event model structure for a single pharmacogenomic scenario

Notes: The figure provides a Petri net representation of the DES model structure for a single-drug scenario. The figure plots a bipartite network in which the nodes represent events (e.g., initial drug indication, adverse event, secular death), and the directed arrows describe the states from which individuals can flow into each node. Time is represented on the bottom axis. All drug scenarios have an identical structure, though with differing values for the underling parameters.

lar death), and the directed arrows describe the states from which individuals can flow into each node. Time is represented on the bottom axis. All drug scenarios in our model have an identical structure, though with differing values for the underling parameters.

3.3.2 Mapping CPIC Level-A Drugs to the Simple Model

The generic pharmacogenomic model described above can be summarized (for a given drug scenario k) using a set of discrete set of parameters π_k. Because the DES modeling structure is modular, we can easily scale up our model to accommodate the $K = 42$ drug scenarios captured in the CPIC Level-A list. That is, our estimates below are the result of simulating the drug experiences of a patient population as they are simultaneously exposed to forty-two specific pharmacogenomic scenarios over the remainder of their lifetimes.

In principle, a different parameter set based on the published literature or based on observed estimates from a genotyped cohort could be defined for each of the forty-two CPIC drug-gene scenarios. Moreover, ideally an "enriched" submodel could be constructed that captures the set of trajectories that could be experienced by a patient under each specific drug-gene scenario.[4]

4. Indeed, in parallel work (available at www.rightsim.org) we construct drug-specific submodels for three common cardiovascular drugs: warfarin, clopidogrel, and simvastatin.

However, to fully model all forty-two drug-gene pairs, the resources, data requirements, and computation time would be prohibitively expensive.

For these reasons we simplify our model by mapping the forty-two CPIC drug-gene pairs to one of seven pharmacogenomic scenarios. These scenarios are characterized by three specific criteria: (a) the frequency at which the drug is prescribed, (b) the frequency of the composite adverse event, and (c) the severity of the adverse event. For each CPIC drug-gene pair, we queried both the literature and our medical home cohort data and assigned values of "high" and "low" to each of the three criteria. For example, the drug-gene pair for warfarin mapped to the high-high-high scenario because warfarin is a commonly prescribed drug, adverse events are frequent (warfarin-related complications are among the most common reasons for emergency department visits in the United States), and the adverse events potentially averted by pharmacogenomically guided therapy are severe (these events include bleeding and blood clots that can lead to stroke or acute myocardial infarction). By comparison, simvastatin is another commonly prescribed drug with a common, but much less severe, side effect (myopathy, or muscle soreness). For these reasons the simvastatin drug-gene pair is mapped to a high-high-low pharmacogenomic scenario. A full listing of the CPIC drug-gene pairs and their mapping to the seven pharmacogenomic scenarios is provided in table 3.1.

3.3.3 Baseline DES Model

Table 3.2 provides a summary description of the baseline parameter values that form the underlying basis for our DES model. For each genetic testing strategy, we model a baseline scenario for ten million patients in which we summarize the average QALYs and costs incurred across the population. We utilize a limited societal perspective (i.e., we consider drug costs in terms of social resource opportunity costs, not prices, but do not directly model indirect effects of lost productivity and wages downstream of adverse events). We also discount all benefits and costs using a standard 3 percent discount rate. All patients in the DES model are tracked from initiation until death, either due to case fatality from an adverse event or secular causes.

3.3.4 Probabilistic Sensitivity Analyses

While DES affords significant modeling flexibility, one downside is its computational burden. To reduce first-order (stochastic) uncertainty in a model where only a fraction of patients experience a drug exposure and where adverse events are rare, millions of patient trajectories must be simulated. Even with optimized computing software, a DES model with multiple pharmacogenomic drug scenarios can take several hours to execute, even in a multicore distributed cluster computing environment.[5] This computation

5. Advanced Computing Center for Research and Education (ACCRE). Accessed Apr. 4, 2018. https://www.vanderbilt.edu/accre/.

Table 3.1 CPIC drug-gene mapping

Scenario name	Prescribing frequency	Adverse event frequency	Adverse event severity	Gene	Drug name	FDA recommendation
LHH	Low	High	High	TPMT	azathioprine	Testing recommended
				DPYD	capecitabine	Actionable PGx
				DPYD	fluorouracil	Actionable PGx
				CFTR	ivacaftor	Testing required
				TPMT	mercaptopurine	Testing recommended
				G6PD	rasburicase	Testing required
				TPMT	thioguanine	Actionable PGx
				IFNL3	peginterferon alfa-2b	Actionable PGx
HHL	High	High	Low	CYP2C19	amitriptyline	
				CYP2D6	amitriptyline	Actionable PGx
				CYP2D6	fluvoxamine	Actionable PGx
				CYP2D6	ondansetron	Informative PGx
				CYP2D6	paroxetine	Informative PGx
				SLCO1B1	simvastatin	
				CYP2C19	citalopram	Actionable PGx
				CYP2C19	escitalopram	Actionable PGx
LLL	Low	Low	High	HLA-B	abacavir	Testing required
				HLA-B	allopurinol	
				UGT1A1	atazanavir	
				HLA-B	carbamazepine	Testing required
				CYP2C9	phenytoin	Actionable PGx
				HLA-B	phenytoin	Actionable PGx
				CYP2C19	voriconazole	Actionable PGx
LHL	Low	High	Low	CYP2D6	codeine	
				CYP2D6	nortriptyline	
HLL	High	Low	Low	CYP2D6	tropisetron	
HLH	High	Low	High	CYP2C19	clopidogrel	
HHH	High	High	High	CYP2C9	warfarin	Actionable PGx
				CYP4F2	warfarin	
				VKORC1	warfarin	Actionable PGx

time severely limits our ability to perform an important component of our analysis: probabilistic sensitivity analyses (PSAs).

In a PSA, model parameters are assigned distributions rather than values; the simulation is then run iteratively by drawing a new set of parameter values from the joint distribution of parameter values each time the model is run. The PSAs are an important tool for identifying parameters with the greatest leverage, understanding variation in the estimated outcomes as parameter values are varied, and performing VOI analyses that can inform future research priorities (Neumann et al. 2016).

Table 3.2 Model parameters

Parameter	Baseline value	PSA distribution
Risk allele (genetic variant) prevalence	0.2	beta(20,80)
Risk reduction from PGx alternative	0.7	beta(7,3)
Probability PGx test ordered	0.5	uniform(0,1)
Probability upstream PGx information used	0.75	uniform(0.5,1)
Ten-year drug indication rate		
Low scenario	0.02	beta(2,98)
High scenario	0.15	beta(15,85)
Three-year adverse event rate		
Low scenario	0.05	beta(5,95)
High scenario	0.15	beta(15,95)
Disutility: Adverse event		
Low scenario	0.02	beta(2,98)
High scenario	0.1	beta(10,90)
Adverse event case fatality rate		
Low scenario	0.001	beta(1,999)
High scenario	0.05	beta(5,95)
Cost: single-gene test	100	uniform(0,200)
Cost: Panel test	250	uniform(0,500)
Cost: Standard therapy (daily cost)	1	
Cost: PGx alternative (daily cost)	3	constant(1,5)
Cost: Adverse event		
Low scenario	2,500	
High scenario	15,000	
Cost: Adverse event (case fatality)		
Low scenario	10,000	
High scenario	10,000	

Representation as Coupled Delay Differential Equation

To facilitate PSA analyses, we converted the DES model structure described above into a set of coupled time delay differential equations (DEDEs). Estimates derived from the numerical solution to the DEDE effectively eliminate stochastic uncertainty from the model, and provide for very fast model executions that return expected average outcomes (i.e., average QALYs and costs for a given strategy).[6]

6. The DEDE approach returns a point estimate within the relative error of the numerical solver (in our case 1e-9) and can represent exactly the same models as DES. The DEDE provides no estimate of variance, however. The DES converges on the DEDE number based on the number of trajectories simulated, that is, each log scale increase in the number of trajectories results in a log scale increase in accuracy of simulation, and can be used to assess the expected variance of a population. For example, a DEDE matched to a DES with two million trajectories would give us four digits of accuracy for the mean outcome value of QALYs or costs. We can further verify the equivalence of the models by comparing cumulative counts of events, as we show in the appendix figure.

A downside to the DEDE modeling approach is that it does not provide details on event counts, patient attributes, or variance in outcomes among the simulated population—all of which are feasible in a standard DES. We therefore view our DEDE approach for PSAs as complementary to the DES model, which can be run to provide rich detail on the value of pharmacogenomic testing (e.g., number of adverse events averted, number needed to genotype to avert an adverse event) that may be of interest to payers, clinicians, and policymakers.

To construct our differential delay model, we treat time as an independent variable and create a series of variables each representing a state that an individual could occupy at a point in time in a manner similar to Markov chain modeling. Each of these variables can take a value from 0 to 1, representing the average expected occupancy of the population at that point in time. We treat each pharmacogenomic drug indication type as a submodel in a series of coupled models, and individual occupancy in any given submodel (including deaths) must total to 1.

If all rates were fixed values, this would be equivalent to solving a Markov chain model. However, in differential equations, rates can depend upon current occupancy of a node. This allows for a richer set of modeling tools. For example, our submodels are coupled by two principal effects: rates of multiplexed panel testing and death rates from other submodels. If a condition in one submodel triggers a multiplexed panel genomic test at a rate proportional to its population, then this transition rate affects all submodels. Further, individuals dying from adverse events in one drug submodel must die in all other drug models. Another benefit is that the secular death rate is a function of time in models, and this time-varying rate is taken from the 2011 Social Security death data and splined into a smooth curve. One could additionally use rates that correspond to probability distributions via the following transform: rate = $\varphi(t; \theta)/(1 - \phi(t; \theta))$ when a distribution represented arrival times. In this simulation, we use exponential arrival times to condition indicators for each submodel.

Inside each submodel, counter variables are also used to keep track of occurrence of indication, adverse events, and adverse events resulting in death. The overall structure of the model facilitates a solution via coupled ordinary differential equations. However, the indicator condition carries a temporary disutility cost that occurs over a period of time and cannot be modeled as a simple fixed cost. To model this, a special tracking variable is used that allows for occupancy entrance based on a fixed rate and exit based upon entering occupancy at a point in the past minus death over that period. This requires the rate to depend on a value at another point in time, and thus requires techniques of delay differential equation for solving this variable.

Figure 3.3 summarizes the parameters in the DEDE model. The PSA distributions for all model parameters are provided in table 3.2.

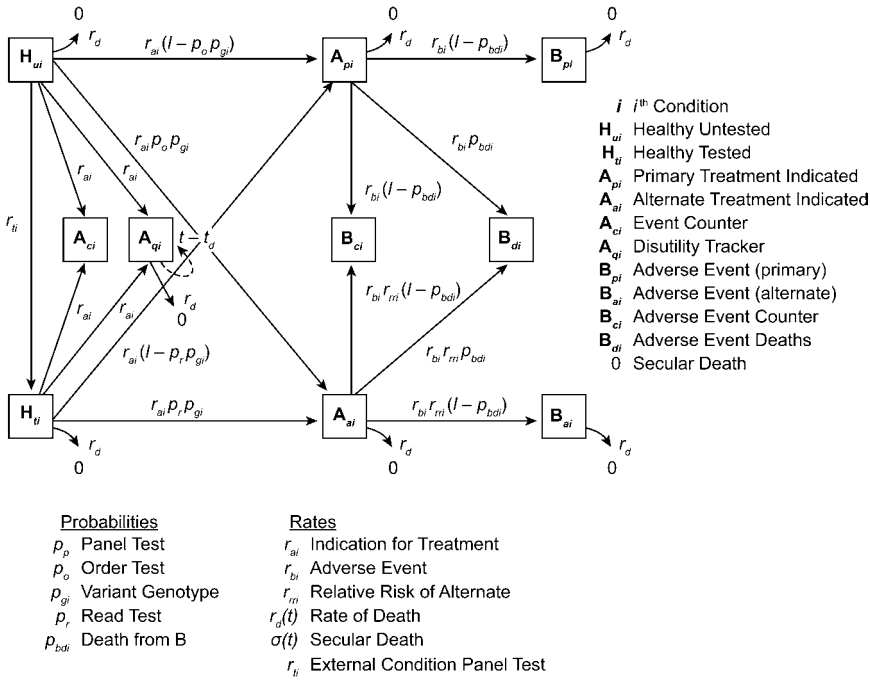

Fig. 3.3 Delay differential equation representation of a single pharmacogenomic scenario

Note: Figure provides a representation of the DEDE for a single-drug scenario.

Metamodel

The numerical solution to the DEDE facilitates a PSA in which we allow each model parameter to vary based on a prespecified distribution. For example, in our PSA we test the sensitivity of the overall average QALY and cost outcomes to differences in the probability that genetic information is ordered and/or acted upon. We do so by allowing these parameters to vary across the PSA model runs. Furthermore, we also assess whether the optimal genetic testing strategy changes if the cost of the pharmacogenomic alternative increases, or if the cost of genetic testing declines, and so forth.

To execute our PSA, we define a parameter space by specifying distributions for nearly all parameters in our model (see table 3.2). We then reestimate the numerical solution to the DEDE model 5,000 times using a Latin hypercube sampling design, each time drawing and fitting the model using a newly sampled set of parameters. The use of Latin hypercube sampling ensures that we efficiently obtain a near-random sample covering the multidimensional parameter space.

Based on the PSA model runs, we then fit a metamodel that regresses the

outcomes for a given strategy (e.g., average QALYs, average costs, NMB, or NHB) on the parameter values, which are first rescaled to have mean zero and standard deviation 1 (Jalal et al. 2013; Jalal, Goldhaber-Fiebert, and Kuntz 2015). Thus, the coefficients and predicted values from the metamodel can be used to assess how the outcome for a given strategy changes as a given parameter value varies, while holding all other parameters fixed at their mean value.

For our sensitivity analyses we are interested in identifying parameters and threshold values that determine whether the optimal genotyping decision changes. To do this, we fit a multivariate metamodel with the net health benefit (NHB) for each genotyping strategy as the outcomes, and with the parameters of interest entering as flexible splines. Following recent work by Jalal and Alarid-Escudero (2017), we fit the metamodel using a generalized additive model (GAM) to flexibly estimate the relationship between the varying model parameters and the outcome. We then use this model to predict the NHB across the observed range of values. At each set of values we identify the strategy with the maximum NHB (i.e., the optimal strategy at that value). These calculations form the basis for the one- and two-way sensitivity plots presented in the results section.

Expected Value of Partial Perfect Information

The metamodel specification previously described provides a linear approximation to the main DES/DEDE model. That is, the metamodel can be used to predict changes in the outcomes given a change in the underlying parameters. However, while this method can be used to identify parameters that yield the largest predicted changes in outcomes, this information may be useful only insofar as it informs decisions on the optimal genotyping strategy. For example, for a societal willingness-to-pay threshold (e.g., $50,000/QALY), varying a given parameter over a plausible range may result in large changes in the outcome, but it may not result in *any* change to the optimal decision; in that case, our decision to genotype or not genotype is mostly uninformed by the specific value of that parameter, whatever it may be.

To identify and prioritize model parameters that drive uncertainty in decision-making, we estimate the expected value of partial perfect information (EVPPI) as a measure of model uncertainty (Campbell et al. 2015). The EVPPI provides a dollar- or health-valued estimate of the cost of resolving all uncertainty in a model (Neumann et al. 2016). Because the EVPPI identifies parameters that contribute to uncertainty in *decision-making*, the estimates can be used to guide future research prioritization for precision medicine.

To estimate the EVPPI for each parameter in our model, we define a metamodel outcome that, for each genotyping strategy under consideration, is the result of a loss function that is the difference between the estimated NMB for the strategy in that PSA model run and the NMB for the (overall) optimal strategy determined under the baseline value run. In other words,

this loss function provides an estimate of the (dollar-valued) opportunity cost of identifying the wrong optimal genotyping strategy

$$L(\alpha, \boldsymbol{\pi}) = \text{NMB}(\alpha, \boldsymbol{\pi}) - \text{NMB}(\alpha^*, \boldsymbol{\pi}).$$

For example, suppose that under the baseline run that for a given λ value, the NMB for the optimal (no genotyping) strategy is $100. Now suppose that for a given PSA model run, the NMB for the preemptive panel testing strategy is $102. In that case, the opportunity loss of identifying the wrong optimal strategy under baseline is $2. By comparison, if the NMB for the preemptive panel strategy were $98, then the opportunity loss would be $0 since the same decision was made under both the baseline and the PSA model run.

To produce our estimates of the EVPPI we fit a metamodel that regresses the opportunity loss outcome on the (varying) model parameters:

$$L(\alpha, \boldsymbol{\pi}) = \beta_0 + \beta_1 + e.$$

We also fit the EVPPI results over a range of values of λ to assess how the estimates change under a range of societal willingness-to-pay thresholds.

3.4 Results

3.4.1 Value of Genomic Information

Before examining the cost effectiveness of specific genetic testing approaches, we first aim to estimate the value of pharmacogenomic information—that is, the (dollar-valued) opportunity cost of not incorporating genetic information into therapeutic decision-making. This estimate is directly linked to the VOGI defined in the previous theory section.

To estimate the VOGI, we utilize our DES model to calculate outcomes under two scenarios: one in which no genetic information is used, and another in which genomic information is obtained at no cost and is acted upon 100 percent of the time (i.e., patients with the genetic variant are always prescribed the alternative therapy). This latter scenario is intended to capture an idealized world in which physicians could observe and optimally act on genetic heterogeneity.

To identify and decompose which pharmacogenomic scenarios drive our value calculations, we repeat this exercise separately for the seven scenarios (i.e., the CPIC mappings) as described above.[7] The difference in average

7. When estimating the VOGI for a specific pharmacogenomic scenario, we allow the other scenarios to run out in our model as well, though without the genomic information being used. This allows for apples-to-apples comparisons of VOGI estimates that are not affected by competing risks (e.g., fatal adverse events) issues that would come up if we only modeled a single scenario at a time.

Table 3.3 Value of genetic information

Prescribing frequency	Adverse event frequency	Adverse event severity	VOGI (λ = $50k/QALY)	VOGI (λ = $100k/QALY)	VOGI (λ = $150k/QALY)
Low	High	Low	–76	–62	–48
Low	Low	High	–43	12	68
High	Low	Low	–608	–552	–496
High	High	Low	–517	–418	–320
Low	High	High	9	108	207
High	Low	High	–279	110	498
High	High	High	–59	628	1,316

NMB between the "no testing" and the "free testing" approaches provides an estimate of the VOGI for each pharmacogenomic scenario.

Our VOGI estimates for the seven pharmacogenomic categories are summarized in table 3.3. The three left-hand columns classify scenarios based on our three criteria: prescription frequency, adverse event frequency, and adverse event severity. Likewise, the three right-hand columns summarize VOGI estimates under the three recommended societal willingness-to-pay thresholds (Neumann, Cohen, and Weinstein 2014): $50,000, $100,000, and $150,000 per QALY.

The VOGI estimates demonstrate that for commonly used societal willingness-to-pay thresholds, only a few drug scenarios accrue (dollar-valued) health benefits that are greater than their downstream costs. The low-high-high scenario (e.g., azathioprine-TPMT) has a positive estimate under all values of λ, while the high-low-high (e.g., clopidogrel-CYP2C19) and high-high-high (e.g., warfarin-CYP2C9/VKORC1) scenarios have large positive values for λ > $100,000/QALY. These results not only highlight which drug-gene pairs are likely to drive overall value in a panel-based or sequencing approach, but also indicate which specific single-gene testing strategies have the highest cost-effectiveness estimates. Notably, our finding that clopidogrel and warfarin are cost-effective, single-gene testing scenarios is consistent with recently published studies on single-gene testing for those two drugs (Verhoef et al. 2016; Kazi et al. 2014)—though it is worth noting that the overall cost effectiveness of pharmacogenomic testing for warfarin in particular remains controversial (Verbelen, Weale, and Lewis 2017; Furie 2013).

3.4.2 Cost Effectiveness of Testing Strategies

We next turn our attention to estimates of the incremental cost-effectiveness ratios (ICERs) for multiplexed and serial single-gene testing strategies. These ICERs, as well as the average QALY and cost estimates

Table 3.4 **Incremental cost-effectiveness ratios for single and multiplexed genomic testing strategies**

	Average QALY	Average cost	ICER
No testing	22.413	12,771	Ref.
Serial single-gene testing	22.427	14,420	117,689
Reactive multiplexed testing	22.428	14,639	Dom. (extended)
Preemptive multiplexed testing	22.434	15,398	139,615

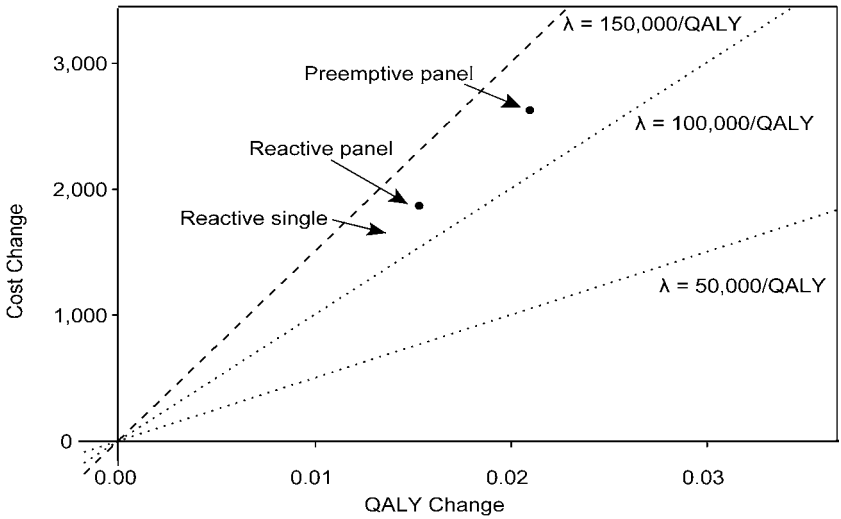

Fig. 3.4 Cost effectiveness of single-gene testing scenarios

Notes: The plane depicted above summarizes the cost effectiveness of alternative single-gene testing strategies. Each strategy's plotted value denotes the incremental change in average quality-adjusted life years (x-axis) and average lifetime costs (y-axis) relative to the reference strategy of no genetic testing. The rays running from the origin have slope equal to alternative societal WTP thresholds: $50,000/QALY, $100,000/QALY, and $150,000/QALY. Points that lie below and to the right of a given WTP line are cost effective at that WTP value.

that underlie them, are summarized in table 3.4 and in the cost-effectiveness plane depicted in figure 3.4.

Here we see that under our baseline model assumptions, all genomic testing strategies result in net average gains in both QALYs and costs in the simulated patient population (i.e., each strategy is in the northeast quadrant of the cost-effectiveness plane in figure 3.4). However, a strategy of reactive multiplexed testing is ruled out by extended dominance—that is, this strategy has an ICER that is greater than that of a more effective strategy (Neumann et al. 2016). By comparison, serial single-gene testing has an ICER of $117,689/QALY, while a preemptive multiplexed testing strategy has an

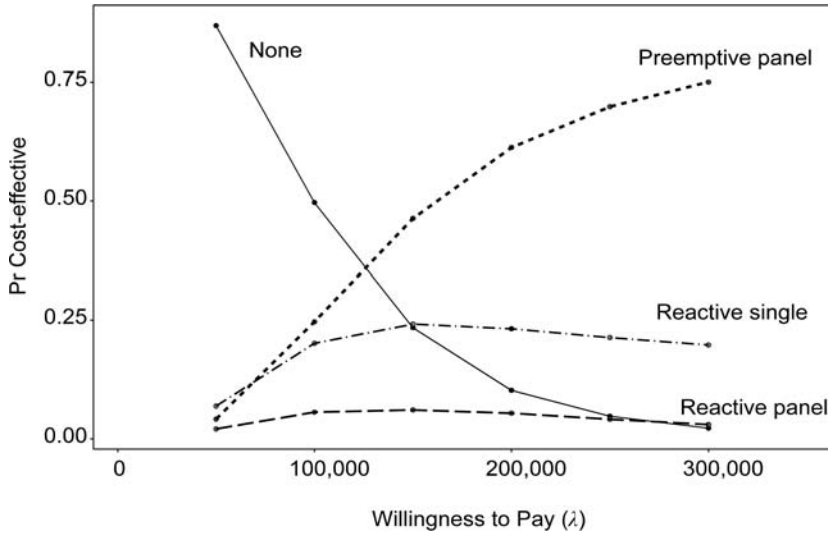

Fig. 3.5 Cost-effectiveness acceptability curve
Note: The figure plots the fraction of (5,000) PSA model runs that are cost effective at a given societal willingness-to-pay value (λ).

ICER of $139,615/QALY—both of which would be deemed cost effective based on the upper end of standard societal willingness-to-pay thresholds ($150,000/QALY) (Neumann, Cohen, and Weinstein 2014).

3.4.3 Sensitivity of Results

Cost-Effectiveness Acceptability Curve

Our results thus far correspond to the average change in QALYs and costs under the baseline model parameters summarized in table 3.2. However, given that only a subset of these parameters are based on direct evidence, and given that the underlying model is built on a relatively simple representation of a pharmacogenomic scenario, a natural question to ask is how sensitive the results are to varying assumptions and parameter values.

We begin our exploration of decision uncertainty in figure 3.5, which plots a cost-effectiveness acceptability curve (CEAC) based on the PSA model runs. This figure summarizes uncertainty by plotting, for varying values of λ (i.e., the societal willingness-to-pay threshold), the fraction of the PSA model runs that are cost effective at that value. For example, at λ = $50,000/QALY a no-testing strategy is optimal in nearly 100 percent of model runs. Thus, even allowing nearly all parameters to vary over a large plausible range does not change our recommendation not to genotype. By comparison, at λ = $100,000/QALY a no-testing strategy is optimal in 49.6 percent of model runs, while the preemptive multiplexed testing strategy is optimal

in 24.6 percent of runs. In this case, and for higher values of λ, it is worth investigating which specific parameters drive decision-making uncertainty.

One- and Two-Way Sensitivity Analyses

In figure 3.6 we draw on the results of the metamodel to examine how sensitive our estimate of the NHB for each strategy is to values of specific parameters for the high-high-high scenario (i.e., warfarin-CYP2C9/VKORC1), all while holding all other parameters fixed at their baseline value. The choice of this scenario and parameters was driven primarily by our finding that it yielded the highest VOGI estimate, and also because these parameters were identified as providing the highest leverage in terms of driving decision uncertainty in our model (more discussion on this point is provided in section 3.4.4).

The left-hand column of the figure provides one-way sensitivity analyses for NHBs estimated for λ = $100,000/QALY, while the right-hand column depicts NHBs based on λ = $150,000 / QALY. The sensitivity of our results for three key parameters—the risk reduction from the PGx alternative, the relative cost of the PGx alternative, and the probability genetic-testing information is used—are depicted in the rows.

The plot in the upper-right corner of figure 3.6 demonstrates that when λ = $100,000/QALY, the optimal strategy changes as the adverse event risk reduction from PGx changes. For example, when the relative risk of an adverse event under the PGx-guided therapy is 0.6 or below, then a preemptive testing strategy is optimal. However, if the risk reduction is 0.7 or above, then a no-testing strategy is optimal; in that case, the additional costs it takes to administer the testing and the alternative therapy are not worth the smaller reduction in the risk of an adverse event. On the other hand, when λ = $150,000/QALY a preemptive strategy remains optimal even at higher relative risk values. To put these findings in context, a recent RCT found a relative risk for a composite adverse event outcome of about 0.85 from PGx-guided warfarin dosing (Gage et al. 2017).

The middle row of figure 3.6 shows outcome sensitivity as the relative cost of the PGx-guided therapy varies. Not surprisingly, we see that the NHB under a no-testing strategy is constant since, under that scenario, no patient receives the PGx alternative therapy. But if the relative cost of the PGx alternative is two times or more when λ = $100,000/QALY, then genetic testing is not the recommended strategy. Again, however, this decision is heavily dependent on the chosen value of λ since, when λ = $150,000/QALY, a preemptive strategy remains optimal.

Finally, in the last row of figure 3.6 we show how sensitive our results are to assumptions on the likelihood that pharmacogenomic information is ordered and/or acted upon. In a reactive strategy, this corresponds to the probability that the physician orders the genetic test at the time of drug indication; in real-world settings, this probability has been demonstrated to

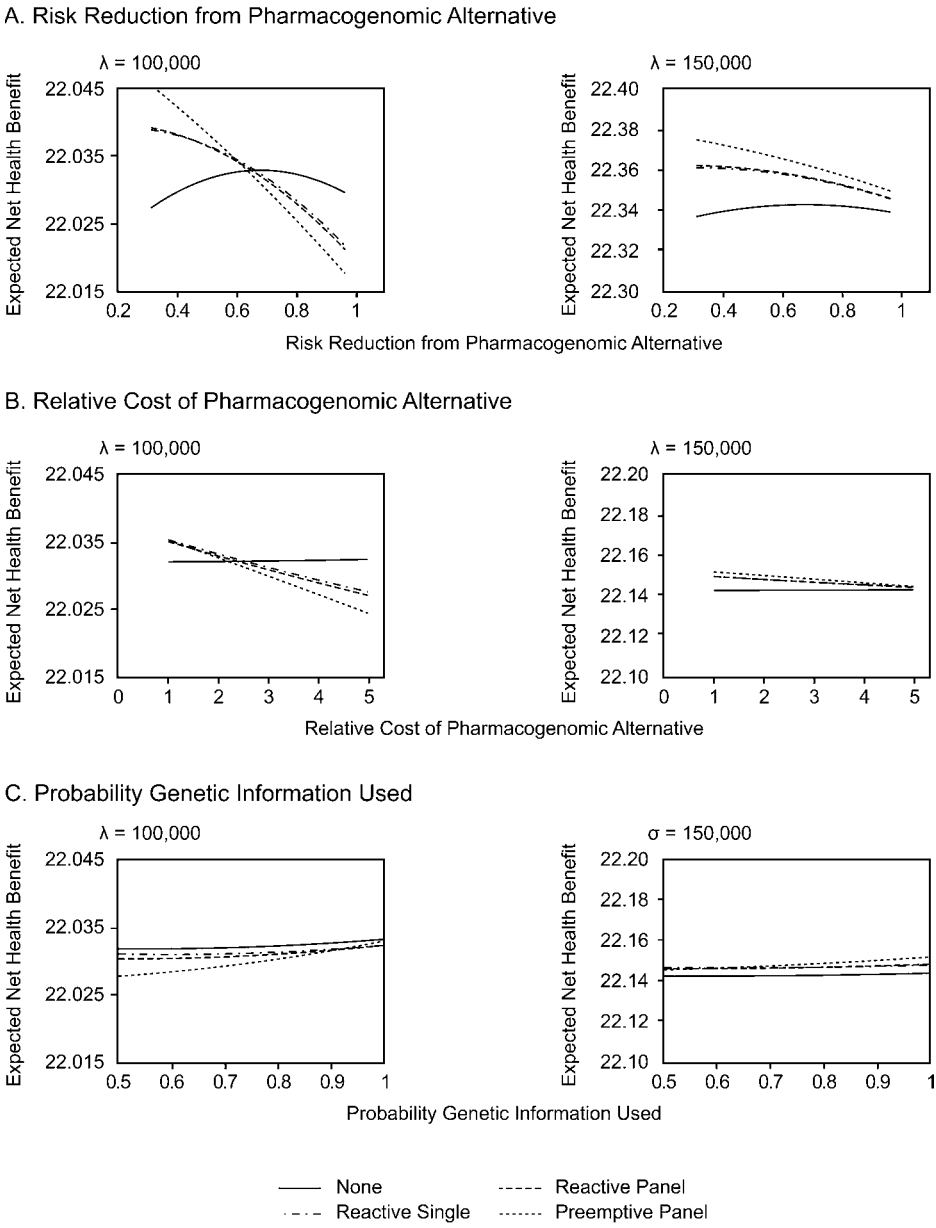

Fig. 3.6 One-way sensitivity analysis for the high-high-high (warfarin) scenario

Notes: The figure plots model sensitivity to individual parameter values. Model sensitivity is measured in terms of NHB using a PSA with 5,000 model runs. Parameters are drawn from fixed probability distributions as denoted in table 3.2. Sensitivity values are fit using a GAM fit to the PSA model runs.

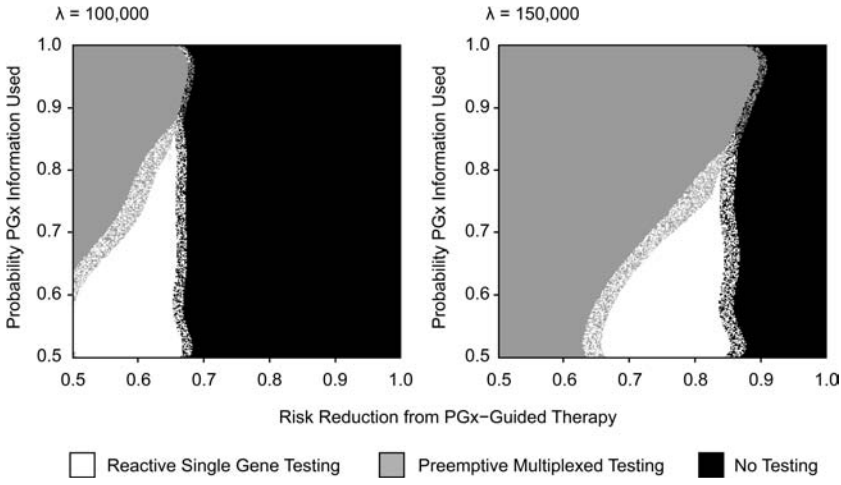

Fig. 3.7 Two-way sensitivity analysis for the high-high-high (warfarin) drug type
Notes: Figure plots model sensitivity to specific jointly varying parameter values. Model sensitivity is measured in terms of NHB using a PSA with 5,000 model runs. Parameters are drawn from fixed probability distributions as denoted in table 3.2. Sensitivity values are fit using a GAM fit to the PSA model runs.

be well below 100 percent in scenarios where a genetic test is not mandated by FDA guidelines (J. F. Peterson et al. 2016). Similarly, in a preemptive strategy this value corresponds to the probability that genetic information obtained upstream is utilized by the physician.

The figure demonstrates that the relative value of reactive testing versus a preemptive approach is heavily influenced by the probability that the physician orders and/or acts on the information. For example, when λ = $150,000 and the probability of use is high, then a preemptive strategy is optimal. However, when this probability is low then the reactive strategies win out.

In figure 3.7 we explore these relationships further by plotting the optimal strategy as a function of *two* varying parameters: the relative risk reduction and the probability that genomic information is used. Again, these estimates correspond to the high-high-high (warfarin) scenario, and are derived from a metamodel fit with an interaction term between the two parameters. The figure is further divided into two panels corresponding to results using λ = $100,000/QALY and λ = $150,000/QALY.

The results in figure 3.7 show, again, that if the risk of an adverse event under the PGx alternative is similar to the risk under the standard therapy, then a no-testing strategy is preferred. However, for low relative risk values (i.e., 0.8 or below) the optimal strategy is preemptive multiplexed testing only if the probability of the physician utilizing the information is high; if this probability is low, then reactive serial single-gene testing is preferred.

3.4.4 Expected Value of Partial Perfect Information

To generalize our sensitivity results we now turn to our estimates of the EVPPI for each of the varying model parameters. The EVPPI estimates for the top twenty-five highest-valued parameters for λ = $100,000/QALY are provided in table 3.5. The top ten parameters are also summarized in the slopegraph depicted in figure 3.8, which visualizes how the prioritization of key parameters based on EVPPI changes over different values of λ.

Again, as noted in the methods section, the EVPPI provides a dollar-valued estimate of the opportunity cost of selecting the wrong strategy. Echoing the result in figure 3.5 (i.e., that a no-genotyping strategy is optimal in nearly all simulations), the EVPPI for almost all parameters is $0 when λ = $50,000/QALY. In other words, because the overall decision to not genotype is robust under nearly all plausible parameter values, there is little value in conducting additional research that can inform knowledge of the specific parameter values.

By comparison, however, at λ = $100,000/QALY several categories of model parameters stand out as influential. These parameters mostly relate to the high-high-high (e.g., warfarin-CYP2C9/VKORC1) and high-low-high (clopidogrel-CYP2C19) scenarios. Moreover, within these categories the most influential determinants of the cost effectiveness of genotyping relate to the risk reduction from a PGx alternative, to the relative cost of the PGx alternative, and to parameters governing physician behavior to genotype and/or act upon genotyping information obtained upstream (see figure 3.8). Taken together, our results on the EVPPI indicate that scientific evidence on PGx should focus on these factors.

Finally, it is also notable that the parameters governing the cost of the genetic tests receive EVPPI estimates of $0 across the entire range of willingness-to-pay thresholds (table 3.5). That is, lowering (or raising) the cost of genotyping rarely, if ever, changes our decision on the optimal strategy. Rather, it is the parameters that govern *downstream* costs and behavior that are key determinants of decision-making.

3.5 Model Limitations

The base case analysis and PSA were conducted using a set of parameters derived from prior cost-effectiveness studies, pharmacogenomic implementations, and other primary literature. The analysis presumes the existence of a theoretical pharmacogenomic panel encompassing all of the pharmacogenes associated with CPIC Level-A drugs; if only a subset of genes are assayed, the overall cost effectiveness could be attenuated. The costs of obtaining biospecimens, performing laboratory procedures, interpretation, point-of-care result delivery, and data storage are assumed to be incorporated into the cost of the test. In actuality, the cost of implementing a genetic

Table 3.5 **Expected value of partial perfect information: top twenty-five parameters**

Parameter	Prescribing frequency	Adverse event frequency	Adverse event severity	λ = $50k/QALY	λ = $100k/QALY	λ = $150k/QALY
Risk reduction from PGx alternative	High	High	High	0.1	172	46.9
Cost: PGx alternative (daily cost)	High	High	High	0	63.9	0
Cost: PGx alternative (daily cost)	High	Low	High	0	57.2	0
Cost: PGx alternative (daily cost)	High	Low	Low	0	55.3	0
Risk reduction from PGx alternative	High	Low	High	0	54.7	1.1
Cost: PGx alternative (daily cost)	High	High	Low	0	41.9	0
Probability PGx test ordered	High	Low	Low	0	40	1.1
Probability PGx test ordered	High	High	High	0	36	75.2
Adverse event disutility	High	High	High	0	26.4	0
Three-year adverse event rate	High	Low	High	0	24.8	0
Cost: Panel test				0	0	0
Cost: Single-gene test				0	0	0

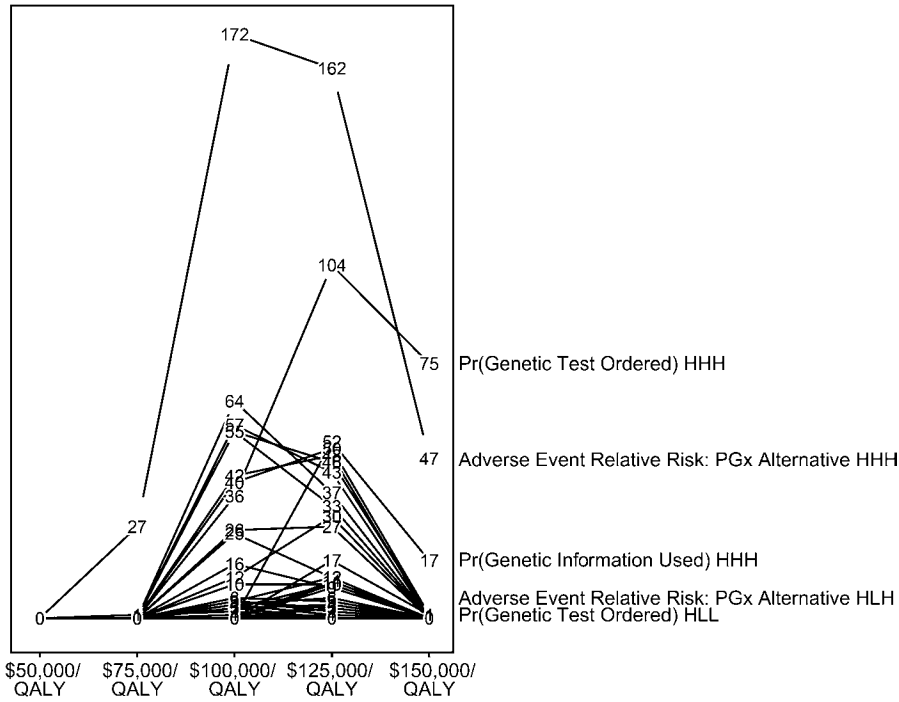

Fig. 3.8 Expected value of partial perfect information by societal willingness-to-pay threshold

Notes: The figure plots a slopegraph showing the expected value of EVPPI for specific parameters and societal willingness-to-pay thresholds. Parameter descriptions listed on the right side denote the magnitude and rank of the most important parameters for λ = $150,000 per QALY; EVPPI values for other values of λ can be found in table 3.5 and in the text.

testing program may vary widely between health systems, and depend heavily on the existing infrastructure to manage genetic data discretely and deliver it across the enterprise to the appropriate prescriber with sufficient clinical decision support. To address this potential limitation, we examined a broad range of test costs in the PSA. Additionally, we recommend that future research on standard pharmacogenomics implementations could estimate costs with sufficient granularity so that subsequent CE analyses incorporate perspectives of health systems with different capabilities.

3.6 Conclusion

The integration of pharmacogenomics into routine clinical practice is key to the overall vision of precision medicine. However, despite a substantial and growing body of scientific evidence and the enthusiasm of many clini-

cal practitioners, funding agencies, and policymakers, pharmacogenomic testing has yet to be broadly and routinely adopted by health care systems. In large part, adoption is hindered by a lack of payer reimbursement and confidence that multiplexed testing will yield downstream improved health care outcomes and acceptable costs over a reasonable time frame.

In this study, we attempt to bridge key research gaps by developing a methodological framework for assessing the long-term value of PGx testing strategies. Our modeling approach overcomes several distinct limitations of past work by broadening both the scope and time horizon for PGx to affect patient costs and health outcomes. Moreover, by coupling real-world evidence on a PGx implementation with novel value of information methods, we are able to identify scenarios where preemptive testing and single-gene testing are each cost effective. Our sensitivity analyses, moreover, clarify the circumstances in which PGx testing strategies may be optimal, and can be used to prioritize future work by highlighting parameters and specific gene-drug scenarios that drive the overall cost effectiveness.

Appendix

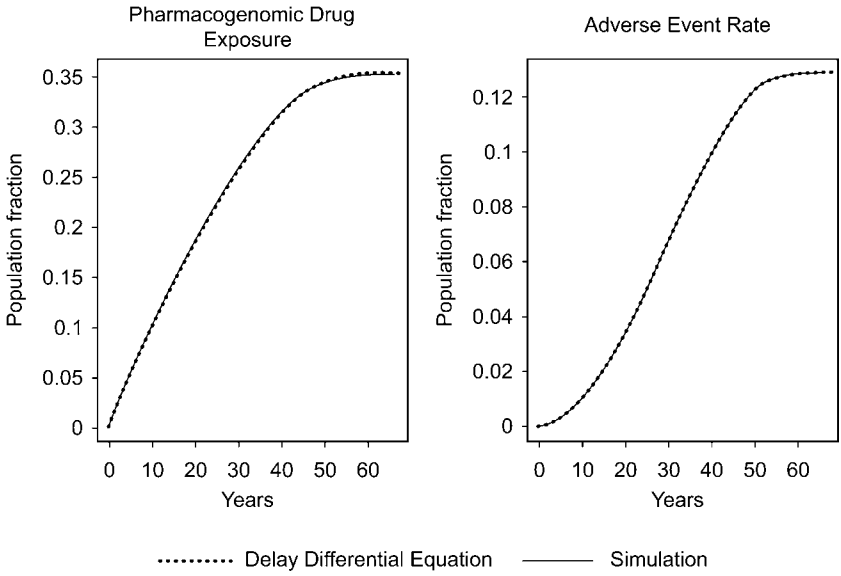

Fig. 3A.1 Benchmarking drug exposure and adverse events: DEDE versus DES

Notes: The above plots show how average drug exposure rates and adverse event rates differ across the DES and DEDE modeling frameworks.

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