A widely-held vision arising from the sequencing of the human genome is to guide health care decision-making with genetic data to improve patient care -- a promise that is fueled by extraordinary advances in the discovery of genomic variation that predicts therapeutic response. Already, the Food and Drug Administration (FDA) recognizes many interactions between gene variants and drug outcomes; currently more than 70 drug labels include references to germline pharmacogenomic information that can affect prescribing across a wide array of diseases and conditions. Yet while scientific evidence underlying pharmacogenomics is expanding rapidly, parallel efforts to understand the economic incentives and behavioral changes related to characterizing individuals’ genetic risks are lacking.

Existing research on the value of pharmacogenomics has largely focused on the short-term cost effectiveness of single gene tests – an approach that ignores the potential lifetime value of multi-gene assays and sequencing. Further, the cascading impact of inexpensive gene panel tests on individual and provider incentives and behavior, new health care spending, and changes in patient outcomes is still poorly understood. Thus, the feasibility and economic value of large-scale genetic testing for current health systems remains unproven. This has slowed translation to clinical practice, and prompted major payers (e.g. Medicare and private insurers) to reassess reimbursements for genetic testing. If these economic challenges are not addressed, it will be difficult if not impossible to capture the potential value of pharmacogenomics in particular and precision medicine more broadly.

Our proposed contribution will address these gaps by leveraging empirical insights from an active, real-world precision medicine program (PREDICT; Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment). Our paper will focus on how physicians respond to multiplexed pharmacogenetic testing – and how this response is mediated by changes in the insurance, payment, scientific, and health system environments. This distinct contribution fits squarely within our ongoing research program funded by the National Institutes of Health Common Fund Health Economics program. Below, we provide background information on PREDICT and on the type of paper and analyses we could contribute to the NBER program.

PREDICT

The PREDICT program (Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment) is a clinical quality improvement initiative at Vanderbilt University Medical Center (VUMC). This program has genotyped almost 15,000 patients since 2010 as a part of routine care. Through PREDICT, we have 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
favorable with a cost per QALY of < $50,000. Health economic studies have determined the value of simvastatin or many of the other well-described equivalent studies have been performed for descent populations.

Pharmacokinetic cytochrome P450 gene polymorphisms (both implemented within PREDICT) can impact the clinical use of genetic data; comparing these strategies is an explicit focus of our RIGHT parent NIH grant. Figure 2 provides a screenshot example of the decision support module that prompts providers to pre-emptively genotype patients under the PREDICT program. Figure 3 provides an example of clinical guidance in a patient with an actionable genetic variant.

Figure 1 provides a conceptual diagram of how different genotyping strategies (both implemented within PREDICT) can impact the clinical use of genetic data; comparing these strategies is an explicit focus of our RIGHT parent NIH grant. Figure 2 provides a screenshot example of the decision support module that prompts providers to pre-emptively genotype patients under the PREDICT program. Figure 3 provides an example of clinical guidance in a patient with an actionable genetic variant.

**Figure 1. Opportunities for Prospective Genotyping**

*Figure 2. PREDICT Prognostic Model estimating risk of requiring future genotype-tailored therapy.*
Preliminary Evidence

As part of a pre-emptive genotyping strategy, PREDICT algorithms electronically evaluated 89,566 patients receiving care within implementation clinics for their propensity, based on a statistical risk score, to receive one of the medications targeted by the program. 23,835 of these patients were flagged for exceeding the risk threshold; of these, clinicians elected to genotype 4,947 in response to a prompt. An additional 5,067 patients were genotyped using the alternate indication based triggers for the program. These patients were followed via their electronic medical records to determine how the genetic data was used as new prescriptions were written.

Our proposed project will leverage these and other data as a lens through which we can investigate physicians’ behavioral responses to genetic information, and how these responses may be mediated by economic incentives and changes to the payment system more broadly.

One example is provided in Figure 4 below. The Figure is based on our analyses of physician prescribing decisions when the physician is given genetic test data on the patient's metabolism status for Clopidogrel. Clopidogrel is a thienopyridine antiplatelet agent indicated for secondary prevention of coronary and cerebrovascular disease, and is a critical component of prophylaxis against thrombotic complications of percutaneous coronary interventions (PCI). Large, high-quality observational studies and meta-analyses have repeatedly shown that CYP2C19 poor metabolizers treated with clopidogrel following percutaneous coronary intervention (PCI) are at increased risk of stent thrombosis and major adverse cardiac events (myocardial infarction, revascularization, stroke
The FDA has added a Black Box warning describing these findings to the clopidogrel label. Alternative therapies include switching to prasugrel or ticagrelor, both drugs with no CYP2C19 dependency and probable superior efficacy but with increased bleeding risk and significantly higher cost.

![Figure 4. Physician Response to Genetic Information -- Drug Switch Rates by Pharmacogenomic Phenotype](image)

The figure shows that among patients identified as poor metabolizers, 48% were placed on an alternative to clopidogrel (Prasugrel or Ticagrelor) by their physician, while 52% received Clopidogrel despite higher risk for stent thrombosis and major cardiac events. There is, moreover, a clear gradient in physician response – intermediate metabolizers were prescribed the alternative just 21% of the time, while those identified as normal metabolizers received the alternative drug 5% of the time.

One the one hand, this evidence makes clear that physicians respond to the genetic information given to them by the precision medicine program. But on the other hand, half of patients still receive Clopidogrel despite being tested and flagged as a poor metabolizer in their electronic medical record. A key question is what incentives or barriers are leading 50% of patients to receive the drug when the scientific evidence points in the direction of giving them an alternative.

Figure 4 provides some insight into the types of economic incentives and behavior that we propose to explore. The figure plots the annual cost of Clopidogrel (which is available in generic form) and one alternative (Prasugrel, which is branded; the other alternative, Ticagrelor, is also branded) for a fully-insured Medicare patient in the Nashville Medicare Part D market. The price under each plan is given by the dots, while prices within each plan are linked using a line.

As the Figure makes clear, the annual cost—even to a fully insured Medicare patient—is much higher for the pharmacogenomic alternative than for Clopidogrel. Clearly, the decision to switch a patient identified as a poor metabolizer carries with it a significant change in out-of-pocket costs. A key question we propose to explore the extent to which these economic considerations are driving physician behavior.
Figure 5. Annual Cost of Clopidogrel and Prasugrel
**Proposed Research**

Our analyses for the NBER program paper will focus on two key questions. First, we will investigate the price sensitivity of clinicians to the cost of genetic testing by leveraging an institutional change in how the PREDICT program was operated. One distinctive feature of PREDICT was that initially, the entire cost of genotyping was paid for by VUMC. This changed later, when VUMC began to bill the patient’s insurer for the cost of the genetic test. From internal PREDICT data we know that change resulted in a significant drop in the number of genetic tests ordered among high-risk patients—suggesting that economic concerns over the cost of genetic testing to patients was partially driving physician decisions to genotype in the first place. For our paper, we have the ability (using historical de-identified patient electronic medical record data) to exploit this institutional change to more comprehensively investigate how price sensitive physicians are to a key component of the patient cost of personalized medicine.

Second, we will utilize the rich array of data available within the Vanderbilt EMR to explore how insurance and formulary design modifies clinician prescribing of genotype-tailored therapies once genetic information is in-hand. Using the unique RxStar tool developed at VUMC, physicians are given real-time data on drug alternatives and their relative position on the patient’s formulary at the point of prescribing. That is, in addition to dashboard information from PREDICT on genetic risk associated with a given therapy, physicians can also see whether the proposed alternative is covered by the patient’s insurance provider. We thus have the capability to capture formulary data not only on prescribed medication for our genotyped patients, but also data on the alternatives that were not prescribed. These data give us the unique opportunity to exploit variation in patient formularies to study how current insurance designs affect personalized medicine interventions in the real-world. The results of our project could be particularly fruitful as evidence for value-based insurance designs that adjust patient copayments based on genomic biomarkers.

Finally, the fact that much of the genotyping under PREDICT was driven by a prediction model (with measurement and prediction error) provides an additional layer of potentially exogenous variation that we can exploit in our analyses. For our proposed project, we will explore whether sufficient variation exists to either use the prognostic model cutoff (which identified candidates for genotyping) in a regression-discontinuity design, or more generally as an instrumental variable that affects whether patients were genotyped. Using either of these designs, we can explore downstream patient utilization and outcomes to provide credible and novel evidence on the effect of precision medicine.

**Summary**

In summary, our proposal is motivated by an emerging view in health economics that much of the observed geographic variation in treatment patterns and spending across the United States can be traced to the so-called “grey area” of medicine (Chandra and Skinner 2011, Wennberg, Fischer and Skinner 2002). This category of “preference sensitive” clinical practice is often characterized by considerable heterogeneity in treatment benefits across different types of patients (Chandra, Cutler and Song 2011). Critically, within this “grey area,” the relevant population for whom personalized treatment could be cost-effective is often poorly identified, and treatment guidelines are frequently contradictory or non-existent. For pharmacogenomics testing strategies, uncertainty around the right populations to target and around the clinical value of testing has contributed to an environment in
which health system investment, reimbursement by insurers and health systems, and genotype-tailored treatment decisions by clinicians are often based exclusively on the cost of testing alone and not based on its economic value. The research proposed here will significantly improve our understanding of these issues by identifying key economic levers that affect and modify the impact of precision medicine on both physicians and patients.


