Exploring Strategies to Optimize the Value of Pharmacogenomic Testing

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Abstract

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The emergence and continual advancement of genomic technologies offer numerous areas that warrant a critical appraisal for integrating new health care services to increase access and improve outcomes for patients. This dissertation examines two strategies in the context of pharmacogenomics (PGx) testing. In the Overall Introduction, we initially focus on identifying clinical utility and economic evidence gaps necessary to inform appropriate clinical adoption of PGx testing across diverse healthcare settings. In Chapter 1, we report our findings from an analysis of real-world evidence from a commercial PGx knowledge resource, which is comprised of data from patients who have undergone PGx testing. Additionally, we characterize gene-drug pair level of evidence as developed by expert groups, and present associated predictive factors that may inform clinical actionability. Following this, in Chapter 2, we focus on a hypothetical clinical cohort of acute coronary syndrome patients undergoing percutaneous coronary intervention. We use decision modeling methods to estimate the projected cost-effectiveness of a multi-gene panel

to guide two treatment decisions for this clinical cohort from the payer perspective. We describe influential parameters in the model, discuss limitations of this work, and denote implications to health policy decision making. In the Overall Conclusions, we summarize and describe future considerations. To increase appropriate clinical PGx testing adoption, we provide evidence that healthcare entities may wish to consider the use of a commercially-developed PGx knowledge resource solution in lieu of delaying implementation awaiting publicly available PGx knowledge resource solutions. Additionally, for the aforementioned patient cohort, we provide evidence that the multi-gene panel estimates are projected to be cost-effective at a $100,000 willingness-to-pay threshold when compared to either a single-gene panel or to no gene testing. These findings build upon the available economic evidence for multi-gene panels that payer decision makers may consider during their health technology assessment evaluations to determine inclusion of covered services within their medical policies. Finally, the contents of this dissertation contribute to the broader discourse regarding value assessments in the interplay between precision medicine and clinical genomics.

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DEDICATION

From the early seeds sown affording intellectual curiosity to the harvesting of an independent mind abetted by critical and constructive thought challenging the status quo, my edification generating this body of work is dedicated to the opportunities for transformation that shall remain constant in our ever evolving societal ecosystem.

OVERALL INTRODUCTION

Health care payers currently have varying reimbursement policies for pharmacogenomic (PGx) testing.[1; 2] This results from varying criteria for both determining clinical utility and discerning evidence sources that demonstrate clinical utility. For instance, the Blue Cross Blue Shield Association's newly established Evidence Street, a web-based platform that provides health care decision-makers access to objective medical evidence reviews for diagnostics, defines clinical utility of a genetic test or technology as one that must "improve net health outcomes," whereas, the Hayes[1] review organization considers the following four factors when evaluating clinical utility of a genetic test: **patient outcomes** - discern whether the results of the test improve health outcomes, prognostic ability -; **diagnostic thinking** - determine whether the test confirms or changes a diagnosis -; **decision-making guidance** - assesses whether the test results inform appropriate dietary, physiological, medical (including pharmaceutical) and/or surgical intervention-; and **familial and societal impacts** - whether the test identifies at-risk family members and evaluates subsequent impact on high-risk populations, and/or health systems.[3; 4] These are only two examples; other payer organizations may have additionally nuanced factors that impact clinical utility decision-making during health technology assessment (HTA) evaluations.

Through its Molecular Diagnostic Services (MolDX) Program, the Center for Medicare & Medicaid Services (CMS) typically makes coverage decisions for PGx tests at the regional level rather than at the national level (i.e., local coverage determinations in the absence of national

[1] Hayes is an internationally recognized leader in unbiased health technology assessment (HTA) research and comparative-effectiveness analysis to better inform decision making and reimbursement policy development.

coverage determinations).[5] As a result, a given decision is made several times for the same test based on different guidelines and processes, and often with differing outcomes.[6] Trosman *et al* found that private payers use a range of HTA methods in reimbursement coverage decisions for genetic testing, and identified shortcomings in HTA methods (i.e., reviews not adequately incorporating nonclinical factors) that could be informative to payers.[7] Furthermore, recent work highlights differing value frameworks that are intended to aid the assessment process for coverage determinations for health care services.[8] Development of standardized guidelines and best practice frameworks could potentially improve the transparency and efficiency of the coverage decision making process, and decrease variability in patient access to PGx testing.[9] The Food and Drug Administration (FDA) guidance for industry of clinical PGx for pre-market evaluation and recommendations for labeling detail numerous examples of clinically-relevant value derived from PGx information for improvements in dosing and safety of drugs and drug development.[10]

Despite the availability of actionability guidelines paired with PGx information, the delivery of PGx testing is not widespread in the clinical care setting. Most of the evidence base has been informed by investigations conducted within the clinical research realm, and due to healthcare decision makers who may be reliant on publicly available clinical PGx implementation guidelines, uptake of PGx testing is limited.[11; 12] The most widely studied sites include medical centers with pre-emptive clinical PGx implementation programs (i.e., St. Jude's Research Hospital, Vanderbilt University Medical Center, University of Florida and Shands Hospital, Mayo Clinic, and Mount Sinai Medical Center).[13] Thus, evidence generated from settings beyond these academic medical centers is necessary to inform PGx implementation.

Challenges to the payer assessment processes may persist due to a lack of publicly available knowledge resources for evidence that aligns incentives against economic barriers for key decision makers. In a comprehensive review of the literature, the Canadian Agency for Drugs and Technologies in Health found limited evidence to establish the cost-effectiveness of PGx testing. Their investigation did not identify any established standardized guidelines specific to clinical applications of the technology.[14] Through additional work in the United States, Berm *et al* conducted a systematic review of the literature on economic evaluations of PGx tests and found that utilizing PGx testing to inform treatment selection was mostly found to be a cost-effective or cost-saving strategy.[15] They noted that future evaluations should include a broad range of scenario analyses to adequately estimate cost-effectiveness of PGx testing strategies.

Without robust actionability data to inform the clinical utility and economic evidence base and widespread implementation programs for PGx testing necessary to identify a subset of responders, some current clinical practices generate inefficiencies in the healthcare system (e.g., through wasteful spending on drugs for which patients do not receive the optimal drug benefit).

Logical next steps to address components of the aforementioned evidence gaps include conducting an analysis on real-world data from a commercial PGx knowledge resource and quantifying the projected economic value of a specific clinical scenario from the payer perspective that evaluates a multi-gene panel approach in clinical decision-making. Chapters 2 and 3 of this dissertation address these two gaps.

Overall impressions and concluding comments can be found in the final section of this dissertation.

Chapter 1. USING REAL-WORLD PHARMACOGENOMICS KNOWLEDGE RESOURCES TO GUIDE CLINICAL DECISION-MAKING

1.1 ABSTRACT

Pharmacogenomic (PGx) testing can help to optimize drug therapy selection. Despite the availability of FDA Guidance and select expert-developed guidelines, however, clinical utility evidence gaps limit the uptake of PGx testing in clinical settings. Commercial PGx knowledge resource solutions may increase adoption. We investigated real-world data from a commercial PGx knowledge resource by characterizing the Clinical Pharmacogenomics Implementation Consortium (CPIC) level of evidence and sought to identify predictive factors for the clinical actionability made at the time of result interpretation. For 99,727 patients who underwent PGx testing, 90% of patients were tested for six or fewer drugs; 41% were male. Predictors that were statistically significant differed across the four clinical subgroups that were evaluated (pain, cardiology, psychiatry, gastroenterology). Twenty-eight of the 33 PGx gene-drug pairs, characterized by CPIC level of evidence less than B, resulted in a warning or critical actionability recommendation (versus informational recommendation). This indicates a possible change in drug selection, and highlights a discrepancy in level of evidence determinations between public and commercial knowledge resources. To our knowledge, this is the largest retrospective study conducted to date on patients undergoing PGx testing in a broad set of clinical settings. Our findings provide a robust characterization of real-world PGx testing utilization data and demonstrate evidence of clinical actionability from a commercial PGx knowledge resource. Healthcare systems may wish to consider commercial knowledge resources to spur appropriate PGx test adoption. These solutions can adapt quicker than can

centralized authoritative resources to synthesize clinical actionability data and inform time-sensitive clinical guidance. They often can be customized to the population of each Learning Health System, rather than rely on publicly available, standardized sets of PGx knowledge resources.

1.2 INTRODUCTION

Pharmacogenomic (PGx) testing is a novel approach to optimize drug therapy [13; 16]. Yet use of PGx-guided treatment in clinical care settings remains limited by numerous barriers including incomplete availability of clinical actionability and utility data, inconsistencies in clinical care policies for pre-emptive PGx testing, and delays associated with receiving results during point-of-care PGx testing (also known as reactive testing).[13; 17-19] Despite the availability of FDA Guidance and select expert-developed guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), with prioritization for assignment of CPIC level of evidence and the development of guidelines for genes/drugs described elsewhere[20]; the Dutch Pharmacogenetic Working Group (DPWG); the Pharmacogenomics Research Network (PGRN); and the Pharmacogenomics Knowledge for Personalized Medicine (PharmGKB)[21]; implementation of pre-emptive PGx programs has largely been limited to academic centers that focus on clinical research.[13; 22] Additional evidence from diverse clinical settings is needed to assess the impact of testing on broader populations.

Evidence reveals genes with PGx variation are associated with the metabolism of approximately 7% of all FDA-approved drugs, affecting over four billion (18%) of all outpatient prescriptions in the US (2013 data).[23] This suggests that numerous PGx high-risk drugs are commonly prescribed for which known genetic information could inform clinical

actionability. Yet, results of a recent retrospective database analysis of over 270,000 drug orders suggest that PGx tests were ordered for fewer than 2% of orders for drugs for which germline (inherited) PGx testing information was available in the FDA drug label.[24] Sixty genes in the cytochrome (CYP) P450 gene family code account for approximately 75% of enzymes involved in drug metabolism, yet clinical actionability evidence is limited to a subset of these genes.[25] Moreover, in another retrospective analysis, Hocum and colleagues investigated a commercial PGx testing database and found that most patients referred for PGx testing were not normal metabolizers of the five CYP450 genes studied (*CYP2D6, CYP2D9, CYP2C19, CYP3A4*, and *CYP3A5*).[26] Finally, in a study of over 73 million patient records from health claims data sources, investigators estimated 20% incident exposure to multiple PGx drugs for which the strength of evidence for a gene-drug association is high (defined by CPIC level A guidelines or high clinical significance according to DPWG guidelines).[27] Together, these studies demonstrate the low adoption of, yet potential for using PGx tests to guide drug orders in routine clinical care.[24; 26; 27] A study of real-world PGx testing data could provide a frequency estimate of PGx testing (and resulting phenotype information) as it is associated with clinical actionability that may inform clinical decision-making, ultimately mitigating patient exposure to drugs to which they will have a limited response. The aim of this study is to address that evidence gap.

Using data collected in real-world clinical settings, the objective of this study was to identify PGx gene-drug pairs, match them to their associated CPIC level of evidence (LOE) guidelines and PharmGKB rank, analyze which PGx drugs were most frequently prescribed across age

groups, and investigate predictive factors for the clinical actionability made at the time of result interpretation.

1.3 METHODS

1.3.1 *Data Sources and Summary*

This was a retrospective database analysis. We used data collected by Translational Software®, a commercial firm that integrates clinical results obtained from laboratories into actionable PGx gene-drug information (for whom patients underwent PGx testing). Laboratory source data includes data from community health systems and independent testing laboratories. Through the use of its proprietary PGx knowledge resource (which includes integration of guidelines from multiple expert groups including the aforementioned CPIC, PharmGKB, and DPWG), the company provides a cloud-based PGx test reporting solution that interprets genetic results and provides clinically-actionable recommendations for over 35 genes.[28] Their service generates clinical recommendations on potential severity of drug-gene interactions using three categories (critical, warning, and informational). These are embedded in electronic health records as clinical decision support (CDS) alerts. This information is intended to inform consideration of drug treatment alternatives, dose recommendation details, and whether a normal response to the drug ordered is expected. Additional information regarding drug-drug interactions is reported depending on the individual service partner and patients' active drug lists. The software application is built utilizing the Fast Healthcare Interoperability Resources (FHIR®) standard. This standard addresses electronic medical record interoperability challenges and allows CDS alerts to be presented using a variety of vendor platforms. Data were collected between January 2014 to September 2016, and were de-identified for this study. The full dataset Translational Software provided included 315,546 observations on 99,727

patients, wherein the data were sourced from 114 labs. Observations were inclusive of a single PGx gene (i.e., one gene-drug pair per observation). Key data elements provided were the following: Lab identifier (ID) brand name drug, age, sex, expected phenotype, PGx gene tested, concomitant drug list, clinical actionability result. To create our analytic dataset, we generated additional key data elements which included clinical subgroup, PharmGKB rank, CPIC LOE, and generic drug name. The analytic data set was inclusive of 90,732 patients (186,228 observations). The University of Washington Institutional Review Board determined this study did not constitute human subjects research, therefore, approval was not required. Translational Software® did not contribute to the design of this study.

1.3.2 *Study Design*

We stratified the data into clinical subgroups and analyzed subgroups that met an *a priori* inclusion criterion for having greater than 23,000 observations in each stratum to ensure ample sample size for our analytic dataset. This inclusion threshold was motivated by evaluation of a different commercial knowledge resource conducted by Hocum *et al* from a commercial PGx testing lab whose total sample was 22,000.[26] Thus, we wanted to expand on their work by employing a larger sample size and analyzing additional PGx gene-drug pairs. The subgroups were pain, cardiology, psychiatry, and gastroenterology (GI). Psychiatric drugs were categorized into those used for schizophrenia (1st generation, 2nd generation) and depression (selective serotonin reuptake inhibitor (SSRI)/serotonin–norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA)), and stimulants (**Table 1**). The only data element for which there were missing data was sex. Missing sex data were assumed to be missing at random; observations missing sex were excluded from the regression analysis.

In each category, we generated models to predict the clinical actionability from generic drug name or drug type, expected phenotype, age and sex. The outcome of interest was the actionability of the clinical recommendation from Translational Software® alerts described above (informational, warning, critical). Displayed in **Table 2** are genes and the corresponding nomenclature for the expected phenotype categories. There is no standard nomenclature across genes tested.

1.3.3 *Statistical Analyses*

We created prediction models for each PGx gene-therapeutic category pair (e.g., *CYP2D6*-cardiology). When multiple drugs were paired with a specific gene, all were included in the same model. When all three outcome levels were represented, we used multinomial logit models.[29] When the outcome consisted of only two categories, we created multinomial generalized linear models for a binomial distribution. Predictors for the models were chosen using the stepwise regression approach, by optimizing the Akaike Information Criteria (AIC), a conventional statistical measure used to determine the best fitting model for the observed data, while minimizing loss of information.[30] Each model was fit on the analytic dataset. Models were not built for genes if the originally partitioned validation set consisted of fewer than 1000 observations.[2] For all models, when we identified zero in some cells across two of the categorical predictor variables (generic name and expected phenotype), we employed penalized maximum likelihood estimate methods, as use of conventional maximum likelihood estimation methods will result in first-order bias. First-order bias occurs when the assumption

[2] We excluded the following genes from the prediction analysis due to not meeting our threshold of having at least 1,000 observations in the originally partitioned validation datasets: pain (*OPRD1, COMT, CYP1A2, CYP2B6*); cardiology (*CYP3A5, CACNA1C, 12q15, ABCG2*); GI (*CYP2D6*); and psychiatry (*ANKK1, CYP1A2, CYP2B6, FKBP5, GRIK4, HTR2A, SLC6A4, UGT2B15, BDNF, ADRA2A*).

of a finite parametric estimation does not hold, thus penalizing the model guarantees finiteness even in cases of data separation or perfect prediction whereby the maximum likelihood estimator is infinite.[31] This is not a concern when using a traditional logistic model.

For each of the clinical subgroups, we explored random effects models by evaluating laboratory ID – to account for different gene tests that may have been ordered by laboratory; however, the random effects variation terms were close to 0. Therefore, we did not include laboratory ID as a random effects variable in our models.

We first estimated each model including both generic drug or drug type and phenotype. However, this resulted in model overfitting due to collinearity of the predictors of interest; thereafter, we generated two models for each gene tested by clinical subgroup. Model 1 estimates the effect of generic drug or drug type, using a multinomial model for the three-level outcome (Equation 1.1) and using a multinomial generalized linear model with a binomial distribution for the two-level outcome (Equation 1.2). Model 2 evaluates the expected phenotype on clinical actionability, employing a multinomial model for the three-level outcome (Equation 1.3), and subsequently, using a multinomial generalized linear model with a binomial distribution for the two-level outcome (Equation 1.4). We did not generate model 1 if there was only one drug or drug type under evaluation. Here, α represents the intercept, β represents penalized parameter coefficients for the odds ratio associated with the predictor for comparison between warning and/or critical to the referent category informational associated with clinical actionability, and X represents an explanatory variable for generic drug or drug type, expected phenotype, age, and sex, respectively.

For a multinomial three-level outcome, here in model 1:

$$\log \frac{\pi_{critical} \text{ or } \pi_{warning}}{\pi_{informational}} = \alpha + \beta X_{\text{generic drug}} + \beta X_{\text{age}} + \beta X_{\text{sex}} \quad \text{(Equation 1.1)}$$

For a multinomial two-level outcome, model 1 includes generic drug, age, and sex:

$$\log(\rho/1-\rho)) = \alpha + \beta X_{\text{generic drug}} + \beta X_{\text{age}} + \beta X_{\text{sex}} \quad \text{(Equation 1.2)}$$

For a multinomial three-level outcome, model 2 includes expected phenotype, age, and sex:

$$\log \frac{\pi_{critical} \text{ or } \pi_{warning}}{\pi_{informational}} = \alpha + \beta X_{\text{expected phenotype}} + \beta X_{\text{age}} + \beta X_{\text{sex}} \quad \text{(Equation 1.3)}$$

For a multinomial two-level outcome, model 2 includes expected phenotype, age, and sex:

$$\log(\rho/1-\rho)) = \alpha + \beta X_{\text{expected phenotype}} + \beta X_{\text{age}} + \beta X_{\text{sex}} \quad \text{(Equation 1.4)}$$

For the primary analysis, any observations in cardiology and *CYP2D6* with expected phenotype of 'Intermediate or Normal metabolizer' were collapsed into 'Normal metabolizer.' For observations that the expected phenotype was collapsed, loss of information was not a concern because there were so few observations to which this applied.[3] In one-way sensitivity analyses, we also considered alternate selected predictor strategies by evaluating collapsed expected phenotype categories. We conducted these one-way sensitivity analyses on the

[3] For the psychiatry-*CYP2D6* model, there were initially seven categories for the expected phenotype predictor variable. We explored ways to consolidate categories without losing information, and since all of the generic drugs with an outcome of 'intermediate or normal metabolizer' had five or fewer observations we re-coded these into a 'normal metabolizer' for the expected phenotype. For the cardiology-*CYP2D6* model, there were initially seven categories for the expected phenotype variable. Since all of the generic drugs with an outcome of 'intermediate or normal metabolizer' had fewer than 20 observations we re-coded these into a 'normal metabolizer' for the expected phenotype.

psychiatry-*CYP2D6* model by generating two new variables that collapsed six categories into four categories. For the first new variable, we recoded 'possible intermediate or ultra-rapid metabolizer' to 'ultra-rapid metabolizer' and recoded 'ultra-rapid or normal metabolizer' to 'normal metabolizer'. For the second new variable, we recoded 'possible intermediate or ultra-rapid metabolizer' to 'intermediate metabolizer' and 'ultra-rapid or normal metabolizer' to 'ultra-rapid metabolizer'.

Model diagnostic methods are not well developed for categorical data when penalized multinomial models are used.[29; 32] Therefore, we simply compared AICs among models to determine best fit.

Analyses were performed using RStudio (RStudio Inc., Boston, MA) and R 3.4.0 statistical software (Vienna, Austria)[33] using the 'nnet' package to build multinomial models, and the 'pmlr' package to build penalized multinomial models.[34; 35] Statistical significant thresholds were set at $p < 0.05$, with additional thresholds assessed.

1.4 RESULTS

For the 186,228 observations on 90,732 individual patients (41% male), an average of three drugs were ordered per patient (range 1 to 23). Over 90% of patients were tested for six or fewer drugs. The majority of patients were between 45-64 years of age and relatively few were younger than 18 years of age. Additional characteristics are presented in **Table 3**. Missing data were limited to the sex variable; across clinical subgroups, fewer than 5% of patients were missing sex.

1.4.1 *Pain*

Age and sex are presented in **Table 4**. The average number of PGx test/drug pairs, per patient, was 1.9. For patients 18 years and younger, codeine and ibuprofen were the most commonly ordered drugs; for patients over 18 years, hydrocodone and oxycodone were most commonly ordered (**Table 5**). For *CYP2D6,* of the five gene-drug pairs modeled, CPIC LOE ranges from "A" to none assigned. For *CYP2C9,* of the six gene-drug pairs modeled, CPIC LOE ranges from "B" to none assigned. For *OPRM1*, of the three gene-drug pairs modeled, CPIC LOE ranges from "C" to none assigned (**Figure 1.1**). For PGx gene-drug pairs with less than a CPIC LOE B, seven pairs resulted in warning and/or critical clinical actionability exhibiting discordance between sources of evidence (**Table 6**).

1.4.2 *Cardiology*

Age and sex are presented in **Table 7**. The average number of PGx test/drug pairs, per patient, was 2.0. For patients 18 years and younger, fluvastatin and mexiletine were the most commonly ordered drugs; for patients over 18 years, atorvastatin and simvastatin were most commonly prescribed (**Table 8**). For *CYP2C19,* of the two gene-drug pairs modeled, CPIC LOE ranges from "A" to none assigned. For *SLCO1B1,* of the six gene-drug pairs modeled, CPIC LOE ranges from "A" to none assigned. For *CYP2D6,* of the eight gene-drug pairs modeled, CPIC LOE ranges from "C" to none assigned. No CPIC LOE was assigned for *CYP2C9,* of the four gene-drug pairs modeled or for *CYP3A4*, of the three gene-drug pairs modeled, respectively (

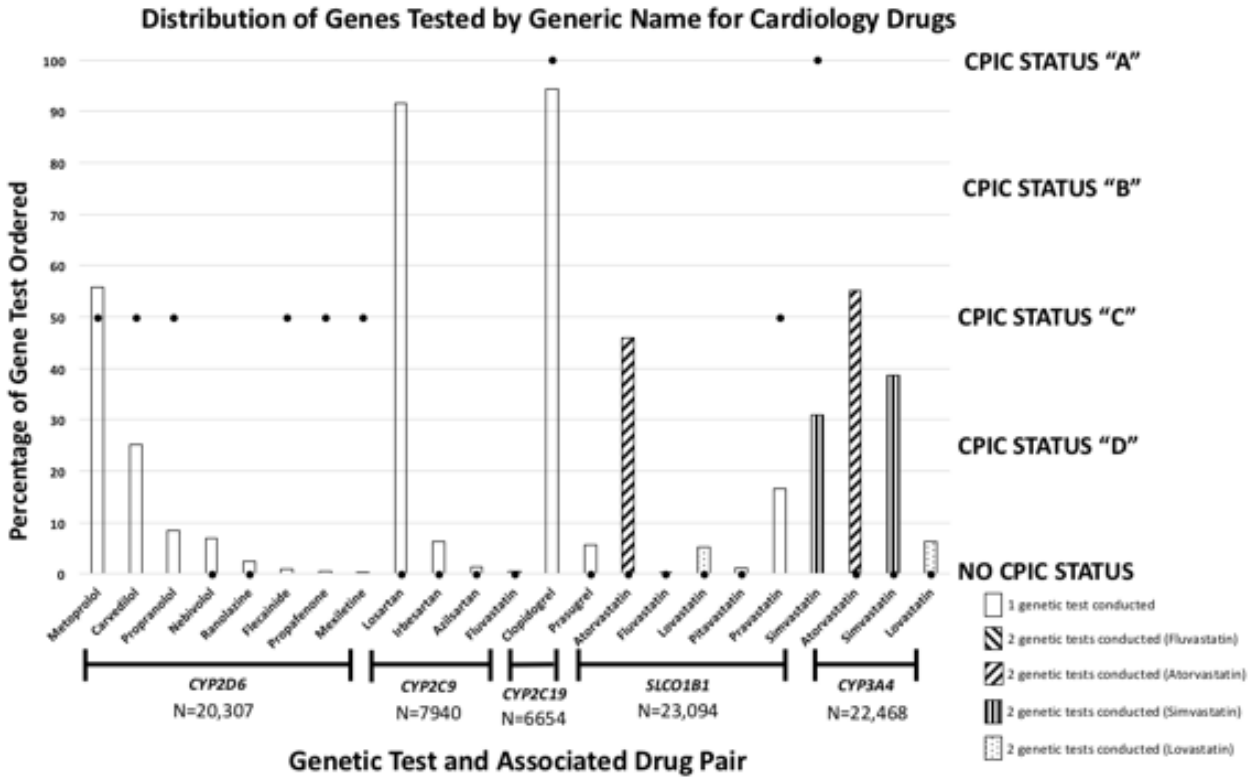

Figure 1.2). For PGx gene-drug pairs with less than a CPIC LOE B, eight pairs resulted in warning and/or critical clinical actionability exhibiting discordance between sources of evidence (**Table 9**).

1.4.3 *Psychiatry*

Age and sex are presented in **Table 10**. The average number of PGx test/drug pairs, per patient, was 1.4. For patients 18 years and younger, stimulant and gamma-Aminobutyric acid (GABA) reuptake inhibitor were the most common drug type categories, and for patients over 18 years, SSRI/SNRI and TCAs were most common (**Table 11**). For *CYP2C19,* of the five gene-drug type pairs modeled, CPIC LOE ranges from "B" to none assigned. For *CYP2D6*, CPIC LOE ranges from "A" to none assigned. For *CYP2C9,* of the six gene-drug pairs

modeled, CPIC LOE ranged from “B” to no LOE. For *COMT*, no CPIC LOE was assigned (

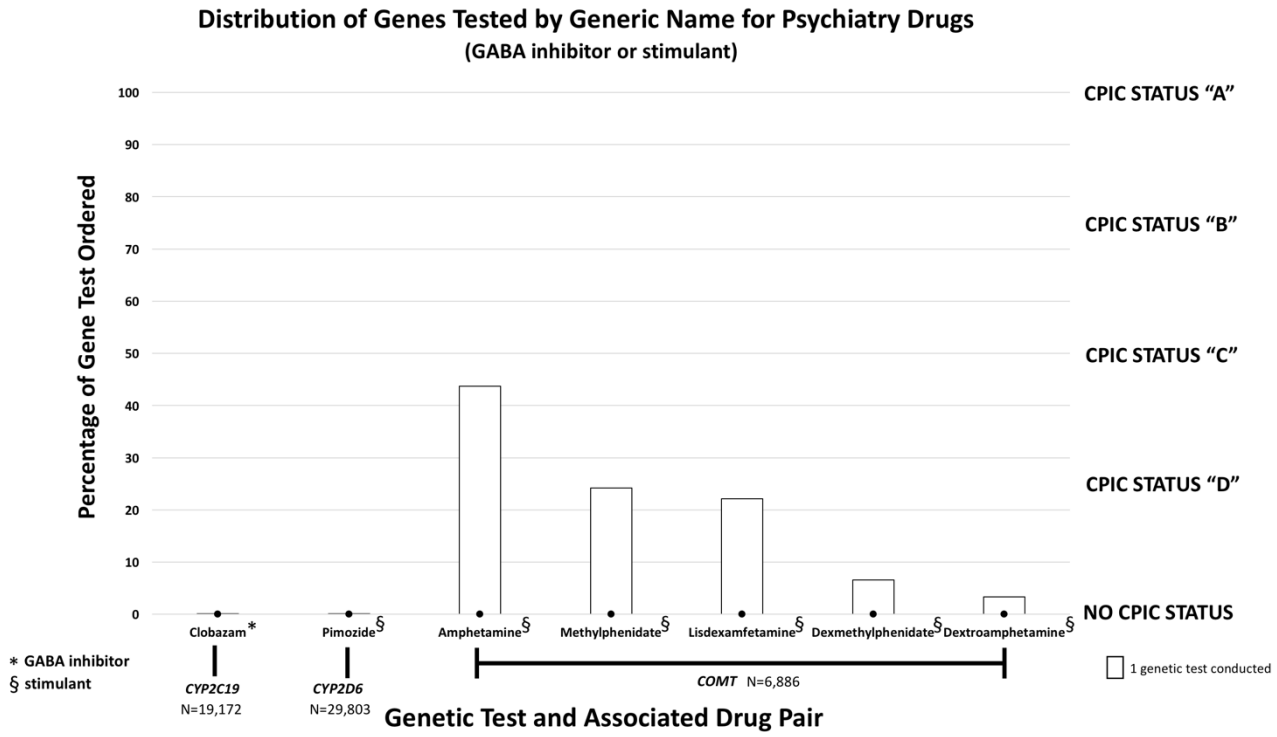

Figure 1.4).

1.4.4 *Gastroenterology*

Age and sex are presented in **Table 12**. The average number of PGx test/drug pairs, per patient, was 1.0. For patients 18 years and younger, omeprazole and esomeprazole were the most commonly ordered drugs; for patients over 18 years, omeprazole and pantoprazole were most commonly ordered (**Table 13**). For *CYP2C19,* of the five gene-drug pairs modeled, CPIC LOE ranges from “B” to none assigned (Figure 1.7). For PGx gene-drug pairs with less than a CPIC LOE B, two pairs resulted in warning and/or critical clinical actionability exhibiting discordance between sources of evidence (**Table 14**).

1.4.5 *Predictors Associated with Clinical Actionability*

1.4.5.1 Pain

We generated models, two each for *CYP2D6, CYP2C9, and OPRM1* (**Table 15**). For *CYP2D6* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly higher for hydrocodone ($p < 0.001$) and oxycodone ($p < 0.001$) versus codeine. For Model 1, the odds of receiving a *critical* versus an *informational* recommendation were significantly lower for every one-year increase in age ($p < 0.05$); for hydrocodone ($p < 0.001$) and oxycodone ($p < 0.001$) compared to codeine. For Model 2, the odds of receiving a *critical* versus an *informational* recommendation were significantly lower for poor ($p < 0.05$), possible intermediate or ultra-rapid ($p < 0.05$), ultra-rapid or normal ($p < 0.05$) compared to normal metabolizer. For *CYP2C9* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for ibuprofen ($p < 0.01$) compared to celecoxib. For Model 2, the odds of receiving a *warning* versus an *informational* recommendation were significantly higher for every one-year increase in age ($p < 0.001$); and significantly higher for intermediate ($p < 0.001$) and poor metabolizer ($p < 0.001$) when each is compared to normal metabolizer, respectively. For *OPRM1* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for morphine compared to fentanyl ($p < 0.001$). For Model 2, the odds were significantly higher for males ($p < 0.05$); significantly higher for every one-year increase in age ($p < 0.01$); and significantly higher for altered OPRM1 function when compared to normal function ($p < 0.001$). **Table 16** displays the predictors with accompanying arrows to depict the direction of the odds ratios.

1.4.5.2 Cardiology

We created models, two each for *CYP2C19, SLCO1B1, CYP2D6, CYP2C9,* and *CYP3A4* (**Table 17**). For *CYP2C19* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for prasugrel compared to clopidogrel ($p < 0.001$). For Model 2, the odds were significantly higher for rapid ($p < 0.05$) and ultra-rapid ($p < 0.05$) compared to normal metabolizer. For Model 1, the odds of receiving a *critical* versus an *informational* recommendation were significantly lower for every one-year increase in age ($p < 0.01$) and significantly higher for prasugrel compared to clopidogrel ($p < 0.001$). For Model 2, the odds were significantly higher for intermediate ($p < 0.05$) and poor ($p < 0.05$) metabolizer when each is compared to normal. For *SLCO1B1* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for fluvastatin ($p < 0.05$) and simvastatin ($p < 0.001$) compared to atorvastatin. For Model 2, the odds were significantly higher for decreased function ($p < 0.01$) and poor ($p < 0.01$) function compared to normal function, respectively. For Model 1, the odds of receiving a *critical* versus an *informational* recommendation were significantly higher for simvastatin compared to atorvastatin ($p < 0.01$), and significantly higher for decreased ($p < 0.001$) and poor ($p < 0.05$) compared to normal function, respectively. For *CYP2D6* (Model 1), the odds of receiving a *critical* versus an *informational* recommendation were significantly higher for metoprolol compared to carvedilol ($p < 0.01$). For Model 2, the odds were significantly higher for poor ($p < 0.05$), ultra-rapid ($p < 0.05$), and ultra-rapid/normal ($p < 0.05$) compared to normal metabolizer. For *CYP2C9* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly higher for fluvastatin ($p < 0.001$) and losartan ($p < 0.001$) compared to azilsartan,

respectively; and significantly lower for irbesartan compared to azilsartan ($p < 0.001$). For Model 2, the odds were significantly higher for poor and intermediate metabolizer when each is compared to normal ($p < 0.001$ for both, respectively); and significantly lower with every one-year increase in age ($p < 0.05$). For *CYP3A4* (Model 2), the odds of receiving a *warning* versus an *informational* recommendation were significantly higher with a one-year increase in age ($p < 0.001$); significantly higher for males ($p < 0.01$); and significantly higher for intermediate compared to normal metabolizers ($p < 0.001$). **Table 18** displays the predictors with accompanying arrows to depict the direction of the odds ratios.

1.4.5.3 Psychiatry

We created models, two each for *CYP2C19, CYP2D6,* and *COMT* (**Table 19**). For *CYP2C19* (Model 1), the odds of receiving a *warning* versus an *informational* recommendation were significantly higher for males ($p < 0.05$). For Model 2, the odds were significantly higher for intermediate, poor, rapid, and ultra-rapid compared to normal metabolizers ($p < 0.001$ for each, respectively). The odds of receiving a *critical* versus an *informational* recommendation were significantly higher for every one-year age increase ($p < 0.05$); and, for SSRI/SNRI ($p < 0.05$) and TCA ($p < 0.001$) drug type compared to GABA reuptake inhibitor drug type. For Model 2, the odds were significantly higher for every one-year increase in age ($p < 0.05$); and, for poor, rapid, and ultra-rapid compared to normal metabolizer ($p < 0.001$ for each, respectively). For *COMT* (Model 2), the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for every one-year increase in age ($p < 0.001$); for males compared to females ($p < 0.001$); and, for intermediate and low *COMT* activity

compared to high/normal metabolizers ($p < 0.001$ for each, respectively)**. Table 20** displays the predictors with accompanying arrows to depict the direction of the odds ratios.

1.4.5.4 Gastroenterology

Two models were generated for *CYP2C19* (**Table 21**). For Model 1, the odds of receiving a *warning* versus an *informational* recommendation were significantly lower for omeprazole compared to dexlansoprazole ($p < 0.05$) (**Table 22**). For Model 2, the odds were significantly lower for every one-year increase in age ($p < 0.001$); significantly lower for males ($p < 0.001$); and significantly lower for intermediate and poor metabolizers and higher for rapid and ultra-rapid metabolizers when each is compared to normal metabolizer ($p < 0.001$ for each, respectively). Model 2 further required penalized binomial regression, however, due to computational constraints, we did not undertake developing that additional model for this study.

1.4.6 *One-Way Sensitivity Analyses*

Results were robust to the different predictor selection strategies (**Table 19**).

1.5 DISCUSSION

For *CYP2D6* (pain); *CYP2C9* (pain); *CYP2C19* (GI, cardiology, psychiatry); *OPRM1* (pain); *CYP3A4* (cardiology); and *COMT (*cardiology); age was correlated with clinical actionability (**Table 23**). For *OPRM1* (pain), *CYP3A4* (cardiology), *COMT* (pain), and *CYP2C19* (GI), male was correlated with informing clinical actionability. For *CYP2D6* (pain, cardiology), *CYP2C9* (pain, cardiology); *OPRM1* (pain); *CYP2C19* (cardiology, psychiatry, and GI); *CYP3A4* (cardiology); *SLCO1B1* (cardiology); *COMT* (psychiatry); at least one category of generic drug

or drug type was correlated with clinical actionability. For *CYP2D6* (pain, cardiology); *CYP2C9* (pain, cardiology); *OPRM1* (pain); *CYP2C19* (cardiology, psychiatry, GI); *CYP3A4* (cardiology); *SLCO1B1* (cardiology); *COMT* (psychiatry), at least one category of expected phenotype was correlated with clinical actionability. When comparing AICs for all models within each designated therapeutic category, Model 2 (included the expected phenotype) performed better than Model 1 (drug or drug type) most often. These findings are logical in that known pharmacokinetics and pharmacodynamics evidence is routinely used to inform clinical actionability.[36] We posit some distribution of the (up to) three clinical actionability categories for gene-drug pairs with CPIC LOE A or B. Importantly however, 28 of the 33 PGx gene-drug pairs characterized by CPIC LOE less than B resulted in a warning or critical actionability recommendation that differed from the CPIC evidence currently assigned (**Tables 12-14**).

Dunnenberger *et al* concisely present the 12 most commonly tested genes (*CYP-2C19*, *2C9*, *2D6*, *3A5*, *DPYD*, *G6PD*, *HLA-B, IFNL3, SLCO1B1, TPMT, UGT1A1, VKORC1*) that have known PGx-associated clinical actionabilitys.[13] Our study generated prediction models for four of these genes, but due to our inclusion criteria of greater than 1000 observations per gene test, we did not model the remaining seven genes. Recognizing that some health systems and clinical laboratories utilize PGx tests for genes beyond the 12 most commonly tested, our study evaluated these additional genes: *CYP3A4, COMT,* and *OPRM1*. Comprehensive PGx panels are used in the research setting; however, limited evidence of clinical utility impedes more widespread implementation in routine clinical practice. Two such panels used in research include PGRNseq, a custom capture sequencing panel that includes 84 genes with associations

to PGx phenotypes and Affymetrix's Drug Metabolizing Enzymes and Transporters genotyping panel, which provides coverage for PGx biomarkers in 231 relevant genes.[37-39] The fact that these panels are much larger, coupled with the call for additional evidence of clinical utility, suggests that adoption of a smaller, more targeted panel may be warranted.

Our results suggest that the PGx test results could inform clinical decision-making regarding selection of alternate treatment, adjusting dose recommendation, and/or identification of potential drug-drug interactions, thereby providing evidence for utilizing PGx tests. Additionally, our findings may meet one criterion for Hayes' health technology assessment definition of clinical utility in that they guide decision-making through the provision of additional PGx-drug evidence.[40] Our results support both testing and timely alerting.

There were two methods challenges that we addressed during this study. Collinearity, where a model describes the random error in the data rather than the relationships between variables, resulted when drug name and expected phenotype were included in the full model. This limited model convergence on the dataset. Subsequently, we built two separate models as discussed in detail in the Methods. Separately, when a zero was identified in some cells across either of the two categorical predictor variables (drug name and expected phenotype), use of conventional maximum likelihood estimation methods resulted in first-order bias. To address this bias, we employed penalized maximum likelihood estimate methods.[31] As denoted in the methods, penalization of the model guarantees finiteness even in cases of data separation or perfect prediction whereby the maximum likelihood estimator is infinite.

Development of PGx tools that easily integrate into provider workflow will lessen the burden for implementation and can provide accessible CDS.[19] Hoffman *et al* describe principles to support publically available, standardized sets of PGx knowledge resources, but limitations to clinical implementation of PGx tests persist if solely relying on expertly developed CPIC guidelines and a single authoritative consensus-based national resource.[41] However, herein lies a rate-limiting barrier to ease implementation and adoption challenges. Further, these guidelines are not able to account for patient-specific level data beyond genetic information and drug in question. Therefore, our work suggests that healthcare systems may wish to consider commercial knowledge resources, as these solutions may adapt quicker to synthesize clinical actionability data to inform CDS, and can often be customized to the population of each Learning Health System. From our evaluation of the Translational Software commercial knowledge resource, the software's ability to integrate patient-specific data by accounting for additional predictive factors, the inclusion of these data provides different clinical actionability evidence. This evidence may differ from the clinical PGx implementation guidelines yet to be defined.

This is the largest retrospective study conducted to date on patients undergoing PGx testing in a broad set of clinical settings and outside of a clinical research setting. Our findings provide a robust characterization of real-world PGx testing utilization data. Our findings of the highest incidence of exposure to PGx drugs in patients 40 years of age and older are similar to those of Samwald *et al*.[27] This seems reasonable for specific age categories because, as the age of an individual increases, one can expect increased demand for drug use. Findings from our study may aid payer decision-makers in discerning value in adopting PGx testing by comparing

patient characteristics of our study sample to those of their enrolled members. As Relling and Evans demonstrated, CPIC LOE can inform evidence synthesis necessary to mitigate a barrier in clinical implementation of PGx testing.[23] CPIC LOE for the genes tested in our sample are displayed in **Figure 1.1 – Figure 1.7**. Integrating the significant drug predictors generated from our models coupled with CPIC, DPWG, PGRN, and PharmGKB guidance could better inform which PGx tests to utilize for specific drugs. Reliance on authoritative guidelines for PGx testing may hinder access to test information that could inform clinical decision-making. Our work demonstrates discordance in centrally-organized expert guideline assignment and changes to a real-time clinical decision for drug treatment selection.

The major limitation of our study is that our dataset did not include associated drug-related outcomes, as these are not routinely collected by testing laboratories. Neither did our data include race/ethnicity; the availability of that data would strengthen the prediction models to better inform clinical recommendations, as there are known differences in actionable PGx variant allele frequencies associated with PGx risks across racially diverse patient populations.[42-44] Further, our dataset did not include ICD-10 codes, which could better inform healthcare resource utilization and may be coupled with future investigations determining clinical utility of PGx testing. We assumed that all drugs mentioned on each patient's drug list (beyond the drug ordered) represented active orders, but laboratory documentation may not be accurate, so we did not investigate drug-drug interactions and the predictive impact of these drugs on clinical recommendations. Additionally, by applying our threshold for generating models for clinical subgroups inclusive of 23,000 observations, we potentially limit the evidence associated with genes for models that were not built; and, future work should explore

gene-drug pairs not included in our analysis. The *CYP2C19*-GI Model 2 overfits the data (**Table 21**). Subsequently, the GI subgroup data required building a penalized binomial regression model; however, due to computational constraints and identifying an approach to ensure model convergence, we did conduct this for the analysis. This warrants caution interpreting the reported model results. Due to our large sample, for Model 2 we would expect to see narrower confidence intervals across each therapeutic subgroup. However, the fact that we intentionally included a limited number of predictors to prevent overfitting each model, may have contributed to wider confidence intervals. [36; 45; 46]

Despite evidence from our exploratory analysis demonstrating potential clinical utility, prospective studies are needed to further demonstrate the impact of the provision of PGx test results on drug-related outcomes. Such data can more robustly inform clinical utility, economic utility, and spur adoption of appropriate testing into clinical practice. A large prospective effort, the Ubiquitous Pharmacogenomics program, is currently underway, but has only just begun enrollment.[19; 47] In the meantime, our study provides estimates of predictive ability of drug and expected phenotype from a large patient sample that may better contribute to clinical recommendations for patients undergoing PGx testing.

1.6 TABLES AND FIGURES

Table 1. Variables included for predictors of interest

Variable	**Type**	**Description**
Age	Continuous	Integer
Gender	Binary	Female, Male
Gene Tested	Categorical	*CYP2D6, CYP2C9, CYP2C19, OPRM1, CYP3A4, SLCO1B1,* and *COMT*
Generic Drug Name	Categorical[a]	Pain: carisoprodol, codeine, dihydrocodeine, hydrocodone, oxycodone, tramadol, ibuprofen, meloxicam, diclofenac, celecoxib, indomethacin, piroxicam, tizanidine, morphine, fentanyl Cardiology: atorvastatin, azilsartan, clopidogrel, fluvastatin, irbesartan, losartan, lovastatin, pitavastatin, prasugrel, pravastatin, simvastatin Gastroenterology: dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole
Drug Type[b] (only for psychiatry drugs)	Categorical	1st generation (1stGen) antipsychotics, 2nd generation (2ndGen) antipsychotics, gamma-Aminobutyric acid (GABA) reuptake inhibitor, selective serotonin reuptake inhibitor (SSRI)/serotonin–norepinephrine reuptake inhibitor (SNRI), Tricyclic Antidepressants (TCA)
Expected Phenotype	Categorical	normal metabolizer, intermediate metabolizer, poor metabolizer, rapid metabolizer, ultra-rapid metabolizer, decreased function, poor function, normal function, ultra-rapid or normal metabolizer, possible intermediate or ultra-rapid metabolizer, low *COMT* activity, intermediate *COMT* activity, high/normal *COMT* activity, altered *OPRM1* function, normal *OPRM1* function
Laboratory identifier	Numeric	114 unique LabIDs

[a] Clinical subgroups that did not meet inclusion criterion of greater than 23,000 observations included the following: endocrinology, immunology, infectious disease, neurology, oncology, rheumatology, urology, and other (other consisted of the following drugs: primidone, zonisamide, brivaracetam, repaglinide, torsemide,

flurbiprofen, nateglinide, fosphenytoin, vevimeline, clonidine, donepezil, eliglustat, timolol, disulfiram, methylene blue, and acamprostat).

[b] 1stGen antipsychotics included chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, pimozide; 2ndGen antipsychotics included aripiprazole, brexpiprazole, clozapine, iloperidone, olanzapine, paliperidone, risperidone; GABA reuptake inihibitor included clobazam; SSRI/SNRI included atomoxetine, amoxapine, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazaodone, paroxetine, sertraline, venlafaxine, vortioxetine; TCAs included amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortiptyline, protriptyline, trimipramine; stimulants included amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate

Table 2. Genes and the corresponding nomenclature associated with the expected phenotype categories.

Gene Name	Expected Phenotype															
	Normal Metabolizer	Intermediate Metabolizer	Poor Metabolizer	Rapid Metabolizer	Ultra-Rapid Metabolizer	Decreased Function	Poor Function	Normal Function	Ultra-Rapid or Normal Metabolizer	Possible Intermediate or Ultra-Rapid Metabolizer	Low *COMT* Activity	Intermediate *COMT* Activity	High/Normal *COMT* Activity	Altered *OPRM1* Function	Normal *OPRM1* Function
CYP2D6	X	X	X		X				X	X					
CYP2C9	X	X	X												
CYP2C19	X	X	X	X	X										
OPRM1														X	X
CYP3A4	X	X													
SLCO1B1						X	X	X							
COMT											X	X	X		

Table 3. Sample distribution of sex, age in years, and PGx tests associated with prescribed drugs.

Overall Male	41%
Mean Age (years)	56
Mean Age, Sex Missing (years)	50
Overall Age Range	1-90
Overall Range of PGx tests/drugs per patient	1-23
Overall Mean of PGx tests/drugs per patient	1.6

Table 4. Sample distribution of sex, age range in years, PGx tests associated with prescribed drug for pain. N = 47,054 (unique patients)

Age Category (years)	Males	(%)	Females	(%)
	1-18	< 1	1-18	< 1
	19-44	8	19-44	12
	45-64	18	45-64	27
	65-80	9	65-80	15
	81+	2	81+	4
	Total	37	Total	59
	Mean (years)	56	Mean (years)	57
Overall Age: Mean (Range)	57 (1-90)			
Overall Tests (Number of PGx tests/drugs per patient): Mean (Range)	1.9 (1-13)			
Observations missing sex data	4%			
Mean age for observations missing sex (years)	49			

Table 5. All ages drug frequency relative to the full sample for the pain clinical subgroup and across patients under 18 years old proportion relative to all drug orders (N=87,662 observations).

	Frequency	
Drug	Total Orders, All Ages (% of All Pain Drugs)[a]	Total Orders, Age <18 (% of Total Orders)
carisoprodol	2042 (2)	9 (<1)
celecoxib	2198 (3)	8 (<1)
codeine	2473 (3)	37 (2)
diclofenac	4377 (5)	10 (<1)
dihydrocodeine	13 (<1)	0 (0)
fentanyl	1538 (2)	7 (<1)
hydrocodone	33180 (38)	120 (<1)
ibuprofen	6705 (8)	138 (2)
indomethacin	456 (<1)	2 (<1)
meloxicam	5719 (7)	23 (<1)
morphine	2571 (3)	17 (<1)
oxycodone	13663 (16)	43 (<1)
piroxicam	139 (<1)	0 (0)
tizanidine	3045 (3)	7 (<1)
tramadol	9543 (11)	29 (<1)

[a] Total percentage will not sum to 100 due to rounding

Table 6. Pain pharmacogenomic gene-drug pairs with associated CPIC Level of Evidence, PharmGKB rank, and actionability of the clinical recommendation. Sub totals are presented for PGx gene tests with a Level of Evidence less than B.

PGx Gene-Drug Pair	CPIC LOE	PharmGKB Rank	Clinical Recommendation					
			N	%	N	%	N	%
			Informational		*Warning*		*Critical*	
***CYP2D6* Total (25,679)**								
CYP2D6-codeine	A	level 1A	2036	8%	152	< 1%	285	1%
CYP2D6-oxycodone	A	level 2A	11211	44%	2452	10%	0	0%
CYP2D6-tramadol	A	level 1B	7964	31%	565	2%	1014	4%
Sub Total of PGx Gene Tests < LOE B (18,212)								
CYP2D6-dihydrocodeine[a b]	none	none	12	< 1%	1	< 1%	0	0%
CYP2D6-hydrocodone[a b]	none	none	14859	82%	3340	18%	0	0%
***CYP2C9* Total (19,594)**								
CYP2C9-celecoxib	B	level 2A	1546	8%	652	3%		
Sub Total of PGx Gene Tests < LOE B (17,396)								
CYP2C9-diclofenac[a b]	none	level 3	3064	18%	1313	8%		
CYP2C9-ibuprofen[a b]	none	none	6463	37%	242	1%		
CYP2C9-indomethacin[a b]	none	none	317	2%	139	1%		
CYP2C9-meloxicam[a b]	none	level 3	3990	23%	1729	10%		
CYP2C9-piroxicam[a b]	none	none	93	< 1%	46	< 1%		
***OPRM1* Total (19,090)**								
OPRM1-fentanyl[a]	none	level 3	1229	6%	309	2%		
OPRM1-hydrocodone[a]	none	level 3	11911	62%	3070	16%		
OPRM1-morphine[a]	C	level 2B	2523	13%	48	< 1%		

[a] Percentages calculated using the Sub Total (all *OPRM1* PGx gene-drug pairs were CPIC LOE < B)
[b] Indicates a Pain PGx-Drug Pair with CPIC LOE < B resulted in a Warning and/or Critical Clinical Recommendation
[c] The red circle indicates a clinical recommendation that differed from the available LOE.
PGx: Pharmacogenomic LOE: Level of Evidence

Table 7. Sample distribution of sex, age range in years, PGx tests associated with prescribed drug for cardiology. N = 40,849 (unique patients)

Age Category (years)	Males	(%)	Females	(%)
	1-18	< 1	1-18	< 1
	19-44	3	19-44	4
	45-64	19	45-64	20
	65-80	18	65-80	21
	81+	4	81+	7
	Total	44	Total	52
	Mean (years)	63	Mean (years)	64
Overall Age: Mean (Range)	64 (1-90)			
Overall Tests (Number of PGx tests/drugs per patient): Mean (Range)	2.0 (1-23)			
Observations missing sex data	4%			
Mean age for observations missing sex (years)	55			

Table 8. All ages drug frequency relative to the full sample for the cardiology clinical subgroup and across patients under 18 years old proportion relative to all drug orders (N=80,363 observations).

	Frequency	
Drug	Total Orders, All Ages (% of All Cardiology Drugs)[a]	Total Orders, Age <18 (% of Total Orders)
atorvastatin	22984 (29)	56 (<1)
azilsartan	112 (<1)	1 (<1)
carvedilol	5097 (6)	10 (<1)
clopidogrel	6188 (8)	62 (1)
flecainide	172 (<1)	2 (1)
fluvastatin	96 (<1)	4 (4)
irbesartan	506 (<1)	4 (<1)
losartan	7273 (9)	11 (<1)
lovastatin	2600 (3)	6 (<1)
metoprolol	11312 (14)	53 (<1)
mexiletine	24 (<1)	2 (7)
nebivolol	1413 (2)	5 (<1)
pitavastatin	257 (<1)	1 (<1)
prasugrel	366 (<1)	2 (<1)
pravastatin	3854 (5)	8 (<1)
propafenone	108 (<1)	1 (<1)
propranolol	1696 (2)	48 (3)
ranolazine	485 (<1)	2 (<1)
simvastatin	15820 (20)	88 (<1)

[a] Total percentage will not sum to 100 due to rounding

Table 9. Cardiology pharmacogenomic gene-drug pairs with associated CPIC Level of Evidence, PharmGKB rank, and actionability of the clinical recommendation. Sub totals are presented for PGx gene tests with a Level of Evidence less than B.

PGx Gene-Drug Pair	CPIC LOE	PharmGKB Rank	Clinical Recommendation					
			N	%	N	%	N	%
			Informational		*Warning*		*Critical*	
***CYP2D6* Total (20,307)**								
CYP2D6-carvedilol[a b]	C	level 3	4828	24%	269	1%	0	0%
CYP2D6-flecainide[a b]	C	level 2A	143	1%	21	< 1%	8	< 1%
CYP2D6-metoprolol[a b]	C	level 3	9246	46%	721	4%	1345	7%
CYP2D6-mexiletine[a b]	C	none	17	< 1%	7	< 1%	0	0%
CYP2D6-nebivolol[a b]	none	none	1321	7%	92	< 1%	0	0%
CYP2D6-propafenone[a b]	C	level 2A	88	< 1%	20	< 1%	0	0%
CYP2D6-propranolol[a]	C	level 4	1696	8%	0	0%	0	0%
CYP2D6-ranolazine[a b]	none	none	458	2%	27	< 1%	0	0%
***CYP2C9* Total (7,940)**								
CYP2C9-azilsartan[a]	none	none	112	1%	0	0%		
CYP2C9-fluvastatin[a b]	none	level 3	32	< 1%	17	< 1%		
CYP2C9-irbesartan[a]	none	level 3	506	6%	0	0%		
CYP2C9-losartan[a b]	none	level 3	7039	89%	234	3%		
***CYP2C19* Total (6554)**								
CYP2C19-clopidogrel	A	level 1A	2439	37%	1832	28%	1917	29%
Sub Total of PGx Gene Tests < LOE B (366)								
CYP2C19-prasugrel[a b]	none	level 3	366	100%	0	0%	0	0%
***SLCO1B1* Total (23,094)**								
SLCO1B1-simvastatin	A	level 1A	5446	34%	0	0%	1679	7%
Sub Total of PGx Gene Tests < LOE B (15,969)								
SLCO1B1-atorvastatin[a b]	none	level 3	8012	50%	2601	16%	0	0%
SLCO1B1-fluvastatin[a]	none	level 3	47	0%	0	0%	0	0%
SLCO1B1-lovastatin[a b]	none	level 3	923	6%	275	2%	0	0%
SLCO1B1-pitavastatin[a b]	none	level 3	184	1%	73	< 1%	0	0%
SLCO1B1-pravastatin[a b]	C	level 2A	2937	18%	917	6%	0	0%
***CYP3A4* Total (22,468)**								

CYP3A4-atorvastatin[a b]	none	level 3	11516	51%	855	4%	
CYP3A4-lovastatin[a b]	none	level 3	1311	6%	91	< 1%	
CYP3A4-simvastatin[a b]	none	level 3	8139	36%	556	2%	

[a] Percentages calculated using the Sub Total (For *CYP2D6*, *CYP2C9, CYP3A4* all gene-drug pairs LOE < B)
[b] Indicates a Pain PGx-Drug Pair with CPIC LOE < B resulted in a Warning and/or Critical Clinical Recommendation
[c] The red circle indicates a clinical recommendation that differed from the available LOE.
PGx: Pharmacogenomic LOE: Level of Evidence

Table 10. Sample distribution of sex, age range in years, PGx tests associated with prescribed drug for psychiatry. N = 38,594 (unique patients)

Age Category (years)	Males	(%)	Females	(%)
	1-18	5	1-18	3
	19-44	9	19-44	18
	45-64	12	45-64	25
	65-80	6	65-80	12
	81+	1	81+	3
	Total	33	Total	61
	Mean (years)	46	Mean (years)	52
Overall Age: Mean (Range)	49 (1-90)			
Overall Tests (Number of PGx tests/drugs per patient): Mean (Range)	1.4 (1-20)			
Observations missing sex data	5%			
Mean age for observations missing sex (years)	41			

Table 11. All ages drug frequency relative to the full sample for the psychiatry clinical subgroup and across patients under 18 years old proportion relative to all drug orders (N=54,117 observations).

	Frequency	
Drug	Total Orders, All Ages (% of All Psychiatry Drugs)[a]	Total Orders, Age <18 (% of Total Orders)
1stGen	823 (2)	26 (3)
2ndGen	5630 (10)	809 (14)
GABA Reuptake Inhibitor	26 (<1)	7 (27)
SSRI/SNRI	33687 (62)	1765 (5)
Stimulant	5142 (10)	1811 (35)
TCA	8809 (16)	210 (2)

[a] Total percentage will not sum to 100 due to rounding

Gen: generation; GABA: gamma-Aminobutyric acid SSRI/SNRI: selective serotonin reuptake inhibitor/serotonin–norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant

Table 12. Sample distribution of sex, age range in years, PGx tests associated with prescribed drug for gastroenterology. N = 22,489 (unique patients)

Age Category (years)	Males	(%)	Females	(%)
	1-18	<1	1-18	<1
	19-44	4	19-44	8
	45-64	15	45-64	25
	65-80	13	65-80	20
	81+	3	81+	7
	Total	35	Total	61
	Mean (years)	61	Mean (years)	61
Overall Age: Mean (Range)	61 (1-90)			
Overall Tests (Number of PGx tests/drugs per patient): Mean (Range)	1.4 (1-5)			
Observations missing sex data	4%			
Mean age for observations missing sex (years)	53			

Table 13. All ages drug frequency relative to the full sample for the gastroenterology (GI) clinical subgroup and across patients under 18 years old proportion relative to all drug orders (N=23,556 observations)

	Frequency	
Drug	Total Orders, All Ages (% of All GI Drugs)[a]	Total Orders, Age <18 (% of Total Orders)
dexlansoprazole	1143 (5)	1 (<1)
esomeprazole	4655 (20)	38 (<1)
lansoprazole	1021 (4)	27 (3)
omeprazole	11540 (49)	99 (<1)
pantoprazole	5197 (22)	25 (<1)

[a] Total percentage will not sum to 100 due to rounding

Table 14. The gastroenterology pharmacogenomic gene-drug pairs with associated CPIC Level of Evidence, PharmGKB rank, and actionability of the clinical recommendation. Sub totals are presented for PGx gene tests with a Level of Evidence less than B.

PGx Gene-Drug Pair	CPIC LOE	PharmGKB Rank	Clinical Recommendation					
			N	%	N	%	N	%
			Informational		*Warning*		*Critical*	
***CYP2C19* Total (25,679)**								
CYP2C19-esomeprazole	B	level 3	3322	14%	1333	6%	0	0%
CYP2C19-lansoprazole	B	level 2A	700	3%	321	1%	1014	4%
CYP2C19-omeprazole	B	level 2A	8336	35%	3204	14%	0	0%
Sub Total of PGx Gene Tests < LOE B (6,340)								
CYP2C19-dexlansoprazole[a b]	none	level 3	783	12%	360	6%	285	1%
CYP2C19-pantoprazole[a b]	none	level 3	3612	57%	1585	25%	0	0%

[a] Percentages calculated using the Sub Total

[b] Indicates a gastroenterology PGx-Drug Pair with CPIC LOE < B resulted in a Warning and/or Critical Clinical Recommendation

[c] The red circle indicates a clinical recommendation that differed from the available LOE.

PGx: Pharmacogenomic LOE: Level of Evidence

Table 15. The adjusted odds ratios and the associated clinical actionability comparison for the pain pharmacogenomic models. AICs and 95% confidence intervals are reported.

		Adjusted Odds Ratio (OR, 95% Confidence Intervals)			
Genetic Test		**Warning vs. Informational**		**Critical vs. Informational**	
CYP2D6	Variable	OR	95% CIs	OR	95% CIs
Model 1 (Drug)	Age	1.00	[1.00, 1.00]	0.995	[0.991, 0.999]
	Male	1.05	[0.99,1.12]	1.10	[0.96, 1.27]
	Referent category: Codeine				
	Dihydrocodeine	0.72	[0.01, 5.7]	0.38	[0.00, 3.05]
	Hydrocodone	3.2	[2.6, 3.9]***	$3.2*10^{-4}$	[$2.5x10^{-6}$, 0.002]***
	Oxycodone	3.1	[2.5, 3.8]***	$4.2*10^{-4}$	[$3.3x10^{-6}$, 0.003]***
	Tramadol	0.94	[0.76, 1.17]	0.90	[0.77, 1.07]
	AIC	-1789			
Model 2 (Expected Phenotype)	Age	1.1	[1.0, 1.1]	1.1	[0.7, 1.1]
	Male	0.6	[0.0, 115]	0.5	[0.0, 88.0]
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	59	[0.3, $1.1x10^{4}$]	0.97	[0, 644]
	Poor Metabolizer	50	[0.2, $1.3x10^{4}$]	1009	[3.3,$6x10^{5}$]*
	Possible Intermediate or Ultra-Rapid Metabolizer	3	[0.0, 567]	86	[0.3, $4.0x10^{4}$]
	Ultra-Rapid Metabolizer	22	[0.1, 4205]	662	[2.4, $3.0x10^{5}$]*
	Ultra-Rapid or Normal Metabolizer	26	[0.1, 5635]	667	[2.3, $3.4x10^{5}$]*
	AIC	-2388			
CYP2C9					
	Age	1.00	[0.998, 1.00]		
Model 1	Male	1.1	[0.97, 1.2]		
(Drug)	*Referent category: Celecoxib*				
	Diclofenac	1.1	[0.9, 1.2]		
	Ibuprofen	0.09	[0.08, 0.11]**		
	Indomethacin	1.1	[0.8, 1.4]		
	Meloxicam	1.1	[0.9, 1.2]		
	Piroxicam	1.4	[0.9, 2.1]		
	AIC	13383			
Model 2	Age	1.04	[1.03, 1.04] ***		
(Expected Phenotype)	Male	0.9	[0.8, 1.1]		

	Referent category: Normal Metabolizer		
	Intermediate Metabolizer	$4.2x10^5$	$[3.7x10^5, 4.8x10^5]$***
	Poor Metabolizer	$1.4x10^{10}$	$[1.4x10^{10}, 1.4x10^{10}]$***
	AIC	4781	
OPRM1			
	Age	1.00	[0.998, 1.00]
Model 1	Male	1.0	[0.90, 1.1]
(Drug)	*Referent category: Fentanyl*		
	Hydrocodone	1.0	[0.89, 12]
	Morphine	0.08	[0.06, 0.11]***
	AIC	12851	
	Age	1.01	[1.00, 1.02]**
Model 2	Male	0.79	[0.64, 0.99]*
(Expected Phenotype)	*Referent category: Normal OPRM1 Function*		
	Altered OPRM1 Function	$1.3x10^6$	$[425, 3.9x10^9]$***
	AIC	2289	

Male is compared to the female referent category AIC: Akaike information criteria

*p < 0.05 **p < 0.01 ***p < 0.001

Table 16. Statistically significant adjusted odds ratios and the associated clinical actionability comparison for the pain pharmacogenomic models. AICs are reported.

	Adjusted Odds Ratio[a] (OR)		
	Warning vs. Informational	**Critical vs. Informational**	*AIC*
CYP2D6			
Generic Drug (Model 1)	↑hydrocodone ↑oxycodone vs. codeine	↓hydrocodone ↓oxycodone vs. codeine	*-1789*
Phenotype (Model 2)		↑poor metabolizer ↑ultra-rapid metabolizer ↑ultra-rapid or normal metabolizer vs. normal metabolizer	*-2388*
CYP2C9			
Generic Drug (Model 1)	↓ibuprofen vs. celecoxib		*13383*
Phenotype (Model 2)	↑intermediate metabolizer ↑poor metabolizer vs. normal metabolizer		*4781*
OPRM1			
Generic Drug (Model 1)	↓morphine vs. fentanyl		12851
Phenotype (Model 2)	↑altered *OPRM1* function vs. normal *OPRM1* function		2289

[a] Derived from model 1 (generic drug) and model 2 (expected phenotype) results across the pain clinical subgroup, each of these predictors has a statistically significantly increased or decreased adjusted OR with the comparison denoted. All models are adjusted for age and sex.

Table 17. The adjusted odds ratios and the associated clinical actionability comparison for the cardiology pharmacogenomic models. AICs and 95% confidence intervals are reported.

		Adjusted Odds Ratio (OR, 95% Confidence Intervals)			
Genetic Test		**Warning vs. Informational**		**Critical vs. Informational**	
CYP2C19	Variable	OR	95% CIs	OR	95% CIs
Model 1 (Drug)	Age	1.00	[0.99, 1.00]	0.993	[0.988, 0.998]**
	Male	0.96	[0.83, 1.10]	1.0	[0.9, 1.2]
	Referent category: Clopidogrel				
	Prasugrel	0.002	[1.9x10^{-5}, 0.02]***	0.002	[1.8x10^{-5}, 0.02]***
	AIC	-5027			
Model 2 (Expected Phenotype)	Age	1.06	[1.01, 1.11]	1.03	[0.98, 1.09]
	Male	1.6	[0.0, 1026]	0.8	[0.0, 488]
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	1	[0, 677]	2783	[10, 1.3x10^{6}]*
	Poor Metabolizer	1	[0, 5626]	478	[1, 1.3x10^{6}]*
	Rapid Metabolizer	3116	[11, 3.4x10^{6}]*	1	[0, 1878]
	Ultra-Rapid Metabolizer	742	[2, 1.3x10^{6}]*	2	[0, 3774]
	AIC	-583			
CYP2C9					
Model 1 (Drug)	Age	1.00	[0.99, 1.01]		
	Male	0.8	[0.6, 1.1]		
	Referent category: Azilsartan				
	Fluvastatin	6.1x10^{4}	[3.7x10^{4}, 1.0x10^{5}]***		
	Irbesartan	2.9x10^{-10}	[2.9x10^{-10}, 2.9x10^{-10}]***		
	Losartan	3324	[2343, 4714]***		
	AIC	1561			
Model 2 (Expected Phenotype)	Age	0.972	[0.949, 0.996]*		
	Male	0.7	[0.3, 1.3]		
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	3.0x10^{4}	[1.7x10^{4}, 5.4x10^{4}]***		
	Poor Metabolizer	3.6x10^{7}	[1.7x10^{7}, 7.7x10^{7}]***		
	AIC	285			
CYP3A4					
Model 1 (Drug)	Age	1.00	[0.99, 1.00]		
	Male	1.0	[0.9, 1.2]		
	Referent category: Atorvastatin				
	Lovastatin	1.0	[0.8, 1.3]		

	Simvastatin	0.9	[0.8, 1.0]		
	AIC	8306			
	Age	1.02	[1.01, 1.02]***		
Model 2 (Expected Phenotype)	Male	1.2	[1.1, 1.5]**		
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	$1.5x10^{6}$	[$1.2x10^{6}$, $1.8x10^{6}$]***		
	AIC	2870			
CYP2D6					
Model 1 (Drug)	Age	1.1	[0.7, 1.1]	1.0	[0.7, 1.1]
	Male	1	[0, 265]	1	[0, 318]
	Referent category: Carvedilol				
	Flecainide	0.1	[$4.6x10^{-4}$, 24]	17	[0, $1.1x10^{4}$]
	Metoprolol	3	[0.02, 551]	2149	[8, $9.8x10^{5}$]**
	Mexiletine	0.1	[$2.0x10^{-4}$, 41]	3	[0, 683]
	Nebivolol	0.5	[0, 97]	1	[0, 858]
	Propafenone	0.1	[$4.5x10^{-4}$, 24]	1	[0, 917]
	Propranolol	0.01	[$7.4x10^{-6}$, 3]	2	[0, 2118]
	Ranolazine	0.1	[$5.5x10^{-4}$, 19]	1	[0, 613]
	AIC	-6284			
Model 2 (Expected Phenotype)	Age	1.07	[0.97, 1.12]	1.06	[0.96, 1.11]
	Male	1	[0, 166]	1	[0, 187]
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	44	[0.23, $1.1x10^{4}$]	1	[0, 994]
	Poor Metabolizer	24	[0.10, $1.1x10^{4}$]	1585	[4, $1.7x10^{6}$]*
	Possible Intermediate or Ultra-Rapid Metabolizer	0.04	[$8.5x10^{-5}$, 12]	103	[0, $5.1x10^{4}$]
	Ultra-Rapid Metabolizer	0.1	[$4.3x10^{-4}$, 21]	607	[2, $2.7x10^{5}$]*
	Ultra-Rapid or Normal Metabolizer	0.1	[$4.8x10^{-4}$, 24]	587	[2, $2.7x10^{5}$]*
	AIC	-2244			
SLCO1B1					
Model 1 (Drug)	Age	1.1	[0.8, 1.1]	1.1	[1.0, 1.1]
	Male	1	[0, 9429]	1	[0, $1.2x10^{4}$]
	Referent category: Atorvastatin				
	Fluvastatin	$5.6x10^{-4}$	[$7.1x10^{-7}$, 0.7]*	2	[0, 6346]
	Lovastatin	0	[$6.1x10^{-4}$, 22]	1	[0, 679]
	Pitavastatin	0	[$1.5x10^{-4}$, 7]	1	[0, 849]
	Pravastatin	0	[0, 65]	1	[0, 655]
	Simvastatin	$2.5x10^{-4}$	[$5.6x10^{-7}$, 0.1]**	2485	[9, $1.2x10^{6}$]**
	AIC	-9492			

Model 2	Age	1.0	[0.9, 1.1]	1.0	[1.0, 1.1]
	Male	1	[0, 8324]	1	[0, 9835]
	Referent category: Normal Function				
	Decreased Function	5994	[22, 2.7×10^6]**	2454	[9, 1.1×10^6]***
	Poor Function	597	[2, 1.9×10^7]**	351	[1, 1.1×10^7]*
	AIC	-2577			

Male is compared to the female referent category

*p < 0.05 **p < 0.01 ***p < 0.001

Table 18. Statistically significant adjusted odds ratios and the associated clinical actionability comparison for the cardiology pharmacogenomic models. AICs are reported.

	Adjusted Odds Ratio[a] (OR)		
	Warning vs. Informational	**Critical vs. Informational**	*AIC*
CYP2D6			
Generic Drug		↑metoprolol vs. carvedilol	*-6284*
Phenotype		↑poor metabolizer ↑ultra-rapid metabolizer ↑ultra-rapid or normal metabolizer vs. normal metabolizer	*-2244*
CYP2C9			
Generic Drug	↑fluvastatin ↓irbesartan ↑losartan vs. azilsartan		*1561*
Phenotype	↑poor metabolizer ↑intermediate metabolizer vs. normal metabolizer		*285*
CYP2C19			
Generic Drug	↓prasugrel vs. clopidogrel	↓prasugrel vs. clopidogrel	*-5027*
Phenotype	↑rapid metabolizer ↑ultra-rapid metabolizer vs. normal metabolizer	↑intermediate metabolizer ↑poor metabolizer vs. normal metabolizer	*-586*
CYP3A4			
Generic Drug	↑intermediate metabolizer vs. normal metabolizer		*2870*
SLCO1B1			
Generic Drug	↓fluvastatin ↓simvastatin vs. atorvastatin	↑simvastatin vs. atorvastatin	*-9492*
Phenotype	↑decreased function ↑poor function vs. normal function	↑decreased function ↑poor function vs. normal function	*-2522*

[a] Derived from model 1 (generic drug) and model 2 (expected phenotype) results across the cardiology clinical subgroup, each of these predictors has a statistically significantly increased or decreased adjusted OR with the comparison denoted. All models are adjusted for age and sex.

Table 19. The adjusted odds ratios and the associated clinical actionability comparison for the psychiatry pharmacogenomic models. AICs and 95% confidence intervals are reported.

Adjusted Odds Ratio (OR, 95% Confidence Intervals)					
Genetic Test		**Warning vs. Informational**		**Critical vs. Informational**	
CYP2C19	Variable	OR	95% CIs	OR	95% CIs
Model 1					
	Age	0.999	[0.996, 1.001]	1.003	[1.0005, 1.005]*
(Drug Type)	Male	1.1	[1.0, 1.2]*	1	[1, 1]
	Referent category: GABA Reuptake Inhibitor				
	SSRI/SNRI	1	[0, 2]	8	[1, 976]*
	TCA	2	[0.8, 6]	19	[3, 2430]***
	AIC	-12934			
Model 2					
	Age	1.003	[0.999, 1.007]	1.009	[1.004, 1.01]***
(Expected Phenotype)	Male	1.1	[0.95, 1.3]	1.0	[0.8, 1.3]
	Referent category: Normal Metabolizer				
	Intermediate Metabolizer	3180	[470, 4.0×10^{5}]***	2	[0, 368]
	Poor Metabolizer	9.1×10^{6}	[4.7×10^{5}, 2.8×10^{9}]***	1.2×10^{4}	[43, 5.2×10^{6}]***
	Rapid Metabolizer	2.4×10^{6}	[2.9×10^{5}, 3.2×10^{8}]***	5.6×10^{6}	[6.7×10^{5}, 7.3×10^{8}]***
	Ultra-Rapid Metabolizer	$9.2*10^{5}$	[9.2×10^{4}, 1.3×10^{8}]***	$2.1*10^{6}$	[2.1×10^{5}, 2.9×10^{8}]***
	AIC	-4601			
CYP2D6					
Model 1	Age	1.01	[0.96, 1.06]	1.01	[0.96, 1.30]
(Drug Type)	Male	1	[0, 165]	1	[0, 196]
	Referent category: 1st Generation				
	2nd Generation	3	[0, 649]	5	[0, 1281]
	SSRI/SNRI	7	[0, 1643]	12	[0, 2627]
	TCA	6	[0, 1299]	9	[0, 1845]
	AIC	-7836			
Model 2	Age	This model could not converge due to linearly dependent columns impeding the invertibility of the design matrix to develop a regression model (indicating exceptionally strong correlated variables within the model)			
(Expected Phenotype)	Male				
	Referent category:				

	Normal Metabolizer Intermediate Metabolizer Poor Metabolizer Possible Intermediate or Ultra-Rapid Metabolizer Ultra-Rapid Metabolizer Ultra-Rapid Metabolizer or Normal Metabolizer AIC				
Sensitivity Analysis A Model 3 (Expected Phenotype)	Age	1.0	[0.7, 1.1]	1.0	[0.7, 1.1]
	Male	0	[0, 107]	1	[0, 127]
	Referent category: Normal Metabolizer Intermediate Metabolizer	16	[0, 2928]	1	[0, 155]
	Poor Metabolizer	24	[0, 4553]	2	[0, 308]
	Ultra-Rapid Metabolizer	1	[0, 102]	1	[0, 213]
	AIC	-4808			
Sensitivity Analysis B Model 4 (Expected Phenotype)	Age	1.0	[0.7, 1.1]	1.0	[0.7, 1.1]
	Male	0	[0, 107]	1	[0, 126]
	Referent category: Normal Metabolizer Intermediate Metabolizer	74	[0, $1.5x10^4$]	50	[0, 9762]
	Poor Metabolizer	117	[1, $2.3x10^4$]	88	[0, $1.7x10^4$]
	Ultra-Rapid Metabolizer	6	[0, 1242]	107	[1, $2.1x10^4$]
	AIC	-3800			
COMT					
Model 1			This model was not generated since there was only one drug type (stimulant) associated with this gene		
Model 2 (Expected Phenotype)	Age	0.97	[0.96, 0.97]***		
	Male	1.5	[1.3, 1.9]***		

	Referent category: High/Normal *COMT* Activity		
	Intermediate *COMT* Activity	$1.3x10^5$	[$1.1x10^5$, $1.4x10^5$]***
	Low *COMT* Activity	$2.1x10^{11}$	[$2.1x10^{11}$, $2.1x10^{11}$]***
	AIC	2928	

Male is compared to the female referent category

*p < 0.05 **p < 0.01 ***p < 0.001

Table 20. Statistically significant adjusted odds ratios and the associated clinical actionability comparison for the psychiatry pharmacogenomic models. AICs are reported.

	Adjusted Odds Ratio[a] (OR)		
	Warning vs. Informational	**Critical vs. Informational**	*AIC*
CYP2C19			
Drug Type		↑SSRI/SNRI ↑TCA vs. GABA Reuptake Inhibitor	*-12934*
Phenotype	↑intermediate metabolizer ↑poor metabolizer ↑rapid metabolizer ↑ultra-rapid metabolizer vs. normal metabolizer	↑poor metabolizer ↑rapid metabolizer ↑ultra-rapid metabolizer vs. normal metabolizer	*-4601*
COMT			
Phenotype	↑intermediate *COMT* activity ↑low *COMT* activity vs. high/normal *COMT* activity	↑intermediate *COMT* activity ↑low *COMT* activity vs. high/normal *COMT* activity	*2928*

[a] Derived from model 1 (generic drug) and model 2 (expected phenotype) results across the psychiatry clinical subgroup, each of these predictors has a statistically significantly increased or decreased adjusted OR with the comparison denoted. All models are adjusted for age and sex.

Table 21. Adjusted odds ratios and the associated clinical actionability comparison for the gastroenterology pharmacogenomic model. AICs and 95% confidence intervals are reported.

		Adjusted Odds Ratio (OR, 95% Confidence Intervals)	
Genetic Test		**Warning vs. Informational**	
CYP2C19	Variable	OR	95% CIs
Model 1 (Drug Type)	Age	1.0019	[0.9998, 1.0041]
	Male	1.0	[0.9, 1.1]
	Referent category: Dexlansoprazole		
	Esomeprazole	0.9	[0.8, 1.1]
	Lansoprazole	1.0	[0.8, 1.3]
	Omeprazole	0.86	[0.73, 0.997]*
	Pantoprazole	1.0	[0.8, 1.1]
	AIC	21217	
Model 2 (Expected Phenotype)	Age	0.11	[0.11, 0.11]***
	Male	$3.3x10^{-38}$	[$3.3x10^{-38}$, $3.3x10^{-38}$]***
	Referent category: Normal Metabolizer		
	Intermediate Metabolizer	0.0	[0.0, 0.0]***
	Poor Metabolizer	$2.3x10^{-71}$	[$2.3x10^{-71}$, $2.3x10^{-71}$]***
	Rapid Metabolizer	Inf	[Inf, Inf]***
	Ultra-Rapid Metabolizer	$6.7x10^{229}$	[$6.7x10^{229}$, $6.7x10^{229}$]***
	AIC	14	

Male is compared to the female referent category Inf: infinity

*p < 0.05 **p < 0.01 ***p < 0.001

Table 22. Statistically significant adjusted odds ratios and the associated clinical actionability comparison for the gastroenterology pharmacogenomic models. AICs are reported.

Adjusted Odds Ratio[a] (OR)		
	Warning vs. Informational	*AIC*
CYP2C19		
Generic Drug (Model 1)	↓omeprazole vs. dexlansoprazole	*21217*
Phenotype (Model 2)	↓intermediate metabolizer ↓poor metabolizer ↑rapid metabolizer ↑ultra-rapid metabolizer vs. normal metabolizer	*14*

[a] Derived from model 1 (generic drug) and model 2 (expected phenotype) results across the GI clinical subgroup, each of these predictors has a statistically significantly increased or decreased adjusted OR with the comparison denoted. All models are adjusted for age and sex.

Table 23. Statistically significant adjusted odds ratios and the associated clinical actionability comparison for age and male across all of the pharmacogenomic models.

Adjusted Odds Ratio[a] (OR)		
Age	**Warning vs. Informational**	**Critical vs. Informational**
CYP2D6		↓pain (model 1)
CYP2C9	↑pain(model 2)	
CYP2C19	↓GI (model 2)	↓cardiology (model 1) ↑psychiatry (model 1, model 2)
OPRM1	↓pain (model 2)	
CYP3A4	↑cardiology(model 2)	
COMT	↓cardiology (model 2)	
Male		
OPRM1	↓pain (model 2)	
CYP3A4	↑cardiology(model 2)	
COMT	↑cardiology(model 2)	
CYP2C19	↓GI (model 2)	

[a] Derived from model 1 (generic drug) and model 2 (expected phenotype) results across all of the clinical subgroups, each of these age and male predictors has a statistically significantly increased or decreased adjusted OR with the comparison denoted.

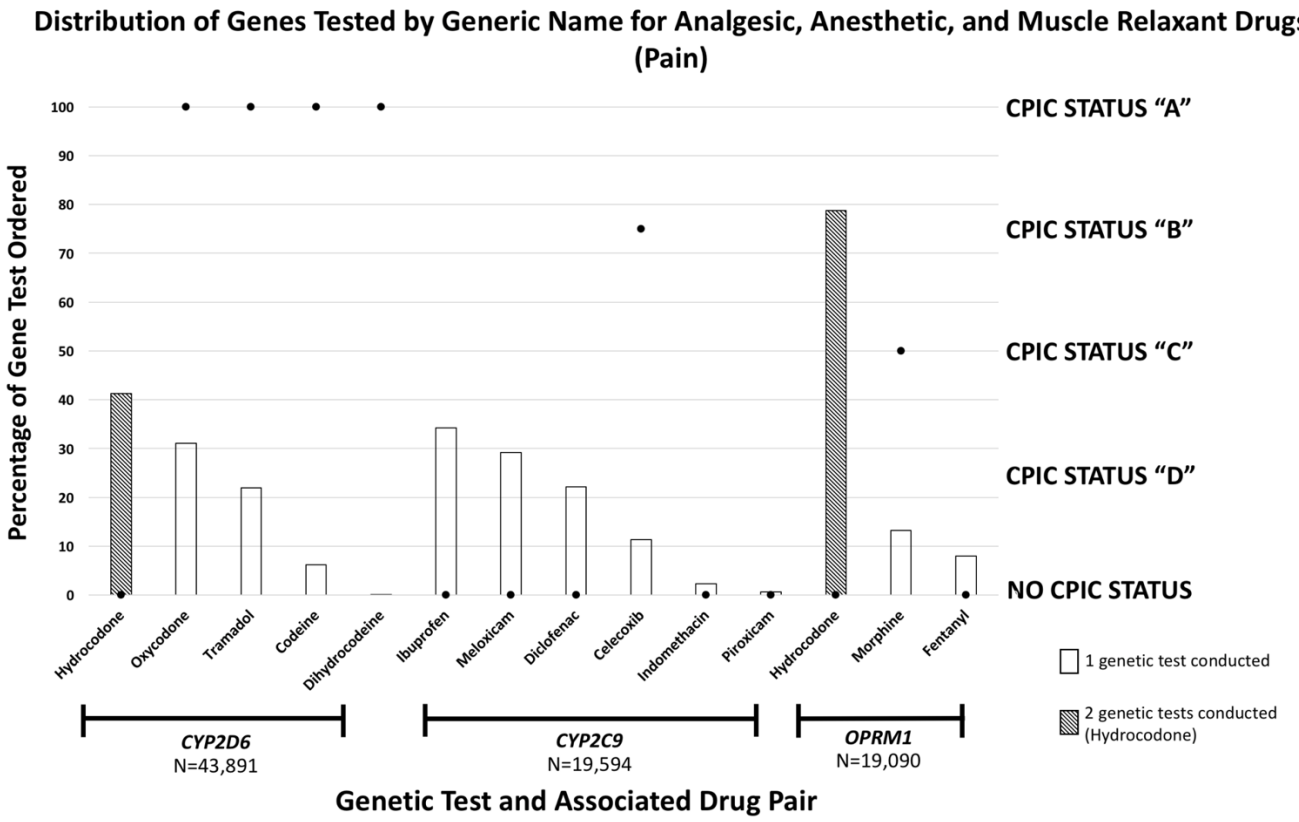

Figure 1.1. Characterization of pain generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

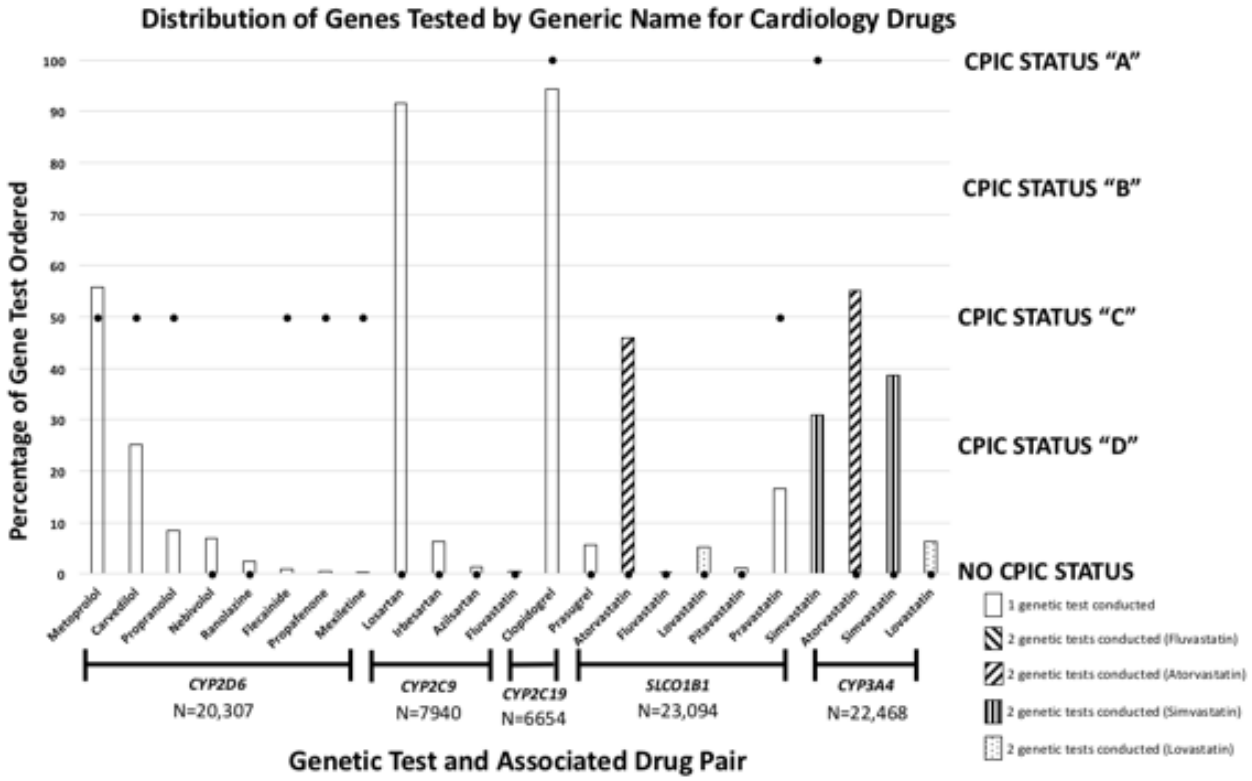

Figure 1.2. Characterization of cardiology generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

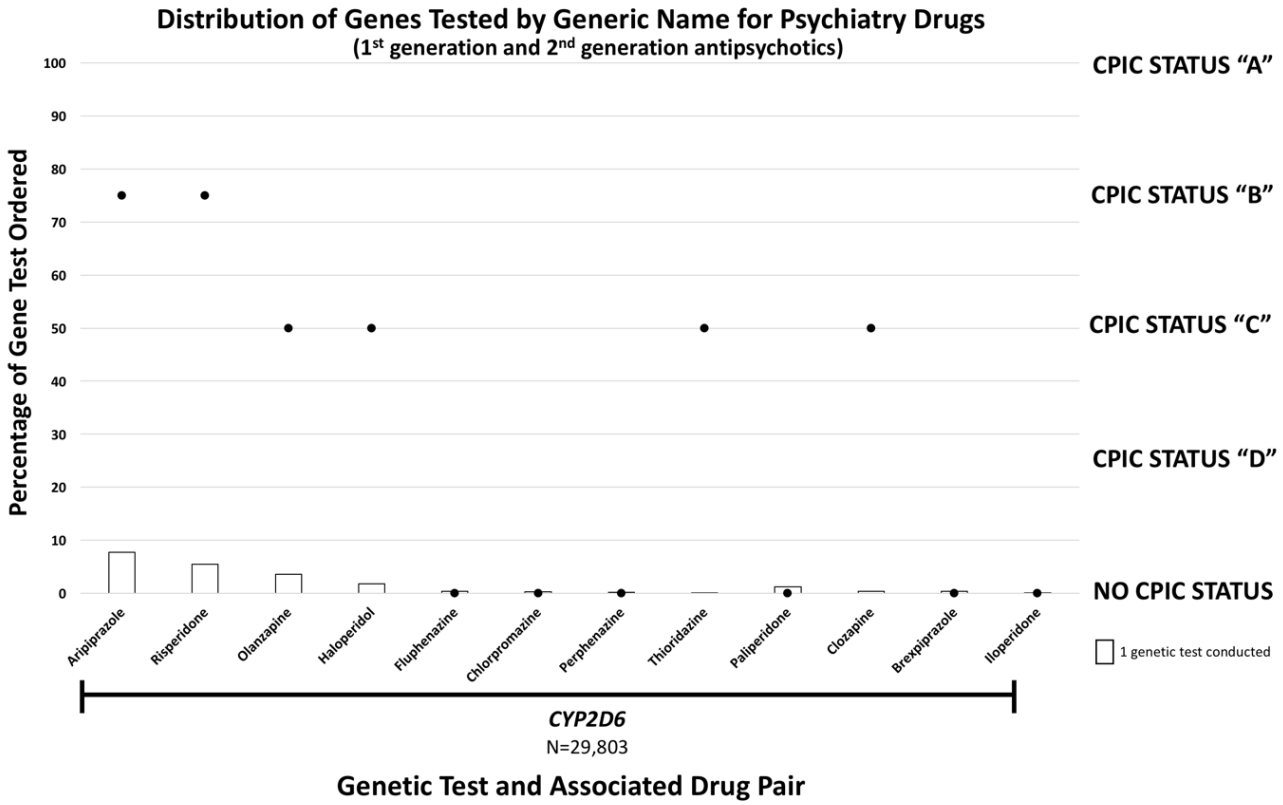

Figure 1.3. Characterization of 1st and 2nd generation antipsychotic generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

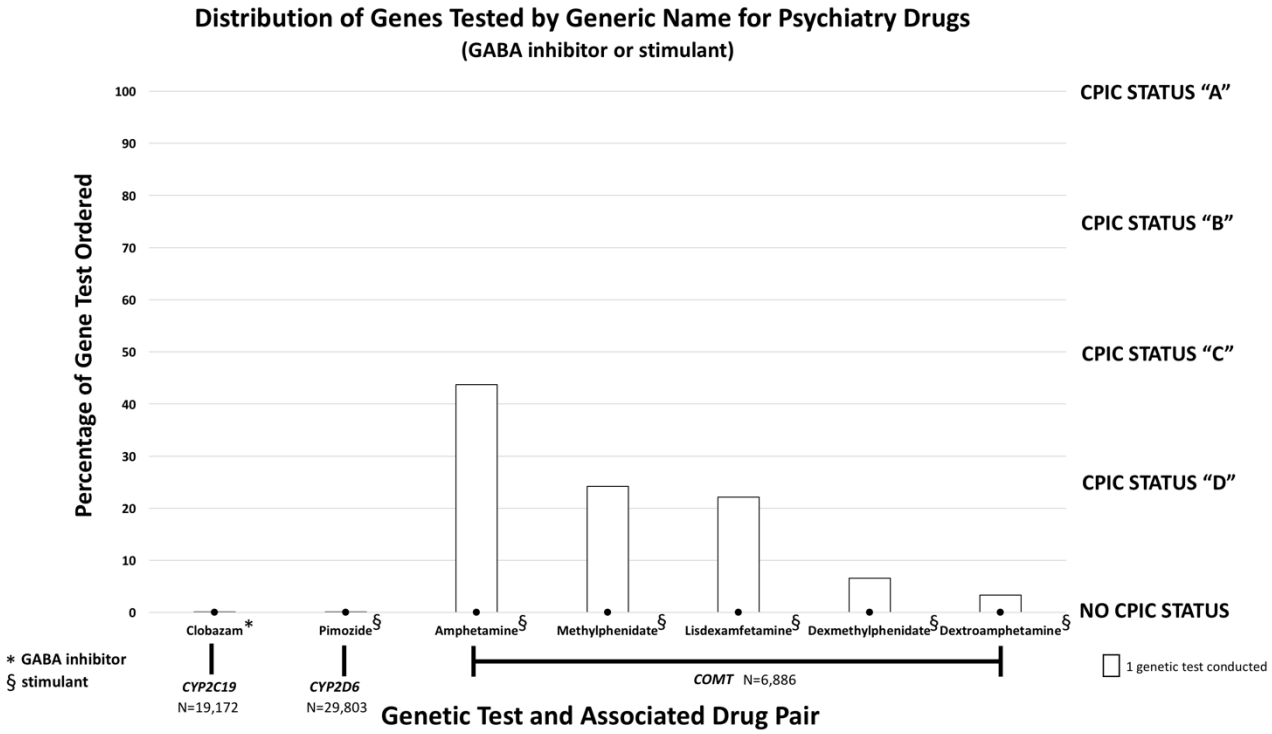

Figure 1.4. Characterization of GABA reuptake inhibitor or stimulant generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

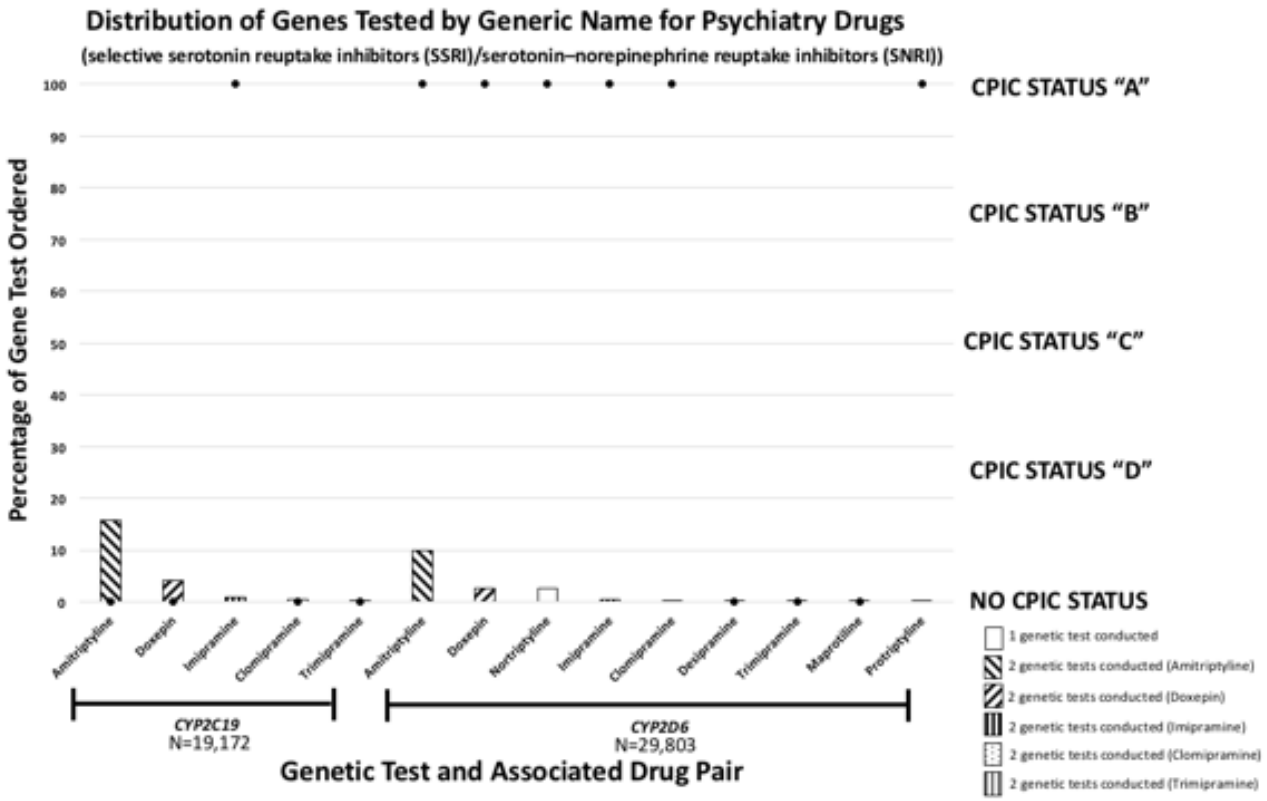

Figure 1.5. Characterization of selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

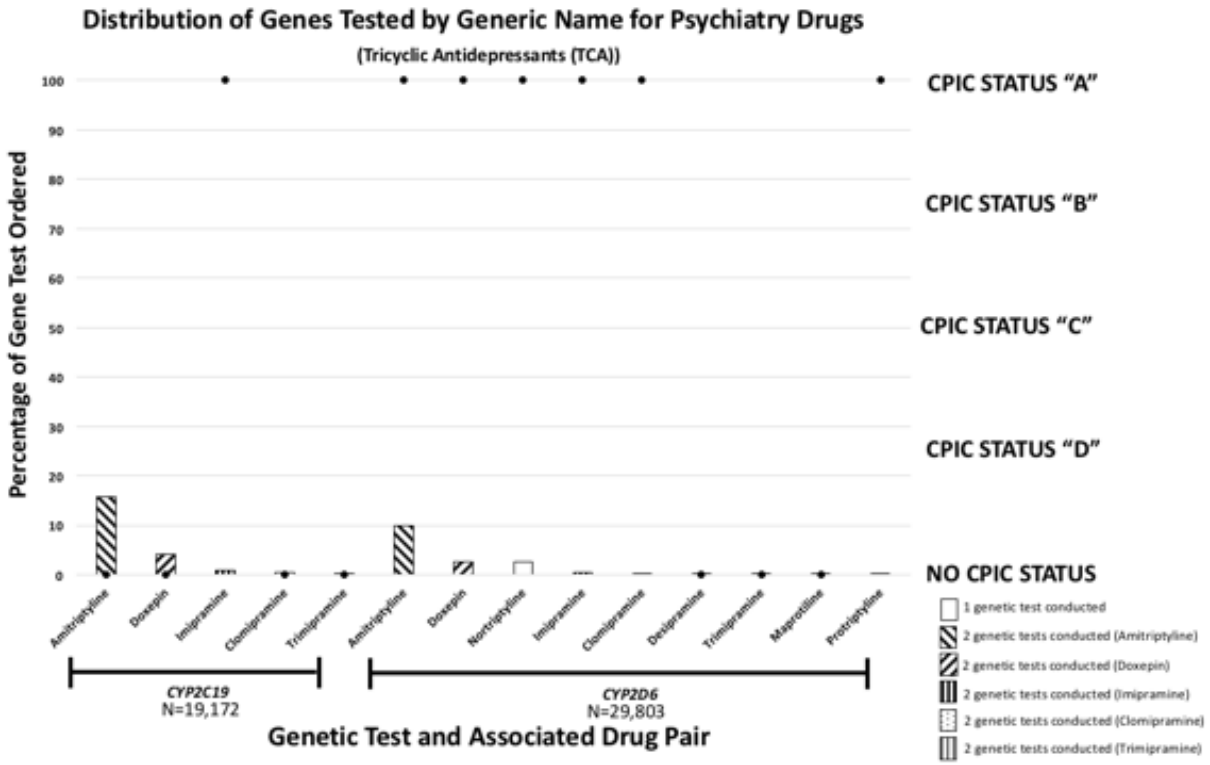

Figure 1.6. Characterization of tricyclic antidepressant generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

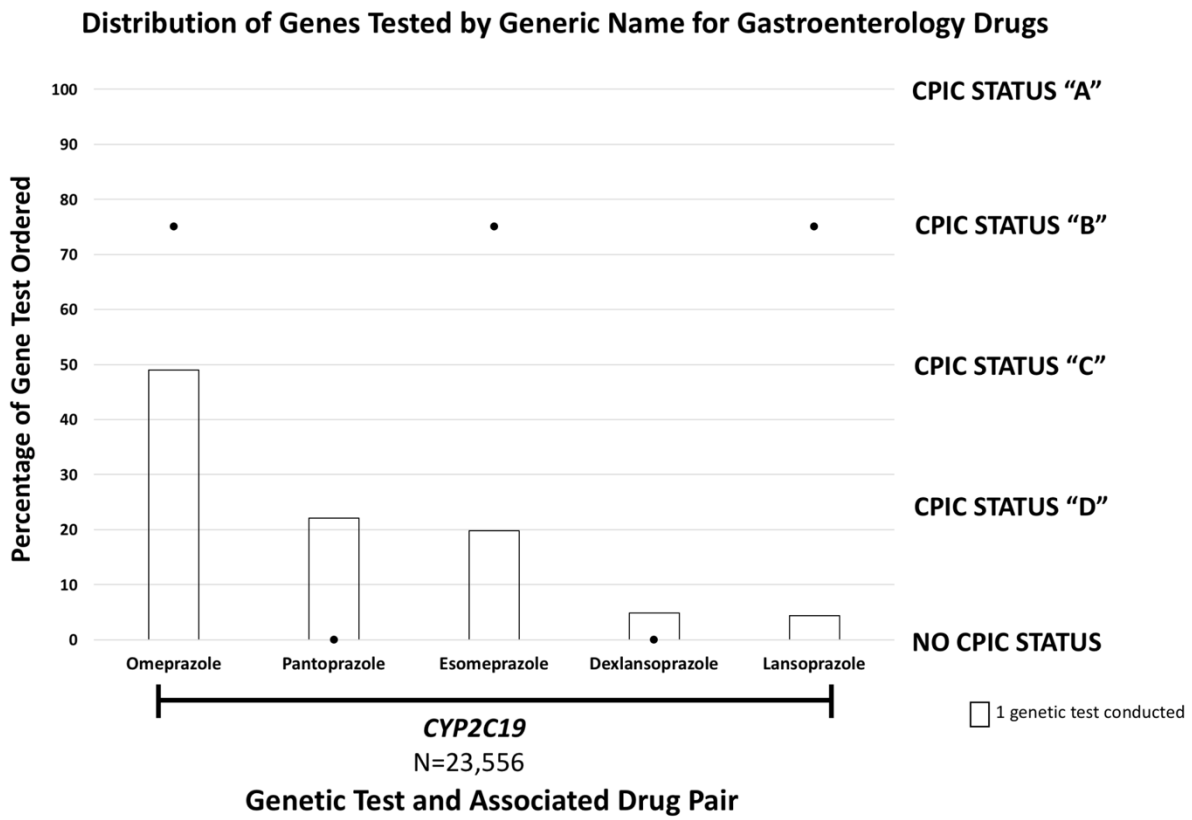

Figure 1.7. Characterization of gastroenterology generic drugs by proportion of gene-drug pair and the associated CPIC guidance.

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TECHNICAL APPENDIX

Methods are not well established in determining diagnostics for penalized multinomial prediction models. Some have proposed using a polytomous discrimination index, as an extension of the c statistic to evaluate goodness of fit (as is comparable to generating the area under the curve), however this is limited in its application. (2012 Van Caster et al DOI 10.1007/s10654-012-9733-3) It is not a straightforward process in performing model diagnostics for multinomial logistic regression models. (Bilder and Loughlin *Categorical Data Analysis in R*). There are methods to detect outliers and influential data points, but these are predicated on running separate logit models and using the available diagnostics tools on each model.

Areas for methods development include building upon common test statistics often used in linear and logistic regression to inform diagnostics of multinomial models.

Since I intended to evaluate goodness of fit (training error) and predictive accuracy (test error), the prediction model results reported in Chapter 1 were generated from 75% of the analytic dataset. Initially the data were partitioned into a training and validation set (75/25 split). I intended to evaluate goodness of fit by generating a c statistic on the training model (which is similar to AUC, where $c > 0.5$ indicates good prediction). Subsequently, I intended to use 10-fold cross validation to assess the model's predictive performance on an independent set of data (the test sample). Noting this, 25% of the analytic dataset were held out for validation.

Future work will analyze the full analytic dataset as this was not initially conducted due to the methods limitations for penalized multinomial prediction models.

Chapter 2. PROJECTED COST-EFFECTIVENESS FOR TWO GENE-DRUG PAIRS USING A MULTI-GENE PANEL FOR ACUTE CORONARY SYNDROME PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

2.1 ABSTRACT

Objective: For patients undergoing percutaneous coronary intervention (PCI), gene-drug associations exist relevant to first-line treatment options–antiplatelet agent, clopidogrel, and pain medication, tramadol. Knowledge of genotype information may allow for avoidance of adverse drug events (ADEs) during critical clinical windows. This evaluation estimated cost-effectiveness associated with a multi-gene panel pre-emptively testing two genes providing *CYP2C19* genotype-guided strategy for antiplatelet therapy, with *CYP2D6* genotype-guided pain management, compared to single gene test for *CYP2C19* with random assignment for pain treatment, and to no testing (empiric clopidogrel with random assignment for pain treatment). **Methods**: Decision analysis modeling was used to project costs from a payer perspective and patient quality-adjusted life years (QALYs) from the three strategies. The model captured composite risks of major adverse cardiovascular events and pain therapy-related ADEs and associated utility estimates. We conducted sensitivity analyses to assess influential input parameters. **Results**: Over 15 months, multi-gene testing was least costly and yielded more QALYs compared to both single gene and no testing; total incremental costs were $1,160 lower with incremental gains of 0.03 QALYs for multi-gene compared with single gene and $9,125 lower with 0.16 QALY gains compared to no test. Base case analyses revealed multi gene was dominant compared to both single gene and no test, as it demonstrated cost savings

with increased QALYs. **Conclusions**: For these patients, a multi-gene-guided strategy yields a favorable incremental cost-effectiveness ratio compared to the other two treatment strategies. Pre-emptively ascertaining additional gene-drug pair information can inform clinical and economic decision-making at the point of care. Future work includes validating these results.

2.2 INTRODUCTION

Among the US population, the prevalence of cardiovascular disease (CD) is as follows: 11% of 18 year olds and older; 12% within 45-64 age range; and 25% within the 65-74 age range.[1] One manifestation of CD is non-ST-elevated acute coronary syndrome (NSTE-ACS), with patients undergoing a percutaneous coronary intervention (PCI). [2] Based on clinical practice guidelines for first-line treatment selection, this patient population often receives antiplatelet therapy (e.g., clopidogrel) and treatment for mild to moderate musculoskeletal pain (e.g., tramadol).[2; 3] There are established gene-drug associations for both of these drugs that hinder optimal efficacy and can result in toxicity that may lead to preventable adverse drug events (ADEs).[3; 4] ACS is associated with significant morbidity and mortality, which puts a substantial financial burden on the healthcare system.[5] Therefore, it is critical that health providers determine individualized approaches for managing ACS patients by considering efficacy and long-term safety of treatment.

Advancements within genomic medicine have ushered in the development of various technologies that generate pre-emptive pharmacogenomics (PGx) testing information at continually decreasing costs (whereby PGx information can be available in advance of treatment selection).[6; 7] The Clinical Pharmacogenetics Implementation Consortium (CPIC), an international collaborative body, develops guidelines for appropriately incorporating known

genetic information into drug treatment strategies when available.[8; 9] As such, genotype information can often be used as a predictor of ADEs.

Existing cost-effectiveness analyses include single gene-drug (SPGx) testing only and multiple-gene drug (MPGx) testing for a single therapy, however there are no such analyses, to date, that model multiple gene-drug pairs for this clinical indication.[10]

2.3 METHODS

2.3.1 *Analytic Overview*

The mean cost of the multi-gene test strategy was the sum of the cost of a multi-gene test, the cost of treatment selected (antiplatelet therapy and pain medication), and the added costs of an ADE or death. The mean cost of the single-gene test strategy was the sum of the cost of a single-gene test, the cost of treatment selected (antiplatelet therapy) and treatment randomly assigned (pain medication), and the added costs of an ADE or death. The mean cost of the no test strategy was the sum of clopidogrel, the cost of treatment randomly assigned (pain medication), and the added costs of an ADE or death.

2.3.2 *Decision-analytic Model*

We used both Microsoft Excel (2016) and R statistical software (RStudio, Boston, MA) to develop a decision model, analyze decision trees, and perform sensitivity analyses. This economic evaluation adopted a US payer perspective to project estimated costs and patient quality-adjusted life years (QALYs). Based on the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) recommendations for economic modeling involving PGx, the models utilized “real-life” decision making and use; however, the

comparators did not fall within the classical method comparing a new medicine "B" to an existing medicine "A." Instead, this analysis compared a "treat-all" strategy, a "test-and-treat" strategy, with the addition of a multi-test-and-treat strategy.[11] The base case was a hypothetical cohort of 55-year-old patients presenting with CD (specifically, patients with NSTE-ACS undergoing PCI) under consideration for antiplatelet therapy, who then were prescribed treatment for pain management. The model compared three strategies to guide antiplatelet therapy coupled with pain treatment: an array-based multi-gene panel that pre-emptively provided genetic information for *CYP2C19* (testing for at least one of the following reduced-function alleles: *2, *3, *4, and *8) and *CYP2D6* (testing for at least one of the following reduced-function alleles: *7, *9, *20, *27, *33, *35, and *41); a single gene test that provided the same *CYP2C19* genetic information, and no test. Figure 1 displays the decision tree comparing the three strategies.

Building from the cost-effectiveness work conducted by Lala *et al* on *CYP2C19*2* genotyping and antiplatelet treatment strategies, this study used similar decision arms (for the single gene test and no test) modelled within the previously published decision tree, but instead incorporated a composite outcome of major adverse cardiac event (MACE) probability estimates ascertained from randomized controlled trial data rather than delineating each possible adverse event[12].

2.3.3 *Probabilities and Costs*

Probabilities and cost data were obtained from the published literature and are displayed in

Table 24. Hazard ratios, relative risk, and rates that were derived from the literature were re-calculated into probabilities using conventional methods.

Given known ethnic differences in allele frequencies for variation within *CYP2C19* and *CYP2D6*, the estimate for population allele frequencies was derived by calculating the average among loss of function allele frequencies across African American, European ancestry, and Asian population estimates[13; 14]. The proportion of the population with a *CYP2D6* reduced function allele is 7%, so this estimate was used[15].

The multi-gene panel cost was estimated from the Affymetrix Price Sheet, Academic Tier 4, 2014 US Dollars, for the Drug Metabolizing Enzymes and Transporters (DMET) Precision Plate, sufficient for 48 reactions [16]. The single gene test for *CYP2C19* was estimated using the 2016 Medicare fee schedule with CPT code 81225 [17]. A composite cost for MACE was used [18]. Costs for tramadol-related ADEs (Drug A) were obtained from a 3-month average [19]; subsequently, a one-month average was calculated and used in the model. Ascertaining direct costs associated with GI toxicity monitoring costs for acetaminophen-related ADEs (Drug B), the average was calculated among all types of inpatient and outpatient surgical and medical management associated with the ADEs [20]. Drug costs were estimated using the 2016 CMS Average Sales Price (ASP) list [21]. Monthly clopidogrel estimates were based on a 75 mg daily dose clopidogrel tablet for a supply of 30 tablets and monthly prasugrel estimates were based on a 10 mg daily dose, as compared in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 Trial, a head-to-head randomized clinical trial of prasugrel

versus clopidogrel [22]. Costs were expressed in 2016 US dollar values. All cost data gathered from the literature prior to 2016 were adjusted using the Consumer Price Index calculator [23]. A generic estimate for clopidogrel of $1 per day was used. The ASP for prasugrel was estimated approximately at $3 per day. The price for monthly pain treatment was estimated to cost $51 and $8 for tramadol and acetaminophen, respectively. Multi-gene testing cost $857 and single gene testing cost $291.

2.3.4 *Health Outcomes*

ACS patients with a *CYP2C19* loss-of-function (LOF) allele have a 50% increased risk for the composite outcome (cardiovascular death, non-fatal MI, or stroke) compared to those with a common allele in *CYP2C19* [24]. The model captured a composite outcome for risks of major adverse cardiovascular events, an outcome for antiplatelet-related complications, and outcome for pain therapy-related persistent and transient adverse events (e.g., cardiovascular events, ulcer, gastro-intestinal bleed, vomiting). Associated utility estimates for all of these outcomes were modelled (Table 1). Following methods used in previous economic evaluation studies investigating cost-effectiveness of genetic testing, utility weights for quality of life after event states were estimated by using the weights for identical heath states within similar populations reported in select articles written between 2000 and 2014 that are included in the Tufts Medical Center's Cost-Effectiveness Analysis Registry [25]. Notably, the estimate used for pain treatment (Drug A) utility was derived from a cost-effectiveness analysis of pain treatments (tramadol included as one of the comparators) for chronic low back pain [19], while the utility applied to the pain treatment (Drug B) was ascertained elsewhere[20]. Quality-adjusted life-years (QALYs) and costs were annually discounted at 3% (for months 13-15).

To determine the ADE probability on tramadol with no genotype information, we used the combined sum total of the sum of 3-month persistent ADE probabilities and sum of the 3-month transient ADE probabilities from the Wielage *et al* analysis since none of the events are mutually exclusive[19]. This enabled a calculation of the likelihood that at least one of the events would happen; subsequently, the average of the sum totals (persistent and transient) was taken, and this resulted in the tramadol-ADE probability.

2.3.5 *Model Assumptions*

An assumption follows for the composite outcome that at least one event within the composite event outcome is symptomatic. Following clinical practice guidelines [2], the alternative pain treatment will be acetaminophen, as metabolism is not grossly affected by the *CYP2D6* pathway [26]. Given that patients on either clopidogrel and prasugrel experience the same probability of having a myocardial infarction (MI) event be symptomatic after 30 days, the 0.90 probability estimate was used to inform the assumption that the MACE will be symptomatic [12]. The monthly rate of a non-CV or non-major-bleed-related death was ascertained from the Lala *et al* analysis and is assumed to be the same across all treatment strategies, input into the model as 0.05. The TRITON-TIMI 38 trial did not assess pain as a study endpoint, nor was it found to be measured as a safety endpoint, thus pain-related data were ascertained elsewhere. Therefore, we used a meta-analysis on efficacy and safety analysis of new P2Y12 inhibitors (for which, prasugrel is categorized) versus clopidogrel in ACS PCI patients[27]. The model thus assumed that all patients within this cohort each experience mild to moderate pain, and that there are no differences in the proportion of patients experiencing pain based on their antiplatelet therapy (i.e., clopidogrel or prasugrel). While evidence has established known efficacy outcome associations for patients on tramadol, explicit rates of safety endpoints categorized by genotype is unknown. Therefore, the

model assumed a 21% probability of ADE on tramadol for a normal metabolizer (as this was calculated by taking the average of all cumulative incidence rates up to 90 days, as described on the FDA tramadol drug label) [28]. The probability estimates for patients with a specific *CYP2D6* genotype assume no ultra-rapid metabolizers, as these patients would require a decreased dose of tramadol or could initially start on an alternate treatment as those receiving acetaminophen. However, the PGx information available from the multi-gene panel would in practice apply that level of detail for return of results to the provider to inform the clinical decision at the point of care. It was also assumed that a patient experiencing a pain treatment-related ADE has a 0.05 decrement of utility, which is a conservative estimate, compared to no ADE.

2.3.6 *Sensitivity Analyses*

For the parameter inputs, β distributions for probabilities and utilities, gamma distributions for costs and log-normal distributions for hazard ratios were used for the sensitivity analyses. These analyses only compared the base case analysis results using the MPGx strategy compared to SPGx (Table 1). We performed one-way sensitivity analyses of selected variables from the model, evaluating a broad range of estimates. We conducted two-way sensitivity analyses to account for potentially correlated parameters over their associated plausible ranges. In two-way sensitivity analyses, we calculated the cost-effectiveness ratios while varying the risks of ADE on acetaminophen and tramadol, respectively, costs of multi-gene and single gene tests, and costs of acetaminophen-ADE. We assessed uncertainty within the model inputs using probabilistic sensitivity analysis with 1,000 Monte Carlo simulations. Unless otherwise stated, high and low estimates derived from the bounds of the 95% confidence intervals (CIs) were used in the probabilistic sensitivity analysis when available. If the bounds of the 95% CIs were unavailable, a range of ±25% for probabilities and utilities, and ±50% for costs were

used. Net health benefit assessments were performed using a $100,000/QALY willingness-to-pay threshold, and we examined alternative threshold values.

2.4 RESULTS

2.4.1 *Base Case Analysis*

Over 15 months, the multi-gene testing strategy was least costly and yielded more QALYs compared to both the single gene strategy and no test strategy. Total incremental costs were $1,646 lower with incremental gains of 0.04 QALYs for multi-gene testing compared with single gene testing and incremental costs of $11,368 lower with incremental gains of 0.17 QALY compared to no testing. The net monetary benefit for multi-gene testing based on a $100,000/QALY willingness-to-pay threshold was $5,65 and $28,391 compared to single gene testing and no testing, respectively. The MPGx strategy dominated both comparator strategies (**Table 25**).

2.4.2 *Sensitivity Analyses*

One-way sensitivity analyses revealed the model was most sensitive to the probability of ADE associated with both acetaminophen and tramadol, not genotype-guided (

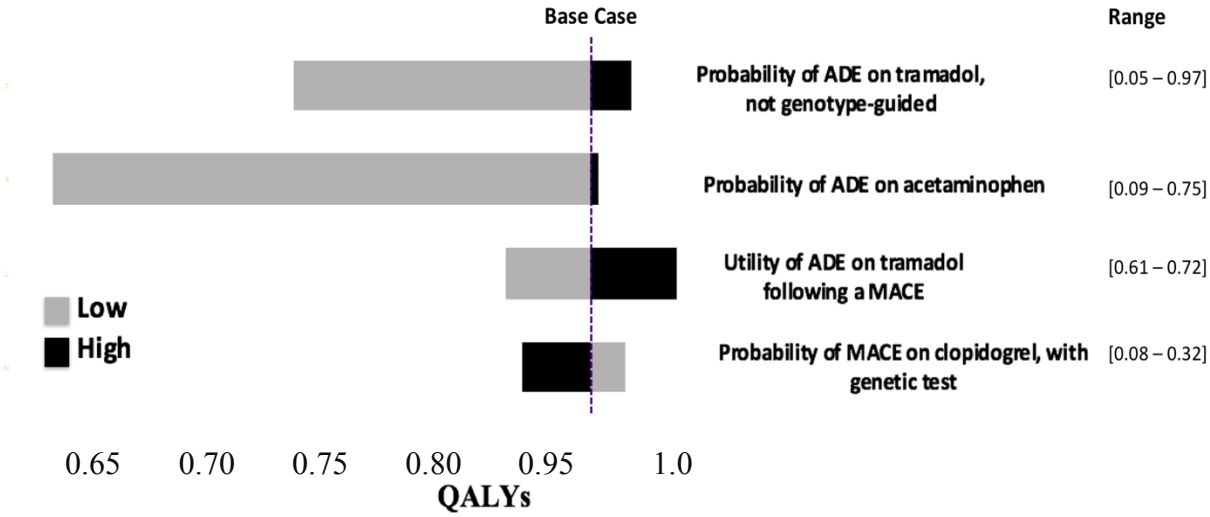


Figure 2.2). Further, the model was sensitive to the cost of the composite ADE from acetaminophen (which included GI toxicity and dyspepsia) (**Figure 2.3**). In these tornado diagrams, individual bars represent the impact of uncertainty in a variable on the incremental net monetary benefit costs. MPGx was still the dominant strategy for the univariate (one-way) analyses. Two-way sensitivity analyses demonstrated when MPGx was the optimal/dominant strategy over SPGx. MPGx is dominant when the probability of ADE on acetaminophen is greater than 0.05 and the probability of ADE on tramadol is greater than 0.48.

2.4.3 *Probabilistic Sensitivity Analysis*

Additionally, a probabilistic sensitivity analysis was performed to assess the robustness of the findings in the base case. For a $100,000 WTP threshold, we found that MPGx was less costly and more effective than SPGx in 73% of the probabilistic sensitivity replicates under a range of cost and outcome probability assumptions to investigate joint uncertainty across the selected

parameters using Monte Carlo simulation (**Figure 2.5**). MPGx was less costly and more effective than SPGx 80% of the replicates when applying a $50,000 WTP, and 71% when applying a $150,000 WTP. The cost-effectiveness acceptability curve summarizes the impact of uncertainty on the result of our economic evaluation, here expressed as the net monetary benefit in relation to possible values of the cost-effectiveness threshold by which the decision-maker is willing to pay for health effects (denoted by the X axis) and the probability of MPGx being dominant over SPGx (denoted by the Y axis) displayed in **Figure 2.6**. Across all WTP thresholds, the MPGx strategy has the highest probability of being cost-effective compared with SPGx.

2.5 DISCUSSION

The chosen gene-drug pairs for the NSTE-ACS patients undergoing PCI were based on "A" designations (highest strength of evidence level) from the CPIC guideline information for both *CYP2C19* testing and clopidogrel, and pain therapies and *CYP2D6* testing [26]. This example is pertinent because of the potential health impact to increase efficacy and/or avoid toxicity, along with ongoing research efforts to establish relevant genotype–phenotype associations and aimed at preventing ADEs.

By generating a scatterplot to assess the degree of uncertainty, this displays the proportion of the 1,000 simulations in which multi-gene test strategy fell into the respective cost-effectiveness plane quadrants. Further, by generating a plot displaying a cost-effectiveness acceptability curve to assess uncertainty, this illuminates the proportion of the 1,000 simulations in which multi-gene test strategy or single-gene test strategy was the preferred strategy at various willingness-to-pay thresholds.

Recently, complementary work evaluated the cost-effectiveness of a pharmacist integrated medical therapy management (MTM) alongside point-of-care single gene testing (POCP) to guide antiplatelet treatment for elderly ACS patients taking the US health care system perspective.[29] The investigators found that the MTM-clopidogrel strategy dominated the POCP strategy with an incremental cost of $195.61 (2016 USD) and incremental effectiveness of 0.05. Our work instead applied the payer perspective and evaluated different strategies compared to their analysis. However, the findings from the SPGx and no PGx test arms in our analysis compare similarly to their two strategies to treat patients with antiplatelet therapy following POCP SPGx testing and to universally treat patients with clopidogrel. Although, the latter arm of their study also included MTM, for which our no PGx test strategy did not consider that concomitant intervention.

This analysis, which economically evaluated two distinct PGx biomarker-drug pairs from a multi-gene panel, generated preliminary results demonstrating the panel is "good value" as it is dominant compared to the other two strategies. It meets the presumably acceptable societal willingness-to-pay cost-effectiveness threshold for $100,000/QALY [30; 31]. We chose to apply a shorter time horizon to generate evidence that may address some of the interpretability challenges payer decision makers asserted limit their usability of cost-effectiveness information in coverage decisions.[32] Future analyses should be conducted from other perspectives (e.g., societal, health care system) and by applying a longer time horizon to model relevant longer-term endpoints for the chosen perspective. Moreover, future work may also

include evaluation of additional gene-drug pairs and extended PGx scenarios from a pre-emptive multi-gene panel.

The results are limited by the parameters set forth in the model. Accordingly, estimates were derived from the literature and assume inherent uncertainty, as does using a hypothetical cohort. The assumptions within the base case limit the generalizability for the findings extending to other clinical situations and hypothetical patient cohorts. This analysis did not model drug-drug interactions, however, the model is extensible to modeling possible interactions that may exist between clopidogrel and proton pump inhibitors (i.e., omeprazole), which often are prescribed together to mitigate the risk of bleeding associated with the antiplatelet treatment [33]. While the *CYP2D6* ultra-rapid metabolizer phenotype is rare in most European ancestry populations, it has 3% and up to 13% frequency rates in Spanish and Ethiopian populations, respectively, demonstrating marked interethnic variation in allele frequency rates; this information would be critical to consider when treating patients from different ethnic backgrounds [34; 35]. These rates should be included into future modelling work as should scenario analyses that were beyond the scope of this study. Adverse drug events averted using empirical data could also be a useful outcome to consider in future work. Additional utility weights for health states involving pain could be collected from the EQ-5D standardized instrument, which includes a pain domain, and provides single index values for health-related quality of life measures [36]. These estimates could be used in future analyses, while it may be worthwhile further to ascertain a more precise estimate (since based on our model, the utilities need to consider both persistent and transient ADEs related to pain treatment).

Numerous comprehensive PGx panels exist in research and clinical settings (e.g., PGRNseq, a custom-capture sequencing panel that includes 84 genes with associations to PGx phenotypes; Affymetrix's DMET genotyping panel, which provides coverage for PGx biomarkers in 231 relevant genes; and Admera Health's PGxOne Plus, which provides information on over 200 genetic variants) [37-40]. However, the majority of the genes included on these panels for certain gene-drug pairs and the associated clinical actionability require more evidence of clinical utility if intended to be used outside of research, used in clinical practice, and reimbursed by payers. Subsequently, Dunnenberger et al concisely presented the 12 most commonly tested genes (*CYP-2C19, 2C9, 2D6, 3A5, DPYD, G6PD, HLA-B*[4]*, IFNL3, SLCO1B1, TPMT, UGT1A1, VKORC1*) that have known PGx-associated clinical actions, that provides an actionable list of genes to conduct pre-emptive PGx testing and from which to expand; more detail is published elsewhere [26]. The framework developed for this clinical case is customizable for various clinical scenarios utilizing additional gene-drug pair information as determined by the Dunnenberger gene list. This analysis took a US health payer perspective, yet, the decision model developed could be used as the basis for evaluations undertaken by other perspectives. Recent work conducted by Peterson and colleagues demonstrated that a pre-emptive multiplexed PGx testing approach for multiple CPIC gene-drug pairs modeled into seven PGx scenarios compared to no testing was not cost-effective as defined by a lower WTP threshold of $50,000 per QALY.[41] However, none of their PGx scenarios explicitly modeled the MPGx scenario described in our analysis; rather, in their work, *CYP2C19* and *CYP2D6* and associated drug pairs only accounted for *CYP219*-clopidogrel and *CYP2D6*-codeine separately.

[4] Some technical challenges persist in testing *HLA-B,* however, such details are beyond the scope of this analysis.

2.6 CONCLUSION

Among ACS patients undergoing PCI with follow on pain management, a pre-emptive multi-gene-guided strategy dominates when compared to a single gene test strategy with a random assignment of pain treatment or to empiric approaches to treatment. By developing a framework using this subset of gene-drug pairs from a full multi-gene panel, future economic evaluations can build upon this decision model. Future work includes validating these preliminary results. Without a robust evidence base and widespread implementation of clinical PGx to identify a subset of responders, some current clinical practices generate inefficiencies (wasteful spending on drugs for which patients do not adequately respond) in the healthcare system. From a societal perspective, such a gap in evidence disables health care providers in appropriately stewarding scarce resources allocated for health care services [42]. Pre-emptively ascertaining additional gene-drug pair information through multi-gene PGx testing may inform clinical and economic decision-making at the point of care.

2.7 TABLES AND FIGURES

Table 24. Summary of parameters included in the model displaying base case probability, utility, and cost estimates, and distributions associated with the probabilistic sensitivity analysis.

Parameter	Estimate (Range)	Distribution	Source
[Probabilities]			
MACE on clopidogrel (not genotype-guided)	0.55 (0.41-0.69)	Beta	CURE Trial [43]
MACE on clopidogrel for reference allele (genotype-guided)	0.16 (0.12 - 0.20)	Beta	[12]
MACE on prasugrel	0.45 (0.43 - 0.47)	Beta	[22]
Survival, given MACE on prasugrel	0.54 (0.40 – 0.68)	Beta	[22]
No MACE on clopidogrel (genotype-guided)	0.79 (0.59 – 0.99)	Beta	[12]
Death, given MACE on clopidogrel (genotype-guided)	0.61 (0.46 – 0.76)	Beta	[12]
Death, given MACE on prasugrel	0.46 (0.41 – 0.53)	Beta	[44]
Death, given MACE on prasugrel	0.46 (0.41 – 0.53)	Beta	[44]
Death, given MACE on clopidogrel (not genotype-guided)	0.46 (0.44 – 0.48)	Beta	[12]
Survival, given no MACE on clopidogrel (not genotype-guided)	0.95 (0.71 – 1.0)	Beta	CURE Trial [43]
ADE on tramadol, genotype-guided	0.07 (0.05 – 0.09)	Beta	[19]
Other death (non-CV, non-major-bleed-related)	0.05	NA	[12]

Parameter	Estimate (Range)	Distribution	Source
[Event costs]			
Composite MACE	$21,885 ($10,943 - $32,828)	Gamma	[18]
Composite death (Average)	$17,370 ($8,685 - $26,055)	Gamma	[12]
Composite pain treatment (tramadol)-related ADE (3-Month Average)	$6,642 ($3,321 - $9,963)	Gamma	[19]
Composite pain treatment (acetaminophen) - related ADE	$5,709 ($2,855 - $8,564)	Gamma	[20]
Genetic test (single gene test)	$291 ($146 - $437)	Gamma	2016 Medicare fee schedule
Genetic test (multi gene panel)	$857 ($500 - $1,500)	Gamma	Affymetrix Price List
Clopidogrel (monthly)	$16 ($12 - $20)	Gamma	2016 CMS ASP List
Prasugrel (monthly)	$82 ($21 - $124)	Gamma	[44]
Event-free survival (monthly)	$319 ($309 - $1,687)	Gamma	[12]
Tramadol (monthly)	$51 ($38 - $64)	Gamma	2016 CMS ASP List
Acetaminophen (monthly)	$8 ($6 - $10)	Gamma	2016 CMS ASP List

No MACE on prasugrel	0.50 (0.38 – 0.63)	Beta	[22]	**[Utilities]**			
No MACE on clopidogrel (no genetic test)	0.40 (0.30 – 0.50)	Beta	CURE Trial [43]	Tramadol utility (No ADE)	0.71 (0.63 – 0.78)	Beta	[24]
Survival, given MACE, on clopidogrel (genotype-guided)	0.39 (0.29 – 0.49)	Beta	[12]	Tramadol ADE utility	0.66 (0.59 – 0.73)	Beta	Assumption
CYP2C19 population reference allele frequency	0.73	NA	[12]	Acetaminophen utility (No ADE)	0.71 (0.63 – 0.78)	Beta	[20]
CYP2C19 population LOF allele frequency	0.27	NA	[12]	Acetaminophen ADE utility	0.66 (0.59 – 0.73)	Beta	Assumption
CYP2D6 reference allele frequency	0.93	NA	[15]				
CYP2D6 population reduced or LOF allele frequency	0.07	NA	[15]				
ADE on tramadol (not genotype-guided)	0.72 (0.54 – 0.90)	Beta	[28]				
ADE on acetaminophen	0.67 (0.50 – 0.84)	Beta	[45]				

MACE: major adverse cardiac event, CV: cardiovascular, LOF: loss of function, ADE: adverse drug event, CMS: Centers for Medicare & Medicaid Services, ASP: average sales price

Table 25. Base case analysis results among the three strategies.

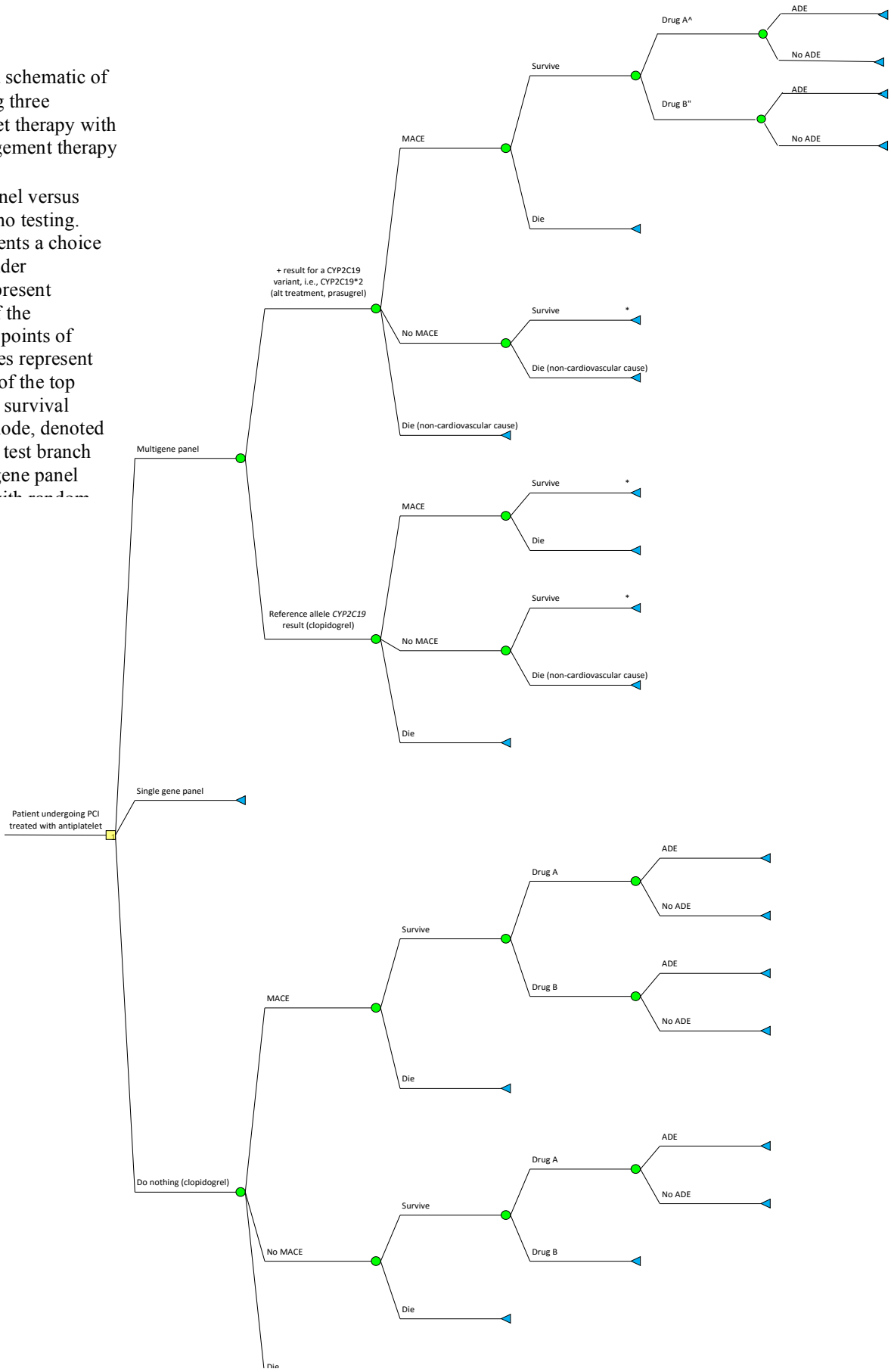
	Mean Cost	Incremental Cost	QALY Gained	Incremental QALY	ICER (cost/QALY)	Multi PGx Strategy Net Monetary Benefit* over Alternative Strategies
Multi PGx Test Strategy	$13,275		0.97			
Single PGx Test Strategy	$14,921	-$1,646	0.93	0.04	Dominated	$5,656[a]
No PGx Test Strategy	$24,643	-$11,368	0.80	0.17	Dominated	$28,391[b]

[a] Comparison between Multi PGx test and Single PGx test strategies

[b] Comparison between Multi PGx test and no PGx test strategies

* Net monetary benefit (NMB) based on $100,000 WTP per QALY. NMB > 0 implies a favorable strategy.

Figure 2.1. Enlarged schematic of decision tree comparing three strategies for antiplatelet therapy with a follow-on pain management therapy evaluated in the model.
The multi-gene PGx panel versus single gene test versus no testing. The square node represents a choice among the strategies under examination, circles represent chance nodes at each of the associated downstream points of uncertainty, and triangles represent terminal states. Clones of the top branch follow all of the survival points with a terminal node, denoted with *. The single gene test branch is a clone of the multi-gene panel branch displayed, but with random



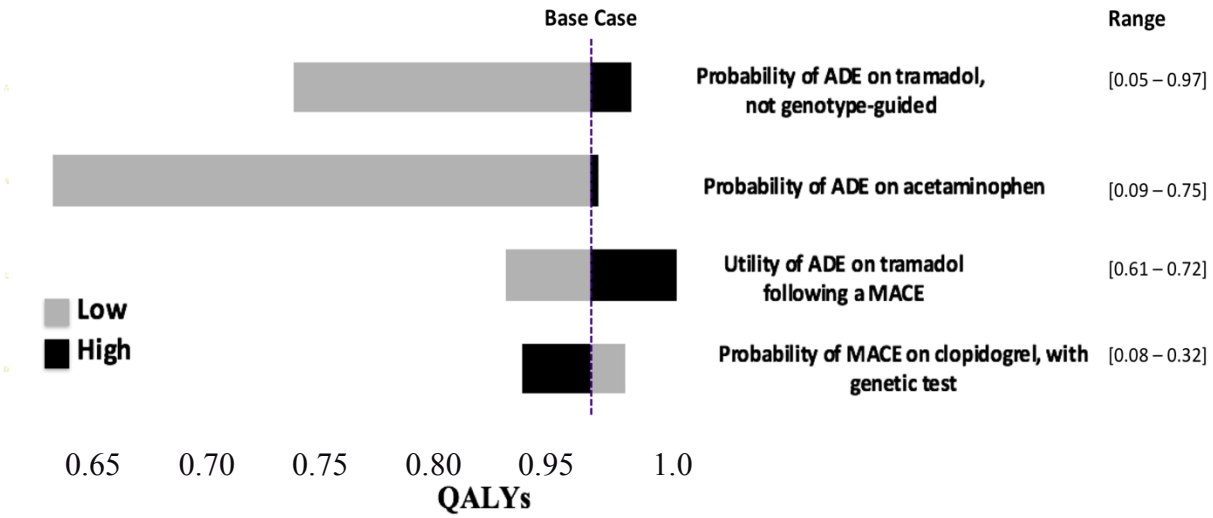


Figure 2.2 One-way sensitivity analysis of select parameter ranges influencing incremental quality-adjusted life years (QALYs).

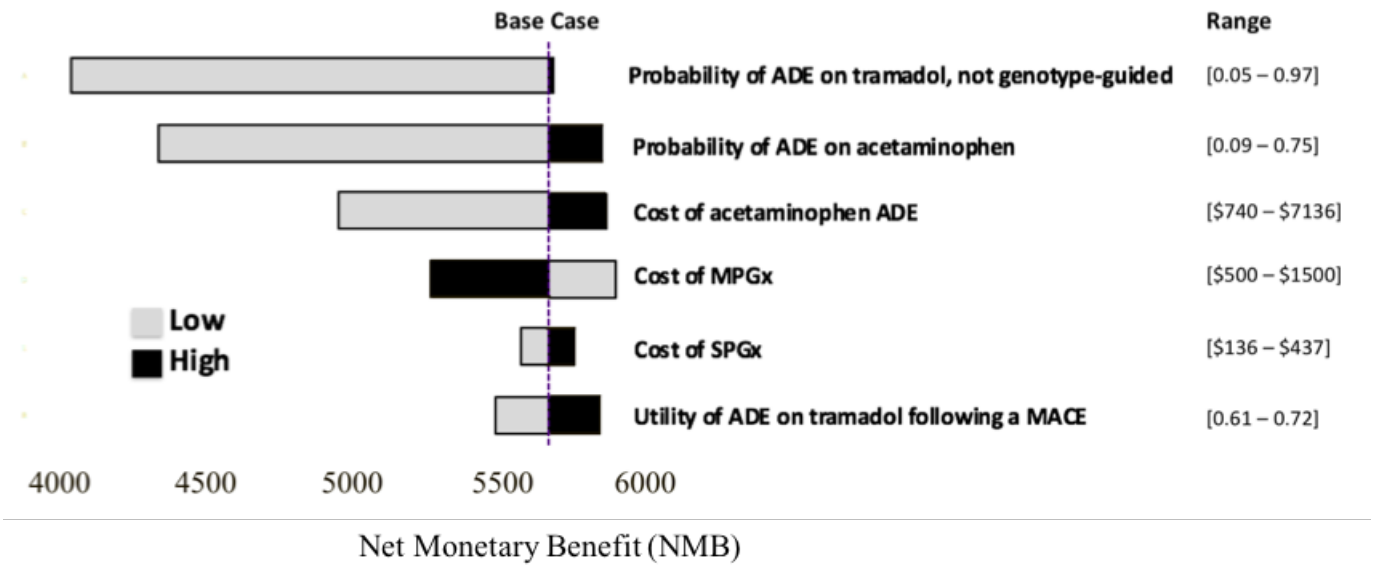


Figure 2.3 One-way sensitivity analysis of select parameter ranges influencing incremental net monetary benefit costs (USD 2016).

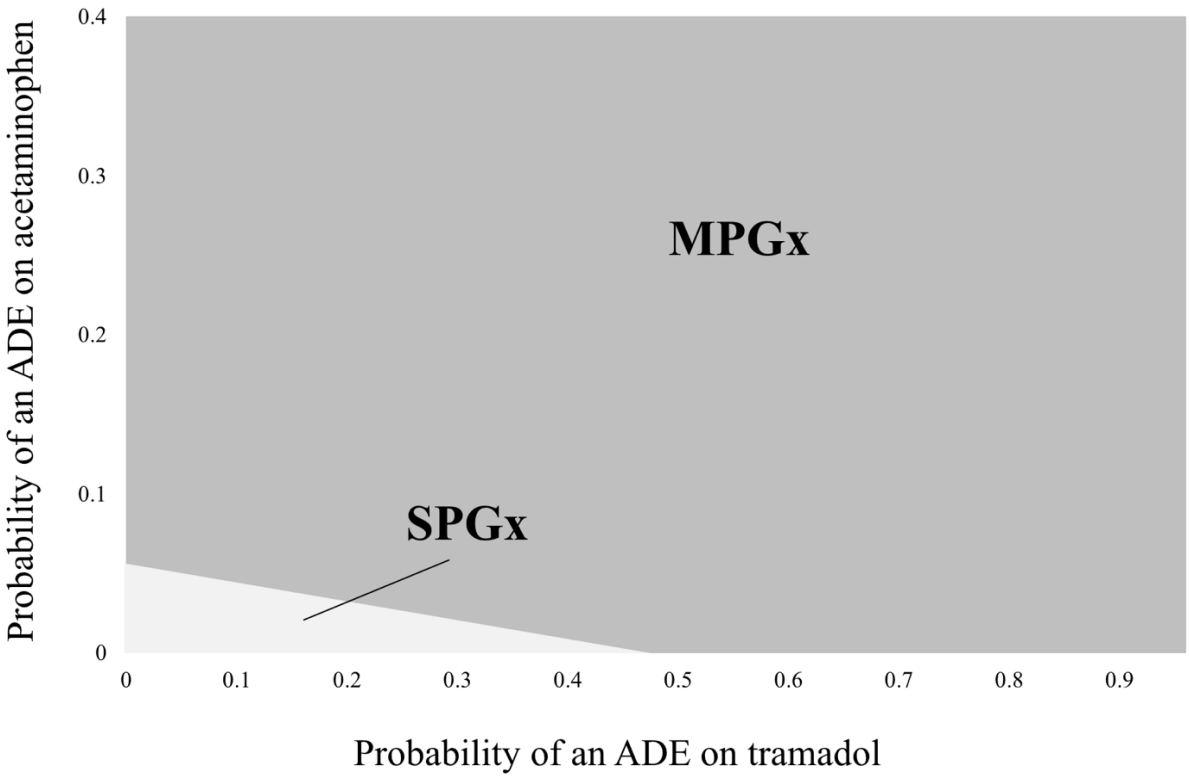


Figure 2.4 Two-way sensitivity analysis of the probability of an ADE on acetaminophen vs. the probability of an ADE on tramadol (not genotype-guided). The shaded region identifies the optimal/dominant strategy. MPGx is superior when the probability of an ADE on acetaminophen > 0.05 and the probability of an ADE on tramadol > 0.48.

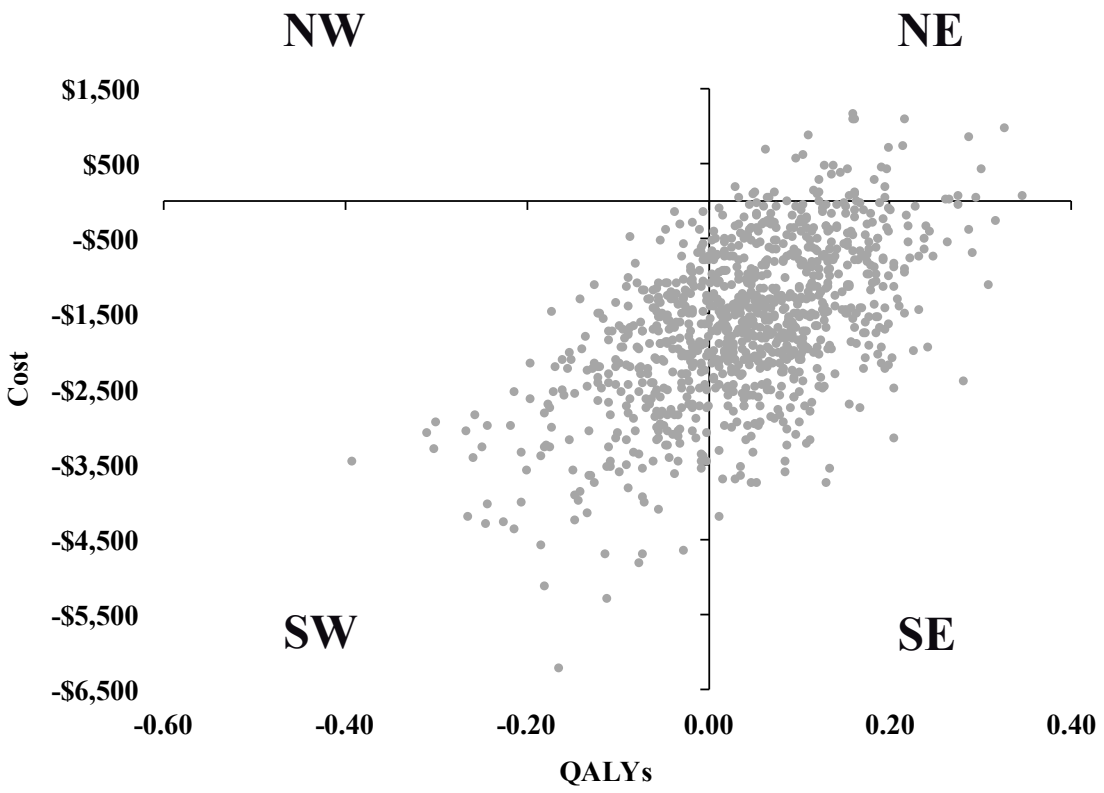


Figure 2.5 This scatterplot displays results from the 1000 trials Monte Carlo simulation evaluating the incremental cost-effectiveness ratio between MPGx versus SPGx under a range of cost and outcome probability assumptions to investigate joint uncertainty across parameters.

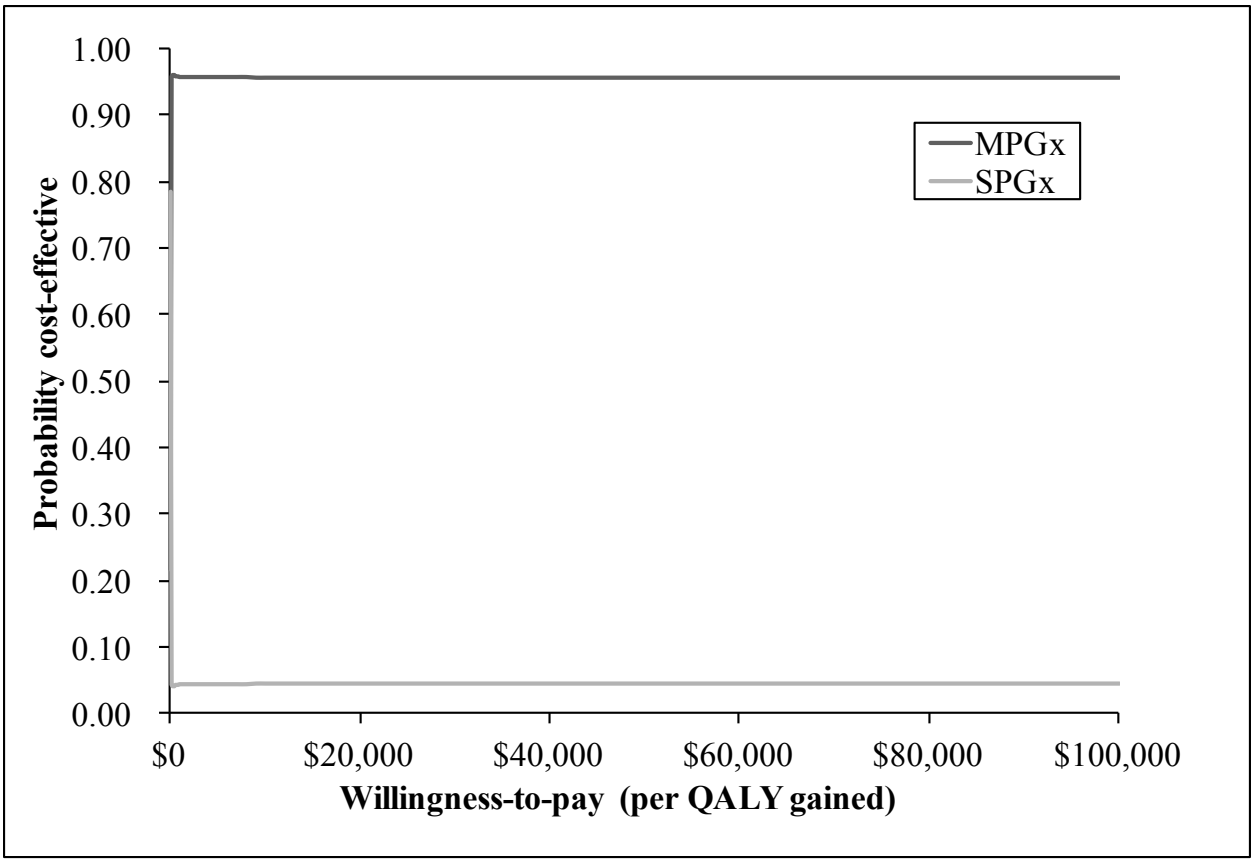


Figure 2.6 Probabilistic sensitivity analyses. The cost-effectiveness acceptability curves representing the probability that either treatment is cost-effective for a given maximum willingness-to-pay threshold per QALY gained over 15 months.

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OVERALL CONCLUSION

The contents of this dissertation have attempted to assess two strategies for optimizing the value of pharmacogenomic (PGx) testing utilizing both an exploratory analysis of real-world evidence and decision modeling approaches. In the context of technology advancements continually evolving and subsequent considerations for clinical practice integration, we found that commercial PGx knowledge resources may meet current evidence thresholds necessary for health care decision makers to adopt health care system policies that support increased adoption of PGx testing. Furthermore, we demonstrated economic evidence for a pre-emptive multi-gene panel testing strategy for ACS patients undergoing PCI and treated for mild to moderate musculoskeletal pain that may be sufficient to inform positive payer reimbursement coverage decisions for this clinical scenario. Notwithstanding, the evidence from this work certainly warrants acknowledgment of payer decision makers' limited use of cost-effectiveness data[1; 2]; and, we assert, the need for future work to consider budget impact analyses if multi-PGx testing approaches are intended to reach their full potential to optimize patient outcomes.

While this dissertation work focused on PGx testing, the evidence contributes to a larger discussion. The discussion described elsewhere, involves approaches intended to assign value to the provision of genomics-based health care services for clinical decision making, regarding evidence-based population and/or clinical practice guidelines[3; 4] and the newly evolving space of optimizing the utility of precision or personalized medicine.[5-7] With the rapid pace of genomics-based technology development, evermore in contention for policy decision makers are efforts to develop authoritative centrally-available knowledge resources[8-11] for standards, best practices, and guidelines for applications of precision medicine, amid constrained resources in the broader

healthcare system. A recent report by a Special Task Force of the International Society for Pharmacoeconomics and Outcomes Research clearly delineates different decision contexts associated with multiple stakeholders involved in health plan coverage and reimbursement.[12] From the report, upon considering various stakeholder positions for the same decision context, different value determinations may result. We assert the following consideration for policy decision makers: Payer, health care administrator, patient/patient advocates, and/or regulatory policy decision makers should appropriately acknowledge the harms and benefits of the more time-intensive, putatively rigorous, publicly-funded efforts, while also honoring credence to commercial innovation aiming to advance practical applications for market consumption. Notwithstanding, transparently communicating technological limitations of commercial solutions may afford an opportunity to balance challenges inherent for decision makers' accepted thresholds of uncertainty.

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VITA

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