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PAYER PERSPECTIVES ON PREEMPTIVE PHARMACOGENETIC TESTING

A Thesis
presented in partial fulfillment of requirements
for the degree of Master of Science
in the Department of Pharmacy Administration
The University of Mississippi

by

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ABSTRACT

Purpose: As preemptive pharmacogenetics expands in the academic healthcare setting, further study is needed to assess the views of additional stakeholders in the marketplace on this technology and the barriers and facilitators to their uptake. The purpose of this study is to investigate the perspectives and opinions about coverage policies for preemptive pharmacogenetic testing of third-party payers.

Methods: A qualitative study utilizing a blended inductive and directed approach was conducted. A screener survey determined interview eligibility as well as demographic data. Semi-structured interviews were conducted with payers from organizations of varying structure and beneficiary populations. Meaning units and codes were used for each interview and aggregated to identify the subthemes and major themes.

Results: A total of 14 payers were interviewed, covering 122,000,000 million lives, or almost 40% of the U.S. population. Positive and negative opinions were noted. Most positive opinions were prefaced with a position that pharmacogenetics held great potential for the healthcare system, but that full implementation was several years away. The work of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Research Network (PGRN) was viewed favorably. However, this would not drive policy decisions. Negative opinions came from a concern of the lack of data that would make these tests actionable for a payer from a policy development point of view. Concerns about the cost of testing large numbers of people was mentioned frequently, as well as the inability to predict

when a patient or physician would use the data from a test or potential cost savings from the technology.

Discussion: Preemptive pharmacogenetic testing remains a cautious pursuit for many payers.

Lacking clinical outcomes data, the inability to evaluate the economic benefits from testing, and high costs are a few central concerns. Real-world implementations from academic institutions and the work of CPIC were seen as promising endeavors. The research community of pharmacogenetic advocates should review this study and focus their efforts on providing the data needed to guide informed policy decision making with regard to pharmacogenetic testing.

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1. INTRODUCTION

Clinical pharmacogenetics has the potential to be one of the next great innovations in precision medicine and tailoring of patient treatments. The phrase, "the right drug, at the right dose, the first time", has become synonymous with pharmacogenetic testing and the improvements that it may possibly bring. This hope has been met with significant barriers to implementation, due to claims by some of insufficient clinical evidence and results which have not been integrated into the decision making process of clinicians.¹

The most common form of pharmacogenetic testing is the point-of-care or "reactive" testing method and it can occur in two forms: the testing of somatically acquired genomic variation and the testing of germline genomic variation. A commonality between the forms is that the patient is diagnosed with a condition and subsequently given the test or the companion diagnostic to determine the appropriate course of treatment. The difference in the reactive form comes from the type of reactive test, the genotyping of the patient or of a tumor. The former corresponds to the germline genomic variation, and the latter to the somatically acquired genomic variation. The genotyping of the patient will identify a specific gene variation that impacts human drug metabolism, transport, distribution, and excretion for certain medications.

Genotyping of the tumor has been used to guide decisions on the type of anticancer agent to use based on the likelihood of a response, and to develop novel therapies that target specific genetic mutations within the tumor. Inherited genome variations in cancer can also influence response. The desired outcome for genotyping the patient or the tumor is to characterize the

corresponding drug response phenotypes such as efficacy, toxicity, or desired pharmacologic effects. This has become the more difficult challenge for pharmacogenetics as well translating these discoveries into clinical practice.²

The development of a newer form of testing for germline genomic variations, preemptive pharmacogenetic testing, takes a broader approach to genotyping the patient by assaying thousands of genetic variants with a single test with the results being entered into a patient's electronic health record for future reference. Current adoption of preemptive pharmacogenetic testing has been limited to a few consortiums composed mostly of academic medical centers. These include the Pharmacogenetics Research Network (PGRN), the Electronic Medical Records and Genomics Network (eMERGE), and Implementing GeNomics in Practice (IGNITE). The costs of implementing the technology, to this point, has fallen predominantly on the individual institution through the pursuit of grants and internal funding. Many of these programs are supported by the National Institutes of Health (NIH) and the National Human Genome Research Institute (NHGRI). This has limited the spread of this technology to only a few locations and clinical settings.

These tests have struggled to gain widespread coverage among third-party payers, although the testing of somatically acquired genomic variation has enjoyed slightly more success in that regard.³ Historically, payers have identified the need for more data on clinical outcomes and prospective comparative-effectiveness studies, ideally randomized-controlled trials, as well as evidence that clinical utility exists to consider coverage for these types of tests.^{4,5} The clinical utility of these tests has become a more important consideration for payers, as they pursue the real-world applicability of medical innovations.^{4,6}

The primary objective of this research is to investigate the perspectives and opinions about coverage and reimbursement policies for preemptive pharmacogenetic testing from third-party payers through a series of in-depth interviews.

2. BACKGROUND

To many health care leaders, an emphasis on value has been the driving force behind decision making in recent years. Value is a relationship between desired outcomes and the cost needed to achieve those outcomes.⁷ Precision or personalized medicine is thought by many health care leaders to be a way to increase value by leaving the population-based treatment approach behind and advancing to a patient-centered model of care.⁷ The Personalized Medicine Special Interest group of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) defines personalized medicine as follows: the use of genetic or other biomarker information to improve safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches.⁸ The NIH has encouraged the adoption of the term "precision" over "personalized" when discussing pharmacogenetics as to prevent the misinterpretation that a treatment or prevention has been developed for an individual.⁹ The term precision medicine is the broadest of all terms and also seeks to include non-genomic factors such as lifestyle and environment.

Overview of Pharmacogenetic Testing

It is important to note that the focus of pharmacogenetics must be distinguished from other areas of clinical genomics that focus on the identification or risk of genetic or chromosomal

conditions. Pharmacogenetics works by determining how germline or somatic mutations affect the metabolic pathways that determine an individual's response to a drug.¹⁰ A germline mutation is a detectable or heritable variation in the lineage of germ cells, while a somatic mutation is a genetic alteration that is acquired by a cell and then passed along during cell division. Somatic mutations, with respect to pharmacogenetics, are mostly involved in the detection of genetic variants in the cells of tumors and related drug response. Pharmacogenetic testing does not focus on the identification of disease risk, and there is little importance that can be gleaned from assessing the genomic variants of an individual and this relationship. In so doing this test avoids some of the ethical issues surrounding other types of genetic testing.¹

The discovery of the hepatic cytochrome P450 in 1977 was one of the most important discoveries for the advancement of pharmacogenetics.¹¹ The CYP450 gene superfamily is involved in the metabolism of about 75% of commonly prescribed drugs. The polymorphic drug metabolism enzymes associated with CYP450 genes are prone to variations in the number of copies, including full gene deletion or duplication, which ultimately effects how a drug would be metabolized within a patient's body affecting the safety and efficacy with some patients. The genotypes of these enzymes are typically categorized as five metabolism phenotypes: ultrarapid, rapid, normal, intermediate, and poor.¹¹ Take the CYP2D6 enzyme, a member of the CYP450 gene superfamily, for example, a patient that presents with multiple copies of this may be classified as a rapid metabolizer of certain medications and will therefore require an increased dose. Conversely, for a patient lacking functional CYP2D6 enzymes the normal dose would exceed the therapeutic target, potentially resulting in an adverse drug reaction (ADR). ADRs are a significant safety risk, causing increased morbidity and associated high costs, as well as being one of the most common causes of death.¹² Many patient factors may contribute to an increased

risk of an ADR, but somewhere between 10-20% of ADRs are due to genetic factors.¹³ By determining the mechanisms and effects of a genomic variation on drug response these kinds of ADRs can be prevented.

Benefits of Pharmacogenetic Testing

Pharmacogenetic testing in clinical practice may benefit the patient in several ways. The use of a pharmacogenetic test can enable more patient-centered care by involving the patient in the decision making process.¹⁴ This involvement in the treatment decisions is likely to be associated with a better patient-physician relationship and increased trust, leading to the potential for greater adherence to the medication therapy.¹⁵ They may perceive the therapy is more beneficial or has less risks, given the pharmacogenetic test results have informed the treatment choice. Also, patients who participate in pharmacogenetic testing may be psychologically affected in a manner which encourages a more active role in their own health management. Because the results of the pharmacogenetic tests inform the selection and dosing of drug therapy, these tests are likely to address patient concerns about therapy. Some patients may perceive little or no need for a therapy or doubt its effectiveness. If the pharmacogenetic test results indicate that this therapy is likely to work in this patient, the patient may be more willing to adhere to the medication therapy.¹⁴

Similarly, using pharmacogenetic test results is a proactive medication safety strategy that can provide information to decrease the risk of adverse drug reactions (ADRs) and improve drug selection. Recall the example of the patient with multiple copies or a deletion of a CYP2D6 enzyme in the CYP450 gene, consequently requiring increased or decreased drug dosing,

respectively, to offset the change in metabolism. The identification of genetic factors that may predispose a patient to an ADR can be helpful in preventing its occurrence.¹⁶ Pharmacogenetic testing will also help select effective therapy initially. A landmark psychiatric clinical trial (STAR-D), completed in 2006 for patients with major depressive disorder, showed that only one-third of patients achieved remission from their initial treatment, meaning that patients generally need to try multiple medications.¹⁷ The burden of switching to different therapies to find an effective treatment can be costly for patients and the entire health care system as well as slow the treatment of their condition.¹⁸ The problem is compounded depending on the number of medication changes, which are required, and the time necessary to find the correct therapeutic approach. Furthermore, early detection and treatment with an appropriate drug lessen the effects of the disease on the body, arriving at better clinical outcomes for the patient.¹⁴ The concomitant research on the economic utility for many pharmacogenetic tests combined with clinical evidence will be a determinant of potential value to the health system.

A study from 2014 identified 59 cost-utility analyses of precision medicine tests between the years 1998 and 2011. The findings from the 2014 study revealed that most studies (72%) showed testing provided better health at higher cost, while 20% showed cost saving.¹⁹ Cost saving in this case means that a negative incremental cost effectiveness ratio (ICER) resulted from the analysis. Roughly half of the studies that provided better health at higher cost fell under the \$50,000/QALY threshold while 80% of the studies fell under the \$100,000/QALY threshold. The former \$50,000/QALY threshold is used as a decision tool by the National Institute of Health and Clinical Excellence in England (NICE) and the \$100,000/QALY threshold is used unofficially in the United States.^{19,20} It is important to note however that there are many factors which can influence the outcomes for the economic value of pharmacogenetic testing, including

test cost, treatment cost, the nature of the indication, treatment benefits with and without the test, and the prevalence of the pharmacogenetic variant.²⁰

In a recent study, Brixner et al. used an observational study design of elderly patients (≥ 65 years old) with a prescription or dose change of at least one of sixty-one oral drugs within 120 days of enrollment that were on 3 or more total medications.²¹ This prospective group was propensity score matched with a retrospective cohort from a claims database. The prospective group was given a CYP 450 pharmacogenetic test and providers used a clinical decision support tool including this new information on patients for a four-month period to measure healthcare resource utilization. Those patients in the tested group showed a significantly lower rate in hospitalizations, 9.8% vs. 16.1%, $p < 0.027$, and in emergency department visits, 4.4% vs. 15.4%, $p < 0.0002$. The rate of healthcare resources utilization was higher in the tested group, most likely due to more outpatient visits, but the potential cost savings were estimated at \$218 per patient in the tested group.

The economics of health care and drug discovery can also benefit from the expansion of pharmacogenetics in the industry. Deverka et al. explain that developing products through pharmacogenetics can reduce the cost of drug development programs by allowing for smaller and less expensive clinical trials, reducing the development time for a product, and increasing FDA approval rates.¹⁸ Moreover, pharmacogenetics could be used to "rescue" certain drugs that may have never made it to market because of severe ADRs. For example, the drug could be made available to the cohort of patients who test negative for the genetic variant leading to the ADR. However, because pharmaceutical companies will be catering to a much more stratified population, incentives such as longer patent life and beneficial pricing contracts will be essential to encourage this type of drug discovery.

Types of pharmacogenetic testing

There exist two broad groups of pharmacogenetic testing: somatic and germline testing, the latter can be subdivided into reactive/point-of-care testing and preemptive testing. The following section provides a brief discussion of each of these types.

Reactive-Somatic/companion diagnostic tests

As pharmacogenetic testing has progressed so has the availability of more advanced types of testing. This has led to the development of what is commonly referred to as “companion diagnostic tests”. These tests are typically developed and tested concurrently with the drug in the early phases of clinical trials.⁵ The goal of these companion tests is to genotype the tumor and break down the complexity, thereby identifying potential tailored treatments for specific types of patients.⁴ It is suggested that the use of the companion diagnostics will facilitate selection of appropriate treatment and lead to better medication-related outcomes. Additionally, it may prevent money being spent on expensive, advanced biologic drug therapy for patients with tumors not likely to respond to the drug therapy. Drug development in oncology products has been an active area of research for pharmacogenetics, particularly in lung and breast cancer. Currently, the United States Federal Drug Administration (FDA) requires pharmacogenetic testing for use of trastuzumab, cetuximab, and panitumumab.

Some companion diagnostics may be co-developed with a drug and by the manufacturer of that drug, while independent companies may develop tests for drugs that are currently used in medical practice. Experts see the development of *post hoc* companion diagnostics growing moderately over the coming years.⁵ The acceptance and use of germline mutation diagnostic

testing has been noticeably less than that of its somatic counterparts used in the treatment of cancer. A major cause of this discrepancy may be the impact that testing in cancer products has on the reduction in utilizing expensive medications in patients where the drug therapy is not likely to work.

Reactive-Germline mutation testing

Germline mutation testing can be divided into two main groups: reactive or point-of-care and preemptive pharmacogenetic testing. Reactive pharmacogenetic testing is the one-at-a-time approach where the test is typically ordered at the point of care when initiating a treatment.²² Support for the use of reactive pharmacogenetic testing comes from the assumption that there is an increased likelihood the results will be applied by the clinician because the prescribing decision will be inexorably linked to the results of the pharmacogenetic test. Furthermore, the gene-by-gene basis of testing allows for the testing to be done on those patients who have been diagnosed with a specified condition.¹ This can have both advantages and disadvantages. One advantage is that unnecessary testing is avoided and the subsequent cost associated by offering the pharmacogenetic test only to those with a specific indication.

A budget impact analysis of CYP2C19 genotyping in patients receiving dual antiplatelet therapy including clopidogrel, which is known to incur serious ADRs for poor and intermediate metabolizers, was recently conducted.²³ The model assumed that patients had been diagnosed with acute coronary syndrome (ACS) and would have received a percutaneous coronary intervention (PCI). The budget impact was considered for three clinical scenarios: no patients received CYP2C19 genotyping, 50% of patients received the genotyping, or all patients received

the genotyping. Demonstrating the feasibility of targeted genotyping, the results showed annual cost-savings to the plan in both the 50% and 100% testing scenarios, \$222,426 and \$444,852, respectively.

There exist several disadvantages to the reactive approach as well. Once the determination has been made to test, it must be "ordered, retrieved, and interpreted by the physician" before applying any changes to the patient's treatment.²² A slow turnaround time can lead to insufficient time being available before a clinical decision for drug therapy needs to be made. Additionally, clinicians may lack the knowledge on gene/drug relations to enable them to even initially order the appropriate tests when needed.¹ Testing on a per-gene basis can lead to an increased cost if repeated tests are needed for complicated patients on multiple genetically dependent therapies. The author of the budget impact analysis described previously only considered the one genotype, he addresses the potential for further cost-savings from a preemptive genotyping approach that enables decreased testing costs for individual genotypes and integration with clinical decision support tools.²³

Preemptive-Germline mutation testing

The alternative pharmacogenetic testing approach is to preemptively test patients for multiple pharmacogenetic variants. A large retrospective study on 52,942 medical home patients conducted by Vanderbilt University Medical Center (VUMC) found that almost 65% of patients were exposed to at least one medication with a drug label indicating a known pharmacogenetic variation in response during the five year time period, and 54% were exposed within a one year time frame. Using probabilities of medication exposure and probability of six possible severe

adverse events, the researchers estimated that 383 adverse events could have been prevented with the implementation of an effective preemptive genotyping program.²²

The ability to assay hundreds to thousands of genetic variants at a time can decrease the cost of individual genotyping, and provide genetic information that can be reused over the lifetime of a patient as other drugs are prescribed. Multi-gene testing in a single assay benefits the patient in another manner due to the fact that the pharmacokinetics and pharmacological effects of a great majority of medications are determined by multiple gene products. The adjustment of dosing based on a single-gene genetic test results, in some cases, can reveal genetic variants in other genes that might be of clinical importance. Additionally, a single gene can affect more than one medication (*TPMT*, *CYP2D6*, *CYP2C19*, *CYP2C9*, *HLA-B*, *DPYD*, *UGT1A1*) and the preemptive availability of these results makes better use of this genetic data.² New drug-gene interactions are discovered continually, and the use of multiplexed preemptive testing and successful clinical support tools will enable clinicians to apply immediately this new knowledge to improve patient outcomes.

The St. Jude Children's Research Hospital protocol, PG4KDS, was opened in 2011 and as of the end of 2013, the results of four genes have been implemented into the EHR. This corresponds to 12 high-risk drugs and 55 clinical decision support systems. The data from this protocol also showed that 78% of patients had at least one actionable genotype result.²⁴ Currently there are seven genes coupled with 17 high-risk drugs that have been integrated into the EHR.²⁵ Another study conducted in the VUMC Predict program preemptively genotyped 10,000 patients and found results, based on five drug-genome interactions, which identified one or more actionable variants in 91% of overall patients and 96% of black patients.²⁶ The genetic data of 9,589 individuals was compared with historical published allele frequencies. The authors point

out that it would have taken 14,656 total tests using a reactive genotyping approach, a nearly 50% increase in the amount of testing. Current thought is that most actionable drug prescribing is linked to 12 genes. Dunnenberger et al. theorized that based on this, 98.5% of whites and 99.1% of blacks, would present with at least one high-risk diplotype.¹ The utility of pharmacogenetic testing is contingent upon the prevalence of patients who receive high-risk pharmacogenetically driven drugs and have phenotypes that predict a variable response. Thirty of the most common prescription drugs considered pharmacogenetically high risk accounted for approximately 738 million prescriptions in 2013.

Implementing Preemptive Pharmacogenetic Testing in Practice

The Pharmacogenomic Research Network (PGRN) is at the forefront of preemptive pharmacogenetics and its successful implementation into the health care system. PGRN is a group of prominent researchers and clinicians at several academic hospitals throughout the U.S. that are coordinating with the National Institute of General Medical Science (NIGMS) and the National Institutes of Health (NIH) to study how genetic variation contributes to interindividual differences in responses to medication.²⁷ Other than VUMC, there are several more highly regarded academic research medical institutions that are undertaking similar preemptive testing strategies. A few of these include St. Jude Children's Research Hospital, Mayo Clinic, Mount Sinai Medical Center, University of Florida and Shands Hospital, the University of Chicago, and Brigham and Women's Hospital.¹

The VUMC PREDICT program was created in 2010 to target "high value genetic variants" that contribute to medication-related adverse events through a preemptive genotyping

of patients. The relationship between variants of *CYP2C19* genotypes and antiplatelet therapy was the initial focus. PREDICT uses the VeraCode ADME Core Panel to genotype their patients, testing for 184 variants in 34 genes associated with drug response.^{1,28} Four of the other institutions listed previously have implemented similar multi-gene preemptive pharmacogenetic testing platforms including Mount Sinai Medical Center (Sequenom iPLEX ADME pharmacogenetic - 36 genes), Mayo Clinic (PGRNseq - 84 genes), St. Jude Children's Research Hospital (Affymetrix DMET Plus Array - 230 genes), and University of Florida and Shands Hospital (Life Technologies Quant Studio Open Array - 120 genes).¹

The actionability of a drug/gene relationship is ultimately dependent upon the translation of genome discoveries into systems that optimize the delivery of medications. An essential aspect of this actionability is the availability of alternative therapies when a high-risk genotype has been identified in a patient. This requires efforts by researchers to not only recognize the drug/gene relationship that may be harmful, but to also identify an alternative therapy.² Work by the Clinical Pharmacogenetics Implementation Consortium (CPIC), has taken a leadership role in addressing this complex issue in pharmacogenetics. Many of these programs rely on the CPIC guidelines to provide the clinical evidence of the drug/gene pair that is being tested and potentially moved into the electronic health record (EHR). The importance of the EHR and clinical informatics in the dissemination of preemptive pharmacogenetics has not been overlooked. Many of the institutions mentioned above have developed clinical decision support tools personalized to the high-risk medications likely to be prescribed based on the preemptive testing results. St. Jude Children's Research Hospital published a detailed report on the development and use of their system.²⁹ Entries are created for high-risk phenotypes that deliver post-test alerts when the high-risk drug is prescribed. The CDS system will also alert the

clinician when a high-risk medication is prescribed prior to genetic results being entered into the patient's EHR. The mission of CPIC is to inform clinicians on how genetic test results should be used to improve patients' outcomes, not when and whether to use them.³⁰

The University of Chicago's "1,200 Patients Project" aimed to determine the relevance of pharmacogenetic results while delivering care in an outpatient clinic. As of 2014, 812 patients had participated and 608 have been successfully genotyped. This protocol used the result signals green light (favorable), yellow light (caution), and red light (high risk) via a genomic prescribing system (GPS). At 268 clinic encounters, 86% of physicians accessed the GPS with 57% green lights, 41% yellow lights, and 1.4% red lights. Also, physician click frequencies were reported as 20%, 72%, and 100%, respectively. This information shows a high rate of physician adoption and widespread use in the patient population.³¹

Approximately 15% of European Union-European Medicines Agency (EU-EMA) and the US-FDA approved medications have some type of pharmacogenetic data in the label.^{32,33} According to CPIC, only about 7% of these medications have actionable germline pharmacogenetics. However, a disproportionate amount of these medications (~18%) represent all prescriptions in the United States.² Though only representing a small portion of the total medications consumed in the U.S., the potential for improving current patient outcomes exist and will be expanding as more actionable drug/gene relationships are identified. The design of CPIC was realized through a collaboration of PGRN and NIGMS, described above, on the view that preemptive genetic testing will become more widespread and clinicians will need the appropriate evidence to make informed and accurate decisions quickly.

The guidance that CPIC provides to clinicians is based on standardized guidelines to understand the types and levels of evidence needed to justify the implementation of pharmacogenetics into clinical practice. This evidence includes:

"...sound scientific rationale linking genomic variability with drug effects, the therapeutic index of the involved medications, the severity of the underlying disease, the availability of alternative dosages or drugs for patients with high-risk genotypes, the availability of CLIA approved laboratory tests, and peer-reviewed clinical practice guidelines that incorporate pharmacogenetics in their recommendations."³⁴

Each guideline contains a summary of the drug dosing addressed from the genotype tests, a literature review, genetic test interpretation for clinicians, population studies to compliment this interpretation if available, genetic test options, possible incidental findings from the test, linkage of genetic variability to variability in drug-related phenotypes, and levels of evidence and strength of recommendations.

The prioritization of CPIC gene/drug pairs uses a subset of two rating schemes adapted from National Academy of Clinical Biochemistry for the quality of the evidence and the National Institutes of Health for the strength of the recommendation.³⁴ CPIC will apply this approach to the development of each guideline.

The schema for evaluating the quality of evidence for a linkage between drug-related phenotypes to specific genetic variations is as follows:

Level 1: the evidence includes consistent results from well-designed, well-conducted studies

Level 2: the evidence is sufficient to determine the effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence.

Level 3: the evidence is insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information.

The schema for evaluating the strength of the recommendation to clinicians involved in decision making is as follows:

A: strong recommendation for the statement

B: moderate recommendation for the statement

C: optional recommendation for the statement

CPIC is a joint project with PGRN and the Pharmacogenomics Knowledge Base (PharmGKB), which is managed by Stanford University and trademarked by the U.S. Department of Health and Human Services (HHS) that "encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships."³⁵ PharmGKB uses a similar rating system to the one listed above but focuses rather on the genotype-based pharmacogenomic summaries of the association between a drug and particular variant. These clinical annotations are assigned a level (1A, 1B, 2A, 2B, 3, and 4), in descending order of strength of evidence for the association, based on population, replication, effect size, and statistical significance.

There are currently 36 variant-drug combinations that are listed level 1A. PharmGKB defines level 1A as the "annotation for a variant-drug combination in a CPIC or medical society-endorsed pharmacogenetic guideline, or implemented at a PGRN site or in another major health system."³⁶ CPIC has designated its levels for gene-drug pairs as either: A, B, C, D. It is important to note that these are not the same as the clinical annotations of PharmGKB, although there is some overlap. There are currently 41 gene-drug pairs that have the designation CPIC Level A and 97 designated CPIC Level B. Level A means that at least one moderate or strong action (change in prescribing) is recommended, while level B indicates at least one optional action is recommended. The PharmGKB annotation levels are incorporated in the prioritization process of CPIC guidelines of new gene-drug pairs. There are currently 30 guidelines available. A flow chart of this process is illustrated in Figure 1.³⁷ For a full list of the clinical annotation levels of evidence from PharmGKB and a visual of the PharmGKB Knowledge Pyramid see Appendix A.

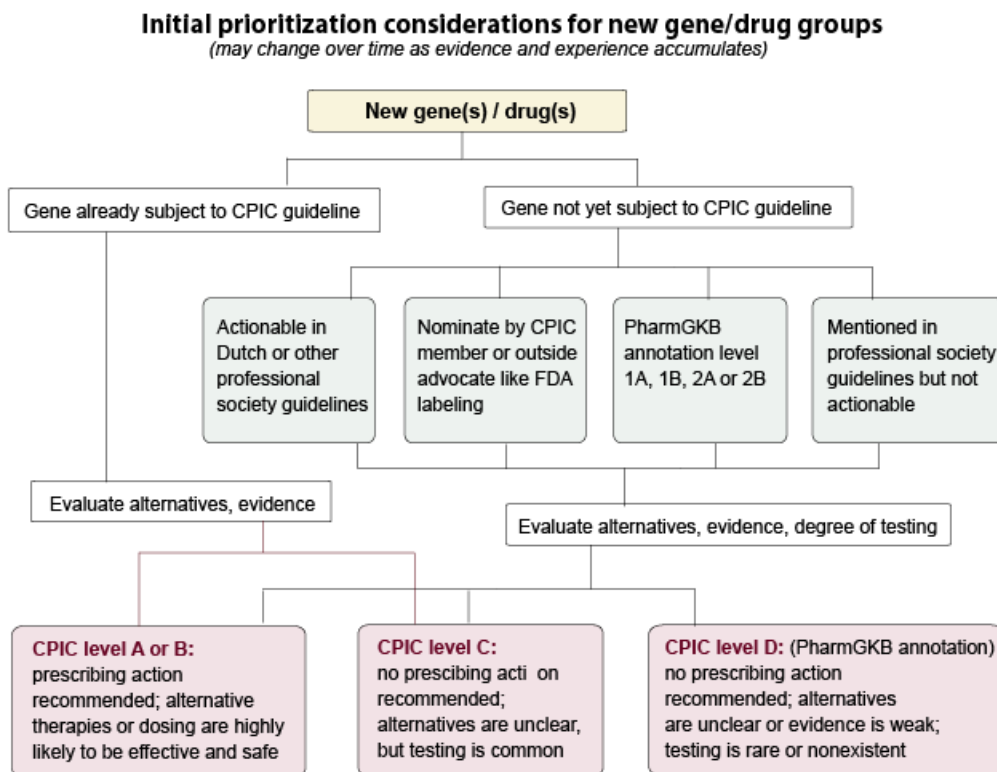


Figure 1. CPIC evidence level selection process flow chart

Although several academic institutions have implemented preemptive testing and efforts are made to provide guidance on how to use the test results, the challenge of implementing a change in routine medical practice is a real issue. The complexity, size, and momentum to resist change can stymie an innovation such as pharmacogenetics from clinical implementation. This can even occur when the change is likely to lead to improved care. For the numerous positives that have been researched and put forth by proponents of pharmacogenetic testing, there still exist barriers to effective implementation. Work by the VUMC PREDICT program identified the following challenges: "the assessment of the potential benefits for clinical pharmacogenomic testing, definition of the target populations, designation of anticipated scope of pharmacogenomic testing, determination of diagnostic methodologies, development of infrastructure to support reporting, interpretation and use of results, and establishment of reimbursement for testing."²⁶

The focus of this research is to gain further understanding of the last challenge identified in the previous list, "the establishment of reimbursement for testing." Third- party payers provide a highly valued perspective on the challenges outlined in the VUMC PREDICT program. The establishment of reimbursement policies for preemptive pharmacogenetics will be facilitated by addressing the other challenges and a detailed look into the decision making process of the payer should reveal some methods to move forward.

The Role of the Payer

The role of the payer cannot be understated in the adoption of pharmacogenetic testing as standard of care. Third-party payers will need adequate evidence to justify coverage decisions

and provide the incentive for clinical practice to adopt this technology so that the potential benefit to patients can be realized. Three types of policies are developed within a third-party payer organization: the medical policy, coverage policy, and payment policy. The first is based on scientific evidence and does not consider financial issues. The second is the most familiar to the average person since it represents the contract between the purchaser and the issuer of the policy and the scope of the benefits therein. The last is the policy between the issuer and the practitioner that receives reimbursement for utilization of the service, in this case, the pharmacogenetic test.

It is important to remember that coverage policies and reimbursement represent two different things.³⁸ Developing these policies requires studies from professional and academic researchers to guide decision-making. The evidence required to build a medical policy is the first barrier that must be overcome for pharmacogenetic testing to move forward. The specific types of studies that payers desire has been ascertained by the research of Leung et al. and ranked according to their importance as evidence: randomized clinical trials (RCTs), systematic reviews (including comparative effectiveness research (CER)), review articles, professional society guidelines, prospective observational studies, budget impact, cost and economic, and retrospective observational studies.³⁹ All of these score somewhere between a 3 and 4 on a 5 point Likert-type scale with the exception of the RCT, which received a score of 4.4. It needs to be noted that the researchers found that the payers did not express concern for using observational data from their own organization in coverage decisions.

Previous literature on how payers are approaching pharmacogenetic testing at their organizations has revealed some fairly consistent themes with regards to the evidence payers require when assessing a new health technology. A health technology assessment (HTA) is

research that is pursued, in this case, by a third-party payer organization, to assess the short- and long-term consequences of the technology. The properties that are evaluated for new health technologies are numerous: safety, efficacy, cost-effectiveness, ethics, legality, and politics. An ISPOR publication identified five activities that define a formal HTA: horizon scanning, topic determination, collection and assessment of evidence, appraisal, and funding and policy implementation.⁴⁰ The adoption of pharmacogenetic testing has been hindered by the third activity, the collection and assessment of evidence, which ultimately hinders the last two activities in the list.

The hindrance in this activity is not that evidence does not exist, but rather the type of evidence that payers find useful in their evaluations does not currently exist. The diversity of available genetic tests corresponds to the variability in how a payer will approach a coverage decision and the strength of the evidence seems to be guiding the process. A study in 2010 examined six case studies of personalized medicine tests of varying types: disease differentiation, pharmacogenetics, and genetic predisposition. They compared coverage decisions among five large private and public payers and found that the pharmacogenetic tests, with current evidence of observational genotype-phenotype studies, were not at all or not usually reimbursed.⁶

Current coverage of disease diagnosis, risk, prognosis, as well as pharmacogenetic tests is low. A study published in 2012 by Hresko and Haga using an online search of the top dozen U.S. health insurers found that 18% of tests for disease diagnosis/risk/prognosis, and 30% of pharmacogenetic tests, were covered. Thirteen of the twenty-seven pharmacogenetic tests that were reviewed included an FDA drug label with pharmacogenetic information. The majority of the pharmacogenetic tests were deemed investigational and not medically necessary.³ The

reluctance to reimburse seems to stem from three major concerns: a lack of clinical utility, tests that are medically unnecessary (defined as lacking the FDA requirement of the test), and lack of cost-effectiveness analysis and/or comprehensive comparative effectiveness analysis.⁴¹

The expectation of clinical utility and comparative effectiveness is evidenced by the fact that payers decline to pay for a pharmacogenetic test costing, many of which are less than \$500, while agreeing to cover drugs (for which the test could be used) that are much more expensive.⁵ The difficulty assessing clinical utility in pharmacogenetics is exacerbated by the complexity and burden of the randomized control trial, the evidence-based driven gold standard of clinical utility. The requirement of a large cohort of heterogeneous patient populations, placebo effects, and drug response variabilities frequently result in a small incremental clinical benefit. Lam attributes this to the fact that pharmacogenetics emphasizes the safety and efficacy of outlier patients, poor and ultrarapid metabolizers, as well as non-responders and those susceptible to ADRs. Suggestions of clinical trials with smaller, targeted patient populations likely to respond or not suffer ADRs have been one of the proposals to address the challenges of traditional RCT assessment for safety and efficacy using pharmacogenomic biomarkers. Scientific and clinical communities continue to debate the balance between the current required level of evidence of clinical utility and those realistically achievable but still scientifically appropriate.⁴¹

An in-depth investigation into the decision making process of six payers provided a look past the basic need for clinical evidence. It examined policies around one genetic test, considered a blend of diagnostic/risk and pharmacogenetics that has received coverage by all insurers, the Oncotype Dx test to assess breast cancer recurrence risk and subsequently guide treatment decisions.⁴² Four of the six payers indicated that they were willing to base their decisions on the intermediate endpoint of clinical utility, defined as evidence the test affected clinical decision

making. While the payers stated that they valued clinical effectiveness most highly, their perceptions of its strength varied greatly. To help the payers overcome a lack of clinical evidence in some instances, patient and provider adoption, of the penis fragment coverage by a California Medicare Administrative Contractor (MAC), and endorsement of a medical society, along with intermediate clinical utility, were considered as important health system factors in developing policy decisions.

Although the Oncotype Dx did have prospective clinical trials, this exposé on the decision-making processes of those who have adopted Oncotype Dx can provide other factors of investigation when a new medical innovation may face uncertainty in clinical evidence. Further study of variations among coverage policies for the technologies associated with precision medicine might facilitate a more homogeneous adoption by educating the decision makers and promoting less discontinuity among physicians and patients.

Slower payer adoption has affected the adoption of pharmacogenetic testing by health care organizations, providers, and patients. Slow payer adoption can be attributed to three main factors: lack of clinical trials to show the clinical validity of the test, little evidence that pharmacogenetic testing has influenced clinical practice decision making and improves patient outcomes, and whether pharmacogenetic testing is cost-effective to their plan. There have been a few studies that have attempted to understand the third-party payer's point of view on this topic through in-depth interviews. To our knowledge, no studies exist to capture the opinions of the third-party payer with respect to preemptive pharmacogenetic testing.

3. METHODOLOGY

Study Objectives

The study purpose is to investigate the perspectives and opinions about coverage and reimbursement policies for preemptive pharmacogenetic testing of third-party payers. The following objectives are to provide the necessary details to achieve the study purpose:

1. Describe the current policies third-party payers have on pharmacogenetic testing and how these policies differ by the type of test
2. Describe the clinical evidence of effectiveness that third-party payers require for policy decisions on preemptive pharmacogenetic testing
3. Describe the third-party payers' perceptions of value with respect to pharmacogenetic testing and the cost factors associated with preemptive pharmacogenetic testing coverage decisions
4. Identify the practice/utility factors that third-party providers are using to make coverage decisions for preemptive pharmacogenetic testing
5. Identify barriers and facilitators to third-party payer coverage of preemptive pharmacogenetic testing.

Sample

Utilizing a payer panel made available by Medical Marketing Economics, LLC, third-party payers were invited to participate. No initial honorarium was offered to participants. A

targeted final sample size of 15 payers was desired for the in-depth interviews, which is consistent with previous work conducted in this area.^{4,5} Interviews were conducted until saturation of topic responses was achieved.

Data collection

Qualitative in-depth interviews were conducted via telephone, bookended by two quantitative surveys administered online (Qualtrics, Provo, UT). A first invitation email (see Appendix B) was sent to all members of the panel along with a brief online screening survey. The screening survey asked about the participant's professional capacity in their institution, size of their plan, and the number of lives covered, as well as the breakdown of plan types for their beneficiaries. The screening survey also assessed levels of familiarity, management, and priority of health technologies and pharmacogenetics at the institution using several Likert-type item questions. The screening survey concluded to assess respondents' familiarity with preemptive pharmacogenetic testing. The survey can be found in Appendix C.

Those respondents who answered "not at all familiar" on the question "Please rate your level of familiarity with *all types* of pharmacogenetic testing" were not be eligible for the interview. All eligible payers received a second invitation email (Appendix D), to participate in the in-depth interview portion of the research. In the second email pre-read material was provided to the participant and included descriptions of different types of genetic testing, diagnostic, pre-symptomatic, and both reactive single-gene and preemptive multi-gene pharmacogenetic testing. The work of the CPIC and PharmGKB on the clinical validity of the drug-gene relationships that drive the actionability of pharmacogenetic testing was also

presented to the participant. An example from the PharmGKB website (<https://www.pharmgkb.org/guideline/PA166128738>) of the clinical decision alerts a clinician might encounter based on the CPIC work was also provided. Non-responsive potential interview respondents were sent a reminder email containing the same information one week after the initial email.

The brief quantitative survey and discussion guide for the in-depth interview were reviewed for face validity with a group of pharmacogenetic experts that have active involvement in the use of these technologies, or are heavily involved in the academic research of pharmacogenetics. After review, the guide and survey were updated to assure concise and informative questions were presented. The first interview acted as a pre-test for the interview guide used in the remaining interviews. Subsequent updates to the guide were made when several questions were found to be unnecessary, and thus removed, while others were rephrased to more accurately convey the intended questions. The interviews were digitally recorded for analysis. Verbatim transcription was completed by a professional transcription service as the interviews were completed. The semi-structured interview guide will be described in greater detail below.

At the conclusion of the interview the participant was instructed to follow a web link to complete a brief survey. This survey contained nine Likert-type questions that were originally included in the semi-structured interview guide, but after the pre-test interview these questions were deemed to function better as a stand-alone survey to summarize the conversation.

Semi-structured Interview Guide

The interview guide has two sections: an introductory section and a section containing three themes found in the pharmacogenetics literature. The first section contains seven questions to assess the participant's attitudes toward pharmacogenetic testing more generally, including any high level perceptions of the precision medicine and current policies they might have on different types of pharmacogenetic testing. This number was reduced from 12 questions to 7 questions after conducting the pre-test discussion/interview. The second section examines barriers to further implementation of pharmacogenetics and key drivers of payers' coverage policies with regards to pharmacogenetics.^{2,4,5,10,39,40,41,43} It originally included 17 questions split among these themes, but was also reduced to 14 and tailored based on face validity and pre-test discussions.

The specific pharmacogenetic themes covered in the second section of the interview guide include: clinical utility and validity of pharmacogenetic tests, perception of value and cost factors associated with pharmacogenetic tests, and coverage and reimbursement issues for pharmacogenetic testing. The semi-structured interview guide can be found in Appendix E.

Data analysis

The results of the screening questionnaire were analyzed and responses to the surveys were aggregated to obtain frequencies. This same information was parsed out for those payers that were eventually interviewed (n=13, one did not complete the post-interview survey) and the data are available in Table 1 and Table 2. A visual comparison was conducted to determine if there were any striking differences among those survey respondents that agreed to the interview and those that did not. An independent samples t-test was run to determine if there was any

significant difference, between the respondents that were interviewed and those that were not, on the items in the screener survey.

The qualitative interview portion of the study was analyzed as a content analysis. This content analysis is a blend of inductive and directed (sometimes referred to as deductive) strategies. As outlined in the description of the interview guide there were a number of pre-identified themes introduced in the interview based on previous literature. However, respondents were allowed to direct the conversation as they saw fit. More specifically, questions in each theme were allowed to shift to another theme and new themes or subthemes were created if the data strongly indicated such. The inductive research approach has been identified as the most appropriate for relatively undeveloped areas of knowledge.⁴⁴ The blend of pharmacogenetics and third-party payer opinions, underdeveloped and developed, respectively drove the decision to pursue a blended qualitative research design. A decision was made to code and analyze the transcripts manually instead of utilizing qualitative data analysis software. Although software may save time and assist in the validity through increased rigor, this process can become deterministic and focused inappropriately on the volume of data instead of the quality, distancing the researcher from their data and potentially losing context and meaning.⁴⁵ With a topic focused on an underdeveloped area of knowledge, this approach seemed inappropriate.

The transcripts were fully analyzed by the study lead and one other author to identify the driving themes of the data. Each transcript was read three times by these two researchers. During the first read through readers highlighted important statements made by the respondent and provided a brief summary of the highlighted portion to identify the topic therein described by the highlighted material. This is also known as meaning units. In a second read, the readers identified codes from the first read through that appeared in a majority of the interviews and

determined main themes and subthemes. A third read through was conducted to ensure no important data were left undiscovered by comparing each interview to the themes and subthemes identified. A third researcher was asked to mediate any disputes between the two other readers to arrive at a consensus.

4. RESULTS

The initial sample included 35 respondents to the screener survey. Six responses were ineligible for any type of analysis due to incomplete responses leading to a final sample size of 29 respondents for the survey. As expected, payers were less familiar with preemptive pharmacogenetic testing. Over three-quarters of respondents were somewhat, slightly, or not at all familiar with preemptive pharmacogenetics.

Of these 29 complete respondents, 14 agreed to participate in the interview by responding to follow-up emails. This consisted of nine pharmacy directors and five medical directors. Three of the five medical directors proved more difficult to recruit and in an attempt to balance the sample, a modest honorarium was offered to three medical directors.

Table 1 provides an overview of the demographics of the interview participants and Table 2 provides data on the remainder of the questions from the screener survey. These 14 payers accounted for nearly 122,000,000 million covered lives or almost 40% of the U.S. population. Plan size ranged greatly from 200,000 to as many as 50,000,000. These individuals interviewed came from various types of organizations including: large traditional payers at the national and regional level, national and regional pharmacy benefit management companies (PBMs), group model health systems, individual medical groups that offer insurance, and others. No two individuals interviewed were from the same health plan. However, some amount of “double-counting” is possible between the PBM and traditional payers. Based on the visual comparison of the data there did not seem to be any differences between those that agreed to the

interview and those that did not. The independent samples t-test comparing the respondents in the two groups did not reveal any significant differences. However, this t-test should be interpreted accordingly due to the small sample size.

Demographics of <u>interviewed payers</u> (N=14)	Mean	Standard Deviation	Minimum	Maximum
Number of lives covered on plan	8,708,898	15,815,280	200,000	50,000,000
Commercial PPO/POS (%)	47.5	35.8	0	100
Commercial HMO (%)	24.3	24.7	0	75
Medicare (%)	11.4	9.9	0	25
Medicaid (any) (%)	16.4	23.1	0	85
Other (%)	0.4	1.3	0	5
Length of time beneficiary stays with organization (years)	4.9	2.7	2	10

Table 1. Screener survey demographics

Results of remaining screener survey questions for <u>interviewed payers</u>	% of respondents	
Organization has official health technology committee (N=13)	Yes	50.0
	No	42.9
	Not sure	7.1
Organization as an adopter of new health technologies (n=13)	Early adopter	7.1
	Early majority adopter	28.6
	Late majority adopter	64.3
Level of familiarity with <i>all types</i> of pharmacogenetic testing	Very familiar	7.1
	Moderately familiar	35.7
	Somewhat familiar	42.9
Level of management of pharmacogenetic testing relative to other health plans (n=13)	Slightly familiar	14.3
	Highly managed	7.1
	Moderately managed	28.6
	Somewhat managed	28.6
	Slightly managed	28.6
Level of familiarity with preemptive pharmacogenetic testing	Very familiar	7.1
	Moderately familiar	14.3
	Somewhat familiar	28.6
Preemptive pharmacogenetic testing discussed at P&T/medical technology meetings	Slightly familiar	28.6
	Not at all familiar	14.3
	Yes	23.1
	No	64.3
	Do not know	7.1
Formal approach to covering preemptive pharmacogenetic testing	Yes	15.4
	No, but in the process of putting one together and will have one in the next few years	46.2
Aware of clinical setting implementation of preemptive pharmacogenetic programs	No, and no current plans for the future	38.5
	Yes	15.4
	No	84.6

Table 2. Screener survey non-demographic data

Content Analysis

The majority of interviews lasted between 30 and 45 minutes, however one lasted 75 minutes. All respondents were given the opportunity to review the material before beginning the interview. The data from the interviews revealed three themes: clinical utility, economic utility, and policy development. These correspond closely with the pre-categorization of the discussion guide. Each of these themes had several sub-themes that will be discussed in detail below.

Clinical Utility – A world of potential with lacking clinical evidence

Payers believe there is potential value in having the pharmacogenetic data available for clinician decision making, but remain skeptical that this data is currently providing evidence that leads to better clinical outcomes for patients. This guiding idea on current clinical utility was a major barrier for widespread adoption and coverage in the payer mind. This concern seemed to come from a lack of objective outcomes level data:

"Now what needs to be tied to...is products A and C work better with this patient, than product B and D for patient two based on the genetic profile as far as outcomes improvement; survival, lower exacerbation, delay in correction, higher level of control, duration medicine." *Pharmacy Director #1 - Large National Health Plan.*

"If there's evidence...[the patient] should get preemptive testing, I'm willing to consider that... Drug reactions are the number one problem and drugs that don't work, drugs that cause more harm than good. I'm open to any of it, I just need to see the evidence." *Medical Director #1 - Large Regional Health Plan*

Many saw pharmacogenetic testing as something that would become standard practice when prescribing medications in the future, but expressed doubts it was going to become pervasive in the next five years.

There were four sub-themes identified under the main theme of clinical utility: potential value of pharmacogenomics, CPIC and actionability, types of clinical data needed, and testing versus monitoring. The “potential value of pharmacogenomics” was asked explicitly to some participants while others offered up their opinion without prompt. Adding to what was

aforementioned; payers see potential value to both patients and the health system but remain apprehensive.

"Tremendous potential, tremendous potential to help us much better refine who we give drugs that often have to be targeted for large populations with a fair amount of variability and drug response. But that being said, at the present time they are relatively low on the value scale." *Medical Director #2 - Drug Benefit Collaborative with medical policy management*

Value was also subject to the type of pharmacogenetic testing payers were using as a basis for their answer. While germline pharmacogenetics, and the pharmacokinetic and pharmacodynamic properties affected by genetics, was the focus of the interviews, payers frequently referred to the companion diagnostics associated with cancer drugs because they were more familiar with them. In fact, several payers made it clear that they desired a test that would provide them with yes or no decision on the reimbursement of a test, "We're looking for a test where we can make the physician accountable, either a yes or a no. Not something that there is a 70% likely response versus a 40% likely a response" *Medical Director #4 - Large National Health Plan*. This led to the observation that many payers were unaware of pharmacogenetic testing outside of scope of companion cancer diagnostics, and as such their expectations were somewhat out of step with the information these tests could provide.

The second subtheme, "CPIC and actionability", focused on payers reactions to the work of this organization and how the data it generates could be used in pharmacogenetics. Interestingly, almost all payers were unfamiliar with CPIC and PharmGKB and the corresponding rating scales and guidelines being developed and payers were pleasantly surprised

by the work being conducted. However, the previous discussion about the ability to make a yes or no decision based on these tests was reiterated in responses to the perceptions of CPIC. Multiple payers used the term "gray area" to describe the lack of clarity on making a yes or no decision with these tests.

"The challenge is if it's A, then can I say, yeah, it should be built in policies; if it's D, then I'm gonna say I'm not gonna cover this. But if it's B or C, I can't make a – I can't enforce a decision or a policy around that. So, no, this is – it might help physicians guide, but, again, it's a guidance and it's not something that a payer can definitively use to make a decision on. That's the challenge."

Pharmacy Director # 5 - PBM w/ medical policy

Given the lack of current use in coverage decision-making, CPIC guidelines were viewed mostly favorable in the context of their incorporation into the electronic health record (EHR). Interviewees felt that CPIC could provide incremental benefit by guiding prescribing.

"If you have a particular drug where a test said this (medication dosage) needs to be reduced, this is not just based on – I would speculate to say that this is compelling data. Those things can be built in as alerts. The electronic record, dysfunctional as it is, can be useful for that." *Medical Director # 3 - Medical group offering insurance*

An unprompted discussion also occurred with several payers on the similarities of CPIC with others such as the National Comprehensive Cancer Network (NCCN) guidelines for cancer treatments. Payers communicated that expanding the breadth of their (CPIC) work could increase their credibility, but stopped short of saying they would reimburse based on these guidelines.

"They (NCCN) started creating interest as far as should you cover this, should you not cover that, we rate this one a 2A, we rate this one a B. They have different ratings for the drugs. That really hadn't happened in a long period of time at all. I think that, that model could be used in something like this." *Medical Director # 3 - Medical group offering insurance*

The next sub-theme “clinical data” specifically focused on the kinds of clinical data that would be useful to payers and stemmed from previous literature suggesting that the RCT may be an unnecessary financial burden, particularly for previously approved and post-marketed drugs. These discussions provided a wide array of responses:

"I quite frankly do think you need the randomized control trials. Those clinical reports may be helpful. If you're going to do this, it really depends on the disease process in terms of that. You have to establish an outcome." *Medical Director #4 - Large National Health Plan.*

"You almost wonder if the best way to do this is in some kind of real-world type of population based study where you test a large group of people and then look retrospectively to see if you can then document a rationale for maybe a drug problem or a failure to respond they had in the past." *Medical Director #2 - Drug Benefit Collaborative with medical policy management*

The number needed to “test” or NNT calculation was a topic frequently brought up by payers without any explicit mention of the topic. A NNT is traditionally known as “number needed to treat” but in this case, interviewees shifted it to be number needed to “test”. More specifically payers defined this as the number of pharmacogenetic tests needed to be

administered to avoid one additional adverse outcome. Payers made it clear that this was something that physicians, and themselves, will use frequently when evaluating the utility of a new treatment or technology.

"You know, again, like anything else, if five percent of the patients are avoided, I don't know if it's worth it. If 40 percent have a drug change or are avoided, depending on the cost of the test, it may be worth it. So, it's going to be the number needed to test, sensitivity, specificity, actionability." *Medical Director #5*
- Large Regional Plan

Some payers also questioned the notion that doing an RCT on only patients who are known to respond would only help those patients, citing a potential benefit for other patients where the drug works but maybe just not as well.

The last subtheme, “testing vs. monitoring”, under the main theme of clinical utility was more inductive in nature as it developed naturally from many of the discussions with interviewees. The debate was one that compared the standard of care for clinical prescribing; dosing and administering one product and waiting to see how the patient responds and if changes need to be made the physician adjusts and waits again, to the use of a preemptive pharmacogenetic test (or reactive) to guide potentially more accurate initial dosing... "If it's a very low cost drug you know, you try one and then maybe try another. Because one of the concerns was some of the testing is that it's going to lead you to maybe pick first line."

Pharmacy Director #6 - Large National Health Plan

This quote shows how payers viewed this testing through the lens of cost by type of drug. Again, the tests payers were most familiar with were the companion diagnostics for high priced

cancer drugs where no generic or low cost alternative exists. One payer challenged the applicability of preemptive pharmacogenetic testing and its benefit to patients by being available in the EHR at the time of initial prescribing...

"The question is, is that test going to delay intervention? We are waiting for the results. How long does waiting two or three days or a week for test results really going to impact outcome? So I don't know. I don't know that I am too concerned about the length of the test - or how long it would take to get the results of a particular test." *Pharmacy Director #7 - Large Regional Health Plan*

Economic utility – The cost burden of organization wide testing and issues in calculating downstream economic benefits

The importance of pharmacoeconomic research in this space is important, most likely as a result of the large upfront costs of widespread testing. Economic utility in healthcare typically refer to cost utility analyses and are considered in concert with a demonstration of clinical utility. There are no subthemes under this major theme as the discussion focused on the topic of the costs of widespread testing and what potential cost offsets could be realized from testing. The payers' familiarity with cancer diagnostic pharmacogenetic tests again seemed to guide their perspectives on this discussion. For example they cited a willingness to pay for a test that costs several thousand dollars when associated with an extremely high priced cancer drug.

"Okay, I'll spend a few hundred dollars or even a couple thousand dollars on a genetic test if it tells me the best way to handle a \$100,000 a year anti-cancer therapy. That's a no-brainer. Now, let's think about pharmacogenetic testing that you're going to apply to large populations. Theoretically, you don't have to do it

multiple times... Let's say it's even a ridiculously low, low price of 100 bucks. If I got a million members that I got to test, I just spent a (hundred) million dollars and I don't know what my return on that investment is going to be." *Medical Director #2 - Drug Benefit Collaborative with medical policy management*

As evidenced by this quotation, payers are either unaware or do not have the sufficient data that the potential economic utility behind the preemptive is the ability to avoid adverse drug events, and subsequent hospitalizations and additional medical procedures. As such the payers were probed on this subject. Still the payers can only conceptualize this idea because of a lack of exposure to that data.

"...if you are going to identify a responder knowing full well that six weeks down the road they may switch to something else, but now you know they are not because you know they are going to respond then yeah I could see some cost savings associated with that...If you know that patients are going to not develop a certain adverse event and therefore going to be more compliant on their therapy because it is better tolerated or they don't have to be hospitalized,... again I see that more as a cost benefit; but downstream though." *Pharmacy Director #7 - Large Regional Health Plan*

This perception of downstream costs being prevented was something that payers valued, but at the same time they find using these cost offsets difficult when making coverage decisions.

"Would we focus it on where we had potential risks either in preventable admissions or hospital readmissions and have offsets? Yes. I think when it trickles down through all that triage, to what's good for society and good for the patient to

get an earlier experience, I'm (going to) suggest probably funding and resources run out before we get to that level of compassion and empathy. Ideally, I think that's great, but I don't think that's real world." *Pharmacy Director #6 - Large National Health Plan*

Payers have demonstrated concern that testing large numbers of people will most likely strain their organization. Although they also speculate that they might realize some cost benefit in avoiding additional medical services from testing, the costs are secondary or downstream in their prioritization. They currently lack the information needed to predict how patients will use this technology, and thus the ability to make an accurate decision on who to cover.

Many payers also had concerns about potentially large upfront cost of the preemptive technology. To investigate this, payers were presented with a hypothetical price scenario in which a multi-gene preemptive pharmacogenetic test was double the cost of a single-gene reactive pharmacogenetic test, \$500 versus \$250. They were asked to consider whether that price difference was enough to deny reimbursement of the more expensive test if ordered by a physician to guide drug selection. All but one payer that was asked to speculate on this scenario concluded that the price difference was not large enough to deny reimbursement of the \$500 test.

"That's a good question. I think again the answer is yes because again, we're not selecting a small subset of the population saying, "Okay, on this subset I'm going to do the \$500 test instead of the \$250 test." You're committing yourself to doing a fairly substantial expense on a large number of patients. The problem you're going to run into there is again a big upfront cost for unknown value down the

road." *Medical Director #2 - Drug Benefit Collaborative with medical policy management*

This scenario was proposed to the payers as a hypothetical to investigate whether current approximate price differences between multi-gene and single-gene tests were substantial enough to affect decision making. The answer appears to be that it is not, and this might allow for some slow integration of multi-gene testing into the system.

Policy development – Population health and the role of other influential stakeholders

Influence from other stakeholders coalesces to provide the payer with another level of considerations beyond just clinical and economic data when evaluating pharmacogenetic testing. The policy development theme evolved from a variety of topics that contributed to the payer decision-making. Numerous subthemes were identified; many of these were drawn from an explicit line of questioning including the effect of CMS and the FDA on third-party payer policies, the stratification of beneficiaries receiving pharmacogenetic testing, and the role of active preemptive pharmacogenetic implementation.

The first subtheme “population health” developed more implicitly due to several particularly interesting conversations examining the potential utilization of preemptive pharmacogenetics as a standard preventive health screening. A recommendation from the U.S. Preventive Services Task Force was discussed as a potentially influencing widespread adoption and coverage of preemptive pharmacogenetics.

"The other way it could be is all plans and payers have annual refreshment and linkage to preventative health guidelines in quality metrics when it's used... If it ever became a part of an annualized preventative health guideline, published and

adopted and/or became a quality metric that will help you, then it would become, and we would pay for it." *Pharmacy Director #9 - Large Regional Health Plan - High proportion of Medicaid beneficiaries*

The concerns being communicated with regard to the high cost of organization or population wide testing, as discussed previously, allowed a probe into potential considerations to attenuate this barrier.

In light of the difficulties with population health widespread adoption, payers were asked to speculate on if they would consider the stratification of beneficiaries to those over a certain age or those with co-morbidities increasing their need for certain pharmaceutical products. This was met with variable response as some payers were willing to consider this as a possibility, while others found it difficult and potentially unethical to choose which beneficiaries might be offered such a technology.

"I think that if you have a patient that's 60 years old and they're relatively healthy, you may have already done this but you may decide that at that age 60, it's time that he has or she has this information in his file so the \$500 gets spent. I think that's going to be really up to the physician on how they view the patient. But I don't think we are going to go out and promote a multi-gene testing for everybody over 65 or everybody over 60 just because the consortium or the guidelines or whatever say that is the right patient for these." *Pharmacy Director #2 - Regional Health Plan*

"I don't think that we would ever do anything like that. I do not think that would be anything legal would ever allow... "Well, if you have these underlying

conditions then you can do a preemptive." If you don't, "Eh, so sorry. Until we develop something, we're not going to test you."... If there was requirements or guidance along those lines, then plans of course would be obligated to comply. That's more or less government taking a stand now." *Pharmacy Director #4 - Large National Health Plan*

The diversity in response to this question again demonstrates the level of uncertainty in this space. In concert with other levels of evidence, payers may be looking to an organization such as CPIC to provide them with information on patient types at a more granular level. One payer was particularly adamant about this concept...

"I think the consortium should really - and again I don't know if that is the intent of what they are trying to do, but I think the consortium should come together and say who should be eligible. At least not just the level of the test itself, but what type of patient, what level of risk, age and things like that." *Pharmacy Director #7 - Large Regional Health Plan*

Payers were probed on the level of influence that the Centers for Medicare and Medicaid Services (CMS) would have on how they went about developing policies for these technologies. As a starter to this conversation, payers were asked if they would consider doing a type of pilot study that CMS has used called "coverage with evidence development". This program allows products or services to be covered by CMS only in the context of an approved clinical study. These studies are conducted when CMS believes that evidence does not support coverage outside of the context of one of these well-designed clinical studies. Payers had mixed reactions to this type of program and the implementation with their own data. Some spoke highly of it and the

potential for CMS to disseminate their findings to the larger payer audience, "Very likely as a pilot we would look at something like that. We do a lot of pilots in conjunction with CMS."

Pharmacy Director #2 Regional Health Plan

Other payers would find the results of such studies from CMS valuable, and instinctively follow their lead...

"I think the learning from that kind of a program probably translates more into the potential that at some point down the road, the tests become part of the things like system pathways or guidelines...we've used CMS actions in the past that changed how we price drugs. I think we could certainly adapt our coverage criteria to if it becomes a standard of care..." *Pharmacy Director #8 - Regional PBM*

The influence of CMS decisions was an undeniable force in the wider adoption by the payers interviewed in this current research. Payers also stressed the impact that a Federal Drug Administration (FDA) approval of pharmacogenetic tests and inclusion on FDA product labels has on coverage decisions. A FDA label that includes a pharmacogenetic test provides substantial evidence to payers that the test provides an additional level of benefit to a (certain) patient above the drug itself. Some indicated that it would be an absolute necessity to have FDA labeling to be considered for reimbursement, "I think it's still going to have to be approved by the FDA. It has to be part of the product labeling. You don't see too many other ways around that."

Pharmacy Director # 5 - PBM w/ medical policy

The requirement of product labeling seems to be driven, in part, by the demonstration of efficacy for products designed for a specific mutation, predominantly somatic.

There was skepticism from several payers on the willingness of the pharmaceutical industry to support pharmacogenetic testing. The skepticism was based in the view that the industry does not realize as much a financial benefit from the sale of drugs in a smaller, more directed population.

"You would think that the pharmaceutical company would come out with it but they don't because they want it to be used in everybody and not just specific patients." *Pharmacy Director #2 - Regional Health Plan*

Tying in the previous subtheme and role of the FDA, one payer provided an interesting insight into future drug development...

What we're hoping to see...before the drug even is allowed to come to market, is suggesting or I guess requiring that manufacturers have some sort of companion diagnostic or predictive test that's going to show whether the drug will work on a given patient. Then, you could probably price your drug more predictably with the expectations of success. I would think they would be in favor of it. *Pharmacy Director #8 - Regional PBM*

Payers also showed some inherent concern that if a pharmaceutical company were to go about developing drugs in much smaller patient populations that they would naturally raise prices to compensate for the lost revenue from treating fewer patients.

"I think they're going to be very cognizant of it as a concern we all have of drugs that are targeted. Having drugs available for small target populations notoriously meant much more expensive so that the cost savings by targeting the drugs may

disappear because the drug prices will go up." *Medical Director # 3 - Medical group offering insurance*

To close out the policy development section, payers were asked about the information presented in the pre-read concerning the active implementation of preemptive pharmacogenetics, the last subtheme. Most payers were pleased that these academic centers had endeavored to pursue this implementation as most were positive on the future for this technology.

"I'd also like to see their data and how it's made a difference, and what specific entity, what diseases they treated, and what were the outcomes based on the choices that they've made. If you're going to proactively do this, tell me what your physicians did with that information. Did they actually change the medication, did they alter the dose of the medication, what were the outcomes, and was the patient discharged sooner or having a shorter length of stay?" *Medical Director #4 - Large National Health Plan.*

Payers believe these institutions can potentially provide a great deal of real-world data on meaningful outcomes that come from the implementation of such programs.

At the conclusion of the interviews, a brief survey was administered using nine likert-type items on a scale of 1 to 5, 1 = strongly disagree and 5 = strongly agree, to summarize some of the major concepts and drivers of payers perspectives on coverage of preemptive pharmacogenetics. All but one payer responded to the survey. The full results of this survey are found in Table 3 below.

Post-interview survey results on five-point Likert-type items (1 = strongly disagree to 5 = strongly agree)	Average score (n=13)
FDA labeling of pharmacogenetic information on approved drugs will impact my coverage decision.	4.6
Clinician adoption and the endorsement of medical societies for preemptive pharmacogenetic testing is/will be an important factor when developing coverage policies.	4.5
Pharmacoeconomic data and the demonstration of cost-effectiveness is/will be important in determining coverage decisions for preemptive pharmacogenetic testing.	4.4
Clinical value is/will be added when clinicians have access to pharmacogenetic data in the electronic health record (EHR) at the time of diagnosis and prescribing.	4.3
Adoption by CMS and other third-party payers would influence my organization to likewise develop coverage policies for preemptive PGx testing.	4.2
The clinical validity of the gene-drug pairs determined by CPIC makes pharmacogenetic testing more actionable for clinicians	3.8
The influence of preemptive pharmacogenetic testing on clinician decision-making is/will be an important consideration when evaluating coverage decision.	3.8
Preemptive pharmacogenetic testing will provide greater clinical value to the patient and clinician by testing hundreds of genetic variants prior to prescribing.	3.5
The constructing of reimbursement policies for preemptive pharmacogenetic testing is likely to be burdensome.	3.1

Table 3. Post-interview survey results

5. DISCUSSION

The examination of the third-party payer's perspectives on preemptive pharmacogenetics provided a diversity of viewpoints on several important topics with which the pharmacogenetic research community should be actively following. The proliferation of more objective outcomes studies from the use of pharmacogenetic testing is the desire of most payers. There is energy from many of these individuals that healthcare and researchers should pursue this, but they cite an inability to make decisions hampered by insufficient evidence. The economic perspectives, particularly on preemptive pharmacogenetics, focused on budget sustainability from widespread organization testing. Not only was the cost from large scale testing a concern, but the difficulty in predicting any potential downstream cost benefits was an issue. Although many payers speculated that the benefits were a real possibility, the ability to integrate that into coverage policies would prove difficult. Third-party payer decision making processes are driven by a myriad of forces including the role of both public and private entities. These forces produce an interesting layer of influence that should be considered in conjunction with clinical and economic data.

The stress placed on the development of further evidence of clinical utility was first and foremost with many payers. Many payers speculated on the future delivery of healthcare and how they thought this technology fit in, but they remained pessimistic on the timeline with which preemptive pharmacogenetics would see widespread adoption and utilization. The American

Society of Hospital Pharmacists (ASHP) 2016-2020 Pharmacy Forecast found that those pharmacists surveyed believed that 51% thought it very likely or somewhat likely that pharmacists in at least half of health systems will be providing treatment recommendations based on pharmacogenetics by 2020.⁴⁶ A recurring sentiment was that preemptive testing, or even germline testing more broadly, did not provide the payer with the appropriate information to make a coverage decision, in contrast to the somatic testing that targets specific mutations within the cancer. This is an inherent difference between cancer companion diagnostics and single-gene or multi-gene germline pharmacogenetic testing, and their use to the payer. Payers desire the "go" or "no-go" indication from a test, but germline testing provides a broader range of data covering multiple pharmacogenes and associated drugs in the case of multi-gene testing. The actionability of these results do indeed point to instances where the drug being administered should be replaced by another drug, in line with companion diagnostics, but in many cases this testing leads to the more accurate dosing of pharmaceuticals to avoid adverse events, and thus a decision to cover the drug in question or not would be nearly impossible.

This cautiousness or pessimism, in part, may stem from a lack of understanding in the developing field of germline pharmacogenetics and corresponding relevant evidence. The work of CPIC stood out to most payers as a positive step toward improving utilization. Payers found CPIC's work encouraging and similar to NCCN guidelines. Payers continued, however, to refer back to the idea that they need information that informs a "yes" or "no" decision to test. This is something that the NCCN guidelines contain, likely a reason for their belief and hope that CPIC would do the same. Language in the NCCN guideline for gastric cancer strongly recommends HER2 testing for those with metastatic disease at time of diagnosis.⁴⁷ Payers believe that providing guidance on prescribing and inputting this information in the EHR was positive, but

not specific enough to guide policy making. However, the current mission of CPIC is not to provide guidance on “when” or “who” should be tested, but rather what providers and patients should do with the results of the tests.

Payers want to see real-world outcomes data from patient populations or randomized control trials. When probing payers on the types of data they needed, a mix of responses ranging from only clinical trials to retrospective studies came out. Most wanted some sort of prospective design where the patient could be followed. The Brixner study described previously that used a prospective cohort propensity score matched to a historical cohort could serve as a methodological model for researchers outside of a traditional RCT.²¹ Payers control vast amounts of patient data and have the opportunity to pilot pharmacogenetic testing rather efficiently if needed or desired. However, payers had mix responses when asked if they would pursue something of this sort, as CMS did in their “coverage with evidence development” program. There was clearly no consensus on proactively moving into these types of studies.

Prospective studies could answer two questions that payers found to be crucially important: what is the benefit of testing and treating over treating and monitoring? And what is the number needed to “test” to realize a benefit in one patient? The first question stems from the assumption that using a potentially expensive test to dose very inexpensive generics, or having the test produce results showing that the patient should be administered a more expensive treatment first-line, without consideration of a cheaper generic, would ultimately lead to higher health care costs for the system. Advocates of preemptive pharmacogenetics would argue that a higher cost pharmaceutical (compared to a drug of lower relative cost) might actually be a cost-saving pharmaceutical because of its precision with the patient in question, thereby avoiding potential adverse events or numerous try and fail strategies with other medications. Large

prospective studies would provide the evidence needed to answer this question and the objective outcomes payers desire.

Answering the number needed to “test” question would provide an objective figure with which to evaluate specific pharmacogenetic tests. This type of data is particularly important for preemptive and germline pharmacogenetics because part of the benefit from this technology comes from avoidance of adverse events and potential re-hospitalizations. According to the interviewees, both physicians and payers find value in this type of information. Member hospitals of the PGRN community are implementing preemptive pharmacogenetic programs and have the opportunity to present information that could help answer some of these pressing questions. Current implementations of pharmacogenetics in clinical practice might be providing enough data to begin calculating NNT's within their patient populations.¹ Recent work by Tonk et al., describes some appropriate methodologies to evaluate measures of population impact from pharmacogenetic tests including the NNT, as well as a population attributable fraction (PAF).⁴⁸ The PAF indicates what proportion of adverse events would be eliminated if patients carrying a variant received a different treatment. These types of data provide strong assessments of clinical validity by predicting adverse events and its impact on broader population health.

The conversation around cost with the payers was consistent and focused on the cost of testing large swaths of the population, the associated upfront cost, and the unpredictability of downstream cost savings. Once again, payers used the cancer companion diagnostics to frame their responses. It was an easy decision for payers to spend several hundred or a few thousand dollars on a test for a drug that cost upwards of six figures, but outside of that it became much more tenuous. Payers indicated little focus on the actual downstream costs associated with preventing adverse events and re-hospitalizations. The variability in how payers evaluate

downstream costs is likely driven, in large part, by the type of organizations. Many traditional insurers indicated a one year time-frame for evaluations of costs, utilizations, and benefits. Recognizing how preemptive pharmacogenetics postulates its benefit, this time-frame of economic evaluation is unlikely to lend itself to positive conclusions. Those from more integrated systems, meaning some higher level of coordination among providers and payers, appeared more willing to move toward preemptive testing.

Stronger assessments of this information might facilitate the adoption of pharmacogenetics into those with value-based purchasing structures looking to avoid ineffective care.⁴ Concerns with when a patient and physician would actually use the data, and what cost offsets might be realized, was another reason for caution as payers evaluated this use. Most of the products or interventions presented to payers for evaluation are designed to address a particular disease state or certain condition, and thus can be prescribed in a treatment plan after an official diagnosis. Preemptive pharmacogenetics demonstrates its value prior to diagnosing and prescribing, but sometimes with an unknown time frame for utilization, and thus presents a challenging assessment of cost tradeoffs. Reactive pharmacogenetics alleviates the concern of paying for a test whose results might not be used for years, but the reach of most reactive tests is usually limited to the single pharmacogene in question for the treatment being prescribed and will likely be not be cost-effective as the price of all types of testing continues to drop. Relling and Evans note this coming crossroad when a decision must be made between a test that is ordered for one gene because of immediate actionability on a diagnosis and a test for genes that includes the former, but also provides genetic information for future diagnoses.²

To probe the topic of large upfront costs further the payers were asked to consider if they would stratify beneficiaries based on age or number of co-morbidities. This was also met with

variable response and hesitancy due to potential ethical or legal issues. However, the use of pilot programs as discussed previously might provide useful prospective information on what types of patient cohorts are benefiting the most from preemptive pharmacogenetic testing. If payers remain apprehensive to the widespread adoption, a strategy such as this could prove useful to gradually increasing the number of patients with pharmacogenetic data loaded into their EHR. However, this could be limited by the type of clinical decision support system employed at the site of care and subsequent usability of the data.

The conversation that implicitly developed and was suggested by several payers concerning the adoption of pharmacogenetic as a preventive health technology endorsed by the U.S. Preventive Services Task Force (USPSTF) was particularly interesting. Some payers suggested that achieving coverage through this course of action was more appropriate for this type of technology, although citing the stringent approval process. However, this is not completely unrealistic. The USPSTF is an independent body that was convened by the Agency for Healthcare Research and Quality.⁴⁹ Recommendations are frequently met with opposition from various clinical groups due to impacts on current practice. For example, a series of exchanges between editors and readers of the journal *Radiology* in 2010 demonstrated strong opinions and dissent on the change in recommendations of appropriate age for regular breast cancer screenings.⁵⁰ It is likely that something such as preemptive pharmacogenetic testing would be met with a similar form of resistance.

The number of preventive services covered expanded with the implementation of the Affordable Care Act in 2010. Some of these services are one-off screenings but many may require recurring screenings to work effectively. Multi-gene pharmacogenetic testing could potentially provide a screening with utilization for an indefinite time period, and thus not require

any re-screening. However, it is likely that even the largest multi-gene pharmacogenetic test will at some point in the future require expansion as more gene-drug relationships are discovered year by year. Whole genome sequencing would ensure the complete mapping of relevant pharmacogenes, but the current widespread implementation of this would be economically untenable.

The impact of CMS was briefly mentioned previously with regards to the “coverage with evidence development” but it is worth noting that payers do stay abreast of policy decisions from CMS and will make many of their own decisions in line with them. Payers also mentioned the importance of pharmacogenetic tests being included on the FDA label. When considering the functionality of a preemptive multi-gene pharmacogenetic test for germline mutations, making a coverage decision based on FDA labeling will likely be a more nuanced process. Almost 200 drug products driven by known pharmacogenes already contain pharmacogenetic data as part of their approved FDA label. Many of these labels, however, do not require pharmacogenetic testing for approval as we have seen in oncology drugs targeting a specific mutation. Again, this demonstrates the payer difficulty in dealing with the disconnect between the obvious yes or no decision and the presentation of pharmacogenetic data in the label as it applies to dosage and administration, precautions, use in specific populations, and adverse reactions. The inclusion of pharmacogenetic data on the majority of FDA labels, outside of the oncology space, does not provide payers with the appropriate level of evidence to make a similar decision. Exceptions include the drug abacavir, which can lead to a fatal hypersensitivity reaction in some patients, specifically mentions screening for the HLA-B*5701 allele before dose initiation.³³ Other medications such as clopidogrel, which has strong clinical support for diminished antiplatelet

effect in some patients, contains a boxed warning but does not specifically require testing prior to administration.

The evolution of policy development for pharmacogenetics is going to be an ongoing and fluid process, requiring tremendous input from sources both private and public. Truly widespread adoption of pharmacogenetic testing will require the work of academic researchers in communities such as PGRN and CPIC to provide that next level of evidence to guide policy decision making.

Future directions

The findings from this study provide the pharmacogenetic research community with several avenues for potential research opportunities. A greater number of prospective real-world population studies testing the impact of preemptive pharmacogenetic testing on measurable outcomes will provide the strongest evidence to facilitate greater adoption. This approach must also include an assessment of those “downstream” costs that payers referenced several times. This type of analysis is not top of mind for many of these decision makers, but as we move more towards value based healthcare, the importance of this type of data will become ever more relevant. Wade et al. stress the importance and role that genomic programs have in developing value-based and patient-centered healthcare.⁷ Several aforementioned methodologies have been described to evaluate pharmacogenetic tests in a manner that produces data that will be of greater interest to payers and policy decision makers, and should be pursued accordingly. Detailed and speculative economic modeling of the pharmacogenetic tests can provide an assessment of potential costs that could potentially be avoided. The granular identification of these costs can

then be applied to real-world studies improving the applicability and dissemination among various care settings.

Several opportunities exist to explore pharmacogenetics role in future health policy. Studying the potential role of the U.S. Preventive Services Task Force would serve as evidence for broad implementation of preemptive pharmacogenetics as a population health policy. Also, the shift towards value-based reimbursement structures might facilitate the adoption of more preventive measures and increase the reach of preemptive pharmacogenetics.

Limitations

The respondent self-selection to participate in the screener survey may suggest that they are more familiar with pharmacogenetics than the average third-party payer, or that their interest might bias their responses in some way. Although this bias would be impossible to ascertain, no biases were identified between those respondents who agreed to participate in the interview and those that did not when comparing responses on the screener survey. Comparability of data may have been reduced due to the different wording and sequencing of each interview. However, richness is gained through this by allowing each interview to gain its own coherence. Qualitative data always come with a question of the level of truth. In this case respondents had no incentive to provide responses that were anything other than accurate. It would be difficult to imagine a scenario in which the respondent personally benefited from providing untruthful data.

Conclusion

Third-party payer opinions of preemptive pharmacogenetic testing indicate a cautious optimism. Concern over the lack of objective outcomes available, an inability to assess economic

benefits, and the potential high costs from widespread testing are the central reasons for this caution. Payers are, however, encouraged by the efforts of organizations such as CPIC that are making the data that is available more actionable and the consortiums that are implementing pharmacogenetic interventions in real-world populations. Expanding reimbursement and exposure of pharmacogenetics to the medical professions should facilitate greater physician adoption and provide further opportunities to study associated outcomes in meaningful ways. This study should be viewed as a call to advocates in the pharmacogenetic research community, both clinically and socially, to continue the pursuit of work directed at addressing the needs described within.

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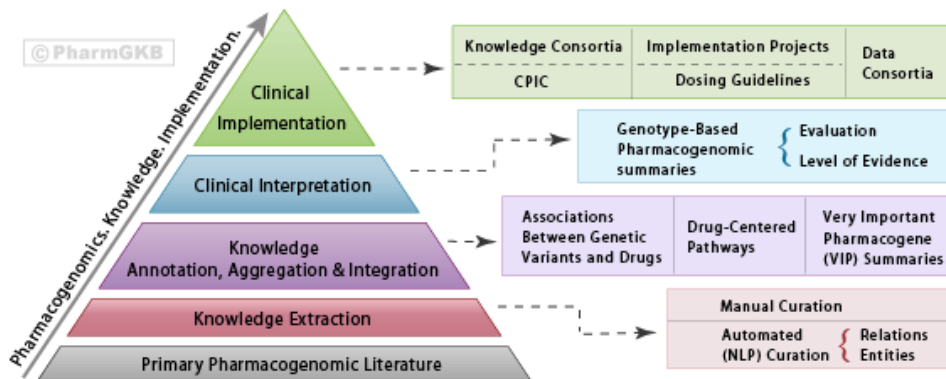
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LIST OF APPENDICES

APPENDIX A – PHARMGKB KNOWLEDGE PYRAMID AND ANNOTATION
LEVELS OF EVIDENCE

The PharmGKB Knowledge Pyramid



Clinical Annotation Levels of Evidence¹

1A	Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.
1B	Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size.
2A	Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.
2B	Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.
3	Annotation for a variant-drug combination based on a single significant (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.
4	Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

¹ PharmGKB: www.pharmgkb.org

APPENDIX B – FIRST INVITATION EMAIL FOR SCREENER SURVEY

Good Morning,

I hope this email finds you well. I have a research opportunity I think you would be interested in.

The research will be conducted in two parts, between the dates of **April 27 - May 18**. It will cover **preemptive pharmacogenetic testing**.

This portion of the research includes a brief online survey that will take approximately 5 minutes to complete. This research is being conducted for academic purposes so we will be asking some questions to ensure alignment with the research objectives.

Please follow the link below to begin the survey.

<<<qualtrics link>>>

Thank you.

APPENDIX C – ONLINE SCREENER SURVEY

Thank you for your participation in this research. You will be required to answer all questions but you may withdraw at any time. Your name and institution will always remain confidential.

By completing the survey/interview you consent to participate in the study.

1. Are you at least 18 years of age or older?
 - Yes
 - No (not eligible to continue)
2. Are you a...?
 - Medical director
 - Pharmacy director
 - Other, please specify _____
3. Approximately how many lives are covered on your plan?
4. What percent of your covered lives fall into each plan type?

	%
a. Commercial PPO/POS	
b. Commercial HMO/IPA	
c. Medicaid (any)	
d. Medicare	
f. Other, please specify _____	
	SUM = 100%

5. What is the average length of time a beneficiary stays with your organization?
6. Does your organization have an official health technology committee?
 - Yes
 - No
 - Unsure
7. **If answered yes to Q7....**have you served on this committee?
 - Yes
 - No
8. How would you rate your organization relative to other health plans regarding adoption/coverage of new health technologies?

Laggard	Late majority adopter	Early majority adopter	Early adopter	Innovator
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. Please rate your level of familiarity with **all types of** pharmacogenetic testing.

Pharmacogenetic testing	<ul style="list-style-type: none"> • Somatic pharmacogenetics - Identification of acquired genomic variants that influence response to drug , this type of pharmacogenetics is mostly relevant in malignancies to guide the choice of anticancer therapy 				
	<ul style="list-style-type: none"> • Germline pharmacogenetics- Identification of inherited genomic variants that influence alterations in a drug's pharmacokinetic and pharmacodynamics properties 				
	Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Very familiar
	○	○	○	○	○

10. Do you currently cover any pharmacogenetic tests or have you reviewed any in the past?

- Yes
- No

11. List any tests you know of that are currently covered: _____

12. How would you rate your organization relative to other health plans regarding your level of management of pharmacogenetic testing?

Not at all managed	Slightly managed	Somewhat managed	Moderately managed	Highly managed
○	○	○	○	○

13. Please rate your level of familiarity with **preemptive** pharmacogenetic testing.

Preemptive multi-gene pharmacogenetic testing	<ul style="list-style-type: none"> • Broad screening of multiple pharmacogenes • Pharmacologic effects of most medications are determined by multiple pharmacogene products • Test results are available in the medical record as a pre-prescription patient characteristic (independent of whether a patient is going to receive a high-risk medicine) • Array-based preemptive testing can include a large number of relevant pharmacogenes that cover most drugs that have a pharmacogenetic implication for dosing 				
	Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Very familiar
	○	○	○	○	○

14. Has preemptive pharmacogenetic testing been discussed at any of your P&T meetings in the last two years?
- Yes
 - No
 - Don't know
15. Does your organization have a formal approach to covering preemptive pharmacogenetic testing?
- Yes
 - No, but in the process of putting one together and will have one in the next few years
 - No, and no plans for the future
16. Are you aware of the clinical setting implementations of any preemptive pharmacogenetic programs?
- Yes
 - No

APPENDIX D – SECOND INVITATION EMAIL FOR IN-DEPTH INTERVIEW

Good Morning,

Thank you for participating in the first portion of the academic research on Preemptive Pharmacogenetic Testing. I am writing to invite you to participate in Part 2 of the research.

This portion of the research includes a 30-45 minute telephone discussion with Nick Keeling to be conducted sometime between Monday, May 23 and Friday June 3. Please contact <<<project coordinator>>> at (XXX) XXX-XXX ext. XXX OR email <<<project coordinator>>> at <<<email address>>> to schedule.

Please be certain to provide <<<project coordinator>>> with the telephone number we should call you at for your interview.

As a reminder, this study has been reviewed by The University of Mississippi's Institutional Review Board (IRB). If you have any questions, concerns, or reports regarding your rights as a participant of research, please contact the IRB at (662) 915-7482 or irb@olemiss.edu.

Thank you.

APPENDIX E – SEMI-STRUCTURED INTERVIEW GUIDE

Thank you for agreeing to participate in this study. My name is Nick Keeling and I am conducting interviews with payer decision-makers regarding their perspectives on pharmacogenetic testing, with an emphasis on germline, preemptive testing, and the coverage policies associated with this technology.

I also want to inform you that I'll be recording this interview so that I don't waste your time taking notes. Your name and the name of your organization will remain confidential. We expect this interview to take approximately 45 minutes. You may withdraw from the interview at any time. Do you have any questions for me before we begin?

Please refer to the pre-read information that was provided to you in the invitation email.

Pharmacogenetic testing	Broad definition: Pharmacogenetics is the study of how genes affect a person's response to drugs.
	<ul style="list-style-type: none"> • Somatic Pharmacogenetics – The study of how acquired genomic variants influence response to drug, this type of pharmacogenetics is mostly relevant in malignancies to guide the choice of anticancer therapy (typically a companion diagnostic)
	<ul style="list-style-type: none"> • Germline Pharmacogenetics - The study of how inherited genomic variants influence alterations in a drug's pharmacokinetic and pharmacodynamics properties
Reactive single-gene pharmacogenetic testing	<ul style="list-style-type: none"> • Single-gene test ordered one at a time when patient is likely to need a pharmacogenetically high-risk drug • Adopted into clinical practice first because of strong monogenic gene-drug associations • Decision based on likelihood that a high-risk drug will be prescribed for a patient or group of patients • Increased likelihood that the genetic test result is applied by the clinician because the prescribing decision is linked to performance of genetic test
Preemptive multi-gene pharmacogenetic testing	<ul style="list-style-type: none"> • Broad screening of multiple pharmacogenes • Pharmacologic effects of most medications are determined by multiple pharmacogene products • Test results are available in the medical record as a pre-prescription patient characteristic (independent of whether a patient is going to receive a high-risk medicine) • Array-based preemptive testing can include a large number of relevant pharmacogenes that cover most drugs that have a pharmacogenetic implication for dosing
Clinical Pharmacogenetics Implementation Consortium (CPIC)	<ul style="list-style-type: none"> • Assesses clinical validity (the ability of the test to differentiate between responders and nonresponders, or to identify patients who are at risk for adverse drug-reactions) of gene-drug pairs to determine those that are clinically actionable • These guidelines adhere to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines • CPIC recommendations are in four levels: A, B, C, D <ul style="list-style-type: none"> ○ A - Genetic information should be used to change prescribing of affected drug ○ B - Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely

	<p>likely to be as effective and as safe as non-genetically based dosing</p> <ul style="list-style-type: none"> ○ C - There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics convincingly makes no difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. ○ D - There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed. <ul style="list-style-type: none"> ● There are currently 41 gene-drug pairs that are listed level A. ● Gene-drug pairs are considered for several reasons: <ul style="list-style-type: none"> ○ Actionable in professional society guideline ○ Nominated by CPIC member or outside advocate like FDA ○ PharmGKB annotation level 1A, 1B, 2A, 2B <ul style="list-style-type: none"> ▪ PharmGKB is a pharmacogenomics knowledge resource managed by Stanford University that focuses on genotype-based summaries of the association between a drug and the gene variant ○ Mentioned in professional society guidelines but not actionable
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<p>Example of Clinical Decision Support from preemptive test CYP2C19 - citalopram</p> <p>(https://www.pharmgkb.org/guideline/PA166127638)</p>	<p>CDS Alert trigger Condition</p>	<p>CDS Context, Relative to Genetic Testing</p>	<p>CDS Alert Text (specific wording of the alert text may differ among programs)</p>
	<p>No CYP2C19 test on file and citalopram ordered</p>	<p>Pre-test</p>	<p>CYP2C19 genetic status may be predictive of an adverse reaction or poor response to this medication. A CYP2C19 genotype does not appear to have been ordered for this patient. Use of an alternative drug or dose may be recommended. Please consult a clinical pharmacist for more information.</p>
	<p>CYP2C19 UM and citalopram ordered</p>	<p>Post-test</p>	<p>This patient is predicted to be a CYP2C19 ultrarapid metabolizer and may be at an increased risk of a poor response due to low plasma concentrations of citalopram. Consider selecting an alternative SSRI not extensively metabolized by CYP2C19. Please consult a clinical pharmacist for more information.</p>
	<p>CYP2C19 EM or IM and citalopram ordered</p>	<p>Post-test</p>	<p>No CDS</p>
	<p>CYP2C19 PM and citalopram ordered</p>	<p>Post-test</p>	<p>This patient is predicted to be a CYP2C19 poor metabolizer and may be at an increased risk of an adverse reaction due to elevated citalopram plasma concentrations. Consider a 50% reduction of the recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. Please consult a clinical pharmacist for more information.</p>

<p>Implementation of preemptive pharmacogenetics in healthcare settings</p>	<ul style="list-style-type: none"> • Pharmacogenomics Research Network (PGRN) formed the Translational Pharmacogenetic Program (TPP) <ul style="list-style-type: none"> ○ Implement routine, pharmacogenetically based prescribing within diverse health-care systems • Vanderbilt University Medical Center (VUMC), Mayo Clinic, Mount Sinai Medical Center, St. Jude Children's Research Hospital, University of Florida, and the University of Chicago have all implemented programs using a preemptive pharmacogenetic approach • VUMC PREDICT program - 5 year retrospective study of 52,942 medical home patients found that 54% of patients were exposed to at least one medication with a known pharmacogenetic response. 383 adverse events were hypothetically avoided. • St. Jude Children's Research Hospital - currently 7 genes coupled with 17 high-risk drugs with upwards of 55 corresponding clinical decision support prescribing guidelines. Approximately 3,500 patients enrolled to date • The University of Chicago - "1,200 Patients Project" - As of 2014, 812 patients enrolled and 608 genotyped. Developed a genomic prescribing system using red (high-risk), yellow(caution), and green (favorable) lights. At 268 clinic encounters, 86% of physicians accessed the GPS with 100%, 72%, and 20% click frequencies for the respective signals • Other preemptive pharmacogenetic implementations <ul style="list-style-type: none"> ○ Inova Health System MediMap™ PGx Test offered to all newborns currently and expanding to all ages soon ○ Northshore University Health System (teaching affiliation) <ul style="list-style-type: none"> ▪ Currently testing pharmacogenes corresponding to 13 drugs
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Introductory questions:

1. Please briefly describe to me your decision making role at your organization. Does your organization have a medication technology/tech assessment committee? How often do you meet?
2. What is your organization's approach to the movement of precision medicine? Is this something that is discussed regularly?
3. What are your current perceptions of the market for pharmacogenetic testing?
 - a. How would you define value for a pharmacogenetic test?
4. How does the evaluation of a pharmacogenetic test differ from other types of health technology? Or does it?
5. How often does your medical technology committee evaluate a new pharmacogenetic test?
6. What evidence does your medical technology committee consider when evaluating a pharmacogenetic test?
 - a. What facilitators and barriers are there to covering pharmacogenetic tests?
7. What is the budget impact of this type of technology? Explain to me if your organization has experienced any budget / financial issues with paying for pharmacogenetic testing.
 - a. Do you currently contract with a major laboratory for these types of testing? (LabCorp, Quest, etc)

Clinical Validity and Utility of Pharmacogenetic Testing

11. Were you aware of the work from CPIC prior to this interview? What impact does this have on your assessment of the clinical validity of pharmacogenetic testing?
12. What type of trial use or data would be most helpful in the decision-making process for your med tech committee? Is the RCT still the "gold standard"?
 - a. **Probe:** Issues with the RCT (affects outliers more and thus incremental benefit appears small in large samples, ethical issues with knowingly giving drug to a non-responder)
 - b. **Probe:** Retrospective studies of before and after preemptive implementation?
13. How do you define clinical utility for pharmacogenetic tests?
 - a. **Probe:** Ability to prevent adverse events more quickly, prescribing the right drug the first time.
14. In the absence of an RCT, what other types of evidence would you consider most influential in policy development?
 - a. **Probe:** Better outcomes, change in prescribing, cost-effectiveness, society guidelines?
 - b. Would you consider CPIC guidelines evidence of clinical utility?
15. What impact could preemptive genetic testing have on patient outcomes?
 - a. Is this different than the reactive/point-of-care pharmacogenetic testing method?

Perception of Value and Cost Factors Associated with Pharmacogenetic Tests

16. Have you reviewed any pharmacoeconomic data on pharmacogenetic testing?
17. What economic impact do you see preemptive pharmacogenetic testing having on your plan?
Probe: A well-known pharmacogenetic assay that tests for 231 genes related to drug metabolism is approximately double the cost of a single gene test.
18. Do you believe preemptive pharmacogenetic testing is a preventive technology?
 - a. Discuss your thoughts on the role of preemptive pharmacogenetic testing value-based payment environment.
 - b. What economic drawbacks can you see from this?
19. Are you familiar with the prices for any pharmacogenetic tests that are currently available, either multi-gene or single-gene assays?
 - a. **Probe:** Provide info that multi-gene assay is \$560 vs. single-gene of \$225
 - b. **Ask if familiar:** Is there a price where you would consider adopting preemptive pharmacogenetic testing more readily? Or does price even matter (i.e. more clinical)?

Coverage and reimbursement issues for pharmacogenetic testing

20. Does your organization approach coverage policy for somatic pharmacogenetic testing (companion diagnostics) and germline pharmacogenetic testing (pharmacokinetics) differently? What are the factors?

- a. Cost of associated drug? Severity of the underlying disease for pharmacogenetic-guided treatment? Potential severity of the adverse effect?
21. Discuss what the coverage and reimbursement decision-making process for a preemptive pharmacogenetic test would look like.
- a. How would the potential time gap between administering a preemptive pharmacogenetic test and clinical utility have an impact on coverage policy?
 - b. Discuss your thoughts on restricting access to sub-sets of beneficiaries that might realize positive outcomes sooner than others from pharmacogenetic testing.
 - c. Is determining coverage of preemptive testing more complex than reactive?
 - d. Is there a certain number of actionable gene-drug pairs or disease areas that need to be covered by the test to make it reimbursable?
22. What is the average amount of time a beneficiary spends with your plan?
- a. What implications might the time-gap have on policy development?
23. Are you familiar with the CMS program called "coverage with evidence development program" to assess the clinical utility of the test in practice?
- a. Has your organization ever addressed this approach or would this be considered?
24. Does the utilization of preemptive pharmacogenetics in practice (Vanderbilt, St. Jude, U of Chicago, Inova Health, etc) have an impact on your decision to cover or not?

That is all the questions I have for you today. Would you like to add anything to our discussion on preemptive pharmacogenetic testing or pharmacogenetic testing more generally?

If you have any further questions about the study feel free to reach to me. My email is njkeelin@go.olemiss.edu. Thank you for your time.

APPENDIX F – POST-INTERVIEW SURVEY

Please indicate your level of agreement or disagreement with the following statements on the following scale.

Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
○	○	○	○	○

1. The clinical validity of the gene-drug pairs determined by the Clinical Pharmacogenetic Implementation Consortium (CPIC™) makes pharmacogenetic testing more actionable for clinicians.
2. Clinical value is/will be added when clinicians have access to pharmacogenetic data in the electronic health record (EHR) at the time of diagnosis and prescribing.
3. The influence of preemptive pharmacogenetic testing on clinician decision-making is/will be an important consideration when evaluating coverage decision.
4. Preemptive pharmacogenetic testing will provide greater clinical value to the patient and clinician by testing hundreds of genetic variants prior to prescribing.
5. Pharmacoeconomic data and demonstration of cost-effectiveness is/will be important in determining coverage decisions for pharmacogenetic testing.
6. The constructing of reimbursement policies for preemptive pharmacogenetic testing may be burdensome.
7. Clinician adoption and the endorsement of medical societies for preemptive pharmacogenetic testing is/will be an important factor when developing coverage policies.
8. FDA labeling of pharmacogenetic information on approved drugs will impact my coverage decision.
9. Adoption by CMS and other third-party payers would influence my organization to likewise develop coverage policies for preemptive pharmacogenetic testing.

VITA

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EDUCATION

B.A., Economics, University of Mississippi, May 2011

B.M., Vocal Performance, University of Mississippi, August 2010

RESEARCH EXPERIENCE

Research Assistant, August 2015 – Present

St. Jude Children's Research Hospital

Patient Safety

TEACHING EXPERIENCE

Teaching Assistant, 2014 – 2015

University of Mississippi

Courses: Pharmacy Ethics, Pharmacoeconomics

HONORS AND FELLOWSHIPS

MME Fellow Grant Recipient – University of Mississippi Department of Pharmacy Administration - 2016

Phi Kappa Phi Honor Society – 2015 initiate

Rho Chi Pharmacy Honor Society – 2015 initiate

PUBLICATIONS AND PRESENTATIONS

Keeling N, Nunna S, Crumby A. Cost-Effectiveness of Once Daily Dolutegravir versus Twice Daily Raltegravir as First-Line Antiretroviral Therapy in HIV-Infected Adults in the US.

International Society of Pharmacoeconomics and Outcomes Research. Montreal, QC, Canada

May 2014.

