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A SUSTAINABLE FUTURE IN THE IMPLEMENTATION OF  
CLINICAL PHARMACOGENOMICS

A Dissertation  
presented in partial fulfillment of requirements  
for the degree of Doctor of Philosophy  
in the Department of Pharmacy Administration  
The University of Mississippi

by

NICHOLAS J. KEELING

December 2019

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## ABSTRACT

**Purpose:** The sustainability of clinical pharmacogenomics requires further study of clinical education on the topic, its effects on clinical workflow, and the responsibilities of different providers for its delivery. Tools from the discipline of implementation science were utilized herein to help achieve the purposes of the three studies. The broad purpose of this dissertation is to advance the work of clinical pharmacogenomic implementation through a more rigorous convergence with implementation science.

**Methods:** Three studies constitute the whole of this dissertation. The first is a scoping review that provides a broad characterization of the methods utilized in available peer-reviewed literature focusing on provider use of and experience with using pharmacogenomics in practice or the study setting. The second study used semi-structured in-depth interviews to elicit strategies and perspectives from leadership in current implementation programs using the Consolidated Framework for Implementation Science (CFIR) Process Domain. The third used a cross-sectional quantitative survey with experimental vignettes to explore the potential for pharmacist-physician collaboration using newly developed implementation science outcomes.

**Results:** The scoping review included 25 studies, with many focused on the interactions of providers with clinical decision support systems and adherence to therapeutic recommendations represented. Results from the interviews were extensive but several highlights included a focus on understanding pharmacogenomic use prior to implementation, high-touch informal communication with providers, and the power of the patient case. The survey analysis revealed

that the primary care physicians believe that it is more appropriate to deliver clinical pharmacogenomics when a pharmacist is physically located in a clinic and is responsible for managing and modifying a drug therapy based on these results.

**Conclusion:** These three studies further the convergence of implementation science and genomic medicine, with particular focus on pharmacogenomics and the foundational concept of implementation science, sustainability. The scoping review should provide future researchers with a landscape of available and previously used methodologies for interventional pharmacogenomic studies. The interview results will help new implementers of pharmacogenomics steer around avoidable hurdles or make them easier to address. The survey results showcase the potential for pharmacist-physician collaboration in clinical pharmacogenomics.

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## INTRODUCTION

### **Precision medicine origins**

In early 2015, the announcement of the Precision Medicine Initiative would make *precision medicine* a nearly ubiquitous term across all sectors of the health care industry pushing an innovative message. This program has since been renamed the “All of Us Research Program”, and focuses on gathering the genomic, environmental, and lifestyle data on over one million Americans across diverse populations ([allofus.nih.gov](http://allofus.nih.gov)).<sup>1</sup> This National Institutes of Health (NIH) program represents one of the largest efforts to integrate rapidly progressing genomic technologies into research and accelerating medical innovation and breakthroughs. However, this program has been preceded by numerous academic, industry, and government driven initiatives pushing this science forward into clinical care.

Prior to genomic information being utilized in clinical care there have been several public initiatives created to curate this complex data. One of these is ClinVar, a freely available archive of information at the National Center for Biotechnology Information (NCBI) on the relationships between genomic variants and phenotypes.<sup>2</sup> A second program, ClinGen, was launched in 2013 to address the clinical relevance of the genomic variants identified in ClinVar.<sup>3</sup> With the majority of the 80 million genetic variants identified in the human genome having no clear link to human disease or health implications, it was discovered that clinical laboratories may be interpreting the importance of variants differently, potentially leading to inappropriate medical interventions. ClinGen is focused on improving how new genomic discovery is used in clinical care by

increasing communication between research institutions. The central questions for the project were: “Is this gene associated with a disease?”, “Is this variant causative?”, and “Is this information actionable?”.

Concurrently developed through requests from the National Human Genome Research Institute (NHGRI) was the Clinical Sequencing Exploratory Research (CSER) program. This program was initiated to create the evidence base for what appear to be the key challenges of *actually* integrating genomic sequencing methods into clinical care across both adult and pediatric patients.<sup>4</sup> Several of these investigation sites focused cancer patients or those at an increased risk of developing cancer, while others focused more on self-reported health patients and those with other medical conditions. Not only was the CSER interested in addressing the issues of generating genomic data and conducting the subsequent analyses, they also dedicated resources to understand provider level education factors, patient and family communications, the clinical utility of testing (ClinGen’s “Is this information actionable?”) and the ethical, legal, and social implications (ELSI). The ELSI has become an important area of focus in the NHGRI’s 2020 strategic vision for genomics (<https://www.genome.gov/27570607/strategic-planning-overview/>).

While these aforementioned projects represent more sweeping initiatives related to genomics, there also exist several other collaborative or consortiums focused on more specific issues. The Electronic Medical Records and Genomics (*eMERGE*) Network was formed in 2007 and focused on exploring how the electronic health record (EHR) may be married with the growing genomic data repositories, and how clinically relevant variants could be made actionable through this to support clinical decision support.<sup>5</sup> The work of *eMERGE*’s diverse network allows for consolidation of genomic data across sites for comparison to already existing,

longitudinal phenotypic data from the EHR. This can lead to the discovery of novel variants in the population, compared then to existing variants, leading to a final determination of those clinically actionable and in need of being placed in the EHR.

### **Genomic medicine implementation and pharmacogenomics**

The Implementing Genomics Into Practice (IGNITE) Network formed in 2013 takes the logical next step in preparing the clinical environment for the inevitability of integrating new patient-level genomic data.<sup>6</sup> Health care research has been steadily moving towards an emphasis on generating more real-world evidence of new health interventions. For real-world evidence to actually exist, the practitioners and researchers the intervention affects must be effectively prepared to use it. The work of IGNITE builds on the *eMERGE* work through point-of-care integration of the data into the EHR and use of CDS tools to guide the clinician. The challenges to genomic medicine most targeted by the IGNITE group include those that can be classified a T3 and T4 translational research practices.<sup>7</sup> These include improving patient outcomes and care quality, evaluating the cost of different testing approaches, enhancing provider engagement and education, and addressing the policy challenges of testing reimbursement and payer support.

The diversity of genomic technologies is both a barrier and facilitator to implementation in clinical care. Genomic sequencing has accelerated with the development of massively parallel sequencing techniques, and includes sub-applications of the technology such as exome sequencing and multigene panels.<sup>8</sup> Exome sequencing includes only those regions of the genome that code for proteins (exons), and has been used more extensively in past years because of its lower cost technical ability, yet there are limitations related to inadequate sequencing depths and identifying genotypes that exist at specific single-nucleotide polymorphisms or SNPs outside of

the exons.<sup>9,10</sup> Multigene panels are typically aimed at specific genes where clinically significant variants are known to exist and may be expressed in certain patient. One of the most common historical uses of genomic sequencing has been the diagnosis of rare Mendelian disease, and is typically indicated for those patients with a suspected monogenic disorder.<sup>11</sup> These diagnoses can help clinicians develop treatment plans and patients make personal decisions on family planning. Additional applications can include screenings of partners prior to the conception of offspring and genetic predisposition screenings for information on predictions of disease risk based on genetics as well, giving clinicians another layer of phenotypic data for the patient.

Included in this last type of predisposition screening are predispositions related to medication efficacy and safety based on genomics, which has become known as pharmacogenomics. This will be the focus of the remainder of this dissertation. Pharmacogenomics works through the identification of variants in the genome that exert some influence on the effects of medication.<sup>12</sup> Variations can occur in the absorption, distribution, metabolism, excretion (ADME) genes, those that affect the medication's pharmacokinetics or the pharmacodynamic genes that modify the target or pathway of the medication in the body.

The pharmacogenomic implications for a patient can apply either to those variants somatically acquired, typically cancer or infectious disease, and variants originating in the germline DNA, that sequence with which you are born. Pharmacogenomics has been the leading the way in operationalizing the benefits of precision medicine. A seminal systematic review in 2001 explored the role for pharmacogenomics in potentially reducing the number of adverse drug reactions, a leading cause of death then and still today.<sup>13,14</sup> Their results showed about 60% of drugs cited in ADR studies at the time had at least one drug-metabolizing enzyme that was genetically encoded with a variant known to cause poor metabolism.

Metabolism classification for these enzymes encoded in the germline has become a key action item from patient's specific diplotypes, one haplotype from each parent.<sup>15</sup> The CYP450 gene superfamily was an early pharmacogenomic discovery and is involved in the metabolism of about 75% of commonly prescribed drugs.<sup>16</sup> The polymorphic drug metabolism enzymes associated with CYP450 genes are prone to variations that ultimately affect how a drug's pharmacokinetics act upon the patient, and the subsequent safety and efficacy to the patient. The phenotypic definitions of the various metabolizer statuses recently reached consensus through work by the Clinical Pharmacogenetics Implementation Consortium (CPIC).<sup>17</sup> We will discuss CPIC in greater detail below. Standardization of these terms is crucial for the reporting and sharing of results across laboratories and EHRs. The final terms are created based on a combination of allele functional status, which include increase, normal, decreased, and no function.<sup>18</sup> The metabolizer terms include ultrarapid, rapid, normal, intermediate, and poor. Those of most interest clinically are the ultrarapid metabolizers, which include two increased function alleles or more than 2 normal alleles, and poor metabolizers, which include combinations of no function alleles and/or decreased function alleles.<sup>18</sup>

Genotyping of tumors or infectious diseases, also known as somatic testing, is another way pharmacogenomics has been operationalized in precision medicine.<sup>12</sup> An ideal state for 'precision medicine' might be circumstance where every medication based treatment is developed specifically for a biomarker(s) known to be causing the disease. Although not there yet, tumor biomarkers appear to be carving a path where companion diagnostic tests can be used to guide the decision to use a specific anti-cancer agent targeted to a specific mutation. This is intended to interfere with the tumor's function to inhibit growth and progression, leading to quicker resolution of the disease.<sup>19</sup> Some of the most well-known mutations are the HER2 target

for breast cancer, EGFR for non-small cell lung cancer, and BRAF for melanoma.<sup>20-22</sup> Germline pharmacogenomics also has a role in preventing adverse events for several commonly used chemotherapy agents that may require dose reductions or drug switches to avoid potentially devastating consequences. The TPMT, DPYD, and UGT1A1 genes are several that contain toxicity biomarkers variants.<sup>19</sup>

Movement towards implementing pharmacogenomics in clinical practice, similar to genomics more broadly, has been driven by academic medical centers funded from public resources such as the NIH. Early on, after the completion of the Human Genomic Project the Pharmacogenomics Research Network (PGRN) began receiving grants from the National Institute of General Medical Sciences to study how genetic variation contributes to interindividual differences in responses to medication.<sup>23</sup> The *eMERGE* network mentioned previously received grants from the NHGRI to dedicate part of their work to coupling the EMR with actionable pharmacogenomic data.<sup>24</sup> Since then the number of supported collaborative, consortiums dedicated to facilitating the implementation of pharmacogenomics have steadily grown. Two highly influential, and coordinated, efforts have been The Pharmacogenomics Knowledgebase (PharmGKB) and CPIC, which was briefly mentioned earlier. PharmGKB works through a process starting with extracting knowledge from pharmacogenomic literature on the associations between variants and drugs to determine those to be “very important pharmacogenes (VIP)”. These lead to pharmacogenomic summaries based on genotypes with different levels of evidence.<sup>25</sup> All this knowledge can then filter into implementation projects and also to CPIC, whose primary responsibility is to turn genotypes into meaningful phenotypes that a clinician can act on. Both PharmGKB and CPIC annotate their levels of evidence across the gene-drug pairs they have evaluated. The highest level of evidence for PharmGKB is level 1A,

which is defined as “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” ([pharmgkb.org/page/clinAnnLevels](http://pharmgkb.org/page/clinAnnLevels)).<sup>26</sup> CPIC has designated its levels for gene-drug pairs as either: A, B, C, or D. Level A indicates that “genetic information *should* be used to change prescribing of affected drug”, while level B indicates that genetic information *could* be used to change prescribing because alternatives are likely as effective and safe as non-genetically based dosing. Lower levels, C and D, indicated that there are no recommended prescribing actions ([cpicpgx.org/prioritization/#flowchart](http://cpicpgx.org/prioritization/#flowchart)).<sup>27</sup> CPIC uses these levels to prioritize their clinical prescribing guideline development, of which there are 35 currently published and more in progress. These guidelines are not intended to help clinicians order a test, rather how to use the results when they become available. More recently, the Pharmacogene Variation (PharmVar) consortium was formed to address the need for a more systematically maintained pharmacogene nomenclature (or language) system as the number of variants discovered continues to grow.<sup>28</sup>

The work of these organizations has served as a crucial foundation for the implementation of pharmacogenomics in the sphere of academic medicine. Efficient and appropriate pharmacogenomic implementation, with a mindset of sustainability, should be the ultimate goal of using public resources to fund discovery such as this. Two of the networks discussed, IGNITE and eMERGE, are actively testing implementation strategies and sharing data. Additionally, PGRN organized the Translational Pharmacogenetics Project (TPP) in 2011 with the stated goals of: harnessing multidisciplinary team expertise and institutional investment, implement routine gene-based drug dosing and selection, and to identify the best implementation and dissemination practices to address remaining barriers.<sup>29</sup> Over a dozen metrics were reported



by the TPP covering everything from the triggers to prompting a test order to the estimated turnaround time, and the roles that different providers play in the implementation.

The IGNITE network set up an internal working group dedicated to pharmacogenomics in 2015.<sup>30</sup> This group set out with to engage both funded network sites and its affiliate members, some of which being non-academic. Measuring the impact of genotype-guided therapy on patient-related outcomes has become the central goal of the institutions involved. Spearheaded by the University of Florida, the group intends to share and disseminate data on effective and non-effective strategies from their individual projects, as well as metrics related to the health care costs involved in the strategy.<sup>30</sup> In this model, more pharmacogenomically-mature institutions have the ability to share their best practices with newer entrants into the science, thus updating prior beliefs and improving the efficiency.

Similarly to IGNITE, the *e*MERGE network initiated a pharmacogenomic specific project, *e*MERGE-PGx.<sup>31</sup> The design of this project was focused on a particular strategy of testing known as preemptive pharmacogenomics, that is, the genotyping or sequencing of a patient prior to diagnosis enabling first point-of-care actionability. This technique was already being implemented among some institutions; however reactive testing still remained the most utilized.<sup>32</sup> *e*MERGE-PGx had three objectives: sequence 84 proposed pharmacogenes in 9,000 patients likely to be prescribed an implicated drug within one to three years, integrate the clinically-valid results into an EHR with the appropriate decision support and assess the outcomes, and develop a repository for those variants with unknown significance back-linked to the clinical phenotypes in the EHR.<sup>31</sup> Early results from approximately 5,000 subjects showed 96.19% of samples had a CPIC level A actionable variant. These high probabilities were also found in an external validation cohort of more than 1,000 patients in a tertiary medical center. A

novel disease-drug association tool was developed to map drugs to distinct diseases, then pharmacogenomically annotated. Ninety-percent of the top 21 diseases in this population and more than 93% of patients could be treated with more than one medication with actionable pharmacogenomic information.

Many of opportunities afforded to the implementers of pharmacogenomics, and noted successes, were enabled by high levels clinical and leadership support at the institution, as well as extensive external funding. The next frontier in the implementation of pharmacogenomics is to address the unique challenges of implementation into ambulatory care settings. These include fewer financial resources, greater fragmentation, and a workforce less familiar with pharmacogenomics than those described in these numerous networks herein.<sup>33,34</sup> The Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics has weighed in, stating we must understand “what factors contribute to the success or failure of a genomic application within a *particular* setting” ([blogs.cdc.gov/genomics/2017/11/27/if-you-build-it/](https://blogs.cdc.gov/genomics/2017/11/27/if-you-build-it/)).<sup>35</sup> There will always be variability in any broadly defined setting, such as tertiary academic or primary care, but the differences between will typically exceed those within.

Given the breadth of diversity in the delivery of health care, approaching implementation of pharmacogenomics in new settings deserves the same level of scientific rigor that allowed it to progress to its current point. The growing field of implementation science may offer this rigor through its theories, methodologies, and frameworks.<sup>36</sup> The need for implementation science was born out of issues in both time it took clinical evidence-based practices to reach usage and the total proportion that ever did, average of 17 years and 50%, respectively.<sup>37</sup> Though its theories and constructs have applications in other industries such as technology or transportation, the original conceptualization for implementation science was health care.<sup>37</sup> A commonly used

definition of the science is “the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services”.<sup>37</sup> Implementation science is most commonly organized into five foundational concepts: 1) diffusion, 2) dissemination, 3) implementation, 4) adoption, and 5) sustainability.<sup>38</sup> These concepts are to be viewed as part of feedback loop with the achievement of sustainability leading to the ability to diffuse new ideas, behaviors, and practices. Effective implementation is at the center of these five concepts as each should be considered during the design process of bringing an evidence-based intervention or practice into usage.<sup>36</sup> As a relatively new science, it is not without its own set of challenges that must be overcome. Some of these include: a lack of common language (a continuing issue in genomics and pharmacogenomics), short-termism, and a lack of embedded evaluation plans. These last two have been highlighted for their application to this dissertation. Short-termism can parallel with the last ‘foundation concept’ of sustainability, and a ‘lack of embedded evaluation plans’ helps illuminate that not only are intervention outcomes important, but also the need to develop implementation-specific outcome measurements.

The foundational concept of sustainability has received increasing attention as one of the most important, yet more misunderstood concepts of implementation science.<sup>39</sup> In fact, recent work attempted to unify the discussion on sustainability through a paper on the development of a comprehensive definition.<sup>40</sup> Although commendable, in the spirit of Proctor et al. sustainability is likely more complex than only one definition.<sup>39</sup> How one defines sustainability in an individual study should be explicitly rationalized or come from a previous publication.<sup>39</sup> The contradiction between this and the just mentioned ‘lack of common language’ exhibit the complexities implementation science researchers are facing. However, this Proctor et al. paper

represents a seminal work to identify the most important issues for research in sustainability. A concept-mapping approach was used that are encompassed in three overarching domains: 1) an agenda unified through answering the high priority research questions on sustainability 2) methodology advancement for sustainability research 3) and advance infrastructure to support this research. These domains are characterized by 91 unique statements within 11 unique conceptual clusters within five larger clusters.<sup>39</sup>

Methodological advancement of sustainability will require the application of individual frameworks in study design and execution. A systematic review of the sustainability landscape revealed 62 publications where a unique sustainability approach was used. These include 32 frameworks, 16 models, 8 tools, 4 strategies, 1 checklist, and 1 process.<sup>41</sup> The obvious observation is that the selection of a framework or model can overload the researcher's choice-set. However, taking a high-level view of multiple disciplines can train the eye to identify where there are overlays in the needs of the discipline being applied to the sustainability framework, as well as ways in which the framework itself can address issues within its own parental discipline of implementation science.

The Dynamic Sustainability Framework (DSF) is a framework built around seven major tenets the authors recommend for explicit testing (Table 1) and a visual model (recreated in Figure 1).<sup>42</sup> The DSF was designed based on previous literature that put forth an alternative conceptualization of sustainability as a cyclical "change process" that provides adaptability in pre-implementation stages such as planning and organizational support rather than an outcome or metric of successful implementation.<sup>43,44</sup> Sustainability is further operationally defined in three more specific constructs: maintenance, institutionalization, and (infrastructure) capacity building.<sup>38</sup> The *sustainability planning model* operationalizes capacity building as both physical

and human infrastructures: structures and linkages, champions and leadership, resources, policies and procedures, and expertise.<sup>43,45</sup> The operationalization of capacity building as a human infrastructure is an important development for this dissertation.

Table 1. Tenets of the Dynamic Sustainability Framework

1	<ul style="list-style-type: none"> <li>• Interventions need not (and should not) be optimized prior to implementation</li> </ul>
2	<ul style="list-style-type: none"> <li>• Interventions can be continually improved, specific to each setting</li> </ul>
3	<ul style="list-style-type: none"> <li>• Ongoing feedback is essential and should be measured over time</li> </ul>
4	<ul style="list-style-type: none"> <li>• More diverse/complex populations does not mean an inevitable loss in benefit</li> </ul>
5	<ul style="list-style-type: none"> <li>• Strong ‘fit’ is essential, but it will likely change over time</li> </ul>
6	<ul style="list-style-type: none"> <li>• Organizational learning should be at the core</li> </ul>
7	<ul style="list-style-type: none"> <li>• Stakeholder involvement throughout all processes</li> </ul>

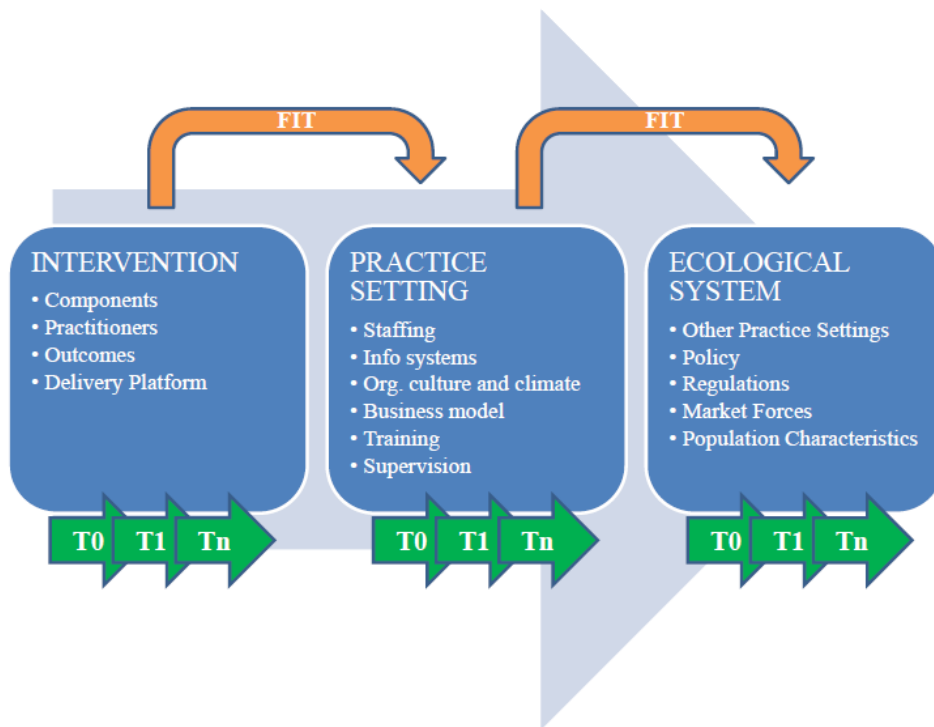


Figure 1. Recreation of the Dynamic Sustainability Framework

Highlighted throughout the DSF is an emphasis on ongoing adaption and evaluation of an intervention with the goal of continuous improvement to determine its optimal ‘fit’ across various ‘practice settings’. Designing implementations with a DSF-type mindset may make headways in addressing the previously mentioned, ‘lack of embedded evaluation plans’ challenge for implementation science. As part of this, valid and reliable outcome measurements for implementation research are being developed. A systematic review found 104 measurement instruments in a core set of outcomes previously identified: acceptability, adoption, appropriateness, cost, feasibility, fidelity, penetration, and sustainability.<sup>46,47</sup> Approximately two-thirds measured acceptability and adoption, with all others having less than 10 measurements. Psychometric strength and quality were also highlighted as being underdeveloped. In response, a follow-up study by some of the authors developed, and psychometrically assessed, three new measures with promising psychometric properties: Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM).<sup>48</sup> These measures are utilized in the manuscript and described in Section III.

Calls to begin cultivating a formal relationship between implementation science and precision medicine, as well as the learning health system, have been made in the past several years.<sup>49</sup> The National Academies of Sciences, Engineering, and Medicine recently held a workshop entitled “Applying an Implementation Science Approach to Genomic Medicine”. The report emphasizes a focus on methods to encourage wider participation from minority and disadvantaged populations, evidence building and clinical research done in parallel (aspects of a learning health care system), and a focus on genomic applications to improving population health.<sup>50</sup> The lack of implementation science frameworks in the National Institutes of Health’s grant portfolio for genomic medicine may be a contributor to these calls. From 2012 to 2016,

only 1.75% of genomic related grants included the formal use of an implementation science framework.<sup>51</sup> This equates to a total of four grants, all of which used the same framework, Rogers' Diffusion of Innovation.<sup>51</sup> This seminal work by Everett Rogers provided the field of implementation science with several key components of innovation diffusion including perceptions of the innovation itself such as compatibility, the degree of innovativeness in the adopter, the environment of the adopter and the systems in place in the environment, and lastly, the actual process of adoption.<sup>52</sup> Implementation science has built on the breadth of Rogers' ideas and created immense depth, as evidenced by the DSF, into each of these components, as well as creating new layers of breadth with frameworks such as the Consolidated Framework for Implementation Research (CFIR) which will be discussed below.<sup>53</sup> Rogers' original work in agriculture has been extrapolated to countless scientific disciplines and thus, this work, and others utilizing the discipline of implementation science, should be read not only as contributing to their specific fields but as important additions to the general pursuit of evidence-based scientific practice.

In addition to the lack of implementation science grants, the CDC's Public Health Genomics Knowledge Base was used to identify published literature where implementation science has been applied to genomics medicine. Although the findings showed a total of 283 articles published in 2014, the inclusion criteria did not specify that a formal implementation science approach be taken, rather that the studies "contributed to our understanding of the implementation of genetic/-omic testing...". In fact, what was discovered was that very few studies actually incorporated a theoretical framework from implementation science, any measure of sustainability, or capacity building (a key component of sustainability).<sup>38,54</sup>

Two working groups from IGNITE, Common Measures and Sustainability, recently put the field of genomics in more rigorous alignment with implementation science, and its foundational concept of sustainability.<sup>53,55</sup> The Common Measures group utilized the CFIR, one of the most robust widely used frameworks of implementation science.<sup>53</sup> This framework is composed of five domains containing 39 constructs or sub-constructs and was built from a large scale evaluation of available implementation science theories, with an end goal of producing a pragmatic way to improve this science. The CFIR now has its own dedicated website ([cfirguide.org](http://cfirguide.org)) which provides both quantitative and qualitative data collection tools, analysis methods, and interpretation resources.

Though the IGNITE work did not specify pharmacogenomics, many of the takeaways are logically applicable to it. The working group evaluated the 39 constructs of the CFIR for their contribution and importance to genomic medicine.<sup>45</sup> The 10 highest-ranking constructs were included in the final list, with the intention to develop data collection tools for the network. Table 2 provides a list of these constructs. The construct “patient characteristics” was included as high-priority although it is a non-CFIR construct. The authors found that the CFIR lacked “well-defined representation of patient-related domains”. While patients do represent a critical aspect of implementing a new intervention effectively, they believe that this impact is less influential than the clinicians and institutional leadership when it comes to initial implementation successes.<sup>45</sup>



Table 2. High-priority CFIR and \*non-CFIR constructs identified by IGNITE CMG

Knowledge and beliefs about the intervention	Self-efficacy	Implementation climate	Readiness for implementation	Relative Advantage
Cost	Engaging	Executing	Reflecting & Evaluating	Patient characteristics*

An effort was made to identify existing measurement tools for these 10 constructs, and to move forward with the development of novel ones where no existing measures had been developed. While many of the ‘patient characteristics’ sub-constructs had reliable and valid measurement tools already in place, most of the high-priority constructs from CFIR did not. This led to an initiative to create these measures, including the pre-implementation provider survey among others freely available in the IGNITE Spark Toolbox ([ignite-genomics.org/spark-toolbox/researchers/](http://ignite-genomics.org/spark-toolbox/researchers/)). The CFIR has also been used in other genomic-focused papers. For example, Lynch Syndrome screening is a condition that can raise the lifetime risk of developing colorectal cancer by as much as 4%, but has faced heterogeneous barriers to implementation that the authors believed implementation science, and the CFIR could address.<sup>56,57</sup> Though not an explicit test of the constructs, the paper focused on Lynch Syndrome matched relevant domains of the CFIR with potential applications for Lynch Syndrome, somewhat similar to the IGNITE work with the framework. The CFIR, and in particular the Process domain, guided the development and data collection of the study described in Section II of this dissertation. The Process domain of the CFIR contains four constructs (Planning, Engaging, Executing, Reflecting & Evaluating). The Engaging constructs is made of up of six sub-constructs (formally appointed implementation leaders, opinion leaders, champions, key stakeholders, innovation participants,

and external change agents). In their original work, the authors of the CFIR describe the constructs of the Process domain as the “essential activities of implementation processes that are common across organizational change.”<sup>53</sup>

In a complementary work, the IGNITE Sustainability Working Group identified 28 constructs most important in sustainability of genomic medicine.<sup>55</sup> Again, these results apply to genomics as a whole, but can be logically extrapolated to pharmacogenomics. These 28 constructs were arrived at by crossing several key drivers of sustainability elicited from an open-ended survey with principal investigators and working group chairs within IGNITE. The second survey collected a ranking of these drivers with applications across patient, provider, payer, and government stakeholders. Table 3 shows the key drivers.

Table 3. Key drivers of genomic sustainability

<b>Key Drivers</b>	Infrastructure (EHR, CDS, lab, manufacturers, community)	Economic measures	Clinical evidence/effectiveness
Regulatory/legal	Research/development	Workforce impact	Education

The top results, those identified as the top five most important of the second survey were (1) expanded genomic education, (2) availability of clinical decision support (CDS) tools, (3) formal recognition of economic data guiding reimbursement decisions (4) the impact of integrating genomic information into workflow, and (5) need for reimbursement decisions and prior authorization regimes. As one can see, these constructs can be easily split into two groups: those that directly affect the provider in the context of delivering genomic medicine and those

that affect reimbursement and coverage policies to pay for genomic testing. The former will be the focus herein.

A recent review of the pharmacogenomic landscape led by many leaders in the field includes brief reflections on things learned, recommendations on improvements, and future directions.<sup>58</sup> Included in these reflections are several of the same things that IGNITE found to be important to sustainability: workforce education, clinical tools for genomic implementation of pharmacogenomic variants, availability of pharmacogenomic testing (often driven by reimbursement), and others. Some of the most pressing issues noted by physicians specifically are the development of effective clinical decision support tools and educational training mechanisms.<sup>59</sup>

One important thing discussed in this review that appears to have been missed by the IGNITE Sustainability group was the importance of stakeholder alignment and transdisciplinary teams (interdisciplinary or multidisciplinary could be used). They list the full gamut of potential partners, from other clinicians to patients to payers to engineers etc. Set forth by the TPP, the implementation of pharmacogenomics was intended to be a multidisciplinary effort, leveraging the expertise of various clinicians and researchers. Clinical collaboration in pharmacogenomics involving the pharmacist has been a particularly important component of its delivery.<sup>60-62</sup> Several pharmacogenomic implementation sites have been initiated and driven by pharmacists and pharmacy departments. These include St. Jude Children's Research Hospital, a co-principal investigator of the CPIC grant, and the University of Florida, which has led the efforts of the IGNITE Pharmacogenomics working group.<sup>60,61,63</sup>

Appropriate education and thus the ability to confidently apply pharmacogenomics to clinical care appear to be lacking among both types of providers.<sup>34,64,65</sup> Those physicians that have been part of one or more of the pharmacogenomic initiatives described throughout here have reported more favorable views toward genetic testing applications and a better sense of preparedness.<sup>59</sup> These results would likely be similar when comparing pharmacists involved in a pharmacogenomic initiative or not. The collaboration of pharmacists may well provide a set of complementary skills, including advanced training in the pharmacokinetics and pharmacodynamics that apply so importantly to pharmacogenomics.<sup>66</sup> Formal mechanisms such as collaborative practice agreements (CPAs) and collaborative drug therapy management (CDTM) programs may be important to creating the appropriate infrastructure to enable this. CPAs and CDTMs expand the role of the pharmacists' involvement with the patient through a team-based approach, and working in a defined protocol that can include assessments, counseling, ordering diagnostics, and managing the patient's drug regime.<sup>67</sup> Several studies have illuminated the benefits of pharmacist involvement in the patient care team and the positive outcomes across the spectrum, from clinical to humanistic.<sup>68-70</sup> These successes in interdisciplinary environments and a well-primed skill set to engage with pharmacogenomics make this a logical investigation.

Given that most health care delivered in the US is not done at an academic institution, there must be greater consideration of how pharmacogenomics can be successfully implemented into ambulatory care, thus sustaining it beyond the externally-funded academic center, and achieving those goals that the National Academies stressed implementation science and genomics should address. Although sustainability may be difficult to define, the definition used in the DSF, taken from Rabin et al., fits this current issue quite nicely: "to what extent an

evidence-based intervention can deliver its intended benefits over an extended period of time after external support from the donor agency is terminated”.<sup>38</sup>

This work is organized in three sections all relevant to the above discussion. Framed by implementation science and the foundational concept of sustainability this dissertation sought to achieve three goals:

1. To provide a characterization of the nature and extent of the peer-reviewed literature on the prospective and retrospective experiences with and actions of health care providers when using pharmacogenomic information through a scoping review. This work is framed around a core research question developed from several tenets of the DSF and constructs related to the sustainability of genomic medicine.
2. Elicit the experiences of early adopter leadership in pharmacogenomic implementation through the questions posed by the CFIR Process domain. The majority of the constructs in the Process domain were identified as high-priority constructs for genomic medicine. Qualitative in-depths interviews served as the data collection methodology.
3. To assess the perceived acceptability, appropriateness, and feasibility of delivering pharmacogenomic in primary care through scenarios of a formal physician-pharmacist collaborative practice environment. A factorial vignette analysis manipulated scenarios of collaboration and other variables important in the considerations of pharmacogenomic testing.

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SECTION I.  
DECISION MAKING IN CLINICAL PHARMACOGENOMICS:  
A SCOPING REVIEW

## 1. BACKGROUND

Barriers to the scale up and spread of pharmacogenomics in clinical practice have been thoroughly discussed over the past decade.<sup>1-4</sup> While many of these barriers have been addressed, numerous obstacles persist that preclude the successful application of clinical pharmacogenomics beyond current institutions enabled by extramural or internal financial support. These obstacles include an underdeveloped clinical decision support infrastructure, lack of third-party payer coverage policies and reimbursement, and limited clinician and patient understanding.<sup>1,5-9</sup> Several of these barriers were also highlighted in a recent work from the Implementing Genomics into Practice (IGNITE) consortium, which ranked 28 important constructs for the sustainability of genomic medicine.<sup>10</sup> Interestingly, three of the top five ranked constructs (1, 2, and 4) focused on provider needs and included: (1) expanded genomic education, (2) making clinical decision support (CDS) tools available, and (3) integrating genomic information into workflow.

A casual scan of the literature reveals numerous descriptive or cross-sectional studies aimed at assessing the attitudes of providers toward pharmacogenomics. The descriptive papers seen throughout the literature come, in large part, from the implementation initiatives established at numerous academic hospitals across the US and abroad.<sup>11-14</sup> Cross-sectional survey work largely focuses on the attitudes, awareness, and concerns of clinical respondents regarding pharmacogenomics. Furthermore, the literature finds that most have positive views of pharmacogenomics, yet feel unprepared to deliver it practice.<sup>6,15-18</sup> These studies highlight the need for further education and intervention. While these papers are helpful in understanding the

nuances and considerations necessary to establish a pharmacogenomic program, they typically do not include a measurement or assessment of the intervention's impact on those delivering it to patients. However, the fact that this barrier continues to persist indicates that there is likely a dearth of studies that actively measure provider response to using pharmacogenomics in clinical workflow, or assessing experiences following actual clinical usage of such pharmacogenomic information.

Real-world assessments and intervention-based studies are crucial as they provide actionable insights to others either currently using or planning to use clinical pharmacogenomics for patient care. The Dynamic Sustainability Framework (DSF) emphasizes the idea of ongoing evaluation and adaptability of an intervention to achieve the goal of continuous improvement.<sup>19</sup> Two tenets of the DSF, the continual improvement of the intervention and a focus on collecting ongoing feedback about the intervention fold together the importance of measuring actual use of an intervention and its impact on the sustainability of the intervention long-term.<sup>19</sup> Learnings and processes from the continuous quality improvement (CQI) literature combined with the rigor of more evaluative research methodologies can lead to a better understanding of what changes are effective in improving clinical delivery of pharmacogenomics while developing generalizable methodologies for application in other settings.

With these considerations, our review is focused on answering the following research question: How have the prospective or retrospective experiences and actions of prescribers, pharmacists, or genetic counselors been measured when using pharmacogenomic information in either real-world practice or a hypothetical research setting? The current objective of this review is to provide a characterization of the nature and extent of peer-reviewed literature that is applicable to the stated question. A scoping review was the appropriate review methodology as it

aims to assess the extent, range, and nature of evidence to summarize heterogeneous methods or disciplines, without pursuing a quality assessment of the literature.<sup>20</sup>

## 2. METHODS

To increase the methodological transparency and uptake of these findings, the recent checklist extension by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) published for scoping reviews (PRISMA-ScR) was used throughout this study.<sup>21</sup>

### **Protocol and Registration**

A registered protocol was not developed prior to beginning the search of the literature. However, the PROSPERO international prospective register of systematic reviews was searched and there was no registered protocol when this project began in December of 2018 that exhibited similarities in research objective or design.

### **Eligibility criteria**

Detailed inclusion and exclusion criteria were developed prior to the first screening of the search results. To be included in the review, papers must include an outcome that measures the experiences of or action by a prescriber (physician or advanced-practice provider), pharmacist, or genetic counselor when engaged in an *actual* or *hypothetical* scenario involving pharmacogenomic testing. Published papers that were descriptive of an implementation project and included provider elements yet do not include formal data collection methods were excluded. Table 1 fully describes the inclusion and exclusion criteria.



**Table 1. Inclusion/exclusion criteria**

<b>Inclusion criteria</b>	Peer-reviewed literature in pharmacogenomics that evaluates the clinical professional’s experience or action taken when using pharmacogenomic information for clinical decision making
	At least 50% of the data must come from responses or decisions made by physicians (MD/DO), pharmacists (RPh/PharmD), or genetic counselors (CGC).
<b>Exclusion criteria</b>	Studies that do not clearly state respondents have used or are using pharmacogenomic information. This includes any study that is descriptive, anecdotal, or opinion in nature.
	Studies published that <i>only</i> include as respondents: patients, advanced practice non-physician providers (nurse practitioners/physician assistants), health profession students, or nurses.
	Studies not primarily focused on pharmacogenomics
	Studies published before the year 2000
	Studies published in a language other than English

**Information sources and search**

In December of 2018, potentially relevant papers were searched in the both the MEDLINE® and Embase® bibliographic databases. MEDLINE® uses the MeSH® (Medical Subject Headings), Embase® uses Emtree®. Search strategies were developed by the lead author

and refined through discussion with other authors. Search results were exported into Microsoft Excel<sup>®</sup> and duplicates removed. Microsoft Excel<sup>®</sup> was used to parse out MEDLINE<sup>®</sup> studies that were duplicated and those that were unique from the Embase<sup>®</sup> search.

A total of 537 studies were pulled from MEDLINE<sup>®</sup>. The search of Embase<sup>®</sup> produced 201 studies unique to the Embase<sup>®</sup> library, and 241 unique studies that were not included in the results of the MEDLINE<sup>®</sup> search. The Embase<sup>®</sup> library searches MEDLINE<sup>®</sup> in addition to its own database. Appendix 1 provides the full search string for each database.

### **Selection of sources of evidence**

Two authors (NK and TD) independently and iteratively reviewed titles and abstracts, then full papers, making decisions to include or exclude at each stage. At the completion of each stage the selecting authors discussed their assessments and came to consensus on the studies to be included. Prior to beginning the selections, a screening form was developed and agreed upon by the authors.

### **Data charting and data items**

The data charting process used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist to determine which variables to extract from the included studies. A data-charting form was developed by the lead author and shared with a co-author (TD). Each author (NK and TD) took half of the included studies and independently charted the data using this form.

In line with the PRISMA-ScR checklist, items 9, 11, and 12 of STROBE will be excluded from the data charting process. These items correspond to sections usually absent from scoping reviews and did not add to answering the stated research questions. Final variables included from

the data abstraction were author and publication year, study location, research aims, study design and methods, population and setting, outcome(s) of interest, and major findings. Table 2 is the subsequent result of this extraction.

### **Synthesis of results**

Lastly, two authors (NK and MR) performed an inductive content analysis of the study design and study methods, as well as the major findings variables from each included article to structure the scoping review findings. In line with the language of the research question, the organization of the findings was determined according to the methodology driving the study. The goal of this analysis was to come to consensus on the number of major methodological groupings and the nature of the methods therein.

### 3. RESULTS

Figure 1 below provides an overview of the number of studies screened, determined eligible (with reasons for exclusion at each stage), and then included in the review findings.

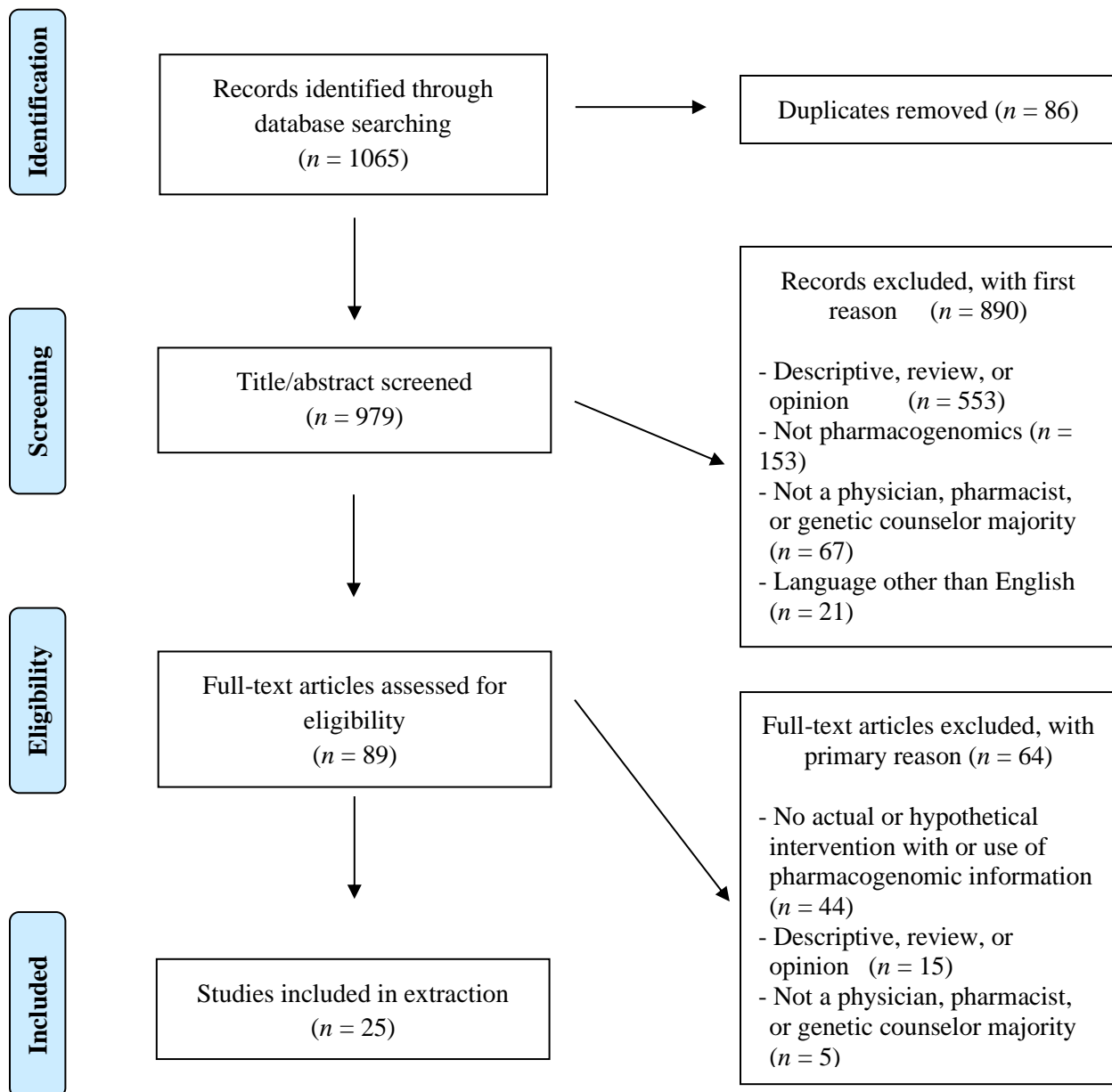


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

## Characteristics of sources of evidence

A total of 25 studies underwent complete data extraction. Most studies (76.0%) were from North America.<sup>22-38</sup> Two studies (8.0%) were conducted in both US and international settings,<sup>39,40</sup> and the remaining were strictly conducted in strictly international settings (24.0%). All studies except for two came from the US and Europe.

Most of this research was quantitative in nature (80.0%).<sup>22,24,25,28-33,35,39-44</sup> Only three studies were strictly qualitative in nature<sup>27,36,45</sup> and two used a mixed-methods approach.<sup>23,26</sup> Study designs ranged from cross-sectional surveys and in-depth interviews to hypothetical clinical case scenarios and timed information-seeking exercises with subjects. One study took a quasi-experimental approach.<sup>25</sup> As outlined in the inclusion criteria, the majority of study participants were physicians, pharmacists, or genetic counselors. Among the 25 studies, almost all (96.0%) were categorized as majority physician<sup>23,25-27,29,31-33,35,36,39-45</sup> while only one study was solely pharmacist.<sup>28</sup>

In a somewhat blended approach, the primary outcome for four physician respondent studies (16.0%) was adherence to therapeutic recommendations from either a pharmacist or pharmacist-led surveillance service.<sup>22,24,30,34</sup> Three additional studies tracked the therapeutic action of a prescriber based on CDS support alerts or another return of results methods.<sup>37,38,46</sup> None of the 25 studies included in the scoping review focused on genetic counselors.

**Table 2. General characteristics of studies included in the review (*n* = 25)**

<b>Characteristics</b>	<i>n</i>	%
<b>Region of origin*</b>		
North America	20	80.0
Europe	6	24.0
Oceania	1	4.0
<b>Years published</b>		
2015 – 2018	17	68.0
2010 – 2014	7	28.0
2005 – 2009	1	4.0
2000 - 2004	0	0.0
<b>General methodology</b>		
Quantitative	17	80.0
Qualitative	3	12.0
Mixed Methods	2	8.0
<b>Study design</b>		
Hypothetical clinical case scenarios	9	40.0
Real-world studies on prescribing/testing decisions	7	28.0
Cross-sectional quantitative surveys	5	16.0
Cross-sectional qualitative interviews	3	12.0
Quasi-experimental	1	4.0

\* Total equals more than 100% due to multi-country studies included

## Results of individual sources of evidence

Table 3 provides an evaluation of each study across all included variables for data extraction. The qualitative content analysis of the study design and methods section revealed five major methodological approaches: hypothetical clinical case scenarios, real-world studies evaluating prescriber response to recommendations or alerts, cross-sectional quantitative surveys, cross-sectional qualitative surveys/interviews, and a quasi-experimental real-world study. In the following sections, each methodological approach will be defined with appropriate sub-sections and aims identified, and a brief mention of major study findings will be provided.

**Table 3. Peer-reviewed articles included in the scoping review**

Author and Publication Year	Study Location	Research Aims	Study Design and Methods	Population and Setting	Outcome(s) of Interest	Major Findings
Bain <i>et al.</i> 2018	United States	To determine the feasibility of implementing a pharmacist led PGx service for the Program of All-Inclusive Care for the Elderly (PACE).	Prospective evaluation of the implementation processes in PACE. This included reviewing policies and procedures, observations documented by the pharmacists, prevalence of genetic variants, and drug-gene interactions, descriptive categorization of the types of pharmacist recommendations, and prescriber acceptances of these recommendations.	The practice setting in which this evaluation was made was a centralized pharmacy in New Jersey that services 15-20% of PACE participants in 21 states. PGx consultations were led by two senior pharmacists and a pharmacy resident. Included prescribers were those who selected testing based on their medical decision.	Rates of prescribers' acceptances of the PGx consultation recommendation s, when feasible.	Eighty-nine percent of pharmacist recommendations were accepted by the referring prescriber. 100% of recommendations were accepted in the categories: <i>continue</i> drug (no change), <i>consider</i> drug dose adjustment, and <i>consider</i> drug regimen change. 38.5% of recommendations were accepted for the category <i>implement</i> drug dose adjustment or drug regimen change.

Blagec <i>et al.</i> , 2016	Austria and United States	To evaluate the perception and usability of a web- and mobile-enabled CDS system (the Medication Safety Code (MSC)) for pharmacogenetic s-guided drug therapy among physicians and pharmacists.	Survey B was a quantitative assessment of physician and pharmacist attitudes toward the MCS system based on two hypothetical use cases. Twenty-five follow-up questions, including a 16 item Likert scale, were used to measure usability, trustworthiness, usefulness, and workflow integration.	Survey B included a final sample of 39 physicians and pharmacists, with an overwhelming majority from Austria or Germany (~90%).	Scores on the usability, trustworthiness, usefulness, and workflow integration subscales and total scale score.	Out of a possible max score of 16, usability scored an average of 10.6, trustworthiness a 10.5, usefulness a 11.4, and workflow integration a 9.9. This equates to a total scale score of 42.3 out of 64. There was no statistically significant difference between physicians (43.7) and pharmacists (38.8), or between respondents aware or unaware of genome guided prescribing and clinical decision support systems.
Devine <i>et al.</i> , 2014	United States	To evaluate an early prototype, commercial CPOE system with PGx-CDS alerts in a simulated environment, to identify potential improvements to the system user interface, and to understand the contexts under which PGx knowledge embedded	The study used a convergent, parallel, mixed methods design. Physicians were given five hypothetical clinical case scenarios featuring a pharmacogenomic alert message triggered by a medication order. Audio-video recordings were coded according to positive and negative evaluation heuristics.	Seven cardiology fellows and three oncology fellows at the University of Washington.	Time to completion of prescribing task. Themes and improvements identified using the heuristic evaluation technique.	Each physician spent between 3.6 to 4.9 minutes per prescribing task. Nine themes and corresponding improvements emerged from the heuristic evaluation. Five included improvement suggestions for the CPOE user interface, two suggested



		in an electronic health record is useful to prescribers.				including PGx information through alerts, and three emphasized the need for relevant guidelines and dosing recommendations
Dunbar <i>et al.</i> , 2012	New Zealand	Feedback from clinicians on their experiences ordering a AmpliChip® CYP450 test kit, receiving results, utilization of the results, and perceived advantages and disadvantage for commencing treatment with risperidone.	Once an appropriate patient was identified, the clinician was directed to prescribe 'as usual', then complete an order form for the patient to get the testing done. Results were fed back to the clinicians directly. Ordering clinicians were contacted to complete a qualitative interview.	Forty-two clinicians ordered the test and a total of 33 were interviewed by a member of the research team. Clinicians worked across three District Health Boards within New Zealand.	Key ways in which the test results were used and the perceived advantages and disadvantages of using the test.	Test results utilization: confirm a clinical decision, provide reassurance, provide additional information on patient response, influence the dose of risperidone, and doctor-patient. Several reasons for not using results were delays in receiving results, inappropriate setting (acute unit with requirement to treat immediately), information deemed unnecessary, and others Dose determination, reduction of adverse effects, and application outside mental health were noted advantages. Disadvantages

included results being used at the expense of clinical judgement, cost, and practicalities of the testing process and results reception.

Ferreri <i>et al.</i> 2014	United States	To determine the feasibility of implementing a PGx service in a community pharmacy.	Prospective evaluation of the program's feasibility following a retrospective data abstraction of prescription fills for clopidogrel between the dates of May 1, 2011 and October 26, 2011.	A single pharmacy within a regional chain known for providing clinical services.	Rate of prescriber acceptance to a Clinical Pharmacist Practitioner (CPP) recommendation across five different genotypes (*1/*1, *1/*2, *1/17, *17/*17, and *2/*17). The number of patients with each were 9, 2, 4, 1, and 2, respectively.	The majority of CPP recommendations were approved by the prescriber. There was 100% approval across genotypes *1/*1 (EM), *17/*17 (UM), and *2/*17 (IM). Genotype *1/*2 (IM) was approved 50% of the time, the other 50% were started on aspirin EC 325 mg daily. For genotype *1/*17 (UM), 75% were approved. Clopidogrel was discontinued in the other patient.
Haga <i>et al.</i> , 2017	United States	To investigate provider utilization of pharmacist support in the delivery of PGx testing in a primary care setting.	Two primary care practices were assessed, one with a pharmacist in the clinic and one with available pharmacist on-call support. Physicians answered a survey assessing attitude, knowledge, and experience with PGx testing before	Twelve primary care providers from two internal medicine clinics within the Duke University Health System	Results from the follow-up survey to assess perceptions and comfort using PGx. Patient charts provided the number of PGx tests ordered in each arm of the trial. Variables of interest recorded by the pharmacist	Five of nine providers strongly or somewhat agreed that felt more informed about PGx testing after the trial. Six felt more comfortable discussing PGx with patients

and after attending a PGx seminar.

included the number of times a pharmacist was consulted (pre-test or post-test), and how the results were applied to treatment.

after. Sixty-three total tests were ordered, 48 being ordered from the pharmacist-in-house arm ( $p < 0.00001$ ). Physicians consulted pharmacists in 13 of the 15 cases in the in-house pharmacist group compared to 7.5 out of 15 in the on-call group.

Heale <i>et al.</i> , 2017	United States	To investigate physicians' information needs and information-seeking behavior when exposed to pharmacogenomics case vignettes.	Mixed methods approach consisting of a pre-study questionnaire of attitudes and knowledge regarding pharmacogenomics, observation of information-seeking in three case vignettes, and a post-study questionnaire and interview.	A purposive sample of six physicians, five male and one female. Three were between 30 and 39 years old, two 40 to 49, and one 60 to 69.	For information-seeking behavior in the vignettes: time spent by physician on information-seeking, time between navigational actions and number, number of searches entered. Categories of the information needs from post-study assessment.	Average number of minutes spent in information-seeking session was 8:22 (2:41 to 15:08), time between navigation was 0:53 (0:03 to 8:27), number of page navigation events per subject per case was 8 (1 to 18), and the number of searches was 2.3 (1 to 8). Follow-up assessment identified six information needs categories from 11 themes: alternative therapies obviating testing, guidance on when and how to test, frequency testing is
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						indicated, evidence of importance of genetic testing, help in understand genetic effects, and aid in searching for information.
Ielmini <i>et al.</i> , 2018	Italy	To identify if the treatment prescribed by the psychiatrist was consistent with the treatment suggested by the PGT at T0 and to assess if clinicians had changed the treatment (in case of discordance) at T1 (3-month follow-up visit) according to the results of the pharmacogenetic test (PGT)	Observational study with a follow-up at 3 months. At baseline (T0), patients received genetic tests and were given 4 scales. At the follow-up (T0), changes to treatment and adverse events were recorded.	Psychiatrist decision making for 30 bipolar type 1 and 2 patients who received PGT Neurofarmagen at 2 psychiatric institutes	Patients' overall assessment and clinical evolution was measured using the Clinical Global Impression. The Hamilton Depression Rating Scale assessed anxiety-depressive symptoms. The Young Mania Rating Scale assessed manic symptoms. The Dosage Record and Treatment Emergent Symptom Scale assessed onset of side effects relating to ongoing pharmacological therapy	At baseline, 13% of patients received optimal therapy. At follow-up, 40% of patients changed to a therapy consistent with the results of the Nerofarmagen test and 32% maintained a therapy disagreeing with the test. A significant within-group reduction in adverse events was observed in patients who received therapy modification
Laerum <i>et al.</i> , 2013	Norway	Develop a prototype for automated interpretation of genetic tests and evaluate hospital physicians' reactions to it in a specific use case.	Algorithm applied to the interpretation of <i>CYP3A5</i> and its impact on the metabolism of immunosuppressive drug tacrolimus. Respondents used the "think aloud" technique to vocalize thoughts and	Nine experienced and less-experienced physicians, five of which completed specialties after qualifying as a Medical Doctor. One physician	Median time to resolve the two scenarios presented and the speech and actions recorded while using the application. Reactions to the application after completing the scenario.	Scenario 1 took on average 164 (110 to 339) seconds to complete. Most of the physicians were observed to not immediately grasp the concept of "interpreted report" versus

			considerations during the application. Scenarios involved viewing and resolving two patient scenarios with regard to tacrolimus treatment. Physician speech and actions on the screen were recorded and they were asked to identify the correct dosing for the given patient.	had a PhD in molecular genetics.		original genetic data. Scenario 2 took less than half the time to resolve on average than scenario 1. Physician attitude to the application was generally very positive. Some details were reported too extensive, unclear, or difficult to understand.
Lemke <i>et al.</i> , 2017	United States	To explore primary care physicians' views of the utility and delivery of direct access to PGx testing in a community health system.	Study participants received complimentary PGx testing kits for themselves and for their patients. 30-minute qualitative semi-structured interviews were conducted to identify viewpoints related to primary care physician PGx clinical decision-making.	Fifteen primary care physicians in the NorthShore University Health System, a four-hospital community health system.	Broad themes and associated sub-themes from the qualitative analysis were the primary outcome.	The three broad themes were perceived value and utility of PGx testing, implementation challenges, and provider and patient needs. The first theme here included two sub-themes: how test findings can be used to guide primary care decision-making, and how information from testing can lead to specific positive outcomes for patients.
Manzi <i>et al.</i> , 2017	United States	To describe the development and implementation of a comprehensive	A retrospective evaluation of the first two years of operation (August 2012 to August	A total of 160 alerts across 31 patients interfaced with 69 unique	Percentage of prescribers who cancelled the order in response to alert, percentage who	23% of prescribers cancelled the order in response to the TPMT

		clinical pharmacogenomics service within a pediatric tertiary care urban teaching hospital	2014) of TPMT single gene sequencing and the subsequent actions of the clinician based on the CDS alert	practitioners. 53% physician, 22% pharmacists, 18% nursing with physician co-sign, and 7% nurse practitioners	initiated a modified dose after alert, and percentage of tests order prior to initial prescription	alert. 71% of prescribers modified the dose after receiving the alert for the initial prescription. 90% of tests were ordered prior to the drug being ordered
McMichael <i>et al.</i> , 2017	Northern Ireland	To demonstrate how attribute nonattendance analysis can be used in medical decision making to assess whether psychiatrists were influenced in their treatment recommendations by information on the genotype of a patient, despite knowing the patient's response to treatment.	Psychiatrists were given patient's pre or post treatment symptom scores on the Positive and Negative Syndrome Scale (PANSS) for two treatments of schizophrenia, were told whether patients had a genotype linked to one of the treatments associated with a 30% increase in effectiveness and were asked to recommend a treatment. Twenty-six vignettes assessed the effect of each attribute on psychiatrists' treatment recommendations.	Sixty-seven practicing psychiatrists from Northern Ireland recruited during continuous professional development meetings in three hospitals.	Psychiatrists estimated probability that they will either ignore or attend to information about the patient genotype when already presented their PANSS scores pre and post.	Across the entire sample, there was an 84% probability that psychiatrists did not consider the patient genotype information and 16% probability they did when already present with the patient's response to treatment. Psychiatrists with less than one year of clinical experience were significantly more likely to incorporate irrelevant genetic information into patient treatment (46% probability). Those with more than 15 years had a 7% probability of incorporating the same information.

Moaddeb <i>et al.</i> , 2015	United States	To characterize the experiences and feasibility of offering pharmacogenetic testing in a community pharmacy setting. These included the time to provide the testing, patient interest, perceptions of patients' post-test comprehension, pharmacists' interactions with prescribing physician, and changes made to prescription based on the results.	Pharmacists completed surveys at two time points for each patient that was offered PGx testing. One for when the testing was offered, and another after testing was completed and test results were communicated. Testing was offered for CYP2C19 and/or SLCO1B1	Community pharmacists in North Carolina across five community pharmacies.	Length of the pre-test counseling, the medium in which results were given to the patients and how long that took, the pharmacist's belief of how well the patient understood the results, and what percentage of result interpretations were done correctly.	Over 80% of pre-test counseling was under five minutes, 84% of results were communicated by phone, pharmacists believed 95% of patients understood the results very well or somewhat well, and pharmacist interpretations were correct just under 90% of the time. Pharmacists reached out to a physician in 4 instances across 56 patients.
Nishimura <i>et al.</i> , 2016	United States	To determine if physicians find clinical decision support alerts for pharmacogenomic drug-gene interactions useful and assess their perceptions of usability aspects that impact usefulness.	A case scenario approach was used where the participant was responsible for prescribing dual anti-platelet therapy. The participant was directed to select a therapy and then regardless of choice a pharmacogenomic alert for clopidogrel and the <i>CYP2C19</i> variant was shown. This was followed by a 15-item questionnaire and open-ended questions on their response to the alert.	Fifty-five physicians at the University of Washington enrolled in the study. 58% of these were attending physicians. Respondents worked in major medical centers, outpatient and specialty clinics, and emergency departments.	Physician response to the alert in an actual clinical interaction. Usefulness of the alert in general, quality of the alert's visual design, appropriateness of the alert in a clinical workflow, and usefulness of the pharmacogenomic content.	40% of physicians would cancel and 49% would modify their initial order for aspirin or clopidogrel after seeing the alert. 4% stated they would override the alert. 7% reported "Other" and responded they would contact a pharmacist. Close to 90% agreed or strongly agreed the alert was helpful, the text was helpful for

decision making, and that the alert came at the appropriate time. 30% of physicians were unsure that pharmacogenomic data was useful for their practice.

Nutescu <i>et al.</i> , 2013	United States	To determine the procedural feasibility of a pharmacist-led interdisciplinary service for providing genotype-guided warfarin dosing for hospitalized patients newly starting warfarin.	Prospective, observational study. Patients that received genotype-guided warfarin therapy provided written, informed consent for use of their data and leftover genetic sample. Recorded information included time of initial genotype and consult order, time to results appearing in EHR, time to initial consult and genotype guided dose recommendation, warfarin doses.	The EHR system for the University of Illinois - Chicago. Clinical dose recommendations are made by the pharmacogenetics consult team.	Adherence of the medical staff to doses recommended by the pharmacogenetics service. Acceptance of the dose recommended defined as within 0.5 mg.	A total of 353 dose recommendations were provided for the 80 patients enrolled. During the initial six months of the service, 73% of warfarin doses ordered by the primary team were within 0.5 mg of the recommended dose by the clinical pharmacist on the pharmacogenetics service. There was a noted increase in adherence to the dose recommendations over time: 66% in months one and two, 76% in months three and four, and 80% in months five and six.
Overby <i>et al.</i> 2015	United States	Pilot study to assess the physician, technology, and	Clinical experts helped develop hypothetical clinical case scenarios that	Fifteen oncology and seven cardiology	Assessments of clinical impact measured by prescribing uptake,	Across both high and low actionable alerts, fellows used the



		task characteristics of effective communication and clinical impact of using a prototype CDS system embedded in the EHR to deliver PGx information.	prompted prescribing tasks, and revisions of scenarios that included presentation of PGx information. Each participant was presented with five scenarios. The third-fifth were deployed in a pseudo-randomized fashion.	fellows practicing at the University of Washington.	prescribing intent, and change in personalized drug dosing (PDD).	gene specific resources 88% of the time and the alert message evidence 74% of the time. Sixty-five percent of physicians changed the prescribed dose after using the PGx-CDS. A significant change (decrease) was only observed for capecitabine and mercaptopurine/thioguanine.
Payne <i>et al.</i> , 2011	United Kingdom	To compare the preferences of patients and health-care professionals for the key attributes of a PGx testing service to identify a patient's risk of developing a side effect (neutropenia) from the immunosuppressant, azathioprine.	A discrete choice experiment through an online survey that consisted of five, four-level attributes resulting in 1024 possible scenarios. This was done alongside a prospective randomized controlled trial (TARGET study).	One hundred thirty-eight healthcare professionals (83% physician) with experience of prescribing and advising on azathioprine.	The five attributes were level of information given, predictive ability of the test, how the sample is collected, turnaround time for a result, who explains the test result.	Health-care professionals were willing to wait 2.2 days on average for a 1% improvement in predictive accuracy. They were willing to wait 8.9 days for high levels of information provision. Health-care professionals preferred the physician over the pharmacist in the delivery of results. They were willing to wait 9.5 days and give up 4.4% in predictive ability of the test. This percentage increased to 6.1

						for the hospital doctor to deliver the result. No significant differences in how the sample is collected.
Peppercorn <i>et al.</i> , 2013	United States	To assess the use of the CYP2D6 test for tamoxifen metabolism outside of clinical trials and the attitudes of community-based oncologists and breast cancer specialists about testing among patients with breast cancer eligible for tamoxifen therapy.	Anonymous cross-sectional survey that evaluated knowledge of the CYP2D6 test, use outside of trials, requests by patients and third parties, and a response to hypothetical test results. Associations between practice setting and CYP2D6 knowledge, use of the test for tamoxifen, and practice patterns were evaluated. Survey was piloted with oncologists at the Duke University Medical Center in Durham, NC.	Final survey was mailed to a random sample of all breast cancer medical oncologists affiliated with the National Comprehensive Cancer Network (NCCNOs) and a random sample of community-based oncologists (CBOs) from the American Society of Clinical Oncology	Response to hypothetical test results presented through three scenarios regarding managing management of patients on tamoxifen who obtained commercially available CYP2D6 results from an external source	For a premenopausal woman with a poor metabolizer (PM) genotype, 33% would make no changes, whereas 56% would change therapy. There were significant differences between NCCNOs and CBOs on what specific change would be made. 66% of respondents made no change when it was a premenopausal woman with an intermediate genotype, 20% would change. The last case involved a PM postmenopausal woman and only 14% of respondents said they would not change therapy.
Peterson <i>et al.</i> , 2016	United States	Solicit clinician's perceptions of clinical utility, preparedness to effectively use	Online survey design with questions based on a previous publication by Stanek et al and	Clinicians at Vanderbilt University within cardiology,	Responses to the question of which providers were responsible for clinical action with	For the clopidogrel and <i>CYP2C19</i> scenario, cardiology and

<p>PGx test results, and questions of responsibility for disclosure and clinical use of multiplexed results</p>	<p>contributions by two authors. Two clinical scenarios were presented to determine which providers should be responsible for clinical action.</p>	<p>primary care, and endocrinology who had previously ordered a PGx test in the implementation program or cared for a patient with a PGx result. Eighty percent of respondents were physicians.</p>	<p>a pharmacogenomic result.</p>	<p>non-cardiology providers agreed multiple providers should be individually notified of results, but less than 50% agreed the patient should be notified directly. Ninety percent of cardiology providers selected the specialist treating the medical condition and the 80% selected the prescriber of the drug therapy affected by test. Ninety-five percent of non-cardiology providers selected the prescriber of the drug therapy. Regarding who is responsible to act on the result, 80% of cardiology and 74% of non-cardiology chose the specialist treating the condition to be responsible for acting on the result. Just above 50% of both groups also chose the provider who</p>
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						ordered the PGx test.
Peterson <i>et al.</i> , 2016	United States	To investigate how physicians respond to an enterprise-wide PGx implementation utilizing either a clinician decision support and a pharmacist-led surveillance system.	In a new implementation program, coronary stent patients receiving clopidogrel were genotyped CYP2C19 variants. Poor and intermediate drug metabolizers were flagged and reported to attending cardiologists to see if alternative antiplatelet agents were prescribed.	Prescribing decisions were tracked for 514 patients with poor or intermediate drug metabolizer status of 2,676 that received a coronary stent in the study period and were discharged on clopidogrel therapy.	Time to a genotype-tailored antiplatelet prescription within 12 months of the stent procedure. Antiplatelet prescription was labeled as genotype-tailored if it matched the PREDICT program recommendations for CYP2C19. Interception rates from the pharmacist surveillance system.	At 12 months, 57.6% of poor metabolizers and 33.2% of intermediate metabolizers received alternative treatment. CYP2C19 was the most predictive factor of prescribing changes. Pharmacist-led surveillance intercepted 481 of 514 candidate patients for alternative therapy. 304 patients were recommended for therapy change and 130 changes were made within 12 months.
St. Sauver <i>et al.</i> 2016	United States	To assess the perspectives of clinicians and the impact of PGx alerts on prescribing practices who received informational materials through a clinical decision support in the electronic drug prescribing system.	In February 2015 respondents were sent an email survey to understand perspectives on implementation and use of PGx testing in clinical practice. Once the survey was returned, the number of PGx-CDS alerts were extracted from the EHR.	One hundred fifty-nine primary care physicians at the Mayo Clinic in Rochester, Minnesota. This physicians care for 1,013 patients participating in the RIGHT Protocol.	Perspectives on clinicians that remembered seeing a PGx alert. Clinician response to an alert if they received one. CDS alerts were grouped into two categories: alert recommended caution with the prescription or the alert recommended an alternate prescription.	Thirty-six clinicians reported on their responses to the PGx alert. 12 had <i>only positive</i> response, 19 had <i>only negative</i> , and five reported <i>both positive and negative</i> responses. EHR and CDS data from 27 clinicians and 50 alerts were

						eligible for inclusion. 26 alerts recommended caution w/ prescription. Three of these resulted in a prescription change, 23 did not. 24 alerts recommended a prescription change. Seven of these resulted in a prescription change, 17 did not.
Ubanyionwu <i>et al.</i> , 2018	United States	To report the results of prescribers' responses to a PGx-based clinical decision support (CDS) alert designed to prompt TPMT status testing.	Retrospective, chart review to evaluate prescriber compliance with a pretest CDS alert that warned of potential thiopurine drug toxicity resulting from deficient TPMT activity.	The Mayo Clinic's Rochester campus electronic health record system between November 20, 2014 and August 31, 2015.	The proportion of patients for whom a test to ascertain TPMT status was ordered and number of guideline-supported doses ordered after CDS alert.	Of 500 CDS alerts generated, 101 cases of <i>TPMT</i> phenotyping or <i>TPMT</i> genotyping were ordered. Alert fatigue from alerts firing in cases of continuing therapy may contribute to this. 24 patients were provided with thiopurine dosing recommendations, only 12.5% received concordant doses
Unertl <i>et al.</i> , 2015	United States	To describe the knowledge and attitudes of clinicians participating in a large pharmacogenomics	Semi-structured interviews. Subjects were recruited through email or in person and compensated for their time. Data collection	Thirteen physicians and two nurse practitioners at Vanderbilt University. These	Key themes categories and the multiple themes representing these categories.	Three high-level theme categories: preparation and knowledge, PGx use in practice, future implementation

		cs implementation program.	continued until data saturation, when additional interviews yielded no significant new information.	individuals came from either a primary care or cardiology practice. They were stratified by the usage patterns: <10 = low, between 10 and 99 = medium, and >100 = high.		challenges. Clinicians acknowledged complexity and unfamiliarity with representations and nomenclature that led to difficulties in using the data. Strong support for ongoing engagement with implementation team. Concerns included the long-term responsibility of actionable results and hand-offs to those outside the program.
Walden <i>et al.</i> , 2015	Canada	To assess physicians' perception of PGx testing and their experience using the test results to help prescribe antidepressant and antipsychotic medication.	Survey sent to physicians six to eight weeks after receiving a PGx report. This coincided with the first patient follow-up visit at six weeks from baseline to allow time for the physician to decide if changes in medication should be made.	One hundred sixty-eight Canadian physicians who ordered at least one PGx test for the prescription of a psychiatric medication. Psychiatrists (33.9%) and general practitioners (40.5%) constituted most respondents.	Physician attitudes towards PGx testing were assessed using the Pharmacogenetics in Psychiatry Follow-up Questionnaire (PIP-FQ).	A vast majority of respondents agreed that genetic testing will become common standard in psychiatric drug treatment and were satisfied with the genetic information provided to them. Clinician scientist respondents (n=12) reported a statistically significant ( $p < 0.001$ ) higher mean in their reported ease of

understand PGx information.

Wegwarth <i>et al.</i> , 2009	Germany and United States	To investigate oncologists' decision making on using PGx tests for cancer treatment and to examine cross-cultural differences between the USA and Germany.	A pilot study was used to reveal the cues which play a role in the decision to order a PGx test. These cues were then used in the main study which consisted of nine scenarios. To determine which information was most important and how it was processed three models were applied: the weighted additive model, the equal-weighted model, and a simple sequential model.	The pilot study consisted of seven US and 12 German oncologists. The main study was comprised of 109 US and 111 German oncologists.	Whether respondents would use the test for making a treatment decision or not, and the type of information most influential in this decision.	US oncologists opted for the test in 6.5 out of nine scenarios, and German oncologists in 5.4 scenarios. The most influential information to US oncologists was the cost of the test, and the guideline recommendation of the test for German oncologists. When side effects of the therapy were described as more severe, a 20% increase ordering of a non-guideline recommended test was noted.
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PGx = pharmacogenomics

### Hypothetical clinical case scenarios

Studies in this section are defined by their approach to engaging a provider in an exercise that mimics real-world clinical decision making in some form. Of the nine studies included in this section, there are three main sub-sections that can be defined. These three sub-sections are: information seeking, prescribing tasks, and other. The first of these sub-sections, “information seeking” includes three studies that aimed to directly measure the time it took to complete certain tasks involving the use of pharmacogenomic information.<sup>23,26,41</sup> All three qualitatively assessed

reactions to the information-seeking process either during or after the exercise. In addition to the time it took to complete the task, one study measured the number of searches and page navigation events that took place as the provider attempted to answer their question.<sup>26</sup> The variability between the findings of each of the included studies was high given the inherent differences among clinical decision support systems (CDS) and study tasks. One study used two scenarios to gauge improvement in the time to complete from scenario 1 to scenario 2.<sup>41</sup> These studies cut across physician specialties, from internists to cardiologists and oncologists, and included multiple disease states and/or pharmacogenes. The sample size was small for these studies, ranging from 6 to 10 physicians. Due to variability in the tasks, it is difficult to make comparisons between the studies. However, physicians spent between three and half to five minutes on the prescribing task and upwards of eight minutes on information-seeking.

The second sub-section, “prescribing tasks”, included three studies wherein the prescriber’s hypothetical actions taken when presented with pharmacogenomic information were evaluated.<sup>29,31,32</sup> Variables measured in these studies included the percentages of physicians who would change a decision or initial orders based on new pharmacogenomic information, response to or dismissal of CDS messages, as well as evaluations of whether the alerts or information were helpful in decision making. All studies in this section were quantitative in methodology. The sample size was larger for this sub-section, ranging from 15 to over 200 physicians. Overall these providers agreed that the alerts were helpful and there was high utilization of the clinical decision support resource. Changes in decision making based on this gene specific information were noted in most of the cases.

The third sub-section, “other”, included three studies which each had unique approaches.<sup>39,40,42</sup> The first aimed to understand different objectives including an attitude



assessment of a CDS tool usability, the second evaluated the use of irrelevant genomic information by psychiatrists with differing experience levels, and lastly, a survey examined the inter-country differences as drivers of oncologist test ordering. Like the previous section, providers involved in the studies cut across specialties and quantitative outcomes were reported. However, the sample in one study included both physicians and pharmacists. Attitudes toward the CDS were moderately positive (42.3 out of 64), younger psychiatrists were significantly more likely to use irrelevant genomic information than their colleagues with more than 15 years' experience, and US oncologists opted for testing more than their German counterparts.

### **Prospective or retrospective real-world studies of prescribing/testing decisions**

This section includes seven of the 25 studies, five of which were prospectively designed and two that used a retrospective chart review methodology. This can be further broken down into two sub-sections: first, studies that explicitly stated the prescribers action being based on the recommendation of a pharmacist or pharmacist-led surveillance service,<sup>22,24,30,34</sup> and secondly, those studies that either prospectively or retrospectively evaluated prescriber decision making based on a CDS alert<sup>37,38</sup> or another form of communication, the type of which was not explicitly stated.<sup>46</sup>

Among the four studies in the first sub-section, those where clinical recommendations either came directly from a pharmacist or from a pharmacist led pharmacogenomic service, the primary aim was to ascertain the frequency with which prescribers accepted these recommendations and for what types of patients (i.e., metabolizer status) did this occur. Prescriber response to the pharmacist recommendation was separated by the metabolizer status of the patient in two of the studies.<sup>24,34</sup> Two studies<sup>30,46</sup> also incorporated an evaluation of the

prescriber response over time and most study outcomes were based on at least six months of data. Study size ranged widely from actions taken on 18 patients up to decisions on 514. Two studies focused on genotype-tailored antiplatelet therapy, one on the dosing of warfarin, one focused on psychiatric medications, and one that cut across therapeutic areas. Acceptance of pharmacist recommendations overall was high, however lower rates can be seen when the recommendation from the pharmacist was to make a therapeutic modification.

In the second sub-section the outcome of interest was not adherence to a pharmacist recommendation, rather it was adherence to an internal CDS system or interpreted results and guidance from the testing lab/company. Two of the three studies in this sub-section produced outcomes from a retrospective chart review to evaluate adherence to testing.<sup>37,38</sup> Interestingly, both studies share additional similarities including a sole focus on *TPMT* testing and the use of a “pretest CDS alert”. This means that the CDS system, rather than guiding the provider on prescribing, informed them that testing is indicated prior to any initial dosing. Pre-test alerts resulted in about 25% of recommended tests being ordered in one study and 90% in another. High rates of modification in doses occurred when prescribers received an alert after the initial prescription.

### **Cross-sectional quantitative surveys**

The cross-sectional quantitative survey section includes five studies that employ unique methodologies to measure response from providers involved in pharmacogenomics.<sup>28,33,35,43,44</sup> Given the uniqueness of each study, no sub-sections were developed here.

One study was based on an actual implementation project across a series of community pharmacies.<sup>28</sup> This study captured a holistic perspective from pharmacists not only on their

experiences with delivering pharmacogenomics but also their perceptions of the patients' experiences as well.<sup>28</sup> The survey of interest was offered after the testing of *CYP2C19* and *SLCO1B1* was complete and test results communicated.<sup>28</sup> A discrete choice experiment was conducted along a randomized controlled trial involving use of azathioprine.<sup>43</sup> This study examined the trade-offs healthcare professionals were willing to make across numerous variables including predictive ability of the test, wait time for results, and information provision.<sup>43</sup> The third study in this section evaluated physician (both psychiatrists and general practitioners) attitudes toward pharmacogenomic testing for antidepressant and antipsychotic medications at the time of a patient follow-up visit, 6-8 weeks after test results were received.<sup>44</sup>

The last two studies were conducted in two large-scale academic implementation programs for pharmacogenomics: Mayo Clinic and Vanderbilt University Medical Center (VUMC).<sup>33,35</sup> The study from the Mayo Clinic's RIGHT protocol assessed the positive or negative aspects of a pharmacogenomic alert.<sup>35</sup> This study also included data similar to the last section that tracked the type and number of alerts that subsequently resulted in a prescription change.<sup>35</sup> The VUMC study aimed to uncover perceptions of both cardiology and non-cardiology providers about who should be notified of the pharmacogenomic results and who should be primarily responsible for managing the patient.<sup>33</sup>

The latter four studies had between 80 and 159 physician respondents while the former never explicitly stated the number of pharmacists responding to the survey.<sup>33,35,43,44</sup> Rather, the reader is informed of the number of participating pharmacies (n=5) and the number of patients engaged by these pharmacists (n=69). The results of the DCE study revealed several interesting tradeoffs physicians were willing to make for higher levels of information and predictive ability of the test.<sup>43</sup> There was rather strong agreement among cardiology and non-cardiology providers

regarding returning results to both the specialist treating and the original prescriber of the drug therapy, as well as agreement that the specialist should be responsible for acting on the result.<sup>33</sup>

### **Cross-sectional qualitative survey methods**

Qualitative survey methodology uses less structured methodologies such as interviews, focus groups, or open-ended surveys. The use of in-depth interviews was the unanimous choice among researchers for studies included in this group.<sup>27,36,45</sup> One focused on mental health providers and elicited specific reasons for and against utilizing test results as well as the advantages and disadvantages of testing more generally.<sup>45</sup> This study contrasts to the other two in that a thematic analysis was not the intent of the findings. A second study targeted primary care physicians to understand more deeply the value and utility of pharmacogenomics, as well as its use to guide clinical decision-making.<sup>27</sup> Participants here were also given complimentary testing kits for themselves and their patients. The last study included both primary care and cardiology providers and utilized a thematic approach in the analysis.<sup>36</sup>

The number of interviews conducted range from 15 to 33 individuals across the studies. The nature of the qualitative methodology seemed to lend itself to a broader assessment of provider involvement with pharmacogenomics, rather than a narrow focus on a specific drug-gene pair. Results of particular interest include the noted advantages of results for decision confirmation and reassurance, however there were perceived disadvantages including the use genomic results at the expense of clinical judgment and worries of handoffs to providers outside established implementation programs.<sup>36,45</sup>

### **Quasi-experimental**

Quasi-experimental studies involve manipulating one or more variables, but without the random assignment of participants to one condition or the other. Only one study included in our search fit this criteria and thus was given its own section.<sup>25</sup> Framing the study as a pilot, the authors designed a two-armed (physician vs. pharmacist-initiated testing) intervention trial with pre-post survey assessments of the primary care physicians involved in each arm. The survey results were supplemented by chart reviews of the 6-month follow-up period from the beginning of the trial. Six different tests (*CYP2D6*, *-2C19*, *-2C9*, *VKORCI*, *HLA-B\*1502*, and *SLCOB1*) were offered and made available for ordering during the trial. Results from this study found that significantly higher levels test were ordered from the pharmacist in-house arm (48 of 63 total tests ordered) and physicians consulted pharmacists at nearly twice the rate in the in-house arm.

## 4. DISCUSSION

This scoping review examined the characteristics of 25 peer-reviewed studies, published since the year 2000 and concentrated on illuminating the prevailing methodologies used to examine the active use of pharmacogenomics (PGx) in practice. The decision to identify methodologies used in implementing PGx in practice was a reaction to the saturation of the literature with cross-sectional health care professional awareness and attitude studies. A common thread in these awareness and attitude studies is that health care professionals find pharmacogenomics useful to patient care, but in most cases lack the requisite knowledge to deliver it effectively.<sup>8,15,16,47,48</sup> While valuable, especially in the early stages of implementing a health innovation, these types of studies tend to lack elements that should be considered for sustainability, as outlined in the DSF.<sup>19</sup>

Our content analysis of the study designs and methods identified five unique groupings that researchers had employed during the time frame of the search. This included hypothetical clinical case scenarios, real-world studies on prescribing/testing decisions, cross-sectional quantitative surveys, cross-sectional qualitative interviews, and quasi-experimental studies. Separating the studies into five-year blocks, a trend of an increasing number of studies fitting our inclusion criteria can be seen, with nearly 70% published in the last four years. Most of these studies produced quantitative outcomes and were conducted by researchers in the United States. Interestingly, our review did not include any studies where the genetic counselor was the health care professional involved in using pharmacogenomic information.

The included studies demonstrate a continued focus on decision making within the confines of the EHR. Most studies of this nature came from the hypothetical case-based scenarios designed to mimic real-world practice. These types of studies fit well at the intersection of the three genomic sustainability constructs outlined at the beginning of this review: clinician education, CDS tools, and workflow integration.<sup>10</sup> The importance of well-designed CDS has been a central focus among leading implementation programs for pharmacogenomics. Research from groups such as the Clinical Pharmacogenetics Implementation Consortium's (CPIC) Informatics Working Group provides suggestions best practices for integrating CDS with pharmacogenomics for clinical delivery.<sup>49</sup> Other leaders in the field point to the importance and challenge of developing standardized representations of results and identifying the right person to receive a CDS alert.<sup>50,51</sup> The feasibility of many of the studies included in this section is driven by the translation of pharmacogenomic information into a discrete data field that can be called upon when applicable. EHRs without this functionality make it impossible for prescribers to use this information efficiently.<sup>52</sup> Given the variability between studies, future research on prescriber interactions with a with pharmacogenomic CDS should pursue comparative and longitudinal study designs to elucidate the *most* effective way to deliver this information.

Additional findings from the review indicate that there has been a concerted effort from several ongoing implementation programs to understand who should be acting on pharmacogenomic information and how well these providers perform. These types of studies are crucially important as they provide the real-world program with a sense of “buy-in” from prescribers. This was typically achieved in one of three ways: by measuring adherence or compliance to a pharmacist- or CDS-based dosing recommendation, measuring engagement with

the platform and any medication changes without the recommendation aspect, or measuring ordering rates based on a pre-test alert to inform the prescriber that a test prior to any dosing is indicated. Following providers over time to see how their adherence behavior changes should be considered for studies in the future. A single cross-sectional assessment would likely miss this trend if applied in other settings. Clinician's limited exposure to pharmacogenomics has been previously noted in the literature.<sup>7,15,47</sup> This unfamiliarity with using the information may contribute to a hesitancy to adopt these suggestions immediately. Supplementing these types of studies with qualitative assessments of *why* adherence to recommendations was higher or lower would strengthen these studies and help the discipline identify areas to intervene and make improvements.

There will be a continued need to communicate the value and validity of pharmacist or CDS based recommendations more broadly. Pharmacist leadership and involvement with crafting the delivery of pharmacogenomics in clinical care has been strong to date and continuing this trend should be maintained for new practice settings when feasible.<sup>5,12,13,53</sup> The infrastructure of the individual institution or practice will most likely guide whether clinical decision support or pharmacist guided recommendation is most appropriate for delivering clinical pharmacogenomics.

Outside of the formal implementation program, the feasibility of delivering pharmacogenomics through the pharmacist and a community pharmacy setting is an ongoing stream of research for the pharmacogenomics community.<sup>17,54,55</sup> Two studies herein illuminate some of the operational considerations such as the time needed for a pharmacogenomic consult, perceived patient understanding, and the ability of the pharmacist to interpret this information correctly.<sup>25,28</sup> Both studies were conducted by the same group of researchers and in the same



state, thus the broader generalizability of the findings may be limited. However, these are excellent models for future researchers to mimic and establish broader validity. Pharmacist engagement in pharmacogenomics has support from their largest professional organizations, the American Society for Health-System Pharmacists and the American Pharmacists Associations.<sup>56,57</sup> Collaborative models of care with physicians, such as formal collaborative practice agreements, is likely the more sustainable path as consistent reimbursement for clinical pharmacy services remains elusive.<sup>58</sup> Furthermore, the integration of the genetic counselor into the physician-pharmacist collaboration would enhance the comprehensiveness of the patient experience and should be experimentally explored in the future.

The findings from our scoping review reveal a plethora of study designs, types of providers involved, and drug-gene pairs serving as the clinical scenario for consideration. Almost all studies from the scoping review included a physician sample, with only one study exclusively focusing on pharmacists. However, several physician specialties (oncology, cardiology, psychiatry, endocrinology, internal and family medicine) were included. While most decision making and prescribing is done by physicians, future research should aim to do the same regarding the pharmacist's actual experiences with using and acting on pharmacogenomic information. This will help achieve one of the research directions of Volpi et al., to study the pharmacist as the "clinical champion" for pharmacogenomics.<sup>5</sup>

The results of this review are not without limitations. First, the timeframe excluded studies published after 2018 and thus likely missed some of the most recent studies. Given the fact that 70% of the included studies were in the last four years, this is highly likely. Many of the studies herein were published from some of the most mature pharmacogenomic implementation programs in the world. The inclusion of many of these studies is likely due to the nature of our

research question and inclusion requirements. More work should be done to explore these same ideas in community practice. The nature of a scoping review does not allow for the synthesis of results across studies and thus this was not our aim. However, the hope is that this review will provide the research community with a keener eye for trends and specific research questions that may lend themselves to such an exploration.

In summary, this scoping review provides the pharmacogenomic research community with a compilation of the studies from the turn of the century that have aimed to collect data on the experiences or actions of health care professionals engaged in using pharmacogenomic information. We further focused the review on the methodologies employed by the authors and broke this down into five separate categories. The interactions of providers with clinical decision support systems and adherence to therapeutic recommendations represented many of the included studies. A broad thematic analysis of the methods and findings provided structure to a discussion that will hopefully guide further research on those factors needed for successful integration of pharmacogenomics into clinical care.

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## APPENDIX



## APPENDIX 1. Search Strategy

MEDLINE<sup>®</sup> MeSH<sup>®</sup> search string was as follows:

((((((("Pharmacogenetics"[Mesh]) AND "Health Personnel"[Mesh])) OR  
(("Pharmacogenetics"[Mesh]) AND "Attitude of Health Personnel"[Mesh])) OR  
(("Pharmacogenetics"[Mesh]) AND "Genetic Counseling"[Mesh])) OR  
(("Pharmacogenetics"[Mesh]) AND "Education"[Mesh])) OR (("Pharmacogenetics"[Mesh])  
AND "Surveys and Questionnaires"[Mesh])) OR (("Pharmacogenetics"[Mesh]) AND  
"Physicians"[Mesh])) OR (("Pharmacogenetics"[Mesh]) AND "Pharmacists"[Mesh]).

Embase<sup>®</sup> Emtree<sup>®</sup> search string was as follows:

('pharmacogenetics'/exp AND 'health care personnel'/exp AND [embase]/lim OR  
'pharmacogenetics'/exp AND 'health personnel attitude'/exp AND [embase]/lim) OR  
'pharmacogenetics'/exp AND 'physician'/exp AND [embase]/lim) OR ('pharmacogenetics'/exp  
AND 'pharmacist'/exp AND [embase]/lim) OR ('pharmacogenetics'/exp AND 'genetic  
counseling'/exp AND [embase]/lim) OR ('pharmacogenetics'/exp AND 'education'/exp AND  
[embase]/lim) OR ('pharmacogenetics'/exp AND 'questionnaire'/exp AND [embase]/lim)) AND  
([article]/lim OR [article in press]/lim OR [short survey]/lim) AND [english]/lim AND  
[embase]/lim AND [2000-2019]/py.

APPENDIX 2. - STROBE Statement—Checklist of items that should be included in reports of *observational studies*

	<b>Item number</b>	<b>Recommendation</b>
Title and Abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p><i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</p> <p><i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>

		<p>(b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed</p> <p><i>Case-control study</i>—For matched studies, give matching criteria and the number of controls per case</p>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias (NOT USED)	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables (NOT USED)	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods (NOT USED)	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed
<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
(e) Describe any sensitivity analyses		

SECTION II.

SUSTAINABLE ADVANCEMENT OF EARLY ADOPTER SUCCESS IN  
HEALTH SYSTEM PHARMACOGENOMICS: STRATEGIES AND  
PERSPECTIVES FROM IMPLEMENTATION LEADERSHIP

## 1. BACKGROUND

From 2012 to 2016, only 1.75% of genomics-related grants included the formal use of an implementation science framework.<sup>1</sup> This equates to a total of four grants, all of which used the same framework, Everett Roger's Diffusion of Innovation.<sup>2</sup> The Center for Disease Control and Prevention's (CDC's) Public Health Genomics Knowledge Base identified 283 articles published in 2014 where implementation science has been applied to genomic medicine.<sup>3</sup> However, the inclusion criteria did not specify that a formal implementation science approach must be taken, rather that the studies "contributed to our understanding of the implementation of genetic/-omic testing..."<sup>3</sup> In fact, what was discovered was that *very few* studies actually incorporated a theoretical framework from implementation science.<sup>3</sup>

In late 2018 the CDC Office of Public Health Genomics blog made an urgent call for the integration of implementation science in genomic medicine. They highlight that although an evidence base is critical, we must also understand "what factors contribute to the success or failure of a genomic application within a particular setting".<sup>4</sup> A recent "priority-setting" study identified 28 constructs of importance for genomic medicine sustainability.<sup>5</sup> Several of the top-ranked constructs have direct implications for the clinical delivery of pharmacogenomics: a need for expanded genomic education, addressing a lack of available genomic-focused clinical decision support (CDS) tools, and improving the integration of genomic information into clinical workflow. In fact, the sixth-ranked construct important for genomic medicine sustainability was the expansion of implementation science research.<sup>5</sup>

Evidence supporting the top rankings of these constructs include many previous studies that focus on the need for robust provider knowledge and seamless integration of information into the workflow. These issues have been consistently recognized as part of best-practice when implementing pharmacogenomics, a leading example of genomic medicine and the science of identifying genetic variants that may influence the safety or effectiveness of a drug in a patient.<sup>6-8</sup> However, as mature and advanced programs still face challenges in this area, it is not difficult to imagine that more pharmacogenomic-naïve health care settings will struggle with these insufficiencies even more.<sup>9-15</sup> Formal training for providers in pharmacogenomics has been reported as low as 11% for physicians, and 17% for pharmacists.<sup>9,10,14</sup> More recent work has qualitatively explored the ongoing physician needs and suggestions for improvement regarding pharmacogenomic clinical decision support (CDS).<sup>15</sup> The nuances of which will require thoughtful design to achieve the seamless integration with current clinical workflows. On a positive note there is consistency throughout the literature that both physicians and pharmacists have favorable attitudes toward the use pharmacogenomics in patient care, but the confidence to use these results appropriately remains an issue.<sup>9,11,16-18</sup>

Leaders in the implementation of pharmacogenomics recently put forth some ‘lessons learned’ and ‘research directions’ needed for the field, including several aligned with these sustainability indicators.<sup>19,20</sup> Two particularly applicable ‘lessons learned’ for clinical implementation of pharmacogenomics are the importance of “stakeholder alignment and transdisciplinary teams” and the need for a “standardization of local factors (e.g. population, clinician workflow, and resources)”.<sup>19</sup> Transdisciplinary teams have been driving pharmacogenomic implementation thus far, with both senior pharmacist and physician providers acting as successful program leads.<sup>21-25</sup> Advancing health system pharmacogenomics will be

improved by identifying an appropriate, local ‘clinical champion’ and aligning transdisciplinary stakeholders based on the resources of the that context.<sup>19</sup> Echoing the tone of the CDC, the application of implementation science can operationalize the ‘standardization of local factors’ by the “collection of data on dissemination and implementation from *early sites of adoption using validated frameworks*”.<sup>19</sup> Despite sparse use of validated frameworks to date, a relationship between implementation science and genomic medicine has continued to develop.<sup>3,5,26-30</sup> Applying an implementation science methodology is essential for advancing pharmacogenomics in local health system contexts, many of which will have fewer resources than previous implementation programs.

The current need from the pharmacogenomic research community is to answer the call for more integration of implementation science into genomic medicine from the CDC and leading clinical implementers. As such, our objective is to provide a qualitative assessment of perspectives and potential strategies for clinical pharmacogenomic implementation from a sample of early adopter leadership in the field. To accomplish this goal and to pursue a focus on the constructs needed for the sustainability of genomic medicine, we have applied the Consolidated Framework for Implementation Science (CFIR)<sup>31</sup>. The CFIR is comprised of 39 constructs across five domains and is described by its developers as a “meta-theoretical” framework that can guide an understanding of where and why an intervention works.<sup>31</sup> With the application of a validated framework, we aim to move the field toward a more robust understanding of local factors to enable success in additional settings.<sup>19</sup>

## 2. METHODS

### **Study design**

Semi-structured, in-depth interviews were used as the specific methodology for this study. In-depth interviews have been suggested for use in the examination of the CFIR ‘reflecting and evaluating’ (Process domain) constructs.<sup>29</sup> They are also critical to uncovering insights for the translation and dissemination of an intervention in resource constrained environments, such as health care.<sup>29,32</sup> The study was approved by the University of Mississippi institutional review board (Protocol #19x-206).

### **Study population and sampling strategy**

Leaders involved at sites that have implemented pharmacogenomics were targeted for interviews using a purposive sampling design. Inclusion criteria include professional credentials of a physician (MD or DO), pharmacist (PharmD or RPh), or a clinical research scientist (PhD), and current or previous leadership involvement in an active pharmacogenomic implementation project. An initial list of potential respondents was brainstormed among two authors (NK and JH) according to one author’s (JH) experience as a member of the pharmacogenomic leadership team at their home institution. Individuals from 18 unique organizations were initially identified, with some organizations having two potential respondents. In instances where two individuals from one institution were identified, authors ensured that these respondents had differing professional credentials (i.e. MD and PharmD) and played differing roles in the implementation of pharmacogenomic programs.



## **Interview guide development**

An adapted version of the CFIR semi-structured interview guide, focusing specifically on the Process domain (cfirguide.org), was deployed in this study and is available in Appendix 1.<sup>33</sup> The Process domain is made up of the four constructs: planning, engaging, executing, plus reflecting and evaluating. The engaging construct is then further broken down into six sub-constructs: formally appointed implementation leaders, opinion leaders, champions, key stakeholders, innovation participants, and external change agents.<sup>31</sup> The Process domain was chosen for two reasons. First, its constructs, and sub-constructs best fit the study objective and ultimate intention to improve the long-term sustainability of genomic medicine. Secondly, the IGNITE Common Measures Working Group (CMG) recently evaluated the CFIR for its potential contribution to genomic medicine and included three of the Process domain constructs (engaging, executing, and reflecting & evaluating) in its list of highest priority CFIR constructs for genomic medicine implementation.<sup>29</sup> Table 1 shows each construct, sub-construct, and corresponding definitions provided in the CFIR Codebook.<sup>31</sup>

The constructs and sub-constructs of the CFIR Process domain are described as the “essential activities of the implementation process...[that] can be accomplished formally or informally...in any order...[and] can be revisited, expanded, refined, and re-evaluated.”<sup>31</sup> The domain is linearly designed starting from the Planning construct through Engaging and Executing and finishing at the Reflecting & Evaluating constructs, yet the framework authors realize a real-world implementation will not always move this way. For example, new planning activities may be necessary as ideas come to light during other execution phases.

The CFIR guide was written using present, future, and past tense at different points. For our purposes, some of the included questions were edited to focus on a retrospective evaluation since many programs were implemented several years ago. For example, in the Reflecting & Evaluating domain, the question “Will feedback be elicited from staff? From individuals served by your organization?” was replaced with “Have you collected structured feedback from clinical staff on their experiences with pharmacogenomics?”. The initial guide was drafted by NK, reviewed and edited by MR and JH, and approved by all authors before use. The interview guide was pre-tested in a question – response – feedback format with a clinical implementer of pharmacogenomics whose responses were then ineligible for analysis. Several questions were removed following this pre-test because the questions were deemed either irrelevant or potentially confusing to respondents.

Construct	Definition
Planning	The degree to which a scheme or method of behavior and tasks for implementing an intervention are developed in advance and the quality of the schemes or methods
Engaging	Attracting and involving appropriate individuals in the implementation and use of the intervention through a combined strategy of social marketing, education, role modeling, training, and other similar activities
<i>Formally appointed implementation leaders</i>	Individuals from within the organization who have been formally appointed with responsibility for implementing an intervention as coordinator, project manager, team leader, or other similar role
<i>Opinion leaders</i>	Individuals in an organization who have formal or informal influence on the attitudes and beliefs of their colleagues with respect to implementing the intervention
<i>Champions</i>	Individuals who dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the innovation may provoke in an organization
<i>Key stakeholders</i>	Individuals from within the organization that are directly impacted by the innovation, e.g., staff responsible for making referrals to a new program or using a new work process
<i>Innovation participants</i>	Individuals served by the organization that participate in the innovation, e.g., patients in a prevention program in a hospital
<i>External change agents</i>	Individuals from within the organization that are directly impacted by the innovation, e.g., staff responsible for making referrals to a new program or using a new work process
Executing	Carrying out or accomplishing the implementation according to plan
Reflecting & Evaluating	Quantitative and qualitative feedback about the progress and quality of implementation accompanied with regular personal and team debriefing about progress and experience

**Data collection**

Once the sample of potential participants was finalized, individuals were invited via email and provided with a link to a demographic survey (Qualtrics, Provo, Utah) and scheduling

poll (Doodle, Zurich, CH) (Appendices 2 and 3). A second “reminder” invitation was sent out one week after the first if there is no response. These individuals were then contacted and successfully interviewed. No incentive was offered.

### **Data analysis**

Analysis of the final transcripts utilized resources and methodology from the CFIR website ([cfirguide.org](http://cfirguide.org)).<sup>34</sup> The CFIR codebook provides a definition of each construct and sub-construct as well as inclusion and exclusion criteria for respondent statements. The definitions provided in the codebook were used to place verbatim quotes in the appropriate construct or sub-construct. Since the question guide was based on the CFIR Process domain, most often the data were coded in the same construct as the corresponding question. However, at times, the elicited response was better coded in another construct. The constant comparative approach was used to compare each new transcript with one another to inductively identify thematic material within the constructs and sub-constructs.<sup>32</sup> Authors NK and JH read each transcript in full twice. A third read through of the transcripts was done to identify which individual quotes best represented the thematic material. No disagreements occurred that required the mediation by a third author.

### 3. RESULTS

Twenty individuals were initially contacted to participate in the interviews. Two of these individuals were unable to participate but recommended a colleague from their institution that they felt fit the inclusion criteria. Seventeen individuals completed both the screener survey and the subsequent in-depth interview. The remaining three individuals were not interviewed because data saturation had already been achieved. Figure 1 presents the results of the demographic survey. A little over half of the respondents were pharmacists (PharmD or RPh), while the remaining participants were either physicians or clinical research scientists. Most participants were CPIC members and came from academic institutions and/or institutions with at least three years of pharmacogenomic implementation experience. The institutions represent by the interview subjects mostly engage in single-gene and panel genotyping, as compared to sequencing, and just under half have implemented a preemptive model of testing.

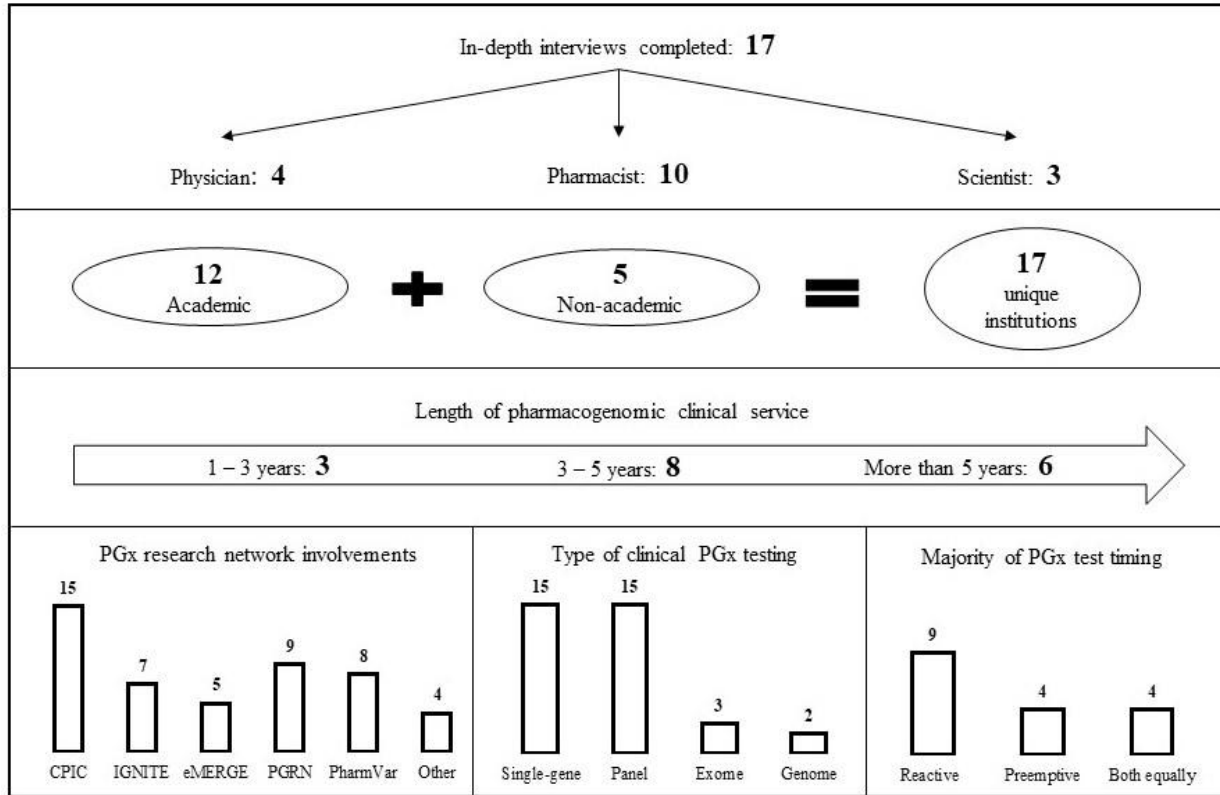


Figure 1. Interviewed individuals' demographics. PGx, pharmacogenomics; CPIC, Clinical Pharmacogenetic Implementation Consortium; IGNITE, Implementing Genomics Into Practice; eMERGE, Electronic Medical Records and Genomics; PGRN, Pharmacogenomics Research Network; PharmVar, Pharmacogene Variation Consortium. Some participants may hold more than one professional credential (MD/DO, PharmD/RPh, and PhD).

## Content Analysis

In the following sections interview participant responses to each of the constructs of the Process domain will be outlined. These findings from the CFIR Process domain should be read as an anecdotal guide for future managers of similar implementation programs. A summary of the key themes can be found in Table 2.

Table 2. Summary of key themes from constructs and sub-constructs of the CFIR Process domain		
CFIR Construct	Key Themes	
<b>Planning</b>	<ul style="list-style-type: none"> <li>• Define leadership and engagement with physicians</li> <li>• Determine where pharmacogenomics is already used and clinician workflow needs</li> <li>• Smart small and get and early win</li> <li>• Formal vs. informal oversight structure</li> </ul>	
<b>Engaging</b>	<i>Formally appointed internal implementation leaders</i>	<ul style="list-style-type: none"> <li>• Multi-disciplinary approach</li> <li>• Dedicated information technology (IT) full-time equivalents (FTEs)</li> </ul>
	<i>Opinion leaders</i>	<ul style="list-style-type: none"> <li>• Support from top leadership or visionary clinician</li> <li>• Cultural/organizational change</li> </ul>
	<i>Champions</i>	<ul style="list-style-type: none"> <li>• Different champions for different clinical services</li> </ul>
	<i>Key stakeholders</i>	<ul style="list-style-type: none"> <li>• Informal, high-touch approach</li> <li>• Utilizing pharmacists for knowledge and communication</li> <li>• Lack of formal education</li> <li>• The patient case</li> </ul>
	<i>Innovation participants</i>	<ul style="list-style-type: none"> <li>• Engagement through the patient portal</li> <li>• Patient referral</li> </ul>
	<i>External change agents</i>	<ul style="list-style-type: none"> <li>• CPIC</li> <li>• Peer organizations with similar EHR systems</li> </ul>
<b>Executing</b>	<ul style="list-style-type: none"> <li>• Lack of dedicated FTEs for pharmacogenomics</li> <li>• Feedback and adjustments to the clinical workflow</li> <li>• Creating a culture of resilience</li> </ul>	
<b>Reflecting &amp; Evaluating</b>	<ul style="list-style-type: none"> <li>• Prevailing goals for many was simply to get the program up and running</li> <li>• Process metrics (alerts fired, tests ordered, adherence to alerts) prioritized over outcome studies</li> </ul>	

### Planning construct

One of the key themes in the Planning construct was the need to have defined leadership and engagement with physicians early on. As one scientist participant said, “*Administrative*

*support is definitely something that was instrumental. The hospital administration gave the financial support and said, 'You have a year, here's some money to get started. Then it needs to sustain itself.'*” (Scientist)

Another important finding was the need to understand where pharmacogenomics was being used and optimizing workflow. A pharmacist participant said, *“Over the past year, we've spent the majority of the time trying to determine where pharmacogenomics is already being used in practice and focusing on optimizing the processes that are being employed.”*

Understanding this will likely enable implementers to lock in one of our key themes of getting an “early win”: *One of the biggest pitfalls that early programs in pharmacogenomics can do is oversell themselves. You're doing something novel. You need to have that win early on, so that people know that you can get something done.*” (Pharmacist)

There are mixed signals about what type of oversight structure is most appropriate and how this should evolve. More specifically, one respondent said, *“When we started, we very quickly got a formal [committee] structure into P&T. That committee lasted about two years. Then, the personalized medicine [group] kind of took over as the oversight”.*(Pharmacist) Some participants noted informal processes that have seemingly worked well, while others have struggled without formal oversight in place. A pharmacist participant shared this, *“Hopefully we will have one [oversight committee] in the near future...because there's no formal group right now...for the new drug-gene pair I'm trying to implement I think I have six different committees I have to present in front of.”*

## **Engaging construct**

The Engaging construct is the only one that contains specifically identified sub-constructs. The major thematic points in each sub-construct will be discussed in turn.



### Formally appointed internal implementation leaders

Since many of the participants were themselves the “formally appointed internal implementation leader”, the interview guide questions were focused on high-level support broadly and where interview participants said they wished more support would come from. At more advanced institutions, formal leadership for genomic medicine has become engrained in the culture. A physician participant stated, *“It goes without saying that the administration has to understand what it is we’re doing...but genomics implementation has been represented on the clinical strategic plan for years. So, we’ve gone through a cultural shift about how to use genomic information, so we don’t have to go to administration to make a sell.”* (Physician)

IT professionals were also frequently mentioned as being a crucial component to implementation leadership. However, according to participants there were not enough of them. In particular, a pharmacist said, *“Essentially all of our precision medicine initiatives are based on trying to use the EHR to its best effect. [This] could be farther along if we had more support for those people. [Those] in charge of the EHRs are overwhelmed with work, overwhelmed with emergencies, overwhelmed with fixing problems rather than working on strategic solutions.”* (Pharmacist)

### Opinion Leaders

Several participants noted that institutional leadership and often a visionary clinician with widespread respect was instrumental in the uptake of pharmacogenomics at their institution. As one participant put it, *“Having institutional leadership from people like deans, CEOs, and whatnot, was incredibly helpful. For specific drug-gene interactions, I think having buy in of*

*either the division chief or other clinical champions in that area has been really helpful.”*

*(Physician)*

Beyond specific individuals, a “systems” mindset was advocated for by one participant that reflected a broader finding that influence is better achieved with a cultural shift by saying, *“Well, I don't think it's one individual. I think you really must think broadly. I'm a systems person, you're still going to have to have the systems in place that are really going to support being able to implement effectively.”* (Physician) Several participants, also noted the integral role and leadership of pharmacists in the implementation of pharmacogenomics. One participant explicitly noted the level of influence pharmacists have at their institution:

*“Our physicians tend to trust the opinions of our pharmacists about how to manage drug therapy. So, if the pharmacists hadn't been on board, the physician probably wouldn't have gone for it. The pharmacists are really the ones who make a lot of detailed decisions on how to adjust drug therapy, so if they hadn't been on board, we wouldn't have been able to do the implementation”* (Pharmacist)

### Champions

The major theme herein was that engagement with a clinical champion is needed on both an institutional level, and an individual service level. One participant said, *“I think in any clinic that you want to use a pharmacogenetic test, there needs to be a clinician champion there. It takes clinician buy-in and not just somebody saying ‘Oh, we have a pharmacogenetic test here we are implementing, and you can use it.”* (Scientist) These physician champions were also useful in promoting pharmacogenomics beyond their own service as one participant described,

*“Several of our docs come to mind right away because they’ve been champions outside of their own division.” (Pharmacist)*

### Key Stakeholders

This sub-construct elicited one of the longest discussions in the interview. An informal, high-touch approach to communication was consistently described by participants as successful and in their opinion the best approach to engagement of key stakeholders. A Physician participant stated, *“We basically use more of a carpet-bombing approach...so we present it at department meetings, we present it through CME, there are online opportunities where we can present this type of information.” (Physician)*. A clinical pharmacist embedded with a physician was seen by several participants as a “catalyst” for encouraging use. A pharmacist leader said, *“I utilized our clinical pharmacist first to really learn about the services, the clinicians, and try to build upon the relationship that was already established with the pharmacy department in those areas ... I was able to be connected by someone that they already knew and trusted.” (Pharmacist)*

Few participants acknowledged formal education initiatives for clinicians, and those that did, said this was typically directed at pharmacists rather than physicians. As one participant mentioned, *“It’s difficult for physicians to commit to formal training ...” (Physician)*. Lastly, the power of the patient case, that matched patients of clinical staff, was mentioned often as a noticeable influence. As another participant stated, *“I think the first thing that was important was [for] someone to hear a case report and say, ‘Oh, you know I have ten patients I can [think] of that are in that exact same boat.’ So, I think after your first win, you become more confident.” (Pharmacist)*

### Innovation Participants

This discussion focused on how to directly engage with patients and through this, provide education that may drive their own engagement with providers. A pharmacist participant said, *“We are hoping to have more engagement with patients through the electronic patient portal where we can actually return results with associated education information...and potentially talk to them about their results...”* (Pharmacist) In line with this, a few participants noted the success of patient self-advocacy for testing saying, *“Getting the patient to advocate to their provider, in a lot of ways would be more effective. Right now our model is relying on providers...but if you are advertising to patients, and they find it interesting, and they ask the provider about it, it's going to be difficult for the provider to ignore.”* (Pharmacist)

### External Change Agents

Widely cited by nearly every participant was the role of CPIC members and the accompanying guidelines produced by the group. As one physician said, *“I'd say CPIC guidelines have been enormously helpful. Having a guideline written by experts outside of [redacted]. That external validity of the summary of the literature, and with a stamp that this is a high level of evidence, is really helpful.”* (Physician) The role of peer institutions with similar EHR programs was also identified by a few participants as a positive influence on their success. A pharmacist participant said, *“You need someone whose been there and done it to ask some questions of, particularly if they're on your same EMR platform, that's hugely helpful.”* (Pharmacist) Table 3 below includes additional verbatim quotes from the Planning construct and each of the Engaging sub-constructs.

<b>Table 3. Additional verbatim quotes from the Planning and Engaging constructs</b>			
<b>Planning construct</b>	<p>“So we did a lot of work on the front end, get [provider] input on what the alert should look like and what workflow should be for those alerts. Because we didn’t have our own system that answered through P&amp;T, we usually had to go through some other group, so we utilized medication use and safety [as our] subcommittee, and then go with them as they presented to P&amp;T. Sometimes we would [also] have to take that to the physician’s informatics group. (Pharmacist)</p>	<p>“One of my first tasks was to build relationships and knowledge, some minimal competency with the pharmacy department. I also started talking to the two groups that were really kind of already doing some pharmacogenomics testing, the first being the hem/onc group and psych group. I visited both clinics and started building relationships with the physicians. I solicited a couple of thought leaders who would support me on the pharmacogenomics oversight committee.” (Pharmacist)</p>	<p>“So the first step, we do a pretty thorough review of both the assay validity and clinical validity of the action, we want to make sure that our panel includes the right variants that provide adequate coverage for our patient population, that those variants are reproducible and all that.” (Physician)</p>
<b>Engaging construct</b>			
<b>Formally Appointed Internal Implementation Leaders</b>	<p>“I think now we’ve got a really good core group of oversight committee members. The one thing I would say is that I got buy-in from our clinical informatics service, but the problem is that they are so overwhelmed that anything I put in takes six months to implement because the backlog is so huge for everything else that’s going on in the institution.” (Pharmacist)</p>	<p>“I might have gone a little heavier on the hospital pharmacist side of things. [We] could have done ‘train the trainer’ instead of doing all the different presentations and the initial education talks between myself and our RN project leader. But I think overall, if you get too big then you’re also straddled by trying to get people together constantly. If you can be small you can be nimble.” (Pharmacist)</p>	<p>“The IT person is helpful because that’s such a major piece of the implementation. It’s really got to be person driven, and I think that the leadership skills are the most important part of a group like this rather than knowledgebase. I’ve come to learn this. I think that you need the people with knowledgebase to be able to push it forward, but leadership skills are the most important.” (Physician)</p>
<b>Opinion Leaders</b>	<p>“I think there is institutional interest, I think that’s a huge, huge thing to have that’s important. But at the end of day too, it’s a patient-physician encounter. We had to spend a lot of time learning about the actual physicians, the point of care, what do they need?” (Scientist)</p>	<p>“Definitely administrators and CMOs. Whenever we were going to a group like cardiovascular interventional or something, we typically found one [person], and we went and talked to them and then they would give an introduction, talk about it, and we would be there for backup for questions. So I think it was really helpful, we had greater success when it was more of a peer-to-peer model.” (Pharmacist)</p>	<p>“IT. For us, that was huge. We have strategic IT partners, and [mine] was aligned with our program, and she just so happened to be the manager of laboratory IT. It fit really well, because a lot of what we were doing had to do with lab results.” (Pharmacist)</p>
<b>Champions</b>	<p>“We identified patterns of pharmacogenomics prescribing, having that clinician be the champion for what we are trying to move forward. (Pharmacist)</p>	<p>“He was here, so he was our physician champion, if you will. He could get a lot of people in our organization motivated to do things, and open doors for me that I otherwise would not have had open.” (Pharmacist)</p>	<p>“As we move towards the larger roll out, we’re making sure that that’s done in large part through pharmacy, because what we found going back to what we were saying before, the physician champions, they’re just so busy that they can never be the person to really drive it. But the pharmacists, they are there and they feel a real sense of ownership over it too. They understand it easier too.” (Scientist)</p>

Table 3 continued. Additional verbatim quotes from the Planning and Engaging constructs			
Key Stakeholders	<p>“What we want to do is want to make the physician’s life easier, not harder. So how do we use pharmacogenomics to make their lives easier, that’s the other reason why I pulled the pharmacy department... They need to know, you got a resource, they got to know that you’re not making their job harder. You know so, believe me, they are happy to order a consult.” (Physician)</p>	<p>“When it came to primary care, that is a much larger group. It’s like 30 different practice sites. We had to a much larger process where we engage the practice managers, we engage the physician leads, and then we actually went to every practice and talked to them about pharmacogenomics, and we still make ourselves available to individual practitioners if they want us to come out and talk to them. I’ll show up over the lunch hour, I’ll show up after hours, have a quick chat with them about what we’re doing in pharmacogenomics, and that was really successful.” (Pharmacist)</p>	<p>“We do know that every outreach that we do, we see an uptick in our volume. This outreach can be to providers or to patients, and it can be a relatively narrow outreach, we will still see an uptick... It’s not you just do it at the beginning, and you’re done. I think that’s something a lot of programs struggle with is they want to hit a grand slam with their first swing of the bat. You can’t do that, right? In baseball, legitimately, on the first pitch, the first swing, that will never be a grand slam. We need to start thinking about small ball, and start thinking about singles, and walks, and doubles, and that’s how we’re going to win the game.” (Pharmacist)</p>
Innovation participants	<p>“Getting the patient to advocate their provider, in a lot of ways it would be more effective. Right now our model is relying on the providers, we are relying on them to be convinced of the utility and to go through and order, but if you are advertising to the patients, and they find it interesting, and they ask the provider about it, it’s going to be difficult for the provider to ignore when the patient is adamant about wanting to be referred to the clinic.” (Pharmacist)</p>	<p>“We have patient education that the clinicians can print directly from the EHR that are specific to the patient, that explains their results. With respect to more public education, that’s our next step. That’s what we want to do, and that’s one of the things that we’re doing as one of our 2019 initiatives” (Pharmacist)</p>	<p>“That’s one that actually we, or I, struggle with at times. Setting expectations, and then afterwards, the return of the results. Sometimes they come in thinking that pharmacogenomics is going to help them figure out why they’ve had an allergic reaction, like a rash, to every medication out there. That’s not something I can help with.” (Pharmacist)</p>
External Change Agents	<p>“We think ClinGen is going to be a dominant for genomic resources relevant to implementation and so integrating CPIC with ClinGen and to some degree also with ClinVar will be important.” (Physician)</p>	<p>“It’s usually specialties that have a statement about testing in their practice guidelines that are more likely to be opposed to using CPIC information. I think clinical groups that have disease states that maybe are not so straightforward are much more willing to try something that might be a little more outside the box.” (Pharmacist)</p>	<p>“We really didn’t have clinical backing or interest initially in expanding to new drug-gene pairs where there wasn’t an awareness of what CPIC was. Proving to some of our leadership that this is already being used in routine patient care and utilizing our services to improve our processes, that’s going to gain us the traction we need to expand into a larger service.” (Pharmacist)</p>

## Executing Construct

A nearly ubiquitous issue in this part of the discussions was the issue of EHR improvements and IT personnel availability. A pharmacist participant said, *“I think the biggest issue is there is no dedicated IT FTE for pharmacogenomics. It's me borrowing people's time to do clinical decision support. So it goes into a bucket with every other IT request and things sometimes move quickly, things sometimes move slowly.”* (Pharmacist) Tangentially related to this was the importance getting provider feedback regarding the workflow changes being made with the implementation of pharmacogenomic testing programs. Frustration with a lack of this was described by a participant:

*“I think failure to understand the clinical infrastructure is the biggest difficulty and my big frustration. My suggestion is to have the clinician champions go through and map the process from beginning to end because otherwise trying to implement a program that is not consistent with clinical practice, how things happen on a day to day basis...it just does not work.”* (Physician)

Understanding current workflow is crucial for effective integration of a new technology like pharmacogenomics, but several participants emphasized incorporating *resilience* into an implementer's mindset. In this case, the term *resilience* here is best explained through this quote: *“So, one of the first early lessons that I learned was just because you think you might use this in this particular service, they may have other ideas. So, one, you have to learn you might have to be patient, an avenue will open up [with] someone else who you didn't even expect to step forward”.* (Pharmacist)

## Reflecting and Evaluating Construct

Thematic material in this construct was dominated by the finding that most programs had few goals beyond the directive to put a pharmacogenomics program into place. As one scientist mentioned, *“They wanted to launch a pharmacogenomics service that would be helpful to clinicians and beneficial to patients. They didn’t feel like they needed to do it as a research project to prove outcomes or to prove cost effectiveness. They really just wanted to get it into clinical care first and foremost.”* (Scientist) The “get it going” mentality seemed to be driven by safety at its core, as a pharmacist mentioned, *“The goal of the program, the primary goal, is patient safety focused- or, medication safety focused.”* (Pharmacist)

In the absence of traditional clinical outcomes, there were other important *process* metrics that were incorporated into many programs. According to a pharmacist participant:

*“We did have some quantitative goals. We still do. We’re supposed to be showing that we have a higher percentage of prescribed drugs that are informed by pharmacogenetics, basically every year. But we did leave the objectives of the protocol quite broad and loose so that we would be able to continue to do the implementation without necessarily meeting very hard specific goals.”* (Pharmacist)

Table 4 below includes additional verbatim quotes from the Executing and Reflecting & Evaluating constructs.



Table 4. Additional verbatim quotes from the Executing and Reflecting & Evaluating constructs			
<p><b>Executing Construct</b></p>	<p>“What we found when we actually looked at the utilization of the drug across the health system is the clinician who wanted to serve as champion, [their] department was actually just a minority user of the drug and gene overall. We had to go back to the drawing board and say, ‘We need greater clinician engagement from some of these other departments that are actually higher utilizers of this drug and gene before we can make effective changes.’” (Pharmacist)</p>	<p>“One of the challenges, the way that budget and strategy happened here, the first year that we were building this, it was made known to the IT leadership that this was a primary initiative, and I was given a lot of resources for the implementation. After the second budget year, specific working about the importance of the implementation was not included in the strategy report that went to the decision makers for IT. My request for implementations were lumped in with every request that went to IT for modifications in the EHR.” (Pharmacist)</p>	<p>“It’s important to get the providers feedback on the workflow before you launch a clinic like this or just any implementation. You start and then you realize certain things don’t work and certain things work. One thing that we noticed is that writing the consult once the results come back, some of the patient medication histories are pretty extensive, and they could have a lot of complex disease states that complicates their overall picture. Some of the actual writing of the consult notes took a lot of time, and we didn’t really have more of a template of what the note looked like.” (Pharmacist)</p>
<p><b>Executing Construct</b></p>	<p>“I would say it actually went better because I never had envisioned an outpatient clinic to start. So that has grown far bigger than I ever thought. I want to say that I wish I had more alerts in place. Right now we cover about 180 drugs I think, but there’s so much more we could do and it just is [an] informatics backlog, that’s the biggest thing.” (Pharmacist)</p>	<p>So any type of implementation has to be equipped to rapidly monitor the difficulties that are inevitably going to arise and to have the ability to rapidly reiterate and revise the program to achieve the desired implementation in a very short time frame. So this is really applying principles of rapid cycle quality improvement.” (Physician)</p>	<p>“But we also are in a situation to where if we lose a little bit of money on a personalized medicine effort that isn’t going to affect the finances greatly, but it improves the patient outcome, then that’s also a step that we can take as well. So, it’s not all numbers. There is the patient aspect of it and that if it’s doable and it’s going to benefit the patients then there’s a pathway forward.” (Pharmacist)</p>
<p><b>Reflecting &amp; Evaluating Construct</b></p>	<p>“They wanted to launch a pharmacogenetics service that would be helpful to clinicians and beneficial to patients. They didn’t feel like they needed to do it as a research project to prove outcomes or to prove cost effectiveness or anything like that. They really just wanted to get it into clinical care first and foremost.” (Scientist)</p>	<p>“The goals and outcomes became... were developed as we moved forward, but I would say it was in fact actually too fluid in a lot of respects. There weren’t great clinical outcomes in place that are easily capturable from the medical record. So really what that requires is our discrete variables added to the medical record and/or a good definition before and after the implementation so that you can monitor the effect of the implementation.” (Physician)</p>	<p>“So, I think that the new challenge... now that we are creating infrastructures, now that we are putting in this practice, how do we demonstrate the value that pharmacogenomics can really offer? And I think my argument would be that it’s more the value the pharmacist can offer, with adding pharmacogenomics to their practice, and making better drug recommendations.” (Physician)</p>

## 4. DISCUSSION

This study represents one of the first primary data studies to qualitatively assess the perspectives of the leading voices in the clinical implementation of pharmacogenomics. Also, this is the first study to apply the rigor of an implementation science framework to pharmacogenomics. The core finding from the Planning construct was the idea that for successful implementation you must first do the appropriate due diligence on the clinical services and clinicians themselves prior to engagement. Following from this, several participants noted the importance of getting an “early win” to demonstrate to leadership that you can accomplish something tangible. It is also important to recognize the limitations of pharmacogenomics at your institution. A narrow, high-evidence focus will prevent a novice program from overselling and causing frustration in the future. The discussion of formal oversight also brought to light several important considerations. First, oversight covered the spectrum from formal committee to very informal, ad-hoc processes. However, it is important to note that there always remained some type of process. While it is unsurprising that newer programs may lack formal oversight, it was surprising to note that some of the most mature programs also lacked formal oversight. This seemed to be a product of pharmacogenomics folding into larger genomic initiatives with their own oversight processes.

Across the sub-constructs of the Engaging construct there was a clear focus on the importance of institutional leadership supporting the implementation. This took shape through C-suite executives who found particular value in pharmacogenomics, visionary clinicians, or in a

broader sense, a cultural shift to one where genomics was integral to all clinical care. At a more detailed level, participants widely noted that having a clinical champion in each service was essential to communication with the broader clinical network. Having a single individual to contact who then forwarded the information to colleagues was both successful and timesaving. However, this did not always have to be a physician-to-physician conversation. Many participants noted that they utilized the clinical pharmacist on service as a communication conduit to prescribers. From both pharmacists and physicians, there was strong opinion that all pharmacists should have some tacit knowledge of pharmacogenomics and be ready to interact with any prescriber when needed.

The lengthy discussions on provider communication led to the ubiquitous opinion that informal, high-touch interactions were optimal. Terms such as “carpet-bombing” and “traveling roadshow” quickly showcase this sentiment. This was typically operationalized through grand rounds, lunch-and-learns, and even the classic “water-cooler” conversation. The importance of the patient case or the patient-driven referral was also a catalyst of provider engagement in pharmacogenomics.

The Executing construct discussion centered around clinical decision support and clinical workflow. A common refrain was the need for more dedicated pharmacogenomic FTEs in the IT profession. Interfacing these individuals with more frequent clinical feedback on CDS language is essential to more effective workflow. *Resilience* should also be a part of every implementer’s toolkit. Perspectives from our participants indicated that even though a first attempt might fail, either opinions in the clinical service may change or a service you did not expect might come to you.

The Reflecting & Evaluating construct revealed a prevailing focus on patient safety and programmatic goals to simply establish and maintain a clinical pharmacogenomic service. Explicit data collection and measurement that did exist were not targeting clinical or economic outcomes, but rather they were process-based metrics for how pharmacogenomics was being used and how providers were responding to the addition of pharmacogenomic decision support alerts in the EHR. In some instances, these initial goals were simply to move pharmacogenomic results into discrete data fields and enable metric tracking. This is an essential step towards outcomes-based studies that reflect real-world clinical practice and decision making.

This study used a popular implementation science framework, the CFIR, to address several issues, including the need for greater clinical education in genomics and improvements in clinical workflow and decision support, that were identified as important for the sustainability of genomic medicine and pharmacogenomics. We decided to focus our efforts on the foundational concept of sustainability in implementation science because it has received increasing attention as one of the most important, yet more misunderstood foundations of implementation science.<sup>35</sup> The study is somewhat limited due to the unbalance in the professional credentials of the respondents. This unbalance is, however, indicative of the current leadership and programs in the field. Also, focusing only on the CFIR Process domain excludes the potential application of other CFIR domains to this topic. Future research should explore other CFIR domains for their insights into clinical pharmacogenomic implementation.

Our decision to study the CFIR Process domain and its operationalization herein can be further understood by connecting this domain with *sustainability*. Sustainability has been conceptualized not just as an outcome or metric of a successful implementation, but also as a cyclical “change process” that provides adaptability in pre-implementation stages such as

planning and organizational support, as well as a concomitant process to the implementation itself.<sup>36,37</sup> Indicators of sustainability have been operationally defined as maintenance, institutionalization, and (infrastructure) capacity building.<sup>38</sup> Capacity-building in the *sustainability planning model* is represented by factors that apply to both physical and human infrastructures which include: structures and linkages, champions and leadership, resources, policies and procedures, and expertise.<sup>29,36</sup> The nature of the constructs and sub-constructs of the Process domain are characterized by a similar set of terms.

Sustainability in pharmacogenomics is particularly important when we consider what several participants described as a research-to-clinical progression of the program. Initial internal or extramural funding supported many programs with the expectation that the program would be self-supporting in the future. The formal implementation programs in pharmacogenomics represented by our participants for pharmacogenomics have been leading the way in the clinical use of genomic medicine and development of the resources necessary to support the delivery of results.<sup>19,39</sup> However, most health care institutions in this country do not have robust clinical pharmacogenomic programs and current implementers of pharmacogenomics have expressed concerns of handoffs outside of their own program.<sup>15</sup> The potential ‘down-the-road implications’ of pharmacogenomic results on future therapeutic decision making will require that local health systems adopt and implement their own programs. They must do this carefully and sustainably from the start because most will not have the luxury of robust institutional or extramural support.

Armed with a deeper understanding of the Process domain and the infrastructure capacities necessary to achieve sustainability of the program, future implementers of clinical pharmacogenomics now have a list of factors to consider in designing their own programs with sustainability at its core. Moreover, they have the ability to avoid some of the roadblocks and

challenges these innovators have faced. Future work should examine more closely the economic implications of revising an initial implementation plan. Future resource-limited institutions must be able to prioritize the initiatives to establish a clinical and operationally effective pharmacogenomic program while keeping costs to a minimum.

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## APPENDIX

## APPENDIX 1. – SEMI-STRUCTURED INTERVIEW GUIDE

Thank you for taking the time to speak with me today. My name is Nick Keeling and I am the principal investigator on this project. I want to inform you that I'll be recording this interview, and that quoted material may be used for a future publication. Your name and the name of your organization will always remain confidential. We expect this interview to take approximately 45 minutes. You may withdraw at any time if you wish.

You were asked to be a part of this study because of your clinical, research, and implementation experience with pharmacogenomics. Please answer these questions as thoroughly as possible. We believe that your insights can guide future implementers of pharmacogenomics and lead to greater standardization across different care settings.

Do you have any questions for me before we begin?

1. To get started, tell me a bit about your general organizational roles: clinical, research, and administrative.
2. Do you know how your organization became involved in using pharmacogenomics in routine patient care? When did it begin?
  - Is pharmacogenomics the primary genomic related initiative? Why was pharmacogenomics chosen over something else?

### PLANNING

3. What were the steps involved in getting a plan in place for implementing the pharmacogenomics program?\*
- Who was involved in the planning process?
4. Tell me how it was communicated to clinicians, leadership, research
5. Was a formal committee put together to direct the implementation of pharmacogenomics?\*
- Tell me about its structure. How and when was it was organized?

### ENGAGING

#### Formally Appointed Internal Implementation Leaders

6. Who has led the implementation of the pharmacogenomics program at your organization (physicians, pharmacists, others clinical or non-clinical personnel)?\*

7. Are there certain groups that you wish had been included at the beginning that would have made implementation more successful?

### **Opinion Leaders**

7. Who were the key influential individuals (or opinion leaders) to get on board with implementing a pharmacogenomics program?
  - o To what extent have these individuals influenced others' use of pharmacogenomics? Success of the implementation?

### **Champions**

8. Other than formal implementation leadership, what people in your organization have taken on the role of a 'champion' for pharmacogenomics?
  - o How has this supported the implementation? What has been most productive?
  - o Who else is needed to 'champion' this successfully?
    1. More administrators, advanced practice, genetic counselors?

### **Key Stakeholders**

11. What steps have been taken to encourage clinicians to use pharmacogenomics?\*
- o What was the most successful way to communicate with or approach them?
- o What types of training were offered to your clinicians?

### **Innovation Participants**

12. What has been the communication strategy for getting the word out about pharmacogenomics to patients and families?
  - o What certain communication processes have worked best?

### **External Change Agents**

15. What role, *if any*, have peers, external organizations, research groups, or individuals played in helping execute the pharmacogenomics program at your organization?\*
- o How were/are they involved? What kinds of activities were/are they doing?

## **EXECUTING**

8. Has your pharmacogenomics program been implemented according to the initial plan?

9. Were there aspects of the plan that created difficulties in the implementation of the plan?
10. What were some of the more significant revisions or refinements to the plan that were developed during the implementation process?
  - How were these shared with other key stakeholders?

## **REFLECTING & EVALUATING**

16. Were there explicitly set goals you and your team developed in relation to the implementation of your pharmacogenomics program?\*
- Were these communicated beforehand? To whom?
- What goals still remain?
17. What data are collected/measures tracked to evaluate progress toward the goals?\*
- Are these clinical, economic, or descriptive?
18. Have you collected structured feedback from clinical staff on their experiences with pharmacogenomics?
  - Was it positive? Negative? Neutral?
  - Was this collected with the intent to publish? Or for internal use?
    1. If yes, was this published and in what setting?
    2. If no, what was this rationale?
19. How have these outcomes been distributed to implementation leaders and other appropriate stakeholders? Mode? Frequency?
  - How has this been used to improve practice?
20. What experience has made the biggest impact in improving the delivery of pharmacogenomics?

That is all the specific questions I have for you today. Is there anything else you would like to add to our discussion? Feel free to be as broad or detailed as you'd like.

Thank you so very much for your time.

## APPENDIX 2. – INVITATION EMAIL FOR SURVEY AND INTERVIEW

Good Morning,

This is an invitation to participate in ongoing academic research focused on the implementation and sustainability of pharmacogenomics. *(If the potential respondent was nominated through snowball sampling the following sentence will be added: “You were nominated by \_\_\_\_\_ as an appropriate person to participate in this research.”)*

This research includes a 5 minute survey and telephone interview expected to last around 45 minutes. The interviews will take place between XXX and XXX. The interviews will be recorded, but your name and organization will remain confidential. We do not believe there are any risks associated with this research. You do not have to take part in this study and you may stop participating at any time.

Please click the link just below to complete the survey. Your responses to this survey will not affect your eligibility to participate in the interview.

<<<Qualtrics link>>>

Please fill out this confidential Doodle poll with your preferred time for the interview.

<<<Doodle poll link>>>

Please contact **Nick Keeling** at [nick.keeling@stjude.org](mailto:nick.keeling@stjude.org) if you have any questions. Nick will reach out to you with a calendar invite at one of your available times.

As a reminder, this study has been approved 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](mailto:irb@olemiss.edu).

I have read and understand the above information. By completing the survey and interview I consent to participate in the study.

Thank you very much for your time.

### APPENDIX 3. – ONLINE DEMOGRAPHIC SURVEY

Thank you for your participation in this research. Responding to this survey serves as your consent to participate. Please answer all the questions. Your name and organization will always remain confidential.

1. Are you at least 18 years of age or older?
  - Yes
  - No (not eligible to continue)
2. Are you a...?
  - Physician (MD or DO)
  - Pharmacist (PharmD or RPh)
  - Clinical research scientist (PhD)
  - Other, please specify \_\_\_\_\_
3. Are you at an academic institution?
  - Yes
  - No
4. Please select any pharmacogenomic research groups/networks/consortiums you are either involved with or a member of (*select all that apply*)
  - CPIC
  - IGNITE
  - eMERGE
  - PGRN
  - PharmVar
  - Other, please specify \_\_\_\_\_
5. How long has your institution been implementing pharmacogenomics into clinical service?
  - Less than 1 year
  - 1 – 3 years
  - 3 – 5 years
  - More than 5 years
6. How many germline variants do you currently have in clinical service?  
\_\_\_\_\_ variants
7. Please select the type(s) of **clinical** pharmacogenomic testing your institution conducts (*select all that apply*)
  - Single-gene genotyping
  - Multi-gene genotyping
  - Exome sequencing for pharmacogenes
  - Genome sequencing for pharmacogenes



8. Is most of your **clinical** pharmacogenomic testing done...
- Preemptively
  - Reactively
  - Both

## APPENDIX 4. – EMAIL TO ASSIST IN SNOWBALL SAMPLING

Good Morning,

Thank you again for participating in the recent interview on pharmacogenomic implementation.

We are reaching out to you again today to ask you to nominate one or more additional potential respondents to complete the same interview. You are under no obligation to nominate additional participants and your choice has no bearing on your previous response.

Please respond to this email with the name, credential, professional job title, and best contact email for your nominated respondent(s).

By responding to this email with your nominations you are also consenting for us to reveal your name to your nominee(s).

Please contact **Nick Keeling** at [nick.keeling@stjude.org](mailto:nick.keeling@stjude.org) with any questions.

As a reminder, this study has been approved 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](mailto:irb@olemiss.edu).

Thank you very much for your time.

SECTION III.

SUSTAINABLE DELIVERY OF PHARMACOGENOMICS IN  
PRIMARY CARE: TESTING THE POTENTIAL FOR PHYSICIAN-  
PHARMACIST COLLABORATION

## 1. BACKGROUND

Implementation programs for pharmacogenomics, and studies of genetic variation and its influence on drug response, continue to increase in number and public funding.<sup>1</sup> As barriers are overcome, the most challenging obstacles to the continued success of this field of study become clearer. Two such obstacles preventing broader use of “clinical pharmacogenomics”, a term used to reflect its application in clinical practice, are provider knowledge/education and testing reimbursement by insurers.<sup>2-6</sup> In fact, the Implementing Genomics into Practice (IGNITE) Sustainability Working Group recently identified the need for expanded (pharmaco)genomic education for providers as the most important construct for the sustainability of the science.<sup>5</sup>

The noted insufficiencies in provider knowledge about pharmacogenomics and preparedness to use these results reaches back several years and stubbornly persist.<sup>7-10</sup> Studies from 2012 found that although nearly all (98%) of physicians believed the patient’s genetic profile influences their response to drug therapy, 90% felt inadequately informed on testing availability and application, and approximately 80% of primary care physicians (PCPs) had never ordered a pharmacogenomic test.<sup>7,11</sup> More recent work shows limited progress in the number of tests ordered, with around 30% of physicians reporting having ordered or recommended a pharmacogenomic test in the past six months.<sup>9</sup> Despite this improvement, family physicians, a first touch-point for many patients, still have a lower likelihood of adopting pharmacogenomics.<sup>9</sup> This compounds concerns from physicians based in academic settings,

actively engaged pharmacogenomic implementation, around patient hand-offs to providers outside of these institutionally based pharmacogenomics implementation programs.<sup>12</sup>

Despite some of these shortcomings, physicians from pharmacogenomic programs within the IGNITE network are reporting improvements in adequate training and confidence regarding the use of pharmacogenomics.<sup>10</sup> Physician attitudes on the clinical usefulness, training and preparedness, and awareness of resources were all statistically significantly more positive for pharmacogenomics as compared to disease genetics.<sup>10</sup> Being able to find and use reliable sources of information to understand and communicate risk also had higher reported odds for pharmacogenomics compared to disease genetics.<sup>10</sup> However, confidence in the ability to use pharmacogenomic results remained low with 30% of physicians responding as such.<sup>10</sup>

Parallel research with pharmacists has demonstrated a pharmacogenomic education need for these providers as well. While nearly all pharmacists had positive attitudes toward pharmacogenomics, and more than half (57%) believe it is their role counsel patients on this information, less than 20% feel their training had been adequate to deliver this information.<sup>13</sup> Early assessments of pharmacists as providers of pharmacogenomics found that 85% felt they should be knowledgeable and 65% said they should be capable of providing information on appropriate use of testing.<sup>14</sup>

The pharmacy profession has also taken lead in the education of providers through pharmacogenomics curriculum development and continuing education programs.<sup>15-17</sup> Researchers from the Mayo Clinic shared their approaches to achieving competencies in pharmacogenomics for healthcare professionals. In particular, they highlighted their work with educating pharmacists, the unmet need to craft “genomic nurses”, and the overall importance of

transdisciplinary care in this field.<sup>18</sup> Successful pharmacogenomics implementation programs at academic health systems have been delivered in a highly collaborative infrastructure, several of which have been led by senior pharmacists.<sup>4,19,20</sup> Additionally, two of the largest professional pharmacy organizations, the American Society of Health-System Pharmacists (ASHP) and the American Pharmacists Association (APhA), have both put out official positions and statements in the past decade on the role of the pharmacist in the delivery of pharmacogenomics.<sup>21,22</sup> Specifically, they highlight the unique skills and abilities of pharmacists, their relation to the delivery of pharmacogenomics, opportunities for integration into medication therapy management (MTM) services, and call on the educational community to prepare pharmacists to apply pharmacogenomic information to therapeutic decision-making.

#### *Pharmacist-physician collaboration in pharmacogenomics*

Pharmacists possess a clinical skill set complementary to the delivery of pharmacogenomics with their specialized training in the pharmacokinetics and dynamics of medications, their interactions, and dosing, all of which can be applied to reduce adverse events driven by drug-gene interactions.<sup>23</sup> The noted successes of institutional pharmacogenomic programs led by senior pharmacists has resulted in recent calls to study the role of the pharmacist as the local ‘clinical champion’ in greater detail.<sup>24</sup>

Collaborative practice agreements (CPAs) or collaborative drug therapy management programs (CDTMs) between physicians and pharmacists may be one way to improve the delivery of pharmacogenomics through a transdisciplinary structure in primary care, and to address those constructs most important to the sustainability of genomic medicine.: expanding provider education and improving the integration of genomic information into workflow.<sup>5</sup> CPAs

and CDTMs expand pharmacists' involvement in patient care by providing a defined protocol under which pharmacists may complete assessments, provide counseling, order diagnostic tests, and manage the patient's drug regimen.<sup>25</sup> It is important to recognize that legislation pertaining to CPAs and CDTMs differs from state to state. Pharmacists may enter into formal collaborative practice agreements in 48 states and the District of Columbia.<sup>26</sup> Of these states, 38 allow pharmacists to initiate drug therapy and 45 allow them to modify an existing therapy. These allowances must be explicitly stated in the agreement, and in 29 states there is a requirement to specify which medications or disease states the pharmacist can manage. Additionally, 31 states currently allow the pharmacist to order and interpret laboratory tests, which could include pharmacogenomics.<sup>26</sup>

A meta-analysis of US pharmacists' involvement in a patient care team found significant improvements in both therapeutic, safety, and humanistic outcomes over comparative services.<sup>27</sup> Recent studies with physicians in active supervisory roles of a clinical pharmacist in a CPA have reported better clinical outcomes, more efficient medication management, clinically helpful recommendations, improved efficiencies in care, and an advanced learning environment which includes newly accessible drug knowledge.<sup>28,29</sup> Limited reimbursement and billing considerations are the most frequently reported barriers; as well as worries over a loss of control and confidence in the pharmacists' clinical.<sup>29,30</sup> Under four percent of responding primary care physicians indicated they would not be accepting of clinical pharmacist practitioners.<sup>29</sup> However, previous literature has shown that 25% of pharmacists feel that acceptance by primary care physicians is a barrier to collaborative practice.

Family physicians and community pharmacists in Canada, a country where the traditional function of a pharmacist more closely mirrors the CPA function of US pharmacists, also report

contrasting perceptions of importance in the function of community pharmacists.<sup>31</sup> There was 44% agreement for the pharmacist function “providing advice regarding drug interactions” and 25% for both “assisting in medication dosage adjustment” and “providing drug information to help select a medication”, suggesting there remains space for improvement.<sup>31</sup> Economic analyses of pharmacist-physician collaborations have also reported positive (cost-saving) findings in addition to clinical improvements across various scenarios.<sup>32,33</sup>

The role and responsibilities of the pharmacist in the delivery of clinical pharmacogenomics has been also been examined. A prospectively designed pilot study measured the clinical support of two different pharmacist models (in-house vs. on-call) at two primary care clinics.<sup>34</sup> A pre-test assessment among the primary care physicians showed that over 90% felt having assistance in interpretation of pharmacogenomic results would increase the likelihood of them ordering a test. Eighty-nine percent thought that the pharmacist or the geneticist/genetic counselor would have “some or a large role in delivery pharmacogenomic testing”.<sup>34</sup> Results from the pilot study also showed that the physical presence of a pharmacist enhanced the pre-held perspectives.<sup>34</sup> Interestingly, when the ‘continued test utilization’ was assessed, one-third of providers reported that they were ‘very or somewhat likely’ to continue ordering. However, when the pharmacist was removed from the clinic there were no new pharmacogenomic tests ordered.<sup>34</sup> This illuminates the role that the pharmacist has in the sustainment of pharmacogenomic test ordering.

Pharmacists appear well-positioned to assist in the clinical delivery of pharmacogenomics. The positive outcomes of using pharmacists in primary care teams, success of pharmacist-led pharmacogenomic implementation programs, a pharmacy profession leading new educational initiatives in pharmacogenomics, and a scope of practice in many states enabling pharmacist



involvement in pharmacogenomics provide support for this statement.<sup>35</sup> Although most physicians perceive collaborating with a pharmacist as being beneficial to their practice and patients, there is little consensus from physicians, and a need for further study, on the level of clinical responsibility they should have, including the pharmacist role in the delivery of clinical pharmacogenomics.

Designing the implementation and delivery of pharmacogenomics in the primary care setting could benefit from similar collaborative infrastructures as those outlined in the pilot studies. The challenge before the pharmacogenomics community will be to design these implementations with a solid understanding of the factors impacting its longer-term sustainability. As such the objective of this study is to understand how primary care physicians currently view the use of pharmacogenomics in practice and how clinical collaboration with pharmacists may influence their perspective.

#### *Implementation science and study hypotheses*

Previous research has provided the field of implementation science, the study of methods to improve the adoption of evidence-based research and practice, with a “working taxonomy” of eight outcomes to use when evaluating successful implementation.<sup>36,37</sup> Three of these outcomes: acceptability, appropriateness, and feasibility, were recently developed into measures with their psychometric properties having been assessed.<sup>38</sup>

- Acceptability is “personal”: individual judgments of ‘clinical pharmacogenomics’ based on differing needs, preferences or expectations.<sup>37</sup>

- Appropriateness is “technical or social”: judgments based on the efficacy of the ‘clinical pharmacogenomics’ achieving some purpose under certain conditions (type of patient, culture, *infrastructure*, etc).<sup>37,38</sup>
- Feasibility is “practical”: judgments based on the perceived ease of implementing ‘clinical pharmacogenomics’ given the individual’s necessary resources (effort, time, or money) and unique circumstances.<sup>37,38</sup>

The three measures of these implementation outcomes are the Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure (FIM).<sup>38</sup> High scores on these outcome measures provide researchers an early indication of the likelihood that staff will adopt a new ‘something’, or if more work is needed to increase scores in one or more outcome measures. Standardizing the use of implementation outcomes has been seen as a critical step for conceptualizing and evaluating the success of a new intervention.<sup>39</sup> The outcomes serve as both indicators of a successful implementation and intermediate outcomes related to the eventual clinical, economic, or social outcomes. Without a successful implementation, the intervention or treatment is likely to be ineffective.<sup>39</sup> To make clinical pharmacogenomics effective to patients, we must ensure the providers delivering the intervention are doing so in such a manner to facilitate its success. Further, these standardized measures make future meta-analyses on this subject possible.

Using these measures, we aimed to collect primary care physicians’ (PCPs) current opinions on the acceptability, appropriateness, and feasibility of pharmacogenomics in their primary care practice. An exploratory analysis was conducted to identify what demographic variables were significant predictors of the baseline AIM, IAM, and FIM scores. As the central analysis herein, we aimed to test the appropriateness and feasibility of delivering of clinical pharmacogenomics

across experimentally manipulated scenarios that reflect realistic, potential variations in the roles of physicians and pharmacists. The following research questions and hypotheses were tested:

**Research question 1:** What level of pharmacist involvement in the functions of delivering clinical pharmacogenomics do primary care physicians find most appropriate?

**Hypothesis 1.** The appropriateness of clinical pharmacogenomics will be positively associated with greater levels of pharmacist involvement and collaboration.

**Hypothesis 1a.** PCPs will consider clinical pharmacogenomics more appropriate when the pharmacist is located in the clinic.

**Hypothesis 1b.** PCPs will consider clinical pharmacogenomics more appropriate when the pharmacist selects and orders the pharmacogenomic test.

**Hypothesis 1c.** PCPs will consider clinical pharmacogenomics less appropriate when the pharmacist modifies the medication regimen and counsels the patient.

**Research question 2:** What level of pharmacist involvement in the functions of delivering clinical pharmacogenomics do primary care physicians find most feasible?

**Hypothesis 2.** The feasibility of clinical pharmacogenomics will be positively associated with greater levels of pharmacist involvement and collaboration.

**Hypothesis 2a.** PCPs will consider clinical pharmacogenomics more feasible when the pharmacist is located in the clinic.

**Hypothesis 2b.** PCPs will consider clinical pharmacogenomics more feasible when the pharmacist selects and orders the pharmacogenomic test.

**Hypothesis 2c.** PCPs will consider clinical pharmacogenomics more feasible when the pharmacist modifies the medication regimen and counsels the patient.

## 2. METHODS

### **Study design**

This study used a quantitative survey methodology that included a series of experimental vignettes. Experimental vignette surveys typically consist of short narrative scenarios or lists of attributes manipulated via the included levels. This allows the researcher to exert a level of experimental control, excluding variables that might confound results, and establish causal relationships if they exist.<sup>40</sup> Incorporating vignettes has been shown to be a practical methodology for the assessment of clinical practice scenarios.<sup>41</sup>

### **Survey instrument**

The survey consisted of two main sections: the first captured participant demographics, practice characteristics, data on the respondent's practice integration with pharmacists and familiarity with collaborative practice, and the respondent's experiences and perspectives on clinical pharmacogenomics. The second was the experimental vignette portion which will be described in more detail below.

Several practice characteristic questions were adapted from a survey instrument developed by the National Cancer Institute for evaluation of primary care physician recommendations and practice for cancer screening.<sup>42</sup> Changes made included the altering the type of response (multiple choice vs. open response) or decreasing number of multiple-choice options available to the respondent. Three items to assess perceived knowledge of

pharmacogenomics in this section come from the IGNITE Common Measures Working Group “Provider Baseline Knowledge of Genetic Testing Survey” and are available online in the IGNITE Spark Toolbox.<sup>43</sup> These items were chosen so that a comparison of respondents perceived knowledge of using pharmacogenomics could be made to their awareness of the leading pharmacogenomic resources such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB). Also, a baseline assessment of ‘acceptability’, ‘appropriateness’, and ‘feasibility’ of clinical pharmacogenomics was measured using the AIM, IAM, and FIM scales. The term ‘clinical pharmacogenomics’ replaced the word “intervention” in the author’s original scales.<sup>38</sup> For the IAM and FIM scales, the language ‘in my primary care practice’ was added. The authors explicitly state in the psychometric study that the items were made as “general as possible” to facilitate adaptation to specific contexts or clinical problems.<sup>38</sup> Each item is measured using a 5-point Likert-type response format and scores were created by averaging responses for all items in each scale.

### Independent variables

The vignette portion of the survey was a 2 x 2 x 2 between-subjects experimental design.

Table 1 describes the levels of the factors in more detail.

Factors	# of levels	Description of levels
Pharmacist location	2 (b/w)	<ul style="list-style-type: none"> <li>• In the clinic</li> <li>• Outside the clinic</li> </ul>
Selects and orders pharmacogenomic test	2 (b/w)	<ul style="list-style-type: none"> <li>• Pharmacist</li> <li>• Physician</li> </ul>
Manages results and modifies the patient’s medication regimen	2 (b/w)	<ul style="list-style-type: none"> <li>• Pharmacist</li> <li>• Physician</li> </ul>

The factor ‘pharmacist location’ mirrors the two pharmacist arms of the Haga et al. trial discussed previously.<sup>34</sup> The remaining factors represent the varying responsibilities a pharmacist might have with the delivery of pharmacogenomic testing in a collaborative practice environment. These include the responsibilities of selecting and ordering the test and the subsequent management and use of the results for modification of drug therapy. Table 3 shows each factor and its corresponding levels, as well as a description of the levels. The survey was pre-tested with two primary care physicians reflective of our target sample and slight revisions to clarify the language in the vignettes were made based on this feedback. The exact language of the vignettes can be found at the end of Appendix 1.

### **Dependent variables**

The outcome measurement following the experimental vignettes was a reassessment of the IAM and FIM scales with the language “delivered this way” inserted into the original measure to better reflect the information presented in the vignettes. Only the IAM and FIM were selected for measurement following the vignettes because the aforementioned ‘criterion’ descriptions of these two scales better capture the objective to understand the potential for collaborative practice in the delivery of clinical pharmacogenomics. The same adaptation to measures described previously was maintained in the reassessment to reinforce the focus on the appropriateness and feasibility of clinical pharmacogenomics to their practice broadly. The AIM scale was excluded from the vignette because the language of the items was not sensible given the objective and focus on collaborative practice environments.

## **Data collection and sampling methods**

A power analysis indicated that to achieve a power of at least 0.90 to detect medium main and interaction effects with a significance level of 0.05, a total of 176 respondents were needed. Given our 2x2x2 design, this required 22 cases for each of the eight treatment groups. To facilitate this data collection, Reckner Healthcare (Chalfont, PA) was engaged to recruit a sample of primary care physicians (family medicine or internal medicine) from their available panel. An invitation email consistent with Reckner Healthcare's policies was distributed to eligible primary care physicians on their panel. These physicians were not offered any incentive but were provided with a summary of the results upon analysis (APPENDIX 2). Participants were randomly assigned to one of the eight treatment groups upon beginning the survey and data collection continued until the required 22 cases per group was achieved.

## **Analysis procedure**

A descriptive analysis provided data on general and pharmacist-related practice characteristics, as well as mean scores on the AIM, IAM, and FIM scales prior to any manipulation. Scale values on these three outcomes range from 1 to 5, have been treated as continuous variables for analysis, and averaged for a single score. Higher scores indicate greater levels of acceptability, appropriateness, or feasibility. Three separate multiple regressions were used to assess if there were significant predictors of the baseline mean scores of the AIM, IAM, and FIM without experimental manipulations. Predictors included questions related to the importance of pharmacists in clinical care, perceived pharmacogenomic knowledge as measured by the three items from the IGNITE Spark Toolbox, and the average score across the familiarity with CPIC and PharmGKB. These predictors were included because of their association with



provider education and pharmacist collaboration. To test the effect of the independent variables on the scores for the IAM and FIM scales after vignette manipulation, the data were analyzed using a three-way analysis of variance (ANOVA) procedure for each of the two dependent variables. All tests were conducted at the  $\alpha=0.05$  level of significance.

### 3. RESULTS

The number of respondents to achieve our desired power and to satisfy equal stratification across our eight groups was achieved with a final sample of 177 family practice or internal medicine physicians. Data collection was closed as soon as 22 respondents were collected for each group. One group or vignette received an extra respondent likely due to another respondent starting the survey and finishing later. This extra respondent was excluded from any analysis.

Nearly two-thirds of respondents were family medicine physicians and close to 90% having practiced more than 16 years. Most were either practice owners or associates and worked in practices with 30 or fewer physicians. About a third of respondents worked in multi-specialty clinics. On average, physicians reported that collaborating with a pharmacist in their primary care practice fell between somewhat and moderately important (3.47 on a 5-point Likert-type item). Physician familiarity with CPAs scored between slightly and somewhat (2.5 out of 5). Just over three-quarters of physicians indicated that they only interact with a community pharmacist, the remaining responded that they had a full-time or part-time pharmacist that worked in the clinic. Fifteen percent of physicians indicated that pharmacist involvement was part of a formal CPA. Of those involved in a formal CPA, 85% granted the pharmacist full access to patient's medical records.

Several questions were asked related to the physician's exposure and experience with pharmacogenomic testing in their practice and revealed some interesting findings. Familiarity

with using pharmacogenomic information scored between slightly and somewhat familiar (2.63 out of 5). On the three items from the IGNITE Spark Toolbox scores were slightly higher than overall familiarity, ranging from 2.96 on the “my training has prepared me to treat patients whose genetics place them at high risk for medical conditions” item and a 3.18 on the “I am confident in my ability to use the results of a pharmacogenomic test” item as well as the I can find/use reliable sources of the information I need to apply pharmacogenomic testing while caring for patients” item.<sup>43</sup> Scores on the items assessing familiarity with Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledgebase (PharmGKB) were much lower, 1.61 and 1.59, respectively. Most respondents (66%) have never had a patient ask about pharmacogenomics and just over half had never used pharmacogenomic information in patient care. Insurance coverage and reimbursement remain top barriers to more widespread use. Close to 80% of physicians indicated that removing selection and ordering of the test from clinical workflow would make delivery more feasible. Appendix 3 contains complete tables of respondent demographics and practice characteristics.

Baseline assessment of the implementation outcomes from Weiner et al., acceptability (AIM), appropriateness (IAM), and feasibility (FIM) scales, are provided below in Table 2.<sup>38</sup> Scores on the AIM were the highest across the three with a slight drop on the IAM scale, and a further drop on the FIM. Only the last item in the FIM scale scored, on average, below a 3 on a 5-point Likert-item.

<b>Table 2. Implementation Outcome Measures Applied to Clinical Pharmacogenomics</b> (1 = Strongly disagree, 5 = Strongly Agree)	<b>Mean</b>
<b>Acceptability of Intervention Measure (AIM)</b>	
Clinical pharmacogenomics meets my approval	3.72
Clinical pharmacogenomics is appealing to me	3.77
I like clinical pharmacogenomics	3.62
I welcome clinical pharmacogenomics	3.73
	<b>Overall Mean = 3.71</b>
<b>Intervention Appropriateness Measure (IAM)</b>	
Clinical pharmacogenomics seems fitting in my primary care practice	3.45
Clinical pharmacogenomics seems suitable for my primary care practice	3.48
Clinical pharmacogenomics seems applicable to my primary care practice	3.60
Clinical pharmacogenomics seems like a good match for my primary care practice	3.49
	<b>Overall Mean = 3.50</b>
<b>Feasibility of Intervention Measure (FIM)</b>	
Clinical pharmacogenomics seems implementable in my primary care practice	3.19
Clinical pharmacogenomics seems possible for my primary care practice	3.54
Clinical pharmacogenomics seems doable in my primary care practice	3.36
Clinical pharmacogenomics seems easy to use at my primary care practice	2.99
	<b>Overall Mean = 3.27</b>

The ANOVA results from the experimental vignette manipulation can be seen in Table 3. Recall, only the IAM and FIM scales were used as the dependent variables following the vignettes.

Independent variables	Dependent Variables	
	Intervention Appropriateness F ratio ( <i>p</i> value)	Intervention Feasibility F ratio ( <i>p</i> value)
<b>Main effects</b>		
<i>Location of pharmacist</i>	1.132 (0.289)	0.947 (0.332)
<i>Provider selecting and ordering test</i>	2.310 (0.130)	3.004 (0.085)
<i>Provider managing results and modify drug therapy</i>	0.59 (0.808)	0.008 (0.927)
<b>Two-way interactions</b>		
<i>Location * Select-order</i>	2.897 (0.091)	1.069 (0.303)
<i>Location * Manage-modify</i>	4.272 (0.040)*	2.900 (0.090)
<i>Select-order * Manage-modify</i>	1.265 (0.262)	0.408 (0.524)
<b>Three-way interaction</b>		
<i>Location * select-order * manage-modify</i>	0.075 (0.785)	0.092 (0.761)

\* Significant at  $p < 0.05$

There were no significant main effects, as well as no significant second-order interactions. However, there was a significant first-order interaction between the location of the pharmacist and the provider responsible for managing and modifying drug therapy. This was only significant for the IAM scale dependent variable ( $F = 4.272$ ,  $P = 0.040$ ). Figure 1 below shows the plot of this cross-over interaction. A simple effects analysis shows that if the pharmacist is managing and modifying drug therapy their physical location does make a statistically significant difference ( $F = 4.829$ ,  $p = 0.029$ ). If the physician is responsible for managing and modifying, the location of the pharmacist does not make statistically significant difference ( $F = 0.492$ ,  $p = 0.482$ ).

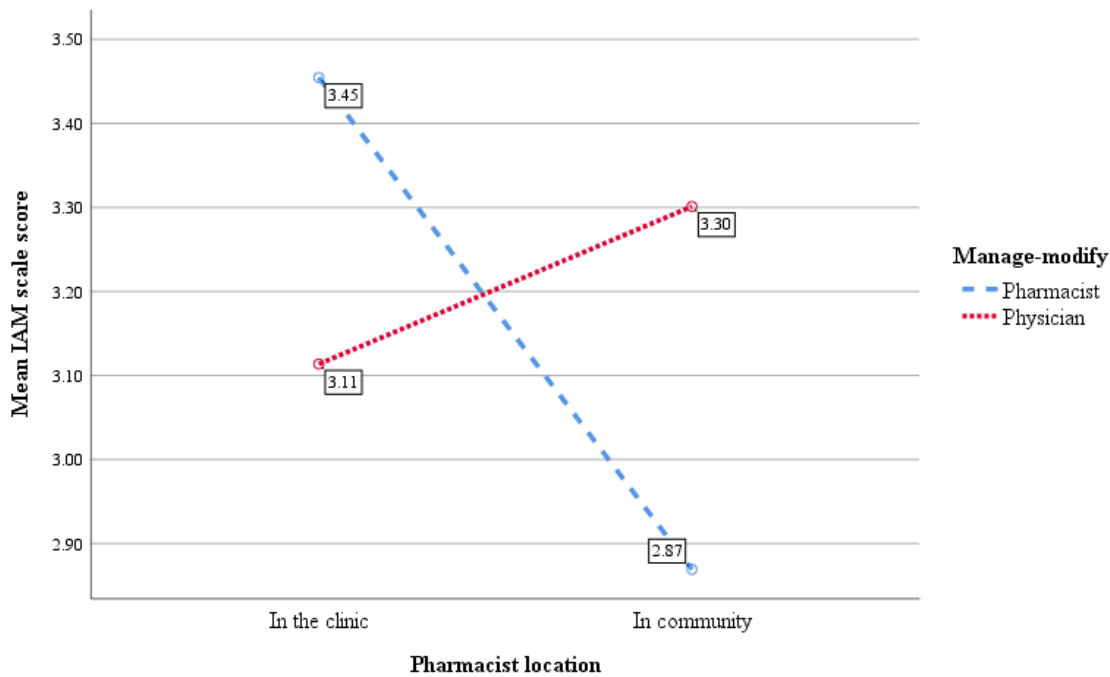


Figure 1. Two-way interaction of Location \* manage-modify on appropriateness (IAM) scores

Although not significant at  $\alpha = 0.05$ , two other potential cross-over interactions were observed. The interaction effect of location of the pharmacist and the person responsible for the selecting and ordering of the pharmacogenomic test on the IAM dependent variable was non-significant ( $F = 2.897, P = 0.091$ ). The plot of this interaction can be seen in Figure 2. A similar pattern emerges in this simple effects analysis as the previous one. If the pharmacist is responsible for selecting and ordering, the location of the pharmacist did make a difference in the appropriateness according to PCPs ( $F = 3.789, p = 0.053$ ).

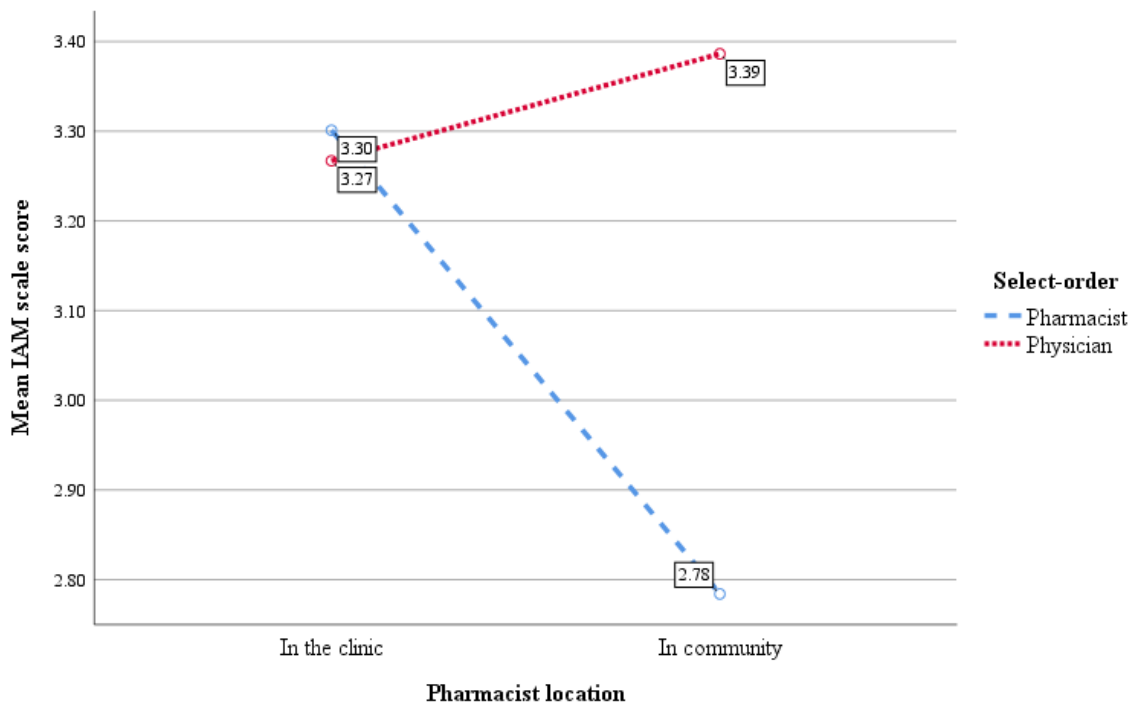


Figure 2. Two-way interaction of location \* select-order on appropriateness (IAM) scores

Another potential crossover interaction was observed between location and the persons responsible for managing the test results and modifying therapy, but this time for the FIM scale dependent variable ( $F = 2.900$   $P = 0.090$ ). The plot for this interaction is shown in Figure 3. Again, the simple effects analysis showed a similar trend although not as strong as the two previous ones. If the pharmacist was responsible for managing and modifying, their location in the clinic seems to have an impact on the feasibility of delivering pharmacogenomics to the responding PCPs ( $F = 3.569$ ,  $p = 0.061$ )

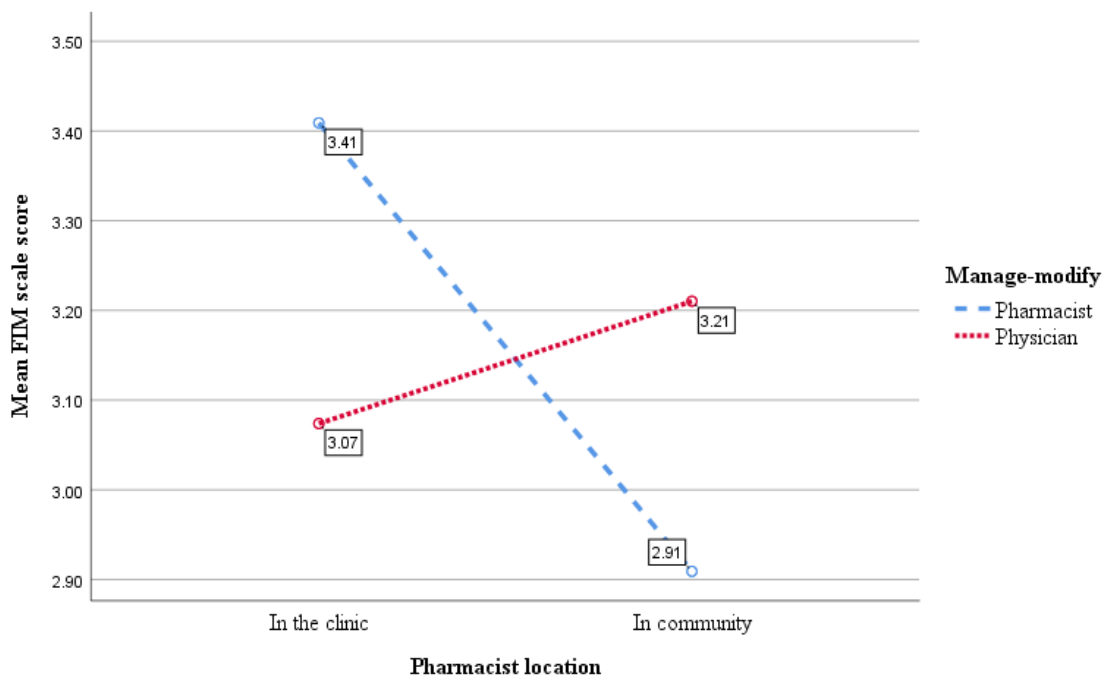


Figure 3. Two-way interaction of location \* manage-modify on feasibility (FIM) scores

As such, both Hypothesis 1 and Hypothesis 2 are not supported. However, as shown earlier, the presence of a statistically significant first-order interaction term changes our interpretation of the main effects associated with Hypothesis 1a and 1c. All three hypotheses, 1a – 1c, are not supported based solely on the main effects. All three sub-hypotheses from Hypothesis 2 are also not supported based on their main effects. Although there was no statistically significant first-order interaction terms for this outcome variable, the potential for cross-over interactions on the basis of the cell means plots were observed and suggest that PCPs do find delivering pharmacogenomics more feasible when the pharmacist is located in the clinic and is responsible for managing and modifying drug therapy.

All three regression models with the baseline AIM, IAM, and FIM scores as dependent variables were significant ( $P < 0.001$ ). Their respective  $R^2$  values can be found in Table 4 along with the full model results. With the baseline scores on the three implementation outcome scales



serving as our dependent variables, the same three independent variables were significant across the three models. These included an item measuring the importance of collaborating with a pharmacist in the responding physician’s practice, as well as the perceived pharmacogenomic knowledge and familiarity with pharmacogenomic resources variables. The only non-significant variable included was actual pharmacist involvement in the primary care practice of the responding physician. This was non-significant across all three models.

**Table 4. Regression results of pharmacist and pharmacogenomic influences on baseline AIM, IAM, FIM scores (n=176)**

	AIM ( $R^2 = 0.317$ ) F ratio ( $P$ value)	IAM ( $R^2 = 0.381$ ) F ratio ( $P$ value)	FIM ( $R^2 = 0.469$ ) F ratio ( $P$ value)
Importance of collaborating with a pharmacist in the primary care practice	0.289 (<0.0001*)	0.348 (<0.0001*)	0.298 (<0.0001*)
Pharmacist involvement in primary care practice <sup>a</sup>			
<i>Full-time in the clinic</i>	0.060 (0.397)	0.025 (0.711)	0.027 (0.664)
<i>Part-time in the clinic</i>	0.033 (0.623)	0.103 (0.104)	0.067 (0.256)
Perceived PGx knowledge <sup>b</sup>	0.270 (<0.0001*)	0.292 (<0.0001*)	0.346 (<0.00001*)
Familiarity with PGx resources <sup>c</sup>	0.163 (0.030)*	0.150 (0.036*)	0.251 (<0.0002*)
	std $\beta$ ( $p$ value)		

<sup>a</sup> Dummy variables: reference group is working with a community pharmacist only

<sup>b</sup> Average score across the three items included from the IGNITE Spark Toolbox

<sup>c</sup> Average score across familiarity with CPIC and PharmGKB questions

\* Significant at  $p < 0.05$

## 4. DISCUSSION

The focal analysis of this study showed that when a pharmacist responsible for managing pharmacogenomic results and modifying drug therapy, primary care physicians found this to be significantly more *appropriate* when the pharmacist was physically located in the clinic with the physician. If the pharmacist was also selecting and ordering a pharmacogenomic test, the PCPs find this to be more appropriate when the pharmacist was located in the clinic as well, as opposed to being in the community. This IAM score was nearly identical to the average score when the physician was responsible for selecting and ordering with a pharmacist in the clinic. These results seem to indicate that the physical presence of a pharmacist is driving physician perceptions of how appropriate delivery of clinical pharmacogenomics is to their primary care practice.

Regarding the *feasibility* outcome, when the pharmacist was responsible for managing results and modifying drug therapy, PCPs found this to be more *feasible* when the pharmacist was located in the clinic. Interestingly, the “pharmacist in the clinic” cell mean differences were identical for this interaction term on both the IAM and FIM scales, with similar overall mean scores. The absence of significance for *feasibility* may be due to a smaller cell mean difference in the “in the community” scenario. However, it is important to note the similarities between the scores for the *appropriateness* and *feasibility* of delivering pharmacogenomics when a pharmacist is physically located in the clinic and is responsible for managing and modifying the drug regimen. Additional investigations of this potential relationship would be needed to confirm this trend.

Results from this study indicate that physicians may be willing to sacrifice some clinical decision-making autonomy when dealing with the delivering of pharmacogenomics. The positive results regarding *appropriateness* of an in-clinic pharmacist handling the management of test results and modification of drug therapy is particularly illuminating. The responsibility of modifying drug therapy is currently the highest levels of clinical practice a pharmacist is allowed to engage in under a CPA.<sup>25,26</sup> These results may be indicative of a larger theme in the literature that primary care physicians lack understanding of pharmacogenomics and may be willing to defer to pharmacists if physical oversight remains possible.<sup>7</sup>

Additional results from the study may provide evidence for why physicians were willing to relinquish some autonomy for the delivery of clinical pharmacogenomics. Results on the “Pre-implementation Provider” items from the IGNITE Spark Toolbox all hovered around the mid-point on the agree/disagree Likert-type item. Scores on the general familiarity with pharmacogenomic question were somewhat lower than the IGNITE items, but more interesting was the drastically lower scores regarding primary care physician familiarity with CPIC and PharmaGKB. More research should be done to reveal where physicians are currently getting this type of information from if not CPIC or PharmGKB, and what can be done to increase awareness and use of these resources.

The results from the three regression models revealed several strong predictors of scores on the baseline assessment of the AIM, IAM, and FIM scales. The reported importance of collaborating with a pharmacist and perceived PGx knowledge demonstrated a stronger effect on the dependent variable than the familiarity with PGx resources. This positive relationship between pharmacist collaboration and scores on the acceptability, appropriateness, and feasibility of clinical pharmacogenomics seems to be in line with the findings from the vignettes. Although

we did not have significant main effects in that analysis, these additional regression results, taken together with the interactions noted previously, show that physicians value the contribution of a pharmacist when delivering clinical pharmacogenomics in primary care.

The findings from this current study are also consistent with the previous work that is available. The two-arm pilot study discussed earlier reported a significantly higher number of pharmacogenomic tests ordered when a pharmacist was located in-house, as well as an increase in the number of pharmacist consultations.<sup>34</sup> The pre-pilot survey found that most physicians already believed either pharmacists or geneticists/genetic counselors were likely to have a role in this clinical delivery.<sup>34</sup> Others have proposed that these two types of non-physician providers can play complementary roles in the effective delivery of pharmacogenomics.<sup>23,44</sup>

It is important to consider the implications of this study in light of how prepared the pharmacist is to take on these additional responsibilities. Pharmacists have generally positive attitudes toward their role in delivering pharmacogenomics, have been instrumental in the development of research-based implementations of clinical pharmacogenomics in the US and abroad, and are continuing to lead efforts in clinical education of pharmacogenomics.<sup>13,17,19</sup> Also, ongoing research is contributing to our understanding of how feasible it is for pharmacists to be the ones delivering this information.<sup>45-47</sup> These studies show that pharmacists are making correct interpretations of test results close to 90% of the time, consultations were timely and patients understand the information, as well as there being high rates of adherence to pharmacist recommendations by patients.

There remains limited literature available addressing the issue of physician-pharmacist collaboration in primary care specific to clinical pharmacogenomics. However, this is of great

importance as patients are becoming increasingly interested and aware of genomic testing and pharmacogenomics.<sup>48</sup> An in-depth qualitative assessment of patient perceptions to genomic testing revealed that patients believe that pharmacogenomics could be helpful in identifying problematic prescriptions and used to inform future prescribing.<sup>48</sup> However, concerns around insurance coverage and who should have access to the information were noted. While patients felt the pharmacist could effectively use the pharmacogenomic data, some thought this interaction was redundant while others rely solely on their physician for medication information.<sup>49</sup>

The findings of this current study support the idea that pharmacists co-located with physicians may be effective collaborators in the delivery of clinical pharmacogenomics and extend our understanding of how appropriate and feasible this scenario is to primary care physicians.

### **Limitations**

This study was hypothetical in nature and asked physicians to imagine themselves essentially engaged in a collaborative practice agreement with a pharmacist. Since familiarity with collaborative practice agreements was relatively low and few respondents were engaged in such an arrangement, external validity of the relationships shown herein should be externally validated in future studies with non-collaborative control groups. About half of the responding physicians had never ordered a pharmacogenomic test and may have also biased the responses. Another limitation in our manipulation may stem from the fact that we did not perform any manipulation checks on the manipulations themselves. This could have led to poor manipulation performance and thus the loss of an effect that may have otherwise been there. However, the

manipulations were piloted with two primary care physicians before distribution. Their comments indicated that they understood the differences in the various scenarios.

## **Conclusion**

When a pharmacist is responsible for managing and modifying drug therapy based on pharmacogenomic results, primary care physicians find this more appropriate for their practice when the pharmacist is located in the clinic. Physicians also responded that this same scenario would likely be more feasible. There is also evidence that it is more appropriate for the pharmacist to be located in the clinic if they are also responsible for selecting and ordering a pharmacogenomic test.

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## APPENDIX

## APPENDIX 1. – SURVEY INSTRUMENT

Welcome and thank you! You are being asked to volunteer for this research study. It is up to you whether you choose to participate or not. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate or discontinue participation. You will be required to answer each question. As a reminder, this study has been IRB approved and we do not believe there are any risks associated with this survey.

By now you will have read both the invitation email and the information above. By continuing to the next page you verify that you are at least 18 years of age and give your consent to participate in this study.

***NEXT PAGE***

### **Part A. Practice and Other Characteristics**

The questions in this section will help us better understand you and your current medical practice.

1. What is your primary medical specialty (i.e., the practice specialty where you spend the most hours per week)?
  - A. Family Medicine
  - B. General Internal Medicine
  - C. Pediatrics
  - D. Psychiatry
  - E. Other

***IF C, D, or E SELECTED IN Q1, THEN END SURVEY***

2. Are you currently licensed and actively practicing in this specialty?
  - A. Yes
  - B. No

***IF B SELECTED IN Q2, THEN END SURVEY***

3. What percent of your time is spent in the following activities?
  - A. Direct outpatient care \_\_\_\_\_ % (***IF LESS THAN 25%, END SURVEY***)
  - B. Hospital inpatient care \_\_\_\_\_ % (***IF MORE THAN 50%, END SURVEY***)
  - C. Administrative activities, teaching, or research \_\_\_\_\_ % (***IF MORE THAN 50%, END SURVEY***)

***IF THE RESPONDENT HAS SATISFACTORILY ANSWERED THE PREVIOUS THREE QUESTIONS, THEY ARE ELIGIBLE FOR THE FULL SURVEY***

4. In what state do you primarily practice?

\_\_\_\_\_

***CAPTURE AT LEAST 20 PEOPLE FROM EACH REGION BELOW IN Q4***

**Midwest** (Ohio, Indiana, Michigan, Illinois, Missouri, Wisconsin, Minnesota, Iowa, Kansas, Nebraska, South Dakota, North Dakota)

**Northeast** (Maine, Massachusetts, Rhode Island, Connecticut, New Hampshire, Vermont, New York, Pennsylvania, New Jersey, Delaware, Maryland)

**Southeast** (West Virginia, Virginia, Kentucky, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Mississippi, Arkansas, Louisiana, Florida)

**Southwest** (Texas, Oklahoma, New Mexico, Arizona)

**West** (Colorado, Wyoming, Montana, Idaho, Washington, Oregon, Utah, Nevada, California, Alaska, Hawaii)

5. How many years have you been in practice since finishing your residency?

- A. Less than 5
- B. 5 – 15
- C. 16 – 25
- D. More than 25

6. Which of the following *most closely* represents your current professional status?

- A. Practice owner/partner/associate
- B. Employed by a hospital or health system
- C. Employed by a medical group
- D. Employed by a *university* hospital or health system
- E. Other

7. Is your practice:

- A. Solo
- B. 2 – 5 physicians
- C. 6 – 10 physicians
- D. 11 – 30 physicians
- E. 31 – 100 physicians
- F. 101 or more physicians

8. How many physicians, including you, work in your main primary care practice location (the location where you spend most of your time during the week)?

\_\_\_\_\_ physicians

9. Is your primary care practice located in a single specialty or multi-specialty practice? (multi-specialty practice includes *physician* specialists other than primary care)

- A. Single specialty
- B. Multi-specialty

10. What percentage of your practice is staffed by non-physician advanced practice providers? (e.g. nurse practitioners and physician assistants)

\_\_\_\_\_ %

11. On average, what is your *best estimate* for the number of patients you see per day in your primary care practice?

\_\_\_\_\_ patients

12. Which of the following options *best describes* pharmacist involvement with your primary care practice?

- A. Full-time staff pharmacist that works in your primary care practice
- B. Part-time staff or consultant pharmacist that works in your primary care practice
- C. I only have interactions with community pharmacists not employed in my primary care practice (i.e., independent, chain, retail, grocery-store pharmacies)
- D. Other; please describe \_\_\_\_\_

13. How important, *to you*, is collaborating with a pharmacist for the care of patients in your primary care practice?

Not at all important	Slightly important	Somewhat important	Moderately important	Extremely important
1	2	3	4	5

14. Please rate *your* level of familiarity with formal collaborative practice agreements between physicians and pharmacists.

Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Extremely familiar
1	2	3	4	5

***SHOW THIS STATEMENT TO ALL RESPONDENTS AFTER Q14.***

- ❖ Collaborative practice agreements (CPAs) are used to create formal relationships between pharmacists and physicians, or other providers. This allows the pharmacist to provide expanded clinical services to patients and the healthcare team.
- ❖ CPAs define certain patient care functions that a pharmacist can autonomously provide under specified situations and conditions. Of important note, CPAs are not required for pharmacists to perform many patient care services (e.g., medication reviews, patient education and counseling, disease screening).
- ❖ A CPA allows qualified pharmacists to assume professional responsibility for performing patient assessments and making referrals, ordering and reviewing laboratory tests, administering medications, and selecting, initiating, monitoring, continuing, and adjusting medication regimens.
- ❖ References – (<https://www.aphafoundation.org/collaborative-practice-agreements>, <https://www.cdc.gov/dhds/pubs/guides/best-practices/pharmacist-cdtm.htm>)

15. Is pharmacist involvement in your primary care practice part of a collaborative practice agreement (CPA)?
- A. Yes
  - B. No
  - C. Not sure

***IF A SELECTED IN Q15, SHOW Q16***

16. What level of access do pharmacists have to patient medical records in your main primary care practice location?
- A. Full access
  - B. Limited access (e.g., only medication related information)
  - C. No access



### **Part B. Clinical pharmacogenomics**

The questions in this section will help us better understand your experience with and perspectives on clinical pharmacogenomics.

17. Please rate your familiarity with using clinical pharmacogenomic information.

Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Extremely familiar
1	2	3	4	5

***SHOW THIS STATEMENT TO ALL RESPONDENTS AFTER Q15.***

- ❖ Clinical pharmacogenomics is the application of pharmacogenomics, a field of medicine that studies how individual genetic differences may govern drug toxicity and/or response, for use in clinical practice.
- ❖ Pharmacogenomics can be classified as either germline pharmacogenomics, which refers to the study of how inherited genomic variants influence alterations in a medication's pharmacokinetic and pharmacodynamic properties, or somatic pharmacogenomics, which studies how acquired genomic variants influence medication response (e.g. cancers and infectious disease).
- ❖ Diagnostic testing to identify these genomic variants includes single-gene testing, multi-gene panel testing, and sequencing. This can be done either reactively, ordering a test when a patient is likely to be prescribed a drug with pharmacogenomic implications, or preemptively, independent of whether the patient is receiving a medication or not.
- ❖ References – Borden et al., *Pharmacogenomics J* 2019, Relling and Evans, *Nature* 2015.

Please rate your level of agreement with the following statements.

18. Clinical pharmacogenomics **meets my approval**

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

19. Clinical pharmacogenomics is **appealing to me**

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

20. **I like** clinical pharmacogenomics

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

21. **I welcome** clinical pharmacogenomics

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

Please rate your level of agreement with the following statements.

22. Clinical pharmacogenomics seems **fitting** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

23. Clinical pharmacogenomics seems **suitable** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

24. Clinical pharmacogenomics seems **applicable** to my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

25. Clinical pharmacogenomics **seems like a good match** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

Please rate your level of agreement with the following statements.

26. Clinical pharmacogenomics seems **implementable** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

27. Clinical pharmacogenomics seems **possible** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

28. Clinical pharmacogenomics seems **doable** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

29. Clinical pharmacogenomics seems **easy to use** at primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

**Please read the following scenario carefully and answer the questions that follow based on the scenario.**

***RESPONDENTS SHOWN ONLY ONE VIGNETTE – EQUAL QUOTA PER VIGNETTE***

***Vignette #1*** - You have a collaborative practice agreement with a clinical pharmacist who works in your primary care clinic. This pharmacist operates under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, this pharmacist may initiate, continue, modify, or discontinue medications, order and review laboratory tests, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while being physically located in your primary care clinic.
- This clinical pharmacist is responsible for selecting and ordering the pharmacogenomic test for the patient.
- The clinical pharmacist manages the return of results and prepares a report for the patient’s medical record. The report includes the results and the potential implications on all relevant medication therapy.
- The clinical pharmacist is also responsible for making any appropriate modifications to the patient’s medication regimen considering the pharmacogenomic information now available.

***Vignette #2*** - You have a collaborative practice agreement with a local pharmacy that provides pharmacogenomic services. The clinical pharmacists operate under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, these pharmacists may initiate, continue, modify, or discontinue medications, order and review laboratory tests, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while not being physically located in your primary care clinic.
- This clinical pharmacist is responsible for selecting and ordering the pharmacogenomic test for the patient.
- The clinical pharmacist manages the return of results and prepares a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- The clinical pharmacist is also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

***Vignette #3*** - You have a collaborative practice agreement with a clinical pharmacist who works in your primary care clinic. This pharmacist operates under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, this pharmacist may initiate, continue, modify, or discontinue medications, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while being physically located in your primary care clinic.
- You, the physician, are responsible for selecting and ordering the pharmacogenomic test for the patient.
- The clinical pharmacist manages the return of results and prepares a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- The clinical pharmacist is also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

***Vignette #4*** - You have a collaborative practice agreement with a local pharmacy that provides pharmacogenomic services. The clinical pharmacists here operate under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, these pharmacists may initiate, continue, modify, or discontinue medications, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while not being physically located in your primary care clinic.
- You, the physician, are responsible for selecting and ordering the pharmacogenomic test for the patient.

- The clinical pharmacist manages the return of results and prepares a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- The clinical pharmacist is also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

**Vignette #5** - You have a collaborative practice agreement with a clinical pharmacist who works in your primary care clinic. This pharmacist operates under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, this pharmacist may order and review laboratory tests, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while being physically located in your primary care clinic.
- The clinical pharmacist is responsible for selecting and ordering the pharmacogenomic test for the patient.
- You, the physician, manage the return of results and prepare a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- You are also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

**Vignette #6** - You have a collaborative practice agreement with a local pharmacy that provides pharmacogenomic services. The clinical pharmacists here operate under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, these pharmacists may order and review laboratory tests, and make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while not being physically located in your primary care clinic.
- The clinical pharmacist is responsible for selecting and ordering the pharmacogenomic test for the patient.
- You, the physician, manage the return of results and prepare a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- You are also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

**Vignette #7** - You have a collaborative practice agreement with a clinical pharmacist who works in your primary care clinic during the week. This pharmacist operates under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, this pharmacist may make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while being physically located in your primary care clinic.
- You, the physician, are responsible for selecting and ordering the pharmacogenomic test for the patient.
- You manage the return of results and prepare a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- You are also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

**Vignette #8** - You have a collaborative practice agreement with a local pharmacy that provides pharmacogenomic services. The clinical pharmacists here operate under a defined protocol that allows them to work autonomously at higher levels of clinical practice. In addition to their medication therapy management duties, these pharmacists may make referrals to other medical providers.

With this collaborative practice agreement in place, delivering clinical pharmacogenomics in your primary care clinic would look like this.

- The collaborative practice clinical pharmacist provides services while not being physically located in your primary care clinic.
- You, the physician, are responsible for selecting and ordering the pharmacogenomic test for the patient.
- You manage the return of results and prepare a report for the patient's medical record. The report includes the results and the potential implications on all relevant medication therapy.
- You are also responsible for making any appropriate modifications to the patient's medication regimen considering the pharmacogenomic information now available.

Please rate your level of agreement with the following statements **based on the previous scenario**.

30. Clinical pharmacogenomics delivered this way seems **fitting** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

31. Clinical pharmacogenomics delivered this way seems **suitable** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

32. Clinical pharmacogenomics delivered this way seems **applicable** to my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

33. Clinical pharmacogenomics delivered this way seems **like a good match** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5



Please rate your level of agreement with the following statements **based on the previous scenario**.

34. Clinical pharmacogenomics delivered this way seems **implementable** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

35. Clinical pharmacogenomics delivered this way seems **possible** for my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

36. Clinical pharmacogenomics delivered this way seems **doable** in my primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

37. Clinical pharmacogenomics delivered this way seems **easy to use** at primary care practice

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

**For the remaining questions, you do not need to consider the information presented in the previous scenario.**

38. In your opinion, what is *biggest barrier* to more widespread use of clinical pharmacogenomics in your primary care practice?

- A. Physician education in the appropriate use of pharmacogenomics
- B. Patient interest and engagement
- C. Insurance coverage and affordability
- D. Evidence base to support routine use of pharmacogenomics
- E. Electronic health record tools for pharmacogenomics

39. If prescribing and ordering a pharmacogenomic test were not part of your clinical workflow, and the information was readily available in your patient’s medical record at the point of prescribing, would this make the delivery of clinical pharmacogenomics more feasible?

- A. Yes
- B. No

40. On average, how often do patients ask you about pharmacogenomic testing?

- a) Every week
- b) Every month
- c) Every 6 months
- d) I have never been asked about pharmacogenomic testing by a patient

41. On average, how often do you use pharmacogenomic information in the care of specific patients?

- a) Every week
- b) Every month
- c) Every 6 months
- d) I have never used pharmacogenomic information

Please rate your level of agreement with the following statements:

42. I am confident in my ability to use the results of a pharmacogenomic test.

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

43. My training has prepared me to treat patients whose genetics place them at high risk for medical conditions.

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

44. I can find/use reliable sources of the information I need to apply pharmacogenomic testing while caring for patients

Strongly disagree	Tend to disagree	Neither agree nor disagree	Tend to agree	Strongly agree
1	2	3	4	5

Please rate your level of familiarity with the following pharmacogenomic resources.

45. CPIC – The Clinical Pharmacogenetics Implementation Consortium

Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Extremely familiar
1	2	3	4	5

46. PharmGKB – Pharmacogenomics Knowledgebase

Not at all familiar	Slightly familiar	Somewhat familiar	Moderately familiar	Extremely familiar
1	2	3	4	5

## APPENDIX 2. SUMMARY OF RESULTS PROVIDED TO RESPONDING PHYSICIANS

TITLE: Sustainable Delivery of Pharmacogenomics in Primary Care: Testing the Potential for Physician-Pharmacist Collaboration

### PURPOSE

Advancement in the clinical implementation of pharmacogenomics can be largely attributed to numerous large-scale academic research programs over the past decade. Most of these programs utilize a transdisciplinary model of physician-pharmacist collaboration for delivering pharmacogenomics. Drawing from literature showing improved outcomes from such collaborations, the successes of ongoing implementation programs, and theoretical work from the field of implementation science, this study sets out to experimentally test this collaboration in the primary care setting.

### METHODS

This study utilized a 2x2x2 between-subjects experimental design with data collected using an online survey and hypothetical vignettes. Responses were received from 176 US-based primary care physicians (PCPs). Primary outcome measures: Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM). Manipulated vignette factors: location of the pharmacist (in clinic vs. not), who selects and orders the test (pharmacist vs. physician), and who manages and modifies the medication regimen (pharmacist vs. physician).

### RESULTS

The main effects on the IAM were not statistically significant at  $\alpha < 0.05$ . However, the two-way interaction effect between location and who manages and modifies the medication regimen was statistically significant ( $p=0.04$ ). Although not statistically significant, a second potential crossover interaction effect was observed between location and who selects and orders the test ( $p=0.09$ ). Results of the manipulations on the FIM scale showed no significance of the main effects or interactions, but a non-significant crossover interaction was observed between location and who manages and modifies the medication regimen ( $p=0.09$ ).

### CONCLUSIONS

PCPs find the delivery of pharmacogenomics significantly more appropriate for their practice when the pharmacist is managing and modifying the patient's medication regimen while located in the clinic. PCPs responded that this same scenario would likely be more feasible. There is also evidence that it is more appropriate for the pharmacist to select and order the test when located in the clinic.

<b>General Practice Characteristics</b>	<b>Frequency (%)</b>
<b>Primary medical specialty</b>	
Family Medicine	111 (63%)
Internal Medicine	65 (37%)
<b>Region</b>	
Midwest	50 (28%)
West	31 (18%)
Southwest	20 (11%)
Northeast	33 (19%)
Southeast	42 (24%)
<b>Years in practice</b>	
Less than 5	4 (2%)
5 – 15	20 (11%)
16 – 25	68 (39%)
More than 25	84 (48%)
<b>Professional status</b>	
Practice owner/partner/associate	91 (52%)
Employed by hospital or health system	43 (24%)
Employed by medical group	31 (18%)
Employed by a university hospital or health system	9 (5%)
Other	2 (1%)
<b>Size of practice (# of physicians)</b>	
Solo	43 (24%)
2 – 5	58 (33%)
6 – 10	25 (14%)
11 – 30	18 (10%)
31 – 100	16 (9%)
More than 100	16 (9%)
<b>Single or multi-specialty clinic</b>	
Single specialty	119 (68%)
Multi-specialty	57 (32%)

<b>Pharmacist related practice characteristics</b>	<b>Mean</b>
Importance of collaborating with pharmacist for care of patients in the primary care practice (1 = Not at all important, 5 = Very important)	3.47
Familiarity with CPAs between physicians and pharmacists (1 = Not at all familiar, 5 = Very familiar)	2.50
	<b>Frequency (%)</b>
<b>Pharmacist involvement in practice</b>	
Full-time staff that works in the clinic	23 (13%)
Part-time staff or consultant that works in the clinic	16 (9%)
Only interacts with community pharmacist not employed by practice	134 (76%)
<b>Pharmacist involvement is part of a CPA</b>	
Yes	27 (15%)
No	124 (70%)
Not sure	25 (14%)
<b>Level of CPA pharmacist access to patient medical records (n=27)</b>	
Full access	23 (85%)
Limited access (e.g. only medication related information)	4 (15%)

<b>Pharmacogenomics familiarity</b>	<b>Mean</b>
(1 = Not at all familiar, 5 = Very familiar)	
Familiarity with using clinical pharmacogenomic information	2.63
Familiarity with CPIC	1.61
Familiarity with PharmGKB	1.59
<b>Pre-implementation Provider Items from IGNITE Spark Toolbox</b>	
(1 = Strongly disagree, 5 = strongly agree)	
“I am confident in my ability to use the results of a pharmacogenomic test”	3.18
“My training has prepared me to treat patients whose genetics place them at a high risk for medical conditions”	2.96
“I can find/use reliable sources of the information I need to apply pharmacogenomic testing while caring for patients”	3.18
<b>Use of pharmacogenomics in practice</b>	<b>Frequency (%)</b>

Frequency with which patients ask PCP about pharmacogenomic testing	
Every week	6 (3%)
Every month	20 (11%)
Every six months	34 (19%)
Never been asked about it	116 (66%)
Frequency with which PCPs use pharmacogenomic information in the care of specific patients	
Every week	11 (6%)
Every month	29 (16%)
Every six months	40 (23%)
Never been asked about it	96 (55%)
Biggest barrier to more widespread use of pharmacogenomics in their primary care practice	
Physicians knowledge regarding appropriate use	33 (19%)
Patient interest and engagement	11 (6%)
Insurance coverage and affordability	93 (53%)
Evidence base to support routine use of pharmacogenomics	34 (19%)
Electronic health record tools for pharmacogenomics	5 (3%)
Pharmacogenomics more feasible if prescribing and orderings were not part of clinical workflow, and information was already in medical record	
Yes	143 (81%)
No	33 (19%)

<b>Implementation Outcome Measures Applied to Clinical Pharmacogenomics</b>	<b>Mean (SD)</b>
<i>(1 = Strongly disagree, 5 = Strongly Agree)</i>	
Acceptability of Intervention Measure (AIM)	
Clinical pharmacogenomics meets my approval	3.72
Clinical pharmacogenomics is appealing to me	3.77
I like clinical pharmacogenomics	3.62
I welcome clinical pharmacogenomics	3.73
	<b>Overall Mean = 3.71</b>
Intervention Appropriateness Measure (IAM)	
Clinical pharmacogenomics seems fitting in my primary care practice	3.45
Clinical pharmacogenomics seems suitable for my primary care practice	3.48

Clinical pharmacogenomics seems applicable to my primary care practice	3.60
Clinical pharmacogenomics seems like a good match for my primary care practice	3.49
<b>Overall Mean = 3.50</b>	
<b>Feasibility of Intervention Measure (FIM)</b>	
Clinical pharmacogenomics seems implementable in my primary care practice	3.19
Clinical pharmacogenomics seems possible for my primary care practice	3.54
Clinical pharmacogenomics seems doable in my primary care practice	3.36
Clinical pharmacogenomics seems easy to use at my primary care practice	2.99
<b>Overall Mean = 3.27</b>	



### APPENDIX 3. DEMOGRAPHIC AND PRACTICE CHARACTERISTICS

<b>General Practice Characteristics</b>	<b>Percentage of respondents</b>
<b>Primary medical specialty</b>	
Family Medicine	63%
Internal Medicine	37%
<b>Region</b>	
Midwest	28%
West	18%
Southwest	11%
Northeast	19%
Southeast	24%
<b>Years in practice</b>	
Less than 5	2%
5 – 15	11%
16 – 25	39%
More than 25	48%
<b>Professional status</b>	
Practice owner/partner/associate	52%
Employed by hospital or health system	24%
Employed by medical group	18%
Employed by a university hospital or health system	5%
Other	1%
<b>Size of practice (# of physicians)</b>	
Solo	24%
2 – 5	33%
6 – 10	14%
11 – 30	10%
31 – 100	9%
More than 100	9%
<b>Single or multi-specialty clinic</b>	
Single specialty	68%
Multi-specialty	32%

Table 1. Practice characteristics among all respondents

<b>Pharmacist related practice characteristics</b>	<b>Mean</b>
Importance of collaborating with pharmacist for care of patients in the primary care practice (1 = Not at all important, 5 = Very important)	3.47
Familiarity with CPAs between physicians and pharmacists (1 = Not at all familiar, 5 = Very familiar)	2.50
	<b>Percentage of respondents</b>
<b>Pharmacist involvement in practice</b>	
Full-time staff that works in the clinic	13%
Part-time staff or consultant that works in the clinic	9%
Only interacts with community pharmacist not employed by practice	76%
<b>Pharmacist involvement is part of a CPA</b>	
Yes	15%
No	70%
Not sure	14%
<b>Level of CPA pharmacist access to patient medical records (n=27)</b>	
Full access	85%
Limited access (e.g. only medication related information)	15%

Table 2. Pharmacist related practice characteristics among all respondents

<b>Pharmacogenomics related questions</b>	
<b>Pharmacogenomics familiarity</b> (1 = Not at all familiar, 5 = Very familiar)	Mean
Familiarity with using clinical pharmacogenomic information	2.63
Familiarity with CPIC	1.61
Familiarity with PharmGKB	1.59
<b>Pre-implementation Provider Items from IGNITE Spark Toolbox</b> (1 = Strongly disagree, 5 = strongly agree)	
“I am confident in my ability to use the results of a pharmacogenomic test”	3.18
“My training has prepared me to treat patients whose genetics place them at a high risk for medical conditions”	2.96
“I can find/use reliable sources of the information I need to apply pharmacogenomic testing while caring for patients”	3.18
<b>Use of pharmacogenomics in practice</b>	<b>Percentage of respondents</b>
Frequency with which patients ask PCP about pharmacogenomic testing	
<i>Every week</i>	3%
<i>Every month</i>	11%
<i>Every six months</i>	19%
<i>Never been asked about it</i>	66%
Frequency with which PCPs use pharmacogenomic information in the care of specific patients	
<i>Every week</i>	6%
<i>Every month</i>	16%
<i>Every six months</i>	23%
<i>Never used it</i>	55%
Biggest barrier to more widespread use of pharmacogenomics in their primary care practice	
<i>Physicians knowledge regarding appropriate use</i>	19%
<i>Patient interest and engagement</i>	6%
<i>Insurance coverage and affordability</i>	53%
<i>Evidence base to support routine use of pharmacogenomics</i>	19%
<i>Electronic health record tools for pharmacogenomics</i>	3%
Pharmacogenomics more feasible if prescribing and ordering were not part of clinical workflow	
<i>Yes</i>	81%
<i>No</i>	19%

Table 3. Pharmacogenomic related practice characteristics across all respondents

## CONCLUSION

We have designed and completed three complementary research studies focused on the clinical implementation of pharmacogenomic testing and the factors contributing to the sustainability of the science within its current environment and its sustainability in future settings. Theory guiding this work has been taken from the discipline of implementation science and one of its foundational concepts, sustainability. Public health organizations in the US including the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) have been leading this call.<sup>1,2</sup> The National Cancer Institute (NCI) at the NIH has been particularly strong in its advocacy of implementation science more generally and not just in genomics.<sup>3</sup> The issue of translating evidence-based research into clinical application reaches all corners of medicine, including pharmacogenomics, and thus the more formal integration of implementation science principles is warranted. These three studies will also continue building the ongoing relationship between implementation science and genomic medicine. Additionally, the two primary data collection studies are the first to formally apply an implementation science framework or implementation science outcomes to the field of pharmacogenomics.

The scoping review study began this three-part work with an examination of the extent to which previous research has explicitly assessed health care provider interactions with and use of pharmacogenomics in hypothetical or real-world practice. While this study did not apply a certain implementation science framework, as in the qualitative piece, the Dynamic Sustainability Framework (DSF) provides the reader with a reflection on the importance of field conducting such studies. In the introduction we mentioned two tenets of the DSF: “interventions

can be continually improved, specific to each setting” and “ongoing feedback is essential and should be measured over time”.<sup>4</sup> These thoughts helped tighten our research question to make this study unique and an important contribution to the literature. The literature has seen a great deal of work targeted to understand the perceptions and opinions of providers toward the use of pharmacogenomics, however cross-sectional studies of this nature miss the mark when we look at those two tenets of the DSF.<sup>5-8</sup> It is methodologies found in the studies included in the scoping review that position implementers to be able to continually improve and assess feedback from the actual experience using a new intervention such as pharmacogenomic testing.

Most of the 25 studies included in our scoping review were published between 2015 and 2018 on the North American and European continents. This was over double the number of studies published the previous five-year block (2010-2014) and demonstrates a promising trend that researchers and implementers are recognizing the importance of such methodologies. It would be intriguing to compare these results with the publication trends of studies that only assess perceptions or opinions regarding pharmacogenomics. We found that the largest number of included studies were those using hypothetical clinical case scenarios closely followed by real-world studies regarding prescribing and testing decisions. Many of these studies were focused on evaluating the clinical decision support (CDS) systems that enable providers to deliver timely and clinically relevant pharmacogenomic information to patients.<sup>9</sup> While understanding how providers interacted with these systems was important, several studies also aimed to measure the adherence or compliance physicians had to the recommendations of their human colleagues, pharmacists, regarding medication use in light of genomic information. In only one study was the pharmacist the primary respondent for data collection, but in many in they were responsible for the clinical action the physician was acting on.<sup>10</sup> In fact, some of the

more robustly designed studies were those with the pharmacists at the center of the research question.<sup>10,11</sup> The discussion over who should be responsible for managing pharmacogenomic results and delivery of information to the patient is ongoing.

The choice to focus on methodology in this review was appropriate for the field currently. As researchers look to answer questions about the best way to deliver pharmacogenomic CDS or which provider is best for delivery this information to patients, the illuminating findings from this study should give future researchers a firm and broad baseline assessment of methodologies to carry forward and build upon. Understanding the methods of current researchers and implementers and their historical applications will hopefully create a sustainable future for clinical pharmacogenomics.

The second research study herein was the most explicit of the three in its use of implementation science to guide the research design and data collection. Researchers in the IGNITE group have led the way with their previous research on genomic medicine and implementation science.<sup>12,13</sup> The work of the Common Measures working group was instrumental in the decision to pursue a focus on the Process domain. Further, the application of the Process domain was strengthened by the identification of several highly ranked constructs of importance to the sustainability of genomic medicine. The connection between the foundational concept of sustainability and the Process domain is underpinned by the operational indicator of sustainability, capacity building. Previous research conceptualized this not only as a physical indicator, but human as well.<sup>14</sup> The constructs and sub-constructs of the Process domain use almost identical language as some of the factors represented by these physical and human infrastructures in previous literature.<sup>15,16</sup>

The findings from this study demonstrated a strong focus throughout on effective communication as a facilitator of success across many of the constructs and sub-constructs. The Planning construct involved numerous discussions on the need to understand the existing interest and testing volume prior to implementing. This was a crucial factor for many as it determined a first gene-drug pair implementation target and the desire to get an “early-win” for their program. The Engaging construct, more than any other construct, dealt with the *human* capacity building indicator of sustainability. Cutting across several types of essential personnel, this construct provided more nuance on the influence certain individuals or types of individuals had on colleagues and the success of the program. The importance of quick, frequent, and informal interactions with providers cannot be understated. This was one of the most ubiquitous findings in the whole study. The Reflecting & Evaluating construct showed that the goals of most of this early adopter programs was simply to provide pharmacogenomics to the patients. Patient safety was cited several times a primary driver of this goal. Outcomes based studies are planned in the future for many of the participant institution, but at this time process metrics and structured provider feedback make up most data collection.

This research represents one the first formal applications of an implementation science framework to the study of clinical pharmacogenomics. Further, we have tied the formal use of such a framework to the one of its discipline’s foundational concepts, sustainability, and the identified constructs necessary to achieve that in genomic medicine. As evidenced herein by the ongoing challenges among pioneers in the implementation of pharmacogenomics, sustainability is not just an economic construct related to coverage and reimbursement policies. Successfully sustaining pharmacogenomics within participant institutions and designing future implementations with a mindset of sustainability will require precision targeting of supportive

administration and clinicians, maintaining dedicated IT support throughout, and remaining resilient in the face of inevitable failures.

The final study of this three-part work explored more deeply the topic that we have already discussed in each of the two previous studies. That is, the question of which health care providers are best positioned to deliver care using pharmacogenomic information. The scoping review included one study that investigated whether specialists or primary care providers should carry this responsibility, but the larger discussion has centered on what level of involvement the pharmacist should have in conducting pharmacogenomic testing and the interpretation of results.<sup>11,17,18</sup> Pharmacist involvement to date in the implementation of clinical pharmacogenomic programs at major academic institutions has been robust. However, there has been little investigation into how the pharmacist's skill set can be utilized in a primary care setting and what is the attitude of primary care physicians towards their use.<sup>19,20</sup> To understand this more fully, we applied three validated implementation science outcome measures (acceptability, appropriateness, feasibility) that were created to enable more standardized assessments of conceptualizing and evaluating the success of an intervention.<sup>21,22</sup>

Results from our cross-sectional survey indicated that primary care physicians were accepting of pharmacogenomics but the feasibility of delivering it in their practice produced somewhat lower scores. Using an experimental vignette methodology, in the second portion of the survey we explored the appropriateness and feasibility of delivering pharmacogenomics in a collaborative practice agreement across different levels of pharmacist responsibility. We tested three main effects: location of the pharmacist (in or out of the clinic), provider responsible for selecting and ordering the test (pharmacist or physician), and the provider responsible for managing results and modifying drug therapy (pharmacist or physician). When the pharmacist



was responsible for managing pharmacogenomic results and modifying drug therapy, primary care physicians found this to be more appropriate when the pharmacist was physically located in the clinic. Also, although not statistically significant at  $\alpha=0.05$ , the same scenario just described was seen as more feasible according to our sample of primary care physicians. Lastly, when the pharmacist was located in the clinic, physicians were indifferent regarding the appropriateness of themselves or the pharmacist selecting and ordering the pharmacogenomic test.

This study builds on previous pilot work that tested the effects of pharmacist integration into a primary care practice on testing volume and utilization of pharmacist consult.<sup>11</sup> However, we have produced results with broader generalizability because the investigation was not restricted to one geographic set of primary care practices. These results clearly show that primary care physicians are willing to give up some clinical autonomy to the pharmacist to enable delivery of pharmacogenomics in clinical practice. The ability for this to succeed will also be partially dependent on robust educational and training initiatives that enable the pharmacist to effectively deliver pharmacogenomic testing. Finally, variability in state-to-state collaborative practice policies should be examined as a crucial factor in the success of such arrangements. Physicians in states with more advanced policies will likely be the innovators in advancing the pharmacist to higher levels of clinical practice, while laggard state policies will require greater intervention and education on the benefits and possibilities of such arrangements.

To close, these three studies have focused on converging the clinical science of pharmacogenomics with the discipline of implementation science. We have more deeply explored this convergence by looking at the foundation concept of sustainability. This work has great methodological breadth as we utilized review, qualitative, and quantitative/experimental techniques. Moving forward the hope is that future researchers recognize the potential for

implementation science as a facilitator of high quality, standardized study designs that address new and existing issues critical to the sustainability of clinical pharmacogenomics in practice.

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## VITA

**Nicholas J. Keeling, M.S.**

### *Curriculum Vitae*

#### **PROFESSIONAL PROFILE AND CURRENT POSITION**

Ph.D. candidate in Pharmaceutical Sciences with emphasis in health services research and marketing. I have four years of experience working at a premiere children's research hospital and three years working in life sciences strategy and market access consulting. My academic research has focused on the implementation of precision medicine and specifically pharmacogenomics, the study of how genetic differences may govern drug toxicity and/or response. This work and others have been published in the peer-reviewed health care journals *Genetics in Medicine*, *Pediatrics*, and *Pharmacogenomics*.

#### **St. Jude Children's Research Hospital**

2015 – Present                      Pharmaceutical Sciences Doctoral Research Assistant – Medication and Patient Safety

- Provide analytical and operational support for department projects to ensure they meet the long-term and institution-wide efforts of the hospital
- Converge the strategic goals of this department with those of the PG4KDS: Clinical Implementation of Pharmacogenetics program
- Manage and coordinate an economic research project between the interdisciplinary departments of Global Pediatric Medicine, Medication and Patient Safety, and PG4KDS
- Report directly to the Chief Patient Safety Officer

#### **SKILLS AND EXPERTISE**

- **Research Design and Analysis:** Review methods, quantitative/experimental surveys, qualitative in-depth interviews, financial modeling
- **Subject Matter Strength:** precision medicine and pharmacogenomics, implementation science, health insurance, health care delivery, market access strategy
- **Professional Recognition:** served as the only graduate student panel member at a precision medicine conference or forum participant in a national health policy recommendation on the financing of precision medicine
- **Creative Leadership:** managed and led a small team through several successful business plan competitions, served as president of the graduate student body
- **Presentation and Writing Skills:** advanced experience presenting across both professional and academic settings including commercial health care companies and NIH funded research groups, three peer-reviewed health care journal publications and several in progress

## **EDUCATION**

### **University of Mississippi School of Pharmacy, Department of Pharmacy Administration**

- 2019            Ph.D. (candidate) in Pharmaceutical Sciences (Anticipated graduation December 2019)  
Dissertation: A Sustainable Future in the Implementation of Clinical Pharmacogenomics  
Paper 1 – Decision making in clinical pharmacogenomics: a scoping review  
Paper 2 – Sustainable advancement of early adopter success in health system pharmacogenomics: strategies and perspectives from implementation leadership  
Paper 3 – Sustainable delivery of pharmacogenomics in primary care: experimentally testing the potential for physician-pharmacist collaboration
- 2016            M.S. in Pharmaceutical Sciences  
Thesis: Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US Payers

### **University of Mississippi**

- 2011            B.A. in Economics  
2010            B.M. in Music Performance (Vocal)

## **HONORS/AWARDS/GRANTS**

- 2018            Outstanding Student Research Paper – Department of Pharmacy Administration  
2017            Gold Medal Winning Abstract – Academy of Managed Care Pharmacy Annual Meeting  
2017            2<sup>nd</sup> Place Social Sciences, Education, Business, and Accounting - Graduate Student Council 7<sup>th</sup> Annual Research Symposium Podium Competition  
2016            Rho Chi Pharmacy Academic Honor Society  
2016            Phi Kappa Phi Love of Learning Scholarship Recipient  
2015            MME Fellowship Research Grant – Department of Pharmacy Administration  
2015            2<sup>nd</sup> Place Overall, 1<sup>st</sup> Place Best Idea for Mississippi – Center for Entrepreneurship and Innovation, University of Mississippi School of Business, Gillespie Business Plan Competition  
2015            1<sup>st</sup> Place University of Mississippi division, 2<sup>nd</sup> Place State division – Blueprint Mississippi Social Business Challenge  
2015            Phi Kappa Phi Academic Honor Society

## RESEARCH EXPERIENCE

### Peer-reviewed publications

- 2019 Hoffman JM, **Keeling NJ**, Forrest CB, Tubbs-Cooley HL, Moore E, Oehler E, Wilson S, Schainker E, Walsh KE. Priorities for Pediatric Patient Safety Research. *Pediatrics*. [Published online January 23, 2019]
- 2018 Caudle KE, **Keeling NJ**, Klein TE, Whirl-Carrillo M, Pratt VM, Hoffman JM. Standardization can accelerate the adoption of pharmacogenomics: current status and the path forward. *Pharmacogenomics*. 2018; 19(10): 847-860.
- 2017 **Keeling NJ**, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. *Genet Med*. [Published online October 26, 2017]

### Other publications

- 2018 AMCP Partnership Forum: Managing Care in the Wave of Precision Medicine. *J Manag Care Spec Pharm*. [Published online May 25, 2018]

### Abstracts and Posters

- 2019 Rogers SL, **Keeling NJ**, Giri J, Gonzaludo N, Jones JS, Formea CM. PARC Report: A Health System Focus on Reimbursement and Patient Access to Pharmacogenomic Testing. Clinical Pharmacogenetics Implementation Consortium (CPIC) Meeting. Memphis, TN, USA.
- 2018 Hoffman JM, **Keeling NJ**, Forrest CB, Tubbs-Cooley HL, Moore E, Oehler E, Wilson S, Schainker E, Walsh KE. Priorities for Pediatric Patient Safety Research. Pediatric Academic Societies. Toronto, ON, CA.
- 2017 **Keeling NJ**, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. Academy of Managed Care Pharmacy Annual Meeting. Denver, CO, USA.
- 2017 **Keeling NJ**, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. Graduate Student Council 7<sup>th</sup> Annual Research Symposium. **Podium**. University, MS, USA.
- 2016 **Keeling NJ**, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. Southern Pharmacy Administration Conference. University, MS, USA.
- 2014 **Keeling N**, Crumby A, Nunna S. 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, CA

### Professional Panels and Presentations

- 2019 Translational Software™ Webinar Series. Exploring the Knowledge and Perspectives of US Payers on Preemptive Pharmacogenomic Testing
- 2017 Academy of Managed Care Pharmacy Partnership Forum: Managing Care in the Wave of Precision Medicine, Participant. Washington, DC, USA.



- 2017 Precision Medicine Leaders Summit: Access and Affordability in Precision Medicine and Disparities of Care, Panelist. San Diego, CA, USA.
- 2017 Implementing Genomics into Practice (IGNITE) Consortium Clinical Informatics Webinar Series: Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US Payers.
- 2017 OneOme® Monthly Company Meeting: Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers.
- 2017 Clinical Pharmacogenetic Implementation Consortium Monthly International Conference Call: Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers.

## **PROFESSIONAL/ACADEMIC WORK EXPERIENCE**

### **Medical Marketing Economics, LLC**

2012 – 2015 Consulting Analyst

- Supported the planning and execution of consulting engagements across various therapeutic areas and among key stakeholders (physicians, pharmacists, payers, and patients) using quantitative and qualitative research techniques, as well as financial modeling

### **University of Mississippi School of Pharmacy**

2015 (January – May) Teaching Assistant  
Pharmacoeconomics, Pharmacoepidemiology, and Medication Safety

2014 (August – December) Teaching Assistant  
Pharmacy Ethics

## **PROFESSIONAL/ACADEMIC AFFILIATIONS AND CITIZENSHIP**

### **Affiliations**

2018 Clinical Pharmacogenetics Implementation Consortium (CPIC)

2018 Pharmacogenomic Access and Reimbursement Coalition (PARC)

2017 Association for the Advancement of Science

2014 International Society of Pharmacoeconomic and Outcomes Research

### **Citizenship**

2018 CPIC Dissemination Working Group member

2018 PARC Health Systems Working Group

2013 – 17 University of Mississippi Graduate Student Council

Election Commissioner ('17)  
President ('14 – '15)  
Director of Social and Philanthropic Affairs ('13 – '14)