This white paper evaluates the current and future state of clinical pharmacist-led precision medicine initiatives, focusing on an overview of pharmacogenomics (PGx) in three key areas: clinical practice, education, and research. These key facets are described in detail, followed by a review of potential and perceived barriers concerning PGx and recommendations for the clinical pharmacist's role in overcoming these barriers. This paper reviews the current state of clinical pharmacist-led precision medicine and presents a vision for the future of pharmacy practice in this quickly evolving field.

KEYWORDS
education, genetics, pharmacists, pharmacogenomics, precision medicine

1 | INTRODUCTION

Precision medicine is the rapidly growing discipline of using patient-specific gene, environmental, and lifestyle data to tailor a personalized approach to treating and preventing disease. Pharmacogenomics (PGx) is a specific area of precision medicine of interest to pharmacists. PGx is specific to using individual genetic information to tailor medication regimens for a specific patient. In 2001, Francis Collins, director of the National Institutes of Health (NIH) and a geneticist, stated that increased PGx knowledge and literature would lead to the routine use of genetic information to inform drug therapy decisions in clinical practice by 2020.1 Although this vision has not fully been realized, significant advances over the past 20 years have begun to close the gap toward delivering precision medicine as the standard of care.

Collectively, the major professional pharmacy organizations, including the American College of Clinical Pharmacy, the American Pharmacists Association, and the American Society of Health-System Pharmacists, believe that PGx can improve medication-related outcomes and that pharmacists should be leaders in implementing it across the health care landscape.2-4 Indeed, clinical pharmacists are well positioned to lead PGx implementation in many clinical disciplines. This paper summarizes the clinical pharmacist's current role in relation to PGx in clinical practice, education, and research and projects the future of precision medicine in each realm. In addition, the paper reviews the many perceived and true barriers of PGx implementation and recommends strategies to overcome them and advance clinical pharmacist-led PGx efforts.
2 | CLINICAL PRACTICE

2.1 | Current applications

Precision medicine is already used in many areas of pharmacy practice. Table 1 shows the PGx drug-gene pairs that represent known examples for which clinical pharmacists can optimize therapy. Examples exist within multiple specialties. In oncology, patient care is often dictated by patient- or disease-specific genetic alterations. For example, tamoxifen is metabolized to its active metabolite (endoxifen) by CYP2D6, which has a great deal of genetic variability. CYP2D6 intermediate or poor metabolizers have subtherapeutic endoxifen concentrations and an increased risk of breast cancer recurrence. Knowledge of these alterations can lead to the use of therapeutic drug concentrations and reduce the risk of cancer. In psychiatry, the PGx of CYP2D6 and CYP2C19 isoenzymes informs initial drug and dose selection of selective serotonin reuptake inhibitors and tricyclic antidepressants, which has historically been difficult because of delayed therapeutic benefit and patient variability in drug response. Similarly, in cardiology, genetic variants in CYP2C9, VKORC1, CYP4F2, and rs12777823 alter warfarin dose requirements. Incorporating these variants into dosing algorithms can improve dose selection. In addition, genetic variants of CYP2C19 affect the metabolism of clopidogrel from prodrug to active moiety and thus its corresponding drug activity. CYP2C19 poor metabolizers have an increased risk of cardiovascular adverse events. Improved drug and dose selection in psychiatry and cardiology can result in an enhanced degree or rate of efficacy.

Infectious diseases (ID) and neurology PGx can be used to minimize adverse effects. For instance, in therapies involving efavirenz, patients with intermediate or poor CYP2B6 metabolism are at greater risk of neurotoxicity, a potential therapy-limiting toxicity. In addition, patients with the specific variant alleles HLA-B*15:02 and HLA-A*31:01 being treated with oxcarbazepine and/or carbamazepine are at higher risk of Stevens-Johnson syndrome, toxic epidermal necrolysis, and maculopapular exanthema. Use of PGx in ID and neurology can reduce these risks.

Indeed, emerging evidence of genetic associations with disease brings with it many opportunities in precision medicine. As keen stewards of the ever-evolving clinical literature in this area, clinical pharmacists can provide contemporary guidance and education on PGx testing, particularly in periods of increased fiscal responsibility and rising drug costs. Current evidence supports that PGx-guided therapy decisions are most often cost-effective and sometimes cost-saving.

To fully use PGx, moreover, technological improvements must also be leveraged. PGx information should be incorporated into real-time clinical decision support (CDS) systems within electronic medical records (EMRs), including custom rules and links to additional clinical information. In addition, EMRs can help provide primary care physicians with guidance on appropriate testing and interpretation. Leveraging technology together with extending the application of PGx in precision medicine can enhance patient care across several domains.

2.2 | Clinical pharmacist-led PGx services

Many studies have shown that clinical pharmacist-led PGx services improve patient outcomes. St. Jude Children’s Research Hospital (SJCRH) modeled the workflow of its established clinical pharmacokinetic (PK) or therapeutic drug monitoring service to incorporate a clinical pharmacist-led PGx service. Under a collaborative practice agreement, pharmacists ordered PGx tests for TPMT (thiopurine methyltransferase), UGT1A1 (uridine glucuronosyltransferase 1A1), and CYP2D6. An experienced pharmacist interpreted the results from each test and relayed any therapy changes in a written consult. Pharmacists identified patients at risk of drug toxicity from thiopurines and intervened to provide empiric dose reductions. This service also identified patients who were likely to respond poorly, or in an exaggerated manner, to codeine and would benefit from alternative therapies. Since implementation, the clinical PGx program at SJCRH has expanded, developing a clinical pharmacist-led research collaborative known as PG4KDS. This collaborative will help researchers better understand and optimize the processes needed to identify relevant preemptive PGx testing and incorporate these findings and potential clinical implications into the care of pediatric patients.

The University of Florida Health Center for Pharmacogenomics and Precision Medicine also supports integrating PGx data to improve patient outcomes, with clinical pharmacists at the forefront. In addition, the center houses the Program for Applied Research and Development in Genomic Medicine (PARADIGM), a 2- to 3-year clinical research program preparing clinician and research trainees for the evolving future of genomic medicine research and implementation.

The Pitt PGx Program at the University of Pittsburgh and University of Pittsburgh Medical Center not only houses the pharmacist-led PreCISE-Rx project targeted at using genotype interpretation to optimize the selection of antiplatelet medications after cardiac catheterization, but also emphasizes the importance of teaching students and practitioners about using PGx in precision medicine through the Test2Learn program.

The NorthShore University Health System PGx clinic provides testing opportunities to patients who wish to visit on their own accord or who are referred by their clinicians. The multidisciplinary team includes a clinical pharmacist, a medical geneticist, a nurse practitioner, and a genetic counselor. At initial visits, patients are presented with information on the benefits, limitations, risks, and costs of PGx testing. If patients wish to proceed, a pedigree is collected, consent is obtained, and a buccal sample is acquired. The clinical pharmacist interprets the results and provides patient education, including gene name tested, the genotype, the predicted phenotype, and a clinical interpretation.

The University of Colorado Anschutz Medical Campus is advancing large-scale PGx research while providing clinically relevant genetic information to individual patients. The Colorado Center for Personalized Medicine (CCPM) at the campus has actively recruited thousands of patients to contribute DNA samples through the Biobank Research Study. The de-identified data obtained are used to enhance large-
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Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium (CPIC); CPNDS, Canadian Pharmacogenomics Network for Drug Safety; DPWG, Dutch Pharmacogenetics Working Group.
scale PGx research, but patients, if they elect, are also provided with their genetic test results, which are uploaded into their EMR. Translating these genetic data into clinical application is the responsibility of Pharmacogenomics Implementation Committee Colorado (PICcolo), which is co-chaired by a clinical pharmacist. PICcolo began by creating an alert that fired when an order for clopidogrel was ordered for a patient known to be a genetically mediated CYP2C19 intermediate or poor metabolizer who had undergone percutaneous coronary intervention (PCI) the previous year. The hard-stop alert also provided actionable information with clinical alternatives (eg, ticagrelor or prasugrel). Since implementation, CCPM has added CDS tools to address nine other drug-gene pairs.24

The precision medicine program at the University of Illinois Hospital & Health Sciences System includes a clinical pharmacist-led PGx consult service. Inpatient orders for antithrombotic therapy generate an alert notifying providers that genotyping and a consultation by the precision medicine service are available. If elected, a clinical pharmacist on the service then provides initial and continued genotype-informed dosing recommendations throughout the patient’s hospital stay. According to self-reported data, 16 months after implementing this service, anticoagulation-related 30-day readmissions were reduced by 77% and anticoagulation-related 90-day readmissions by 68%. Overall, the annualized cost reduction was estimated as $600,000.25

Clinical pharmacist-led population health PGx interventions have also been shown beneficial. Using data claims from the Medicare/Medicaid program known as the Program of All-Inclusive Care for the Elderly (PACE), clinical pharmacists reviewed the medication profiles of 296 older adult patients (mean age 74.5 years) who were prescribed an average of 14.5 medications. Using the PGxB panel consisting of phenotypic assessment of 11 genes, clinical pharmacists identified at least one drug-gene reaction for nearly 75% of the patients. This resulted in a total of 436 recommendations, including drug dose adjustment (11.2%), drug regimen change (23.2%), or a choice between a drug dose adjustment and change (17.9%).26

The impact of PGx medication management in research environments is also well established. However, translating this to a scalable clinical practice has been challenging. In a survey of 15 of the 20 NIH-funded, early-adopting institutions, primarily led by clinical pharmacists, in the Implementing Genomics in Practice (IGNITE) trial, all 15 sites reported performing at least one PGx drug-gene test clinically, with an average of 6.93 drug/gene tests clinically available.27 However, third-party billing was only implemented for an average of 3.2 PGx drug-gene tests. The authors concluded that adoption continues to lag, even at sites with early and robust implementation, and that insurance reimbursement is key to expanding PGx use.27

Successful programs have laid the groundwork for defining best practice; however, the PGx landscape is rapidly evolving both within and outside pharmacy practice. Best practice is thus likely definable as an evolving, multidisciplinary approach that integrates clinical decision-making with patient education.

2.3 | Resources guiding PGx

Pharmacists can broadly affect PGx implementation efforts by collaborating on clinical practice guidelines, including the Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines, which facilitate a better understanding of PGx testing and clinical implementation. CPIC, cofounded by the clinical PGx program at SJCRH and Stanford University, is an international consortium composed of hundreds of volunteers and a small staff that aims to facilitate the use of PGx tests in patient care by curating PGx evidence and detailed drug-gene clinical practice guidelines.28,29 CPIC’s efforts are funded by the NIH.28 Currently, several pharmacists serve as members of CPIC, its steering committee, and its scientific advisory board. At the time of this publication, 24 CPIC guidelines had been published.28 Of these, 23 (95.8%) listed a pharmacist as a contributing author—many serving as first or senior author. Each guideline reviews the current literature to provide a background on the specific genes and drugs in question and ultimately provides detailed recommendations for interpretation, metabolizer status, and action according to the level of evidence.

Several electronic resource databases have also been developed with pharmacist contributions. The Dutch Pharmacogenetics Working Group (DPWG) established by the Royal Dutch Pharmacists Association is a literature database with graded evidence related to PGx.30 The database is designed to develop “pharmacogenetics-based therapeutic (dose) recommendations and assist drug prescribers and pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance.”31 Currently, a pharmacist is on the DPWG scientific advisory board. Pharmacists are also on the editorial board of the Genomics/Genomics Competency Center, which houses peer-reviewed collections and online genomic educational resources.32

2.4 | PGx consult services

Beyond establishing services, pharmacists currently provide and lead PGx consultative efforts. Pharmacists are uniquely positioned within the health care team to anticipate and examine PGx-related complications, identify appropriate alternative therapies, and educate patients and providers about clinical implications. Pharmacists have distinct knowledge, skills, and abilities related to pharmacotherapy, which can assist with test selection (specific genes and preferred PGx laboratory assay according to the variants tested), posttest interpretation, counseling, and clinical decision-making.3 Foundationally, these consultative skills provide insight into how genetic variations affect a drug’s PK and pharmacodynamic (PD) properties in specific diseases and/or populations.

Pharmacists are also uniquely educated and trained to interpret PGx test results in the context of other patient-specific factors that may influence drug response. This includes concurrent medications—specifically CYP450 inhibitors that may cause phenocconversion—as well as other factors such as age, weight, and tobacco use.
Pharmacists have the knowledge to use phenotypic information (on the basis of genotype and other patient-specific information) before dose adjustments or selection of alternative therapies. If alternative therapy is selected, pharmacists can use PK/PD profiles to predict whether a similar therapeutic effect will be observed. Accordingly, pharmacists are ideally suited to discuss with patients and providers the test benefits, risks, and potential limitations. Although several medical disciplines can affect patient care, pharmacists are uniquely positioned to lead interprofessional teams pertaining to PGx and optimal medication selection, given these nuanced complexities. This has, in turn, allowed pharmacists to develop clinical consult services and clinics that allow for interpretation of PGx results.\(^{15,17,26,32,33}\)

### 2.5 Future of clinical pharmacy practice in precision

The future clinical practice of pharmacists will likely place greater emphasis on precision medicine. Currently, PGx tests are often ordered on an as-needed basis. As more drug-gene pairs are outlined, pharmacists will need to decide whether to continue PGx testing in a reactive manner for therapy selection or adjustment, allowing the results to be available and applied during initial therapy selection. As evidence of the efficacy and economic benefit of PGx testing continues to emerge, routine preemptive testing will likely become standard practice.

Commercially available direct-to-consumer (DTC) genetic testing kits further will increase patient access. Although these tests have limitations for clinical decision-making, pharmacists will continue to be responsible for ensuring their appropriate use.\(^{34}\) Hence, pharmacists’ expertise continue to be needed to critically evaluate testing companies, alleles tested, and appropriateness of star allele conversion to metabolizer status to allow for integration into clinical practice.

In addition to evaluating drug-gene pairs, pharmacists are well positioned to incorporate evaluations of disease-significant genes into as comprehensive medication management (CMM).\(^{35}\) For example, specific genotypes of apolipoprotein L1 are risk factors for chronic kidney disease in the African American population, which can influence therapy decisions related to potentially nephrotoxic agents.\(^{36,37}\)

Finally, for PGx implementation to be as successful as possible, pharmacists will be critical in leading efforts to develop the PGx informatics infrastructure, databases, and CDS tools needed.

### 3 EDUCATION

#### 3.1 Current state of pharmacist education

The field of PGx is rapidly evolving—perhaps even faster than education in this area. Integrating PGx into Pharm.D. programs will help prepare future pharmacists to incorporate PGx knowledge into practice. In 2016, the Accreditation Council for Pharmacy Education added PGx as a requirement to a didactic program for accreditation. Currently, less than half of Pharm.D. programs offer a stand-alone PGx course. Rather, many have integrated PGx within the Pharm.D. curriculum, yet these programs are not standardized, and their curriculum content is inconsistent.\(^{38,39}\) A stand-alone course would emphasize the importance of PGx and provide application opportunities but has not been shown superior to integrating PGx into the curriculum.\(^{40}\) Exposure to PGx education influences student perceptions and knowledge about the importance of PGx information in prescribing decisions. Given a patient case regarding warfarin and PGx, a study found that, before taking a PGx course, 40% of students recommended genomic testing, which increased to 90% after completing the course.\(^{40}\) Similarly, another study showed that third- and fourth-year Pharm.D. students who completed a PGx course had statistically significantly improved knowledge regarding the CPIC guidelines \((P = .04)\) and implications of the CYP2C19 genotype for selection of antiplatelet therapy \((P < .01)\).\(^{41}\)

Various methods have been used to teach PGx in the classroom. At the West Virginia University School of Pharmacy, first-year students in a required biopharmaceutics and PGx course wrote papers, gave oral presentations related to PGx, and practiced genetic counseling in addition to other traditional coursework.\(^{42}\) Student confidence in discussing PGx increased significantly after the course. Faculty at the University of Florida described two elective courses (pharmacogenomics and genomic medicine).\(^{43}\) Students in the PGx course could undergo personal genotyping in addition to more traditional didactic methods. Informed consent for genotyping was reviewed on the first day of class, and a study coordinator unaffiliated with the class handled all student information. Student scores on a PGx knowledge assessment significantly increased after the course. After undergoing personal genotyping, most students reported a better understanding of PGx, believed that genotyping was an important part of their learning process, and stated that the course helped them better understand patients’ experiences with genetic testing. Other institutions have used techniques such as flipped classrooms and genetic software systems to teach PGx content.\(^{44,45}\)

### 3.2 Future of pharmacist education

Successful educational programs will prepare future pharmacists to apply their knowledge of PGx in practice as well as educate their peers and other members of the health care team. Didactic education on PGx should be supplemented by case-based application opportunities and experiential education.

Pharmacists will need to provide comprehensive PGx-based care beyond understanding the role of a single polymorphism and its effect on drug response. Pharmacists are trained to assess multiple pieces of information to ensure appropriate and safe drug therapy, but education will need to continue to evolve to ensure pharmacists can integrate complex genetic information into clinical decision-making.
4 | RESEARCH

4.1 | Current states of PGx research

Clinical pharmacists play a key role in PGx research because of their extensive knowledge of PK/PD and adverse drug reactions. Moreover, clinical pharmacists have recently begun to capture PGx implementation outcomes (scientific, financial, educational, and informatics) and evaluate implementation metrics, which will be useful for health care systems seeking to establish their own PGx testing programs. For example, one large multisite study led by pharmacists who investigated outcomes with clinical implementation of CYP2C19 genotype-guided dual antiplatelet therapy after PCI found a significant reduction in major adverse cardiac events in patients with a loss-of-function allele stemming from alternative medication prescribing. This underscores the major impact that clinical pharmacists can have in examining and disseminating PGx outcomes data through translational research and publication.

Clinical pharmacists can also play a key role in using CYP2C19 and multigene PGx results to optimize medication prescribing beyond antiplatelet therapy in patients undergoing PCI, given pharmacists' extensive knowledge of PK/PD and adverse drug reactions, as shown in another recent evaluation. In this study, pharmacist investigators completed a simulation analysis, which projected that 17.5 PGx-guided medication interventions per 100 patients undergoing PCI could have been made, had multigene PGx results been available at the time of PCI. Further studies are needed to show improved outcomes with multigene PGx testing, given that there are many commonly prescribed medications with actionable PGx recommendations such as proton pump inhibitors, antidepressants, and opioids. However, PGx implementation research is in a relatively early stage.

Clinical pharmacist-led PGx services in addition to traditional medication reviews can avoid substantial costs for payers. Research in this area can help drive payer decisions and support clinical pharmacists as integral members of health care teams. Increasingly, pharmacists' recommendations are being accepted leading to an overall mean cost avoidance of $1063 per actionable drug-gene pair according to the PHARM-GENOME-PACE study. Subtherapeutic drug concentrations lead to treatment failures and increase treatment costs. For example, treatment with voriconazole, an antifungal agent used as prophylaxis in hematopoietic stem cell transplant populations, commonly fails in CYP2C19 rapid/ultra-rapid metabolizers. In one evaluation, however, clinical pharmacist-led genotype-guided dosing resulted in fewer subtherapeutic voriconazole concentrations, prevented invasive fungal infections, and provided an estimated $4700 cost savings per patient compared with simulated controls.

The NIH/National Human Genome Research Institute-funded IGNITE Network is leading pragmatic clinical trials to examine outcomes with genotype-guided management of chronic pain, acute pain, and depression. This network consists of five distinct research sites, each contributing to the greater goal of incorporating genomics into health care. One site is pharmacist led, and all sites have clinical pharmacists as members of the study team.

Studies have also assessed integrating metrics into PGx testing as part of CMM services. A pilot study examining the feasibility and satisfaction of patients receiving CMM plus PGx testing in a cardiology outpatient clinic. It found that PGx testing incorporated into a pharmacist-delivered CMM service was feasible and that patients were very satisfied. The study hence opens the door for larger studies in various ambulatory clinics to show the usefulness of PGx plus CMM programs. Clinical pharmacists are ideally positioned to conduct these studies.

4.2 | Future research

4.2.1 | Diverse populations; large databases

Actionable genetic variants (ie, variants that can lead to alterations in drug selection or dosing) often differ in frequency across ancestral groups, which is particularly important to consider in PGx studies. Like most clinical studies, PGx research aims to recruit patients of diverse ancestry backgrounds. Meta-analyses of some drug-gene pairs may help show the clinical usefulness of genetic testing in multiethnic groups. However, high-powered prospective PGx studies are difficult to conduct, especially when rare variants are being tested, which may limit advances in understanding the genetic influences of drug response—a notable concern when rare variants exist in underserved populations.

However, these limitations may in time be overcome by the ongoing All of Us Research Program, which is dedicated to building a robust research resource from over 1 million participants. Institutions can access the database to explore biological, social, and environmental determinants of health. In addition, the All of Us project is harmonizing and reconciling EMR data to accelerate research interoperability and machine-learning applications to predict drug response and develop precision treatments. Pharmacists in the All of Us partner sites have many opportunities to conduct retrospective, prospective, and cross-sectional studies that will provide insights into causality and help researchers and practitioners better understand diverse populations, provide more rational use of existing therapeutics, and develop new treatments.

Consortia like CSER (Clinical Sequencing Evidence-Generating Research) will contribute to the actionability and return of results, EMR integration, and, more importantly, investigation of psychosocial, behavioral, and economic outcomes related to genomic sequencing. Future studies should examine potential disparities among populations with various socioeconomic backgrounds to inform efforts to ensure equitable use of genomic medicine.

Even as the All of Us project is building a large, diverse database to study many diseases, various other organizations are working in the discovery areas relative to specific disease. The Metastatic Breast Cancer Project as part of the Count Me In nonprofit organization is focused on discovering and applying cutting-edge genomic science for people living with metastatic breast cancer. Count Me In empowers patients with cancer to contribute to breakthroughs and increase the
pace of biomedical research. Pharmacists working in PGx cancer research can partner with such organizations and leverage the resources needed to further personalize therapies.55

Globally, studies such as the 100 000 Genomes Project in the United Kingdom and the Southeast Asian Pharmacogenomics Research Network (SEAPharm) have begun to concentrate on specific precision medicine initiatives.56 Pharmacists can play a significant role in providing precision therapy by becoming involved in research as whole-genome sequencing becomes part of mainstream clinical practice in the future.

4.2.2 | Evaluating outcomes and costs for patients

For PGx testing to be useful and sustainable in the long term, cost justification of PGx programs will be required to ensure third-party payers reimburse for services. Feasibility and patient satisfaction studies will be needed. Demand for PGx services within CMM programs in ambulatory settings continues to grow. This is especially true in older adult populations, where polypharmacy is common.33,57 Investigators from the INGenious trial suggest the need for studies focused on providing data on the cost-effectiveness of PGx programs and their ability to capture and quantify adverse events, compare adverse event rates with national averages, benchmark costs per adverse event, and analyze the accuracy of adverse event recording.58 Funding for PGx programs, grant opportunities, and mentor-mentee participations is also required to facilitate research.59

4.2.3 | Opportunities for PGx discovery

As more molecular data from panomics (the integration of genomics, proteomics, metabolomics, and transcriptomics) and clinical data from EMRs become available to pharmacists, the possibilities for discovery and rapid translation into clinically and biologically meaningful outcomes are tremendous. With the addition of artificial intelligence and machine learning, the future of precision medicine will be led by translational bioinformatics.60 Pharmacists, especially those with careers dedicated to research, will play a critical role in researching and applying panomics-focused approaches to understand patient factors that contribute to variability in drug response. Innovative models for implementing PGx services will need to be developed to integrate this information. Further outcomes studies will be required to understand how implementation of precision pharmacotherapy affects health outcomes and costs.59

5 | PERCEIVED AND TRUE BARRIERS OF PRECISION MEDICINE

5.1 | Clinical practice-related barriers

Clinical pharmacists may face many technological-related barriers when incorporating precision medicine into clinical practice. Currently, many institutions lack the advanced technology infrastructure needed to support the safe and efficient incorporation of precision medicine services into the pharmacist’s workflow. Substantial resources, including pharmacists with expertise in precision medicine and/or informatics, will be important to develop and establish an EMR that contains PGx data, stores large genomic data sets, and displays the most pertinent clinical content in an actionable format.4,59,61-67 Using such advanced systems, pharmacists will no longer have to extract patient data from charts manually or use web-based PGx dosing algorithms—processes that can introduce errors or inconsistencies in final drug selection and dosing. Using patients’ clinical data, EMRs should be able to automatically recommend PGx tests and assist with drug dosing on the basis of the test results.62,65,66 Moreover, EMRs will ideally integrate or communicate between institutions to ensure smooth transitions of care.26

Barriers that may limit the implementation of these services include gaps in knowledge and acceptance of precision medicine and PGx among various health care providers and patients.62,67 Pharmacists as well as other health care providers will require education and training on when to recommend a PGx test, how to interpret the results, and how to translate the results to drug prescribing recommendations.63 Providers may resist PGx implementation because they lack awareness of the positive patient outcomes obtained with precision medicine and the clinical usefulness of PGx testing.57,68 Moreover, PGx guidelines from various organizations may have inconsistent information or lack clarity, further adding to confusion, hesitation, or resistance to precision medicine.62,66,69,70 In addition, patients may refuse PGx testing because of concerns regarding privacy, genetic discrimination, and cost.63

Other barriers include inconsistent reimbursement for PGx services by payers, extended time needed to obtain the testing results, and limited institutional or corporate support to provide precision medicine services.2,4,61,62,68-73 Many payers currently consider PGx testing and services nonessential or experimental; thus, costs for these tests shift to patients and institutions. Pharmacists may also need to wait several days to obtain PGx test results, delaying patient care and interventions.62 In addition to their current workflow, pharmacists providing PGx services may face time pressures to collect samples, interpret data, educate patients and providers, and then document interventions.61,73 However, because regulations allowing pharmacists to order tests vary from state to state, advocating with state representatives may help expand pharmacists’ ability to provide services in these areas.74

5.2 | Education-related barriers

A substantial barrier to incorporating PGx into routine clinical practice is current practitioners’ lack of confidence.61,75 A survey of hospital pharmacists revealed that only 25% felt confident in their ability to interpret PGx test results.76 Variations in PGx test extend and depth of content included in Pharm.D. curricula among pharmacy schools affect pharmacy students’ levels of readiness and comfort in providing precision medicine services.39,67 Moreover, opportunities for
APPEs in PGx concepts remain limited. As a result, pharmacy students may lack in-depth PGx knowledge upon graduation.

Although PGx-focused residencies, fellowships, and in-house training programs provide application-based training, only a few such programs exist. Because of limited postgraduate training, the number of faculty and specialists with expertise in PGx is also limited, which in turn limits the dissemination of knowledge in this practice area. Although most pharmacy schools recognize the need for PGx training, many do not prioritize faculty development in this area. Individual health-system institutions have administered in-house PGx education programs for their pharmacists but acknowledge that successful implementation and delivery of such programs may vary depending on locations and practices of pharmacists.

Online and in-person certification programs in PGx are attempting to fill knowledge gaps for pharmacy students, already-practicing pharmacists, and other health care providers. These programs reach a wider net of learners than PGx-specific residencies, fellowships, or graduate programs but may have a higher barrier to entry. Many continuing education programs provide home-based or live training, which typically last for an hour but do not allow for practice-based application of information. These limitations contribute to the partial retention of information and lack of changes in practice behavior that currently exist.

5.3 Research-related barriers

Researchers, including research pharmacists, may face several challenges before data and results can be incorporated into clinical practice, such as prioritizing the key biomarkers and technologies to study, incorporating novel research methods (eg, N-of-1 studies, drug matching trials, rapid learning systems), and performing cost-effectiveness and health economic studies to advocate for precision medicine. Moreover, research institutions may only offer traditional modeling technologies and methods for research, limiting the exposure of future researchers to newer methods. Research training may not focus on applying quasi-experimental and/or epidemiologic designs in research—two common methods used by researchers working directly for payers.

Establishing collaborations among academia, health care, industry, and payers will remain essential for identifying pertinent genetic markers among large clinical data sets for further explorations, linking these genetic markers to clinical outcomes, and monitoring for these markers in a clinical setting. For example, collaborations are necessary among academic and health care institutions to study PGx associations in rare diseases that affect smaller populations, such as pediatric patients. Partnering with industry helps translate precision medicine research results into medical products, services, and

**FIGURE 1** The pharmacist as the center/leader of a pharmacogenomic program
software programs used in direct patient care. Cooperating with payers will help produce the necessary health outcomes and economic data to advocate for precision medicine.

6 | OVERCOMING BARRIERS TO PRECISION MEDICINE

Clinical pharmacists can overcome barriers and play a vital role in incorporating PGx into precision medicine and health care (Figure 1). In the academic setting, published evidence calls for pharmacists to lead PGx programs and participate in activities such as ordering PGx testing, selecting drugs and doses, medication safety, referring patients to clinical trials, teaching students and health care providers from various health disciplines, and developing research programs while using concepts of precision medicine. In the community setting, pharmacists, as the most accessible health care provider, can educate and counsel patients on PGx testing. Other areas for clinical pharmacist involvement related to PGx include pharmacy informatics; development of CDS tools; database management; creation of medication use policies, processes, and guidelines; and design of clinical usefulness, validity, and cost-effectiveness analyses. For example, a pharmacy informatics specialist in conjunction with a PGx-trained pharmacy specialist can initiate the development of an EMR system that contains PGx data and displays the information in a user-friendly format, including PGx-specific protocols. Developing and implementing a universal EMR system accessible to all health care providers, including community pharmacists, can further accelerate pharmacists’ opportunities to effectively apply PGx data in direct patient care.

Establishing multidisciplinary collaborations will remain essential to advocate and educate about precision medicine. Pharmacists can serve in leadership roles to facilitate the advancement of clinical PGx application and research. Although some providers hesitate to implement PGx because of limited data on its clinical usefulness, others have advocated that pharmacists assume an active role in PGx testing and implementation because they are better equipped for this role than other providers. Many pharmacists have already served as lead authors on CPIC guidelines for PGx and should continue to seek out such leadership roles on multidisciplinary committees.

Clinical pharmacists with additional education in PGx through residencies, fellowships, continuing education, or certificate programs will be best positioned to assume roles in PGx. Thus, an increase in didactic courses, student rotations, continuing education, residencies, and fellowships focused on PGx is needed to prepare generalists and specialists to apply concepts and advance practice related to PGx.

7 | SUMMARY AND CONCLUSION

The field of PGx continues to grow and is becoming a useful tool in the pharmacist’s armamentarium to optimize pharmacotherapy for individual patients. The number of drug-gene pairs continues to grow, and PGx spans many disciplines, including oncology, psychiatry, cardiology, ID, and neurology. Continued research into both current medications and those in development is expected to elevate the prevalence of PGx in practice.

Pharmacists continue to lead in this area as PGx programs are instated at various practice sites around the world. Most commonly, pharmacists help with dose adjustments, regimen changes, or both. Furthermore, clinical pharmacists possess the education and training to integrate PGx data with other patient-specific factors (eg, renal function, hepatic function, age, concomitant medications) into a patient-centered, evidence-based therapy plan. Beyond daily patient care, pharmacists can provide important insight on incorporating these concepts into guideline development and various consultative services.

Research and education remain vital to breaking through PGx implementation barriers. As knowledge continues to grow in these areas, both perceived and true barriers will diminish, and PGx will become an expectation of the medical community. Implementation of a PGx program will require a complex level of coordination among ordering clinicians, clinical pharmacists, and physicians interpreting the tests; information technology experts building CDS; and key personnel in billing and revenue cycles to oversee reimbursement. Commitment of resources in research and education will be key to successfully implementing new PGx programs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

6. Goetz MP, Suman VJ, Reid JM, et al. First-in-human phase I study of the tamoxifen metabolite Z-endoxifen in women with endocrine-