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Precision pharmacotherapy: Integrating pharmacogenomics into clinical pharmacy practice

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Abstract

Precision pharmacotherapy encompasses the use of therapeutic drug monitoring, evaluation of liver and renal function, genomics, and environmental and lifestyle exposures; and analysis of other unique patient or disease characteristics to guide drug selection and dosing. This paper articulates real-world clinical applications of precision pharmacotherapy, focusing exclusively on the emerging field of clinical pharmacogenomics. Precision pharmacotherapy is evolving rapidly, and clinical pharmacists now play an invaluable role in the clinical implementation, education, and research applications of pharmacogenomics. This paper provides an overview of the evolution of pharmacogenomics in clinical pharmacy practice, together with recommendations on how the American College of Clinical Pharmacy (ACCP) can support the advancement of clinical pharmacogenomics implementation, education, and research. Commonalities among successful clinical pharmacogenomic implementation and education programs are identified, with recommendations for how ACCP can leverage and advance these common themes. Opportunities are also provided to support the research needed to move the practice and application of pharmacogenomics forward.

KEYWORDS

clinical pharmacy, personalized medicine, pharmacogenomics, pharmacy practice, precision pharmacotherapy, precision medicine

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1 | INTRODUCTION

Pharmacists have long recognized that using unique patient characteristics to guide pharmacotherapy decision-making can improve drug response and mitigate drug-associated risks. Age, weight, and dietary habits were among the first patient-specific characteristics used to individualize pharmacotherapy. As technologies advanced, analytic tools that measure surrogate markers of liver and renal function, together with drug concentrations in biological fluids, were adopted to optimize therapeutic regimens. Cutting-edge genomic technologies are now being integrated into patient care for the selection of targeted therapies and identification of those at increased risk of poor pharmacotherapy outcomes. The term *precision pharmacotherapy* has been coined to refer to the use of genetic, environmental, lifestyle, and other unique patient or disease characteristics to guide drug selection and dosage.[1]

The American College of Clinical Pharmacy (ACCP) charged the 2018 ACCP Clinical Practice Affairs Committee to develop this white paper, which focuses exclusively on the emerging field of clinical pharmacogenomics as one component of precision pharmacotherapy. The recommendations provided in this paper are intended to serve as a guide for ACCP to support clinical pharmacists' efforts to advance clinical pharmacogenomics and precision pharmacotherapy. The ACCP Practice and Research Networks have written a companion paper published in this issue of *JACCP* that provides a broader analysis of the application of precision pharmacotherapy across therapeutic specialties.

2 | EVOLUTION OF PHARMACOGENOMICS IN CLINICAL PHARMACY PRACTICE

The concept of genetic variations affecting drug response dates back to at least the 1940s,[2,3] with Friedrich Vogel coining the term *pharmacogenetics* in 1959.[4] Initial research mainly focused on how inherited genetic variations (ie, germline variations) in a single gene could influence drug response, termed *pharmacogenetics*. After decades of research focused on discovering genetic variations that influence drug response and the subsequent validation of these findings, evidence became sufficiently strong to warrant the application of pharmacogenetics to clinical practice.[5,6] One of the earliest and most well-known examples of clinical pharmacogenetics is the screening of patients for variations in the thiopurine methyltransferase (*TPMT*) gene to guide thiopurine (eg, azathioprine, mercaptopurine, thioguanine) dosing. Clinical data analyses published in the 1990s showed that reducing thiopurine doses in pediatric patients with acute lymphoblastic leukemia who harbored genetic alterations predictive of TPMT intermediate or poor metabolizer phenotypes prevented severe, life-threatening myelosuppression.[7,8] Subsequent studies of patients with autoimmune diseases suggested that *TPMT* genotyping could prevent thiopurine-induced toxicities in a cost-effective manner.[9,10] These findings propelled the integration of *TPMT* genotyping strategies into patient care.

Throughout the 2000s, clinical use of other single gene-drug pairs to guide drug selection and dosage increased. Examples included *CYP2C19*-clopidogrel, *CYP2C9/VKORC1*-warfarin, *CYP2D6*-opioids, *CYP2D6*-tamoxifen, *DPYD*-fluoropyrimidines, *HLA-B*15:02*-carbamazepine, and *HLA-B*57:01*-abacavir. However, the integration of pharmacogenetics into routine patient care was slow. High genotyping costs, a lack of consensus guidelines for tailoring pharmacotherapy on the basis of genetic test results, and limited options for informing clinicians of genetic test results at the time of drug prescribing (beyond a paper-based laboratory report) made large-scale implementation models impracticable.

The Human Genome Project bolstered DNA genotyping and sequencing technologies, resulting in a drastic decline in costs by the mid-to-late 2000s.[11] Affordable Clinical Laboratory Improvement Amendments (CLIA)-certified array-based genomic panels capable of interrogating hundreds of genes and thousands of variants facilitated the expansion of genetic testing into clinical practice. As more genes were tested on a single platform, the term *pharmacogenomics* (ie, the study of how the genome influences drug response) became more common than *pharmacogenetics* (ie, the study of how a gene or genes influence drug response). By the early 2010s, several large-scale pharmacogenomic implementation science programs had been launched that used array-based genomic panels to preemptively genotype patients.[12-16] Simultaneously, the Centers for Medicare & Medicaid Services (CMS) started an electronic health record (EHR) incentive program that promoted the adoption of EHR software. EHR software platforms in turn enabled the development of clinical decision support (CDS) tools that communicated important genomic information at the time of drug prescribing and verification.[17-20] The Clinical Pharmacogenetics Implementation Consortium (CPIC; https://cpicpgx.org/) was established during this time to provide evidence-based guidelines for optimizing drug therapy on the basis of genetic test results.[6] By the middle 2010s, pharmacist-managed pharmacogenomic clinical services were becoming more widespread, including the establishment of pharmacogenomic ambulatory clinics.[21,22]

In addition to germline variations, precision pharmacotherapy strategies were emerging to identify genetic mutations driving cancer (ie, somatic mutations) to guide targeted drug therapy.[23,24] Among the first targeted cancer therapies introduced into clinical practice were trastuzumab for HER2-positive breast cancer and imatinib for *BCR-ABL* positive chronic myeloid leukemia.[25-27] During the 2010s, the number of anticancer drugs targeting specific somatic mutations increased exponentially.[28,29] Clinical trials were introduced that enrolled patients to receive targeted therapy on the basis of molecular profiling, agnostic of histology (ie, cancer type).[30-32] The 2017 FDA approval of pembrolizumab for any advanced solid tumor with microsatellite instability highlights the paradigm shift of selecting anticancer agents on the basis of molecular alterations instead of histology. Cancer genomic profiling is now emerging as standard of care for numerous cancer types, with CMS recently issuing a national coverage determination for a comprehensive genomic profiling assay as a companion diagnostic for advanced, recurrent, or refractory solid tumors.[33]

Clinical genomics has expanded beyond human germline and somatic genomes to include microbial genomes as well. Antimicrobial stewardship programs are adopting microbiologic molecular rapid diagnostic tests to identify the presence of bacterial or fungal organisms (eg, *Staphylococcus* spp., *Klebsiella* spp., *Candida* spp.) and associated antimicrobial resistance genes.[34] These tests are often performed in patients with life-threatening infections who are most

TABLE 1 Key components of clinical pharmacogenomic implementation initiatives

Engaging with key stakeholders	Prioritizing gene-drug pairs for implementation	Selecting a pharmacogenomic test	Establishing EHR infrastructure	Maintaining sustainability and demonstrating value
Identify and engage multidisciplinary institutional champions and stakeholders	Review clinical evidence and select gene-drug pairs with sufficiently strong evidence to warrant clinical implementation	Determine whether a single gene or multigene panel test is most appropriate for the gene-drug pair(s) selected for implementation	Identify methods for discretely curating pharmacogenomic data in the EHR	Develop continuing education for clinicians and patients to sustain ongoing pharmacogenomic efforts
Determine the value proposition of the pharmacogenomic initiative for the institution	Evaluate drug-prescribing frequencies and which providers are prescribing the drugs of interest	Engage with the institutional laboratory medicine department to determine whether genetic testing should be performed internally or specimens sent to an external laboratory	Collaborate with clinical informatics teams to develop CDS tools that alert clinicians of important genomic information	Maintain and further develop CDS tools to support ongoing pharmacogenomic efforts
Identify potential barriers to implementing clinical pharmacogenomics and formulate solutions	Evaluate the demographics of the patient population and calculate the expected frequencies of actionable genetic variants	Evaluate the demographics of the patient population to determine whether a genetic test provides appropriate variant coverage, given the expected allele frequencies in the population	Obtain provider input on clinical recommendations found in CDS tools	Perform systematic evaluations of operational metrics and deliverables to demonstrate value
Organize a formal precision medicine or pharmacogenomic oversight committee	Align gene-drug pair selection with institutional deliverables and patient care goals	Formulate billing and reimbursement matrices, including the need for a reference laboratory that provides billing services	Obtain provider input on CDS workflows, including when to use active vs passive CDS	Integrate pharmacogenomics into institution-specific quality improvement projects
Engage with pharmacy leadership to integrate pharmacogenomics into existing clinical pharmacist services		Select a test that is suitable for workflow logistics, including turnaround time and specimen type (eg, blood sample or buccal swab)	Establish standard operating procedures for evaluating, maintaining, and updating CDS tools	Communicate findings of value assessments to key stakeholders and institutional leadership
Engage other institutional groups and task forces (eg, anticoagulation task force, CDS committee, risk management)		Verify that a selected laboratory has appropriate state and federal certification/licensure		

Abbreviations: CDS, clinical decision support; CPIC, Clinical Pharmacogenetics Implementation Consortium; EHR, electronic health record.

likely to benefit from earlier organism identification and initiation of targeted therapies. Similarly, viral genotypes are now routinely used to guide antiviral therapy for diseases such as HIV and hepatitis C.

Moreover, numerous publications now provide detailed descriptions of clinical pharmacogenomic implementation models, educational programs, and clinical research methods.[21-24,35-44] A 2015 American Society of Health-System Pharmacists position statement delineated pharmacists' responsibilities and functions in clinical pharmacogenomics.[45] A goal of the present paper is to identify commonalities among successful clinical pharmacogenomic implementation and educational programs and provide recommendations for how ACCP can leverage and advance these common themes. Opportunities for supporting the research needed to move clinical pharmacogenomics forward are also discussed. The following sections on clinical pharmacogenomic implementation, education, and research focus on the inherited (germline) human genome. However, the recommendations can be extrapolated to the entire field of precision pharmacotherapy.

3 | CLINICAL PHARMACOGENOMICS IMPLEMENTATION SCIENCE

The goal of clinical pharmacogenomics implementation science is to improve pharmacotherapy outcomes by seamlessly integrating evidence-based genomic data with other unique patient- and disease-specific characteristics to guide drug selection and dosing. Numerous clinical pharmacogenomic implementation models have been used to integrate genomic information into patient care. Early implementers, primarily at academic health centers, deployed reactive testing (ie, at the time of drug prescribing) and focused on only one or two gene-drug pairs. These early implementation models typically used pharmacist-managed consultation services to guide gene-based dosing recommendations.[22,35,46-48] Later, implementation models expanded to include preemptive, panel-based approaches that interrogate numerous genes at once.[49] Other examples of implementation models include the establishment of standalone ambulatory pharmacogenomic clinics,[21,22] together with efforts to integrate pharmacogenomics into medication therapy management.[50,51] Irrespective of the implementation model used, five common themes underlying these successful implementation efforts have emerged (Table 1): engaging with key stakeholders, prioritizing gene-drug pairs for implementation, selecting a pharmacogenomics test, establishing EHR infrastructure, and maintaining sustainability and demonstrating value.

3.1 | Engaging with key stakeholders

Cultivating strong institutional support, ranging from executive leaders to end users (eg, physicians, pharmacists, and patients), is essential for implementing pharmacogenomics into patient care. Obtaining institutional support typically involves understanding how a new clinical service will be evaluated and aligning the deliverables with those valued by the institution. Executive leaders, together with other key stakeholders such as the department of laboratory medicine, often request a budget impact analysis. This analysis should quantify the resources needed from the stakeholders and summarize the expected costs, benefits, and potential savings.[52] This may involve evaluating the institutions' payer portfolio, patients' interest in and ability to pay for pharmacogenomic testing, and whether implementation will occur in a bundled payment or a fee-for-service environment.

A strategy for obtaining buy-in from physicians and other health care professionals is providing educational programs focused on clinical evidence supporting clinical pharmacogenomics implementation and its benefit to patients. Another common theme among successful implementation programs is collaborating with existing groups (eg, pharmacy and therapeutics committees) and/or creating a pharmacogenomics oversight committee. Members of an oversight committee may include, but are not limited to, pharmacists, physicians, pathologists, nurses, genetic counselors, clinical informatics personnel, and billing specialists.

3.2 | Prioritizing gene-drug pairs for implementation

CPIC guidelines, FDA prescribing information (eg, boxed warnings), and literature searches can be used to identify drugs with sufficient evidence to warrant clinical implementation of pharmacogenomics. A shared characteristic among successful pharmacogenomic implementation programs is understanding the prescribing patterns of drugs significantly affected by genetic variants, and the expected frequencies of actionable genomic results. The percentage of patients exposed to a particular drug, the severity of the gene-drug interaction, and the availability of alternative therapies can be used to prioritize implementation efforts. The frequencies of genetic variants that influence drug response can differ by race and ethnicity. Therefore, obtaining race and ethnic demographics of patients and calculating the expected frequencies of actionable genetic variants within a patient population should also be used to prioritize implementation efforts. Resources such as CPIC or the Pharmacogenomics Knowledgebase (PharmGKB) can provide information about genetic variant frequencies among races and ethnicities.[6,53]

3.3 | Selecting a pharmacogenomic test

The number of genetic variants interrogated and their associated interpretations can vary among clinical pharmacogenomic testing platforms.[54] Similar to how race and ethnicity can influence the prioritization of gene-drug pairs for implementation, race and ethnicity influence the selection of a pharmacogenomic testing platform. Pharmacogenomic testing options should be evaluated to determine whether a particular test provides adequate coverage of the variants observed among the patient population of interest. If the CPIC guidelines are used to guide implementation, selecting a reference laboratory that provides interpretations concordant with CPIC should be considered. Other factors to consider when selecting a pharmacogenomic test include turnaround time, sample collection

logistics (eg, blood sample or buccal swab), need for a single gene test or genomic panel, and costs.[55] Certain reference laboratories may provide billing services together with financial assistance programs that are based on a patient's income.

For early adopters of clinical pharmacogenomics, selecting a pharmacogenomic test has mainly been a well-thought-out process that considers several clinical factors. However, direct-to-consumer (DTC) testing can add a "Wild West" component to pharmacogenomic implementation. The FDA has recently approved DTC tests for cancer risk (ie, *BRCA1* and *BRCA2*), pharmacogenomics, and certain conditions such as G6PD deficiency, Parkinson's disease, and Alzheimer's disease. DTC tests allow individuals to purchase pharmacogenomic panel testing, typically for a few hundred dollars. The quality of a DTC test in the context of variant coverage and its associated interpretations may vary among reference laboratories. DTC genomic tests may potentially have a large effect on pharmacies, particularly in community settings where patients typically have easy access to pharmacists.

3.4 | Establishing EHR infrastructure

Most clinical pharmacogenomic implementation models have focused heavily on EHR infrastructure. EHRs allow genomic data to be incorporated into continuity of care as patients transition between care settings within health care organizations. However, using the EHR for curating and disseminating genomic data remains one of the most challenging steps in implementation. EHR terminologies and standards (eg, LOINC, SNOMED, HL7, FHIR) are limited to support the discrete transfer of pharmacogenomic results from laboratories to EHRs.[56] Furthermore, genomic information may be relevant throughout a patient's life. For example, a *CYP2D6* result obtained to guide antidepressant drug selection may be important several years later to guide pain management pharmacotherapy. Simply scanning a document or entering other nondiscrete pharmacogenomic information into the EHR is insufficient, given that end users, including physicians and clinical pharmacists, may find it almost impossible to retrieve the pharmacogenomic results years later. In addition, nondiscrete data may hamper the ability to appropriately manage changes in the clinical application of a genetic result over a patient's lifetime. CDS tools have emerged as the primary method to deliver EHR-integrated genomic data in a meaningful way.

Several groups and organizations have developed methodologies to support the integration of pharmacogenomic data into the EHR, including CPIC, the Implementing Genomics in Practice network (IGNITE; https://ignite-genomics.org/spark-toolbox), and the Electronic Medical Records and Genomics Network (eMERGE; https://emerge.mc.vanderbilt.edu/ and https://cdskb.org/).[14,57,58] Efforts have focused on curating discrete pharmacogenomic data in a patient-centric, time-independent manner to support active and passive CDS.[59] Active CDS tools focus primarily on interruptive "pop-up" alerts that provide clinicians with meaningful information at the point of care (eg, drug-genotype-specific recommendations).[17] Passive CDS tools include result portals, comments, and interpretations, which reside in the background waiting for the user to access them.[22] Target audience, alert fatigue, practice setting, and clinical importance determine which tools are most appropriate in a given situation. Irrespective of the tools used, it is critical to follow the '5 Rights of CDS' (ie, the right information to the right people through the right channels in the right intervention formats at the right points in workflow) and to engage clinical informatics specialists early in EHR integration and CDS build efforts.[60]

3.5 | Maintaining sustainability and demonstrating value

Ongoing efforts are needed to sustain the pharmacogenomic clinical services that have been implemented and to demonstrate value. Continuous provider education, maintenance and further development of CDS tools, and genomic test reimbursement are key considerations for sustainability.[61] Although reimbursement of pharmacogenomic tests may minimize the financial burden for institutions and patients, it often fails to provide significant revenue. In an era of DTC genomic tests and lowered costs of whole exome sequencing, reimbursement models for cognitive services related to reinterpreting data and applying these data to patient care may emerge as key drivers for sustainability.

Transitions from fee-for-service to value-based care also affect the sustainability of pharmacogenomic services. In a value-based care system, reimbursements are bundled into a lump-sum payment for all services performed during an episode of care. Clinical services that do not demonstrate value are less likely to receive lump-sum reimbursement dollars. In a value-based health care model, pharmacogenomic clinical services are unlikely to be sustainable if value propositions such as improved pharmacotherapy outcomes and reduced costs to treat drug-induced toxicities are not met.[52,62] Thus, systematically evaluating operational metrics on a regular basis is essential for demonstrating value and promoting long-term sustainability.

ACCP can help sustain the role of clinical pharmacists in implementing clinical pharmacogenomics. Moreover, ACCP can endorse and promote existing resources such as the CPIC guidelines and implementation tools developed by IGNITE and others. Opportunities also exist to provide educational resources that describe how to perform pharmacogenomic-specific budget impact analyses and evaluate operational metrics to demonstrate clinical value. Recommendations for ACCP support of clinical pharmacogenomic implementation efforts are summarized in Table 2.

4 | PHARMACOGENOMICS EDUCATION

Effective clinical pharmacogenomics implementation begins with effective education of students, postgraduate trainees, clinicians, and patients. There is a growing need to expand pharmacogenomics education and share best practices for each of these groups. As the field of pharmacogenomics continues to evolve, educational strategies

TABLE 2 Recommendations for ACCP support of clinical pharmacists' efforts to advance clinical pharmacogenomics

Clinical Pharmacogenomics Implementation Science
• Curate and disseminate pharmacogenomics implementation science education resources - Endorse the CPIC guidelines together with publicizing new or updated guidelines - Create a page on the ACCP website that summarizes pertinent resources and provides links to implementation guides and templates (eg, IGNITE and CPIC) - Provide webinars from content experts related to implementation strategies (eg, budget impact analysis, engaging key stakeholders), clinical informatics, and quantitation of operational metrics
• Promote and support the development of short "sabbaticals" or traineeships at sites implementing pharmacogenomic clinical services to provide hands-on training
• Engage with other professional organizations to advocate the clinical pharmacist's role in providing pharmacogenomic services - For gene-drug pairs with strong evidence warranting implementation, jointly advocate reimbursement of pharmacogenomic testing - Advocate reimbursement of medication optimization that includes cognitive services for interpreting and applying pharmacogenomic results
Clinical Pharmacogenomics Education
• Support the inclusion of pharmacogenomics education in pharmacy curricula (eg, didactic and experiential courses) and residency training programs • Foster the continued development of pharmacogenomic specialty postgraduate training programs • Develop and disseminate pharmacist-oriented education resources - Update the 2016 ACCP Pharmacotherapy Didactic Curriculum Toolkit (https://www.accp.com/docs/positions/misc/AM_Pharm_Toolkit_2016_revised.pdf) to include "pharmacogenomic considerations" as a tier 1[a] topic for each disorder that includes actionable gene-drug pairs - Offer a variety of knowledge-, application-, and practice-based CPE programs, including certificate programs - Update the text of ACCP's *Pharmacogenomics: Applications to Patient Care*, when warranted, and consider developing an abbreviated version of the book for home study, knowledge-based CPE credit
• Curate and disseminate patient education and other health care professional–oriented education resources - Build a page on the ACCP website that summarizes pertinent resources and provides links to patient-oriented pharmacogenomics education (eg, IGNITE) - Create a page on the ACCP website that summarizes pertinent resources and provides links to health care professional-oriented pharmacogenomics education (eg, IGNITE, G2C2)
• Engage with other organizations to promote interdisciplinary education models (eg, NIH/NHGRI Inter-Society Coordinating Committee for Practitioner Education in Genomics)
Clinical Pharmacogenomics Research
• Advocate research funding and provide grant opportunities for clinical pharmacogenomics research • Recruit mentors and mentees interested in clinical pharmacogenomics research to participate in ACCP's MeRIT and FIT programs
• Support the development of pharmacogenomics-related practice-based research and network studies

Abbreviations: CPE, continuing pharmacy education; FIT, Focused Investigator Training; G2C2, Genetics/Genomics Competency Center; IGNITE, Implementing Genomics in Practice; MeRIT, Mentored Research Investigator Training; NHGRI, National Human Genome Research Institute; NIH, National Institutes of Health.

[a]Tier 1 = Students receive education and training on this topic to prepare them to provide collaborative, patient-centered care upon graduation and licensure.

must evolve in parallel to meet the needs of contemporary clinical pharmacogenomic practices.

4.1 | Pharmacogenomics education for pharmacists

Inclusion of pharmacogenomic principles and clinical applications in pharmacy curricula is stipulated by the Accreditation Standards and Key Elements for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree,[63] and the North American Pharmacist Licensure Examination includes pharmacogenomics as a required competency.[64] Pharmacogenomics education provided within pharmacy curricula is diverse. Pharmacy programs continue to explore the optimal quantity, delivery, and placement of pharmacogenomic content.[35,65] Pharmacogenomic content may be integrated (ie, threaded) throughout the required pharmacotherapeutic coursework or offered as a standalone or elective course. More recently, novel approaches such as participatory (ie, student) genotyping have emerged in the classroom.[43,66] Independent of the format used, case-based examples provide an excellent learning tool, particularly cases that require students to integrate evidence-based genomic data with other unique patient- and disease-specific characteristics to guide drug selection and dosing. Case-based teaching can also be integrated into introductory and advanced pharmacy practice experiences (IPPEs, APPEs). In addition, the Genetics/Genomics Competency Center (G2C2) provides pharmacogenomic competencies for pharmacists, which may serve as a blueprint for developing the educational content in pharmacy curricula.[67]

There is currently much debate regarding postgraduate training in pharmacogenomics. One side of the debate is that all postgraduate training should integrate pharmacogenomics to the level pertinent to the generalist clinician. Proponents of this viewpoint argue that pharmacogenomics, much like pharmacokinetics, is a clinical tool relevant to all clinical pharmacists rather than its own specialty area of practice. The other side of the debate is that specialized pharmacogenomic residency and fellowship programs may help train future clinical and

research faculty leaders. It can be argued that both viewpoints are valid. For the pharmacy profession to fully embrace precision pharmacotherapy, every pharmacist needs a basic understanding of pharmacogenomics that, at the minimum, encompasses knowledge about the CPIC guidelines and FDA genomics-based dosing recommendations. Integrating pharmacogenomic competencies and training into existing postgraduate year one (PGY1) and PGY2 residency curricula will help ensure that future clinical pharmacists can appropriately interpret and apply pharmacogenomic test results to patient care as they pertain to future clinical pharmacists' areas of practice.

Investing in specialized postgraduate training programs is essential to address growing needs in the emerging field of clinical pharmacogenomics. Implementing a sophisticated clinical pharmacogenomics service requires expertise across genomics, pharmacology, therapeutics, clinical informatics, and, in many instances, unique legal and ethical issues (eg, identification and reporting of incidental genomic findings). It is unlikely that a PGY1 or nonpharmacogenomics PGY2 residency can effectively teach all aspects of clinical pharmacogenomics and its successful implementation, particularly given that use of pharmacogenomics in clinical practice is not yet widespread. In addition, faculty members with specialized training in pharmacogenomics can be valuable resources for other faculty and preceptors teaching student pharmacists, both in the classroom and as part of IPPEs and APPEs. By incorporating pharmacogenomics into student and residency curricula, together with further developing specialized postgraduate training programs, the pharmacy profession will have the basic knowledge to embrace precision pharmacotherapy and the needed leaders to advance clinical pharmacogenomics implementation, education, and research.

Given the rapid developments in the field, many practicing clinical pharmacists may feel inadequately prepared to integrate pharmacogenomics into their practice settings.[68] Different strategies exist to enhance a practicing clinical pharmacist's knowledge and skills in pharmacogenomics, such as traditional continuing pharmacy education (CPE) programs, institution-specific training programs, online resources, and certificate programs.[35] The number of hours that a clinical pharmacist must devote to these resources can vary depending on the scope of the training and the educational needs of the individual. Certificate programs, also known as certificate training programs or advanced training programs, have recently emerged and are offered by several professional associations and educational institutions,[69,70] including ACCP with its Precision Medicine: Applied Pharmacogenomics Certificate Program (https://www.accp.com/PGx). Although the available certificate programs vary considerably in design and scope, they generally offer application- or practice-based clinical pharmacogenomics content.

4.2 | Pharmacogenomics education for patients and other health care professionals

Educating patients about pharmacogenomic testing, what the test results mean, and the lifelong implications of such testing should be considered an essential function of clinical pharmacists providing precision pharmacotherapy. Although patients find value in pharmacogenomic testing, there are potential concerns related to privacy, cost, and the psychological consequences of testing. Pharmacists should play a key role in patient education initiatives including in-person, telephone, or telemedicine counseling to explain pharmacogenomic test results to patients. Additional tools to provide patient education may include web-based educational videos, letters/pamphlets, and integrated patient portals.[71,72] As testing for genetic variants that are predictive of both drug response and disease risk evolves, pharmacists should collaborate with genetic counselors to enable a broader scope of genomics education. For example, discussions regarding risk of disease and associated family implications for *BRCA1/2* testing should be conducted by a genetic counselor, and discussions about opportunities for targeted therapy (ie, PARP inhibitors) should be conducted by a clinical pharmacist.[73]

The primary methods of delivering education for health care providers have been institution-specific online or live modules (including grand rounds), point-of-care CDS tools, and continuing education programs. Online modules and CDS tools often provide links to other educational resources (eg, PharmGKB, CPIC, and G2C2).[74] Various models, including ground rounds and web-based continuing education modules, have shown positive outcomes related to pharmacogenomic education.[75,76] However, inherent barriers such as provider time constraints and learner attitudes, together with financial and personnel resources, necessitate a multimodal approach to delivering education. Combining the use of point-of-prescribing resources embedded in the EHR with ongoing live educational opportunities provides clinicians with multiple points of exposure to support and reinforce pharmacogenomic education.[77]

All clinical pharmacists should possess a basic and functional knowledge of pharmacogenomics to adequately support application at their practice sites. ACCP can support educational needs through continued advocacy for the inclusion of pharmacogenomic education in pharmacy curricula and continued development of clinical pharmacist-oriented educational resources (eg, CPE and certificate programs). Providing up-to-date patient and clinician education resources will further support the role of clinical pharmacists in delivering precision pharmacotherapy. A summary of recommendations for how ACCP can support pharmacogenomic education initiatives is provided in Table 2.

5 | CLINICAL PHARMACOGENOMICS RESEARCH

Pharmacogenomic implementation models have mainly focused on integrating genomics data into patient care, with limited resources available to measure outcomes. Thus, data are limited to establish whether current pharmacogenomic implementation efforts unequivocally improve patient outcomes and do so in a cost-effective manner. This issue highlights both a critical need and an excellent research

opportunity to evaluate the value of pharmacogenomic-based interventions in patient care.[44] To overcome current health care disparities, future clinical pharmacogenomic research studies should include more diverse patient populations (eg, minorities, children, patients of low-socioeconomic status) to ensure that all patients benefit from pharmacogenomics.[44] At the same time, assessments of how to most effectively deliver pharmacogenomic test results at the point of care and provide patient and provider education are also fruitful research directions. Clinical pharmacists are well positioned to lead and participate in these endeavors.[78]

5.1 | Implementation

As the field of clinical pharmacogenomics continues to evolve, there is a corresponding need for well-designed research studies that systematically assess implementation-related outcomes.[79] Examples include acceptability, adoption, appropriateness, cost, coverage (penetration), feasibility, fidelity, and sustainability of an intervention or program.[80] Implementation metrics such as these are often crucial for ongoing institutional support of a clinical pharmacogenomics program. Along the same lines, there is an increased need for rigorous qualitative research studies to evaluate patient and provider perspectives about the clinical usefulness of pharmacogenomic testing.[81]

The current era of precision medicine extends beyond genomics and seeks to integrate patient health data (eg, kidney and liver function) with genomic, epigenomic, transcriptomic, proteomic, and metabolomic data to improve the prevention and treatment of disease. Integration of various omic-based platforms, coined "panomics," into patient care will require innovative implementation models.[82] Clinical pharmacists will play a critical role in researching and applying panomic approaches to understand patient factors that contribute to variability in drug response. As new and clinically meaningful biomarkers are adopted in clinical practice (eg, PD-L1 expression and tumor mutation burden status for immunotherapy treatment opportunities),[83] clinical pharmacists will have to remain nimble and adapt their practice models to incorporate these discoveries.

5.2 | Value

Determining the value of pharmacogenomics implementation is complex and includes variables such as test costs, cost and effectiveness of alternative treatment, frequency of variant alleles, prevalence of adverse drug reactions, scope of the evaluation (eg, single gene-drug evaluation vs panel testing that may affect future outcomes), and evidence of the clinical effectiveness of pharmacogenetic testing.[84] As preemptive testing becomes more common and less expensive, the cost-effectiveness of testing is hypothesized to become more favorable.[84] However, this hypothesis does not settle debates in the field—the major one being what constitutes "high-quality" evidence of clinical effectiveness. In particular, randomized controlled trials (RCTs) remain the gold standard for clinical research and are often relied on to show the benefit of an intervention; however, conducting RCTs to evaluate the benefit of clinical pharmacogenomics is expensive and logistically complex. RCTs require large diverse patient cohorts to capture rare variants/phenotypes and have ethical considerations.[85] Therefore, innovative trial designs are critical for future clinical pharmacogenomic research efforts and will likely include the use of pragmatic studies, quality improvement projects, well-designed retrospective studies, and meta-analyses. A multitude of evidence, rather than a single RCT, will likely be needed to demonstrate the value of clinical pharmacogenomics.[86] Such evidence will also be essential in expanding reimbursement models and advancing the roles and responsibilities of clinical pharmacists in pharmacogenomics.

There remains a critical need for outcomes-based research to establish value and evaluate clinical pharmacogenomic implementation initiatives, with a future need for sophisticated models that can integrate panomics into patient care. Innovative study designs will be needed, together with funding mechanisms to support these initiatives. ACCP can help support these efforts by providing grant funding and training resources for clinical pharmacogenomic-based research as described in Table 2.

6 | THE PROMISING FUTURE OF PRECISION PHARMACOTHERAPY

Application of pharmacogenomics to clinical practice has already yielded success by avoiding untoward drug effects and improving efficacy. In the near future, epigenomics, transcriptomics, proteomics, and metabolomics information will likely be integrated into precision pharmacotherapy implementation models as well. These advances will require sophisticated EHR and clinical informatics solutions. Outcome studies will be warranted to further understand how precision pharmacotherapy implementation efforts influence health outcomes and costs. As technologies quickly advance, pharmacist education will be of upmost importance, with the need for innovative methods to support clinical pharmacists' efforts to educate other health professionals and patients on complex precision pharmacotherapy topics. These continued efforts will conceivably translate to greatly improved pharmacotherapy outcomes that are cost-effective.

7 | CONCLUSION

The field of pharmacogenomics and precision pharmacotherapy is evolving rapidly. Clinical pharmacists can play an instrumental role in these efforts ranging from leading clinical pharmacogenomic implementation initiatives to stewarding the prudent use of pharmacogenomic data across the spectrum of care. Clinical pharmacists have the potential to sustain leadership in pharmacogenomic implementation, education, and research efforts. ACCP is well positioned to advance clinical pharmacist knowledge/skill development in pharmacogenomics and the broader field of precision pharmacotherapy. The recommendations provided herein are intended to serve as a guide for ACCP to support clinical pharmacogenomic implementation, education, and research as an essential component of precision pharmacotherapy.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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