**Precision medicine: Opportunities for health-system pharmacists**

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Historically, the term *pharmacogenetics* described variability in drug response resulting from patients' germline genetic characteristics. *Pharmacogenomics* has been used as a broader term in reference to any genetic factor that impacts drug response, including somatic mutations in cancer, the role of pathogen genomes in infectious diseases, etc. *Precision medicine* has been defined by the National Research Council as "the tailoring of medical treatment to the individual characteristics of each patient."[1] In practical terms today, precision medicine should be considered any care that is guided by individual patient characteristics, including genetic characteristics and other factors such as diet and lifestyle, that maximize treatment benefits while minimizing adverse effects and cost.

In 2015, the United States embarked on a national research agenda to advance precision medicine.[2] A major component of this initiative is the All of Us study, which is establishing a cohort of 1 million individuals with full genomic sequencing and extensive surveys of lifestyle, health, and family medical history.[3] While the focus of the All of Us study is research, a second initiative, the Cancer Moonshot, recognizes that precision medicine is already a clinical reality for many patients with cancer and focuses on accelerating clinical use of precision medicine. The 21st Century Cures Act was passed by Congress in December 2016, authorizing $1.8 billion in funding for the Cancer Moonshot and $215 million for the All of Us study.[4]

Pharmacists have a long-standing interest in optimizing care by individualizing therapy. Pharmacokinetic dose adjustment is an early example of precision medicine, pioneered by clinical pharmacists. As far back as 1998, ASHP published a statement that pharmacists' responsibilities included "designing patient-specific drug dosage regimens based on pharmacokinetic characteristics of the drug product."[5] At the ASHP Pharmacy Practice Model Summit, at least 10 recommendations related to pharmacogenomics and

pharmacy practice were made.[6] Given the anticipated transformative nature of the current efforts in precision medicine, the purpose of this article is to describe current pharmacist roles in genomic aspects of precision medicine, to assess barriers and facilitators to implementing precision medicine, and to discuss emerging trends likely to impact health systems.

**Current pharmacist practice models in germline, or hereditary, pharmacogenomics.** In the United States, few academic medical centers and even fewer community pharmacies have implemented pharmacogenomics programs led by pharmacists, despite pioneering programs being in existence as early as 2007.[7] Characteristics across successful programs include preemptive and indication-triggered testing with a focus on well-defined drug-gene pairs, commonly focusing on clopidrogel, warfarin, and thiopurines.[6] Road maps for implementing pharmacogenomics into clinical practice include addressing educational gaps, engaging a multidisciplinary team, garnering strong institutional support (including informatics support), and tracking of quality metrics. Securing the resources needed to launch these programs remains a challenge, as most pioneering programs used research grant funds to implement pharmacogenomic testing and therapeutic alternatives to clopidrogel and warfarin are readily available. Overcoming logistical hurdles, particularly obtaining test results quickly at the time of prescribing, also remains a challenge.[6]

**Barriers to implementing germline pharmacogenomics.** Currently, there are hundreds of medications with genomic information in their Food and Drug Administration (FDA)–approved labels or in practice guidelines,[8] and a federally funded clinical trials network has been created to support the implementation of genomics.[9] Despite these efforts, pharmacogenomic testing is not routinely performed in most institutions. An illustrative case is that of codeine and cytochrome P-450 (CYP) isozyme 2D6–guided dosing,

whereby instead of implementing guided dosing prior to codeine use, clinical workarounds, including contraindicating use and recommending alternative agents, are currently recommended. Codeine is the oral prodrug of morphine, and CYP2D6 is required to convert codeine to morphine.[10] Patients who are CYP2D6 rapid or ultrarapid metabolizers are able to convert codeine to morphine faster than their counterparts with normal CYP2D6 function, and they are at increased risk for adverse effects caused by excessive exposure to morphine. After the publication of a number of case reports[11-14] of respiratory depression and deaths associated with codeine in CYP2D6 rapid and ultrarapid metabolizers, FDA reviewed data collected in its Adverse Event Reporting System from 1965 to 2015 and identified 24 codeine-associated deaths, prompting FDA[15] to contraindicate codeine use in children under 12 years of age. This move was supported by the American Academy of Pediatrics, which recommended against CYP2D6-guided genotyping, citing insufficient evidence to support the practice, and suggested use of alternative agents for pain management in children.[16] In addition, in a prospective study evaluating CYP2D6 genotyping and codeine use, providers were likely to prescribe alternatives for ultrarapid and rapid metabolizers, but uncontrolled pain was more frequent in poor metabolizers.[17]

Major barriers to implementation of pharmacogenomic testing include a lack of provider and administration buy-in, logistical challenges around testing, and poor reimbursement.[6] Both buy-in and reimbursement are heavily influenced by evidence, typically in the form of prospective randomized trials, demonstrating clinical benefit with meaningful financial implications, which are important to providers and payers. Currently, there is strong evidence associating particular genotypes with drug outcomes, and guidelines developed and published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) discuss appropriate dosing adjustment and use of alternative agents for

specific genotypes.[8] However, there is limited data to suggest that performing genotyping, in and of itself, improves overall patient outcomes, and the CPIC guidelines stop short of recommending genotyping, instead focusing on dose adjustment or the substitution of alternative agents if a patient has a known problematic genotype. In other words, there is strong evidence for many drug-gene pairs that for an individual patient, with a variant genotype, dose adjustment or drug substitution improves individual patient outcomes. However, with the exception of TPMT genotyping and 6-MP dose adjustment,[18] there is limited evidence to suggest that population-level or indication-specific genotyping improves care over standard approaches. Even when evidence is sufficient to gain the support of clinicians and administrators, implementing pharmacogenetic testing requires resources and motivation, and using an alternative therapy that is not affected by genetic anomalies, like codeine, is often simply an easier therapeutic path.

**Facilitators and recent trends impacting pharmacogenomic implementation.**

Direct-to -consumer (DTC) pharmacogenetic testing may overcome barriers associated with implementing pharmacogenomics, as a patient presenting to a provider with results in hand eliminates the buy-in, reimbursement, and logistical challenges discussed previously. DTC testing is available outside the health system, is paid for by the patient, and does not require a physician order. While there are concerns related to test accuracy and clinical utility, the DTC testing industry is experiencing strong growth.[19] In a survey of Kaiser Permanente physicians, 35% of physicians reported receiving DTC test results related to health risks, and 13% received DTC test results for pharmacogenomic testing from a patient over the last year. DTC health risk testing and pharmacogenomic testing were most common in oncology practices, with 48% and 33% of physicians receiving such test results, respectively. Among physicians receiving DTC pharmacogenomic testing results, 39% made

at least 1 referral, most often for clinical genetics services. Referral to a clinical pharmacy professional was less frequent, at 14% of all referrals.[20]

Population genotyping efforts by health systems may also overcome barriers to pharmacogenetic testing. While currently focused on disease predisposition genes, Geisinger Health has established a cohort of more than 200,000 individuals with whole exome sequencing data.[21] The cohort (formed under the MyCode Community Health Initiative) was established for research purposes; however, results are returned to individual patients if they have an alteration in one of 59 genes associated with known disease risk, as recommended by American College of Medical Genetics and Genomics guidelines.[22] Results are communicated to both the patient and the treating physician, who determine the follow-up plan. Geisinger is not currently reporting pharmacogenetic data to the patient, pharmacist, or physician; however, given that whole exome sequencing is being performed, those data exist.

**Somatic mutation testing.** Cancer is unique in that somatic mutations, occurring only in the cancer cell, are both the cause of the disease and a therapeutic target. In head-to-head clinical trials comparing targeted therapies to standard chemotherapy, targeted therapies have been found to be both more effective and to have fewer adverse effects than other forms of treatment.[23,24] This approach has revolutionized cancer drug development. In 2019 alone, of the 48 new drugs approved by FDA, 9 were new anticancer agents and all but one were targeted therapies and indicated only for patients with a specific biomarker.

Cancer clinical practice has also been revolutionized. For example, the 228,000 patients[25] who were expected to be diagnosed with non–small cell lung cancer (NSCLC) in the United States in 2020 are candidates for clinical next-generation sequencing (NGS)

assays. These assays provide comprehensive mutation profiling, typically a panel of approximately 300 to 500 genes and the presence of a mutation or biomarker determines the therapy a patient will receive. Approximately 30% of patients with NSCLC will have a mutation in the genes *EGFR* (15%),[26] *ALK* (5%),[27] *ROS1* (2%),[28] *BRAF* (5%),[29] and *NTRK* (<1%),[30] making them candidates for treatment with a targeted therapy. Approximately 50%[31] of patients with NSCLC will express programmed death ligand 1 (PD-L1) and are candidates for pembrolizumab. In the United States alone, approximately 100,000 patients with NSCLC will be treated with pembrolizumab in 2020, and at an average cost per dose of $10,000[32] the implication for health systems is substantial.

**Current pharmacist practice models in cancer precision medicine.** Oncology pharmacists have been integral to implementing cancer precision medicine, having led the development of molecular tumor boards[33,34] and precision medicine services.[35] In addition, many oncology pharmacists are joining precision medicine teams and developing additional roles, including serving as a medication resource, facilitating interactions with pharmaceutical companies for drug assistance and specialty pharmacies for dispensing, and providing direct patient care to patients receiving precision medicine–based therapies.[36] Pharmacists have also implemented pharmacogenomic dose adjustment services for pertinent oncology germline drug-gene pairs like fluorouracil and *DPYD*,[37] and therapeutic drug monitoring programs for fluorouracil.[38]

**Recent trends impacting cancer precision medicine implementation.** By 2030 the number of new cancer cases is expected to increase by 45%. As the US population ages and is increasingly health insured and as new cancer therapies extend survival, demand for oncology care is expected to increase by 42% by 2025[39] while the American Society of Clinical Oncology expects shortages of medical oncologists.[40] Increased demand is coupled

with an explosion of novel precision therapies. Between 1949 and 2018, there were 203 FDA approvals of new anticancer agents. Considering only breast cancer, 10 drugs were approved in the last 10 years and all but one were targeted therapies,[41] with the majority of drugs in development being either cell based, checkpoint inhibitors, or targeted therapies.[42] Increased demand and increased personalization is expected to drive cancer care for the foreseeable future, and oncology pharmacists are needed to deliver this care.[43]

Specialty pharmacy practitioners should also consider an expanded role in cancer-targeted precision medicine, as their expertise is particularly important in meeting the needs of patients undergoing gene and cell-based therapies. Many of these products require careful and precise storage, distribution, and monitoring—processes specialty pharmacists are comfortable assuring. Patient adherence is important in many areas of therapeutics, but lack of adherence is particularly challenging and wasteful when products are complex, costly, and inconsistently reimbursed; again, these are therapeutic issues specialty pharmacy practitioners deal with often. Many therapies guided by precision medicine accompany other treatment components, and fragmenting gene or cell-based aspects of patient care from everything else individuals require will result in a higher risk of poor outcomes. Specialty pharmacy practitioners' ability to reduce fragmented care delivery will be critical in ensuring successful care of many patients.

**Implications for health-system pharmacy.** In several past ASHP Pharmacy Forecasts,[2,44,45] health-system pharmacy leaders have been encouraged to take the lead in developing, implementing, and maintaining clinical precision medicine programs in their organizations. While such programs require collaboration with a number of other departments, in particular clinical laboratory, pathology, and information technology, and also must engage physicians, pharmacy departments are well placed to successfully manage

programs. In particular, pharmacists have experience overseeing similar clinical processes, in particular therapeutic drug monitoring programs. Pharmacists routinely provide guidance and consultation to physicians about optimizing mediation therapy, and pharmacists can assist with the interpretation of (often) complicated reports of genomic data, leading to impactful clinical recommendations for individual patients. Further, pharmacy leaders are adept at developing financial models that identify and then exploit financial benefits associated with new technology, and they can help articulate the value of new technologies to the payer community, reducing barriers associated with limited insurance coverage and demonstrating the downstream advantage of additional testing as a means of reducing the total cost of care. The role of the pharmacy and therapeutics committee, charged in most health systems to ensure both appropriate and cost-effective care of patients, can be further charged with an expanded responsibility of overseeing precision medicine—taking advantage of clear governance, evidence-based decision-making processes, the ability to calculate and consider financial implications of policy decisions—and ensure that policy decisions are implemented and respected (often relying on clinical pharmacists to serve as the stewards of therapeutic interventions those decisions affect). The use of advanced computing techniques and artificial intelligence models and reliance on large data sets are also critical to the future of precision medicine, and these are also areas where pharmacy has increasing expertise.

In order for health-system pharmacy to establish a leadership position in precision medicine, pharmacists and pharmacy leaders must deepen their understanding of molecular diagnostics and therapeutics; must build new relationships with disciplines that they may not have worked with in the past, such as genetic counselors who help patients understand the implications of their genetic health; and must be prepared to venture into areas that are

perhaps only peripherally related to medication management, such as in areas where genetic data suggest interventions other than medications. However, these challenges are all far easier to overcome for the pharmacy profession and pharmacy departments than for other disciplines and departments that are not as well positioned to meet the other requirements needed to successfully lead in precision medicine, as described above.

**Conclusion.** Pharmacists currently lead the development of guidelines for hereditary pharmacogenomic testing and were early implementers of hereditary pharmacogenomics into clinical practice. However, significant barriers to widespread implementation, including resources and logistics, remain. Current trends that potentially overcome these barriers include DTC and population-level genotyping, and pharmacist roles must continue to evolve with current trends. Somatic mutation testing in cancer has revolutionized cancer drug development and clinical care. Interdisciplinary teams, often led by pharmacists, have widely implemented cancer precision medicine initiatives. Given current deficits in the workforce of medical oncologists, the potential to expand oncology pharmacist roles is exponential, and specialty pharmacy practitioners are important partners. Health-system pharmacy should establish leadership roles in precision medicine.

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