HHS Public Access

Author manuscript

Pharm Res. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Pharm Res. 2017 August ; 34(8): 1551–1555. doi:10.1007/s11095-017-2163-x.

Preemptive Panel-Based Pharmacogenetic Testing: The Time is Now

Kristin W. Weitzel[1,2], **Larisa H. Cavallari**[1,2], and **Lawrence J. Lesko**[3]

[1]University of Florida College of Pharmacy, Department of Pharmacotherapy and Translational Research, and Center for Pharmacogenomics, Gainesville, FL

[2]UF Health Personalized Medicine Program, Gainesville, FL

[3]University of Florida College of Pharmacy, Department of Pharmaceutics, Orlando, FL

Abstract

While recent discoveries have paved the way for the use of genotype-guided prescribing in some clinical environments, significant debate persists among clinicians and researchers about the optimal approach to pharmacogenetic testing in clinical practice. One crucial factor in this debate surrounds the timing and methodology of genotyping, specifically whether genotyping should be performed reactively for targeted genes when a single drug is prescribed, or preemptively using a panel-based approach prior to drug prescribing. While early clinical models that employed a preemptive approach were largely developed in academic health centers through multidisciplinary efforts, increasing examples of pharmacogenetic testing are emerging in community-based and primary care practice environments. However, educational and practice-based resources for these clinicians remain largely nonexistent. As such, there is a need for the health care system to shift its focus from debating about preemptive genotyping to developing and disseminating needed resources to equip frontline clinicians for clinical implementation of pharmacogenetics. Providing tools and guidance to support these emerging models of care will be essential to support the thoughtful, evidence-based use of pharmacogenetic information in diverse clinical practice environments. Specifically, the creation of efficient and accurate point-of-care resources, practice-based tools, and clinical models is needed, along with identification and dissemination of sustainable avenues for pharmacogenetic test reimbursement.

Keywords

pharmacogenetic; pharmacogenomic; preemptive; genomic medicine; implementation

Pharmacogenetics involves the identification of genetic variants that influence drug response. While the science of pharmacogenetics has been studied for decades, the accumulating evidence coupled with technological advances have reached the point of supporting increasing clinical use of pharmacogenetic information to guide drug therapy decisions. For most non-specialist clinicians, germline pharmacogenetic variations that

Corresponding Author: Kristin Weitzel, University of Florida College of Pharmacy Department of Pharmacotherapy and Translational, Research, PO Box 100486, Gainesville, FL 32610–0486, 3652-278-1489, kweitzel@cop.ufl.edu.

affect a drug's pharmacokinetic properties (e.g., activity of cytochrome P450 drug metabolizing enzymes), and subsequently the drug's ability to induce toxicity or elicit therapeutic effects are most likely to have clinical relevance.(1)

As scientific and technological advancements increasingly support the use of genotype-guided prescribing in clinical practice, there has been considerable debate around the optimal approach to implement clinical testing in diverse health care practices, including significant discussion regarding the timing and methodology of genotyping in a clinical environment. Specifically, there has been disagreement on whether genotyping should be performed in a reactive manner for a gene(s), with implications for a single drug at the time it is prescribed, or preemptively using a panel-based approach prior to drug prescribing, with genotype information for potentially hundreds of pharmacogenes readily available in the patient's medical record to inform future drug therapy. (1)

Proponents of a preemptive, panel-based approach cite the significant prevalence of clinically actionable genetic variants and widespread use of drugs with potential pharmacogenetic relevance. (1–4) In an analysis of five drug-genome interactions in over 10,000 patients, a multiplexed test revealed an actionable variant (defined by authors as a variant that prompted clinical decision support to suggest a change in dose or medication) in 91% of genotyped patients, with more than 40% of these exposed to at least one associated medication over a 3-year follow-up period. (2) Although limitations exist for this type of study, including varying definitions of 'actionability' and limited follow up to assess actual adverse events that occurred, this and similar studies highlight the large, diverse patient population for whom preemptive genotyping could prompt a drug therapy change. As genetic information is increasingly used in routine practice, there are also unarguable clinical advantages to having genetic information available at the point of care to guide decision making in real time, as opposed to potentially delaying drug-therapy decisions with reactive pharmacogenetic testing. (1,4) Advocates of a preemptive approach also point out that as the cost of panel-based genotyping decreases over time, preemptive testing becomes more cost-effective compared to repeated testing of one gene at a time. (1–3) However, in the current climate of little to no reimbursement for preemptive, panel-based testing, this potential cost-effectiveness benefit for preemptive testing remains a long-term possibility, rather than an immediate reality for most clinicians. (5)

Critics of a preemptive genotyping approach argue that a panel-based genotyping model that includes drug-gene pairs with varying levels of evidence and inconsistent insurance reimbursement is fundamentally flawed. (6,7) In addition to potential patient harm that may arise from clinical decision making based on gene-drug pairs that lack robust evidence of clinical utility, critics cite potential downstream costs to the health care system incurred through interpretation, storage, use of, and patient counseling on large amounts of pharmacogenetic data. (6,7) Notably, most current preemptive genotyping models prevent such issues by limiting genotyping to variants with the highest level of clinical evidence, such as those supported by peer-reviewed, evidence-based clinical guidelines. (8) Nonetheless, for critics of preemptive genotyping, the potential drawbacks outweigh its benefits, and these drawbacks could ultimately have a negative impact on payer

reimbursement for pharmacogenetic testing and slow the adoption of testing in a clinical environment. (6,7)

The optimal approach to genotyping in a clinical environment will likely continue to be debated for some time among researchers, clinicians, administrators, and payers. However, in spite of the complexity and validity of key points on both sides of this debate, we argue that the time has come to develop much-needed practice-based resources, electronic health record capabilities, educational strategies, and reimbursement models to support thoughtful, pragmatic, evidence-based use of the pharmacogenetic data that is increasingly available to clinicians. To do this, researchers and clinicians must a) recognize current progress in developing and implementing models of care that demonstrate the feasibility of a preemptive, panel-based approach to pharmacogenetic testing across diverse environments; b) identify clinically relevant knowledge gaps and practice-based challenges to expanding the use of preemptive testing; and c) increase efforts and resources towards developing usable solutions and practice models that overcome these barriers on a large scale.

The Changing Landscape of Preemptive, Panel-Based Pharmacogenetic Testing

Initial models for clinical implementation of pharmacogenetic testing were largely based in academic health centers and instituted by multidisciplinary teams of clinicians, researchers, informaticians, administrators, and others. (5) Although each of these models is unique, there are notable commonalities among them, including multidisciplinary collaboration among researchers, administrators, and clinicians to build institutional infrastructure; reliance on an advisory body to integrate an evidence analysis process and development of clinical recommendations into the health system's existing formulary/medication use system; and a systematic process for genetic testing and migration of test results into the electronic health record with development of clinical decision support. (5) In addition, there are examples of centers that have had institutional participation in developing and validating multi-gene arrays that target pharmacogenes most likely to be useful within that institution. (9)

Although these preemptive pharmacogenetic testing models have led to successful uptake of pharmacogenetic testing and use of these data to inform medical decision making within these institutions, some have questioned whether such approaches are scalable for the health care system at large. (5) Specifically, these models have been associated with significant elements of institutional support and financial resources that enable programs to develop custom solutions to overcome implementation barriers, such as pursuing large-scale research funding, writing custom logic and language for clinical decision support, or creating new software or systems to translate and store genomic data within the electronic health record. (5,9)

More recently, researchers and clinicians have built on these initial successes to develop scalable clinical models that can be adapted to a more widespread community-based model of care, such as in community health systems, primary care physician offices, or community pharmacies. (10–14) In many ways, these community-based care models have taken the

essential elements needed for pharmacogenetic testing identified in early clinical academic models and developed pragmatic solutions individualized to their own practice environment to overcome implementation barriers. Such adaptations include outsourcing some aspects of preemptive, panel-based pharmacogenetic testing and interpretation to a commercial laboratory that provides evidence interpretation, recommendations for clinical decision making, an external platform to store test results, and capitated patient payment models to encourage test uptake (11,14); prescriber partnership with trained physician extenders (e.g., nurses, genetic counselors, pharmacists) to communicate test results to patients (12–14); exploration of patient self-pay models to overcome the immediate cost barrier of preemptive testing (10,14); increasing patient access by providing pharmacogenetic testing in nontraditional settings, such as community-based pharmacies and community hospitals (10, 12, 14); and leveraging technological advances, such as the ability to link test results to an evidence-based prescribing decision support system for clinicians. (11,14)

Supporting Development of Pragmatic, Preemptive Pharmacogenetic Testing Models

It can be argued that the organic development and persistence of innovative practice models that incorporate pharmacogenetic data into clinical care across diverse health care environments demonstrates that the time for clinical use of preemptive pharmacogenetic data has already arrived. However, these emerging practice models also propel new and important questions to the forefront of the conversation around preemptive pharmacogenetic testing. Namely, given the increasing accessibility of such testing to community-based practitioners and their patients, what are the most important knowledge gaps and challenges that remain to the widespread adoption of preemptive pharmacogenetic testing and what is required to overcome these challenges? Although not a comprehensive listing of needs and challenges, we propose important and immediate steps that must be taken for clinical adoption of a preemptive pharmacogenetic testing strategy.

First, gaps in clinical knowledge and clinicians' lack of readiness to use, interpret, and apply pharmacogenetic data to clinical decision making must be recognized and addressed. These gaps extend beyond simply an understanding of discipline-specific genotype-informed drug therapy changes into a working knowledge of clinical laboratory testing (Table 1). Although frontline clinicians need not be experts in molecular pathology, as evidence supporting the clinical use of pharmacogenetic tests continues to develop, we assert that clinicians do need to have an awareness of factors that influence the interpretation and application of pharmacogenetic test results.

In the short term, development of clinical decision support tools within the electronic health record to provide distilled, patient-specific information and education at the point of care will be crucial to overcoming this and other knowledge barriers. (3,15,16) Specifically, mechanisms must exist within the EHR to allow for documentation, interpretation, and storage of genetic data with appropriate drug-specific recommendations provided at the point of prescribing and/or dispensing. (15) Clinical laboratory tools or platforms that are self-contained or able to be integrated into the existing EHR are in use in some specialty

areas (e.g., oncology) and may be an option to bridge this gap in some practice environments. However, integration of meaningful, durable clinical recommendations into the EHR is particularly challenging in pharmacogenetics given the growing evidence base for clinical utility with some gene-drug pairs, the changing nomenclature (e.g., star-allele naming conventions) for communicating pharmacogenetic test results, and ethical and legal concerns that may arise regarding tested pharmacogenetic variants that are later found to be clinically relevant.

Until these and other challenges are overcome, it is essential that clinicians are aware of and equipped with practice-based resources that can be used to guide clinical decision making in pharmacogenetics. In the current climate of direct-to-consumer and direct-to-clinician marketing of pharmacogenetic testing panels, we project that clinicians in the primary care setting will be at the forefront of considering and ordering these tests. For these clinicians, there is an immediate need to assess options for genotyping; to understand ethical, legal, and social implications of pharmacogenetic testing; and to be aware of documentation and/or patient education needs with return of test results. This need is increasingly being met by the development of practice-based resources targeted to clinicians. To date, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published 19 guidelines for clinically actionable gene-drug pairs that address barriers to implementation of pharmacogenetic tests into clinical practice. CPIC uses a standardized, peer-reviewed, process and systematic evidence rating to develop guidelines that translate pharmacogenetic test results to prescribing recommendations for specific medications. (8) CPIC guidelines, along with practice-based informatics and other implementation tools for individual gene-drug pairs, are available at cpicpgx.org. A collection of clinical guidelines, including those from CPIC, the Dutch Pharmacogenetics Working Group, and the Canadian Pharmacogenetics Network for Drug Safety; supporting scientific evidence; and pharmacogenetic information included in the approved drug label are also freely available to clinicians through the Pharmacogenomics KnowledgeBase (www.pharmgkb.org). These resources can be invaluable to the frontline clinician, but it is essential that clinicians are aware of and know how to use them in practice. (17)

In the long term, a significant shift in undergraduate and continuing medical education is needed from teaching about genetics in a knowledge-based manner to equipping trainees and clinicians to apply and use genetic and pharmacogenetic data in applications-based routine practice. (17) Educational and practice-based competencies and other efforts are in place to help move these efforts forward, but there is a continued need for novel teaching resources and approaches to increase the accessibility and clinical relevance of educational materials. A growing number of online resources exist to meet these educational needs, including the NIH-funded Genetic and Genomics Competency Center (www.g-2.c-2.org), the Global Genetics and Genomic Community (http://genomicscases.net/en), practice and educational resources developed by multi-site collaborative efforts supporting genomic medicine implementation (e.g., IGNITE Network [www.ignite-genomics.org]).

Most importantly, there is an immediate need to develop and disseminate sustainable reimbursement models for preemptive, panel-based pharmacogenetic testing that are cost effective for providers, payers, and patients. Although there are examples of reimbursement

for pharmacogenetic testing for individual gene-drug pairs in targeted populations (e.g., *TPMT* testing for thiopurine prescribing in patients with acute lymphoblastic leukemia, *CYP2C19* testing to guide antiplatelet therapy after percutaneous coronary intervention, or *HLA-B*15:02* testing to predict risk for carbamazepine-induced severe cutaneous reactions), insurance reimbursement for panel-based preemptive testing remains limited. In addition, the path to pursuing reimbursement for pharmacogenetic testing is often complex, and few resources exist to guide clinicians down a road that leads to a successful practice and billing model for pharmacogenetic testing. (18, 19).

A significant challenge in the development of reimbursement models for preemptive pharmacogenetic testing is limited real-world knowledge regarding the cost-to-benefit ratio of preemptive versus reactive pharmacogenetic testing that payers can use to meaningfully inform economic modeling (i.e., the number of patients needed to genotype preemptively to prevent one adverse event or rehospitalization). In addition, economic models that place a "value" on changes in outcomes are heterogenous and go beyond cost-effectiveness analyses alone.

Efforts to quantify some important measures, such as the frequency of exposure to relevant medications in patients who have pharmacogenetic variants, and therefore may benefit from preemptive testing, are expanding to include more diverse settings. (2,4) For example, a recent retrospective analysis of EHR data in a safety-net health system found that 7,039 patients across a 73-site system initiated a prescription for at least one of 30 clinically actionable pharmacogenetic medications during the 12-month study period (the most common identified medications included tramadol, clopidogrel, and codeine). (20) As costs of panel-based genotyping become comparable to or even lower than single-gene assays because of the ability to batch samples from multiple patients to genotype together, it is logical that a preemptive model would become increasingly cost effective on a large scale, but definitive data supporting this assumption do not exist.

While additional information is needed to address this crucial element to preemptive pharmacogenetic testing, a number of innovative payment models are being explored to meet immediate patient care needs, including patient self-pay, capitated-risk models, integration of pharmacogenetic testing into self-funded health care systems, and pursuit of expanded coverage for panel-based testing by third party payers through traditional avenues of obtaining necessary Current Procedural Terminology (CPT) and other codes for test reimbursement. Increased awareness and exploration of these models among clinicians, administrators, researchers, and payers is needed to help support further advancement in this area. As with the growing body of educational resources, innovative practice models are being developed and adopted internationally that incorporate preemptive testing in a real-world billing and practice environment, including collaborative efforts led by members and affiliate sites of the IGNITE (www.ignite-genomics.org) and eMERGE (https://emerge.mc.vanderbilt.edu/) networks in the United States, the Ubiquitous Pharmacogenomics program (http://upgx.eu/) in Europe, and others.

Conclusion

With the emergence of pharmacogenetic testing in clinical practice in recent years, the debate and questions surrounding preemptive, panel-based pharmacogenetic testing over a reactive genotyping approach are shifting and intensifying. Instead of asking whether or not preemptive testing should be incorporated into clinical care, many clinicians are increasingly aware such testing is at their fingertips and are asking how do I order a pharmacogenetic test and how best can I use these data in my practice? There are significant needs within the health care system that must be bridged to equip clinicians with the knowledge and skills needed to use such testing routinely in their clinical practices. These are important not only for those in the primary care setting, who are likely at the forefront of ordering pharmacogenetic testing, but also for those in specialty care who may be faced with prescribing decisions for patients with available pharmacogenetic information.

Acknowledgments

Funded by NIH grants U01HG007269, UL1TR001427 and institutional support from the University of Florida

References

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015; 526(7573):343–50. Available at: https://dx.doi.org/10.1038/nature15817. [PubMed: 26469045]
2. Van Driest SL, Shi Y, Bowton EA, Shildcrout JS, Peterson JF, Pulley J, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther. 2014; 95(4):423–31. Available at: https://dx.doi.org/10.1038/clpt.2013.229. [PubMed: 24253661]
3. Bell GC, Crews KR, Wilkinson MR, Haidar CE, Hicks JK, Baker DK, et al. Development and use of active clinical decision support for preemptive pharmacogenomics. J Am Med Inform Assoc. 2014; 21(e1):e93–9. Available at: https://dx.doi.org/10.1136/amiainl-2013-001993. [PubMed: 23978487]
4. Schildcrout JS, Denny JC, Bowton E, Gregg W, Pulley JM, Basford MA, Cowan JD, Xu H, Ramirez AH, Crawford DC, Ritchie MD, Peterson JF, Masys DR, Wilke RA, Roden DM. Optimizing drug outcomes through pharmacogenetics: a case for preemptive genotyping. Clin Pharmacol Ther. 2012; 92(2):235–42. Available at: https://dx.doi.org/10.1038/clpt.2012.66. [PubMed: 22739144]
5. Dunnenberger HM, Crews KR, Hoffman JM, Caudle KE, Broeckel U, Howard SC, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annu Rev Pharmacol Toxicol. 2015; 55:89–106. Available at: https://dx.doi.org/10.1146/annurev-pharmtox-010814-124835. [PubMed: 25292429]
6. Janssens ACJW, Deverka PA. Useless until proven effective: the clinical utility of preemptive pharmacogenetic testing. Clin Pharmacol Ther. 2014; 96(6):652–4. Available at: https://dx.doi.org/10.1038/clpt.2014.186. [PubMed: 25399713]
7. Koch BC, van Schaik RH, van Gelder T, Mathijssen RH, Rotterdam Clinical Pharmacology-Pharmacogenetics Group (RCPPG). Doubt about the feasibility of preemptive genotyping. Clin Pharmacol Ther. 2013 Mar.93(3):233. Available at: https://dx.doi.org/10.1038/clpt.2012.191. [PubMed: 23232547]
8. Caudle KE, Klein TE, Hoffman JM, Whirl-Carrillo M, Gong L, McDonagh EM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014; 15(2):209–17. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3977533/. [PubMed: 24479687]
9. Johnson JA, Burkley BM, Langaee TY, Clare-Salzler MJ, Klein TE, Altman RB. Implementing personalized medicine: development of a cost-effective customized pharmacogenetics genotyping array. Clinical Pharmacol Ther. 2012; 92(4):437–9. Available at: https://dx.doi.org/10.1038/clpt.2012.125. [PubMed: 22910441]

10. Ferreri SP, Greco AJ, Michaels NM, O'Connor SK, Chater RW, Viera AJ, et al. Implementation of a pharmacogenomics service in a community pharmacy. J Am Pharm Assoc. 2014; 54(2):172–80. Available at: https://dx.doi.org/10.1331/JAPhA.2014.13033.

11. Dawes M, Aloise MN, Ang JS, Cullis P, Dawes D, Fraser R, et al. Introducing pharmacogenetic testing with clinical decision support into primary care: a feasibility study. CMAJ. 2016; 4(3):E528–E534. Available at: https://dx.doi.org/10.9778/cmaio.20150070.

12. Haga SB, LaPointe NM, Cho A, Reed SD, Mills R, Moaddeb J, et al. Pilot study of pharmacist-assisted delivery of pharmacogenetic testing in a primary care setting. Pharmacogenomics. 2014; 15(13):1677–86. Available at: https://dx.doi.org/10.2217/pgs.14.109. [PubMed: 25410893]

13. Mills R, Haga SB. Clinical delivery of pharmacogenetic testing services: a proposed partnership between genetic counselors and pharmacists. Pharmacogenomics. 2013; 14(8):957–68. Available at: https://dx.doi.org/10.2217/pgs.13.76. [PubMed: 23746189]

14. Dunnenberger HM, Biszewski M, Bell GC, Sereika A, Holley M, Hulick PJ, et al. Implementation of a multidisciplinary pharmacogenomics clinic in a community health system. Am J Health-Sys Pharm. 2016; 73(23):1956–66. Available at: https://dx.doi.org/10.2146/aihp160072.

15. Hicks JK, Dunnenberger HM, Gumpper KF, Haidar CE, Hoffman JM. Integrating pharmacogenomics into electronic health records with clinical decision support. Am J Health-Sys Pharm. 2016; 73(23):1967–76. Available at: https://dx.doi.org/10.2146/aihp160030.

16. Hicks JK, Stowe D, Willner MA, Wai M, Daly T, Gordon SM, et al. Implementation of Clinical Pharmacogenomics within a Large Health System: From Electronic Health Record Decision Support to Consultation Services. Pharmacotherapy. 2016; 36(8):940–8. Available at: https://dx.doi.org/10.1002/phar.1786. [PubMed: 27312955]

17. Johansen Taber KA, Dickinson BD. Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. Pharmgenomics Pers Med. 2014; 7:145–62. Available at: https://dx.doi.org/10.2147/PGPM.S63715. [PubMed: 25045280]

18. Graf MD, Needham DF, Teed N, Brown T. Genetic testing insurance coverage trends: a review of publicly available policies from the largest US payers. Pers Med. 2013; 10(3):235–43. Available at: https://dx.doi.org/10.2217/pme.13.9.

19. Hefti E, Blanco JG. Documenting pharmacogenetic testing with CPT codes. J AHIMA. 2016; 87(1):56–9.

20. Carpenter JS, Rosenman MB, Knisely MR, Decker BS, Levy KD, Flockhart DA. Pharmacogenomically actionable medications in a safety net health care system. SAGE Open Med. 2016; 4:2050312115624333. Available at: https://dx.doi.org/10.1177/2050312115624333. [PubMed: 26835014]

Table 1

Clinician Knowledge Gaps for Use of Preemptive Pharmacogenetic Testing

1	Working knowledge of differences among analytic validity, clinical validity, and clinical utility and awareness of the types and levels of evidence that are needed to establish these.
2	Awareness that not all commercially-available pharmacogenetic tests have demonstrated analytic validity, and only tests performed in accordance with College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) accreditation/certification requirements should be used clinically.
3	Ability to critically evaluate available laboratories and/or platforms for genetic testing, including but not limited to assessment of: • Appropriateness of the specific genes and variants in relation to the target drug, disease state, and/or patient population; • Robustness of testing (e.g. whether copy number variation is detected for *CYP2D6);* • How test results are documented (e.g., in star-allele form or as interpreted phenotypes); • How test results are made available (e.g., electronic or paper, to clinicians and/or patients); • Whether clinical guidance is provided with test results, and if so, what process is used to ensure clinical recommendations are current; • Reimbursement policies and the potential cost to the patient if he/she is uninsured or if testing is not covered by insurance (e.g., if patient's out-of-pocket costs are capped); • Turnaround time for test results
4	Awareness of resources to identify available commercial laboratories or find evidence-based guidance for interpreting clinical pharmacogenetic test results, including: • Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (https://cpicpgx.org/) • Pharmacogenomics KnowledgeBase (https://www.pharmgkb.org/) • Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/)