# Personalizing medicine with clinical pharmacogenetics

**Stuart A. Scott, PhD**
Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, New York.

## Abstract

Clinical genetic testing has grown substantially over the past 30 years as the causative mutations for Mendelian diseases have been identified, particularly aided in part by the recent advances in molecular-based technologies. Importantly, the adoption of new tests and testing strategies (e.g., diagnostic confirmation, prenatal testing, and population-based carrier screening) has often been met with caution and careful consideration before clinical implementation, which facilitates the appropriate use of new genetic tests. Although the field of pharmacogenetics was established in the 1950s, clinical testing for constitutional pharmacogenetic variants implicated in interindividual drug response variability has only recently become available to help clinicians guide pharmacotherapy, in part due to US Food and Drug Administration-mediated product insert revisions that include pharmacogenetic information for selected drugs. However, despite pharmacogenetic associations with adverse outcomes, physician uptake of clinical pharmacogenetic testing has been slow. Compared with testing for Mendelian diseases, pharmacogenetic testing for certain indications can have a lower positive predictive value, which is one reason for underutilization. A number of other barriers remain with implementing clinical pharmacogenetics, including clinical utility, professional education, and regulatory and reimbursement issues, among others. This review presents some of the current opportunities and challenges with implementing clinical pharmacogenetic testing.

### Keywords

clinical pharmacogenetics; pharmacogenomics; genetic testing; personalized medicine; molecular genetics

Clinical DNA-based testing began in 1978 with the diagnosis of sickle cell disease by interrogating the causative p.G6V (Hb S) mutation in the β-globin gene.[1] Since then, as the genetic basis of many disorders have been identified, molecular testing has grown to include population carrier-screening programs for autosomal recessive disorders (e.g., cystic fibrosis), particularly among certain ethnicities (e.g., Ashkenazi Jewish panels[2] and thalassemia and the hemoglobinopathies in the Mediterranean[3]). Today, targeted genotyping and gene sequencing are routinely used for molecular diagnosis, prenatal mutation analyses, and preimplantation genetic diagnosis. Although these testing scenarios predominantly involve Mendelian disorders, many recent genome-wide association studies (GWAS) have identified genes and variant alleles that contribute to some common diseases and complex traits, prompting the possibility of predictive genetic testing to evaluate personalized disease risk. Moreover, the increasing use of whole-exome and whole-genome sequencing strategies

Stuart A. Scott, PhD, Department of Genetics and Genomic Sciences, Box 1497, Mount Sinai School of Medicine, 1428 Madison Avenue, New York, NY 10029. stuart.scott@mssm.edu.

will undoubtedly identify additional common and rare genetic variants that significantly influence disease phenotypes. As these genetic associations become more sophisticated and robust, it is likely that predictive genetic testing will eventually move from the direct-to-consumer (DTC) market to the medical genetics community, including the associated challenges with its appropriate implementation.

Although not as controversial as predictive genetic testing for later-onset complex diseases, another class of genetic testing that struggles with similar issues of clinical utility and acceptance is pharmacogenetic testing.[4] The role of heritable genetic variation in drug response has been studied since the 1950s,[5] and clinical testing for selected genes known to influence drug efficacy and/or toxicity has been available for a number of years. However, clinical adoption of pharmacogenetic testing has remained slow despite US Food and Drug Administration (FDA) product insert relabeling of some drugs to include relevant pharmacogenetic information. Recent and ongoing efforts from the pharmacogenetic community to facilitate clinical adoption include guidelines on implementing pharmacogenetic testing in a clinical laboratory[6] and, importantly, practice guidelines for clinicians on how to interpret test results.[7–10] This review is aimed at introducing the topic of pharmacogenetics and discussing some of the current opportunities and challenges for implementation of clinical pharmacogenetic testing. Testing for somatically acquired sequence variants with respect to drug response is considered beyond the scope of this review, which is limited to testing for constitutional pharmacogenetic alleles.

## PERSONALIZED MEDICINE AND GENOMICS

The concept of "personalized medicine" was anticipated in the late 1800s by Canadian physician Sir William Osler who noted "the great variability among individuals"[11]; however, the more modern definition has evolved to incorporate personal genomic information into a patient's clinical assessment and family history to guide medical management. Major areas of applied research in this field involve identifying the genetic basis of common diseases, studying how genes and the environment interact to cause human disease, and using pharmacogenetic biomarkers to facilitate more effective drug therapy. Although understanding the genetic contribution to human disease is far from complete, hundreds of "normal" DNA variants have been associated with diseases and phenotypic traits, and DTC companies have exploited this information to offer DNA-based testing that provides insight into personal traits and disease risks. Interestingly, when compared against each other, different risk calculation methods and choices of genetic markers have resulted in discrepant results between DTC companies.[12] As a result, practice recommendations have been made to the DTC companies, which included a strong endorsement to incorporate as many informative pharmacogenetic markers as possible,[12] which most DTC companies now do.

Pharmacogenetics has become one of the leading and potentially most actionable areas of the personalized medicine paradigm, as evidenced by the increased availability of clinical pharmacogenetic testing among CLIA-approved laboratories over the past few years. In contrast, CLIA-approved clinical laboratories do not typically offer testing for variant alleles associated with complex diseases to estimate personal risk. Many excellent reviews have been dedicated to personalized medicine and the potential of pharmacogenetics (for recent reviews, see Refs. 13–15). Moreover, the corresponding exponential growth in applied pharmacogenetics literature over the past 10 years (Fig. 1) has recently been acknowledged by the US FDA with drug label revisions to include relevant pharmacogenetic information and additional published commentary on clinical implementation and drug development programs.[16–18] Further information on personalized medicine-based initiatives can be found

at the Personalized Medicine Coalition Web site
(http://www.personalizedmedicinecoalition.org/).

# PHARMACOGENETICS AND PHARMACOGENOMICS

## Pharmacogenetics: History and origins

Although early observations of unusual drug reactions based on biochemical individuality
were noted in the 1930s, the field of pharmacogenetics was not officially recognized until
1959 when the term "pharmacogenetics" was first published by the German physician
Friedrich Vogel.[19] This was in response to earlier observations of interindividual variability
in phenylthiocarbamide taste perception and isolated cases of drug-induced porphyria.
Additional landmark scientific discoveries in the 1950s included the identification of
primaquine-induced hemolytic anemia among African-Americans (later shown to be due to
glucose-6-phosphate dehydrogenase [*G6PD*] variant alleles[20]), succinylcholine-induced
prolonged apnea during anesthesia (due to autosomal recessive butyrylcholinesterase
deficiency[21]), and severe adverse effects after antituberculosis treatment with isoniazid (later
shown to be due to *N*-acetyltransferase [*NAT2*] variant alleles[22]). In addition to the article by
Vogel, two other seminal publications at that time included the American Medical
Association-initiated review of available pharmacogenetic studies by Arno Motulsky[23] and
the first textbook dedicated to the discipline in 1962 by Werner Kalow.[24]

One of the most influential discoveries for pharmacogenetics and its potential clinical utility
was the identification in 1977 of the hepatic cytochrome P450 oxidase that controls
debrisoquine and sparteine metabolism.[25] Subsequent population and family studies
identified specific drug metabolism phenotypes and suggested that the "poor metabolism"
trait was inherited in an autosomal recessive Mendelian fashion. The responsible enzyme,
CYP2D6, was eventually purified, cloned, and extensively sequenced and is now believed to
be directly involved in the metabolism of ~25% of all commonly used drugs. More than 80
variant *CYP2D6* alleles have since been discovered worldwide, many of which encode
deficient enzyme activity, and these are carefully cataloged by the Human Cytochrome P450
(CYP) Allele Nomenclature Committee.[26] Importantly, *CYP2D6* is also prone to copy
number variation, including full gene deletion and duplication, which can significantly
influence the interpretation of *CYP2D6* sequencing, genotyping, and phenotype prediction.
Since the initial discovery of CYP2D6 and its important role in drug metabolism, *CYP2D6*
genotypes have been correlated with four general metabolism phenotypes: ultrarapid,
extensive, intermediate, and poor. Now that clinical DNA-based *CYP2D6* testing is
available, interpretation of a patient's genotype typically includes one of these predicted
metabolism phenotypes (Table 1); however, it should be emphasized that this is only a
prediction and not based on individual pharmacokinetic measurements.

In addition to *CYP2D6*, many other important *CYP450* genes have been discovered, and
polymorphic variant alleles continue to be identified in different populations. Notable
discoveries include two enzymes from the CYP2C subfamily: CYP2C19 and CYP2C9. The
*CYP2C19*2* (c.681G>A) variant allele was originally identified as the cause of impaired
mephenytoin metabolism,[29] and since then, a number of other *CYP2C19* alleles have been
discovered and characterized. Importantly, the common *CYP2C19*2* allele has recently been
associated with reduced active clopidogrel metabolites, resulting in higher on-treatment
platelet aggregation compared with noncarriers and adverse clinical outcomes in certain
clopidogrel-treated cardiovascular patient populations.[30,31] CYP2C9 metabolizes many
clinically relevant drugs including phenytoin, S-warfarin, tolbutamide, losartan, and others,
and like the other *CYP450* genes, it is highly polymorphic. Importantly, variant *CYP2C9*
alleles have been strongly associated with interindividual warfarin dosing variability[32] and

pharmacogenetic-guided warfarin dosing is now a clinical option for patients initiating anticoagulant therapy (http://www.warfarindosing.org; see Table 2).

In addition to the *CYP450* genes, other polymorphic drug metabolism enzymes and their clinically relevant substrates include thiopurine *S*-methyltransferase (*TPMT*; thiopurines), UDP-glucuronosyltransferase (*UGT1A1*; irinotecan), and dihydropyrimidine dehydrogenase (*DPD*; fluorouracil), among others. However, drug efficacy is not influenced solely by genetic variation in drug metabolism genes. Polymorphisms in genes that encode drug transporters and drug targets have also been shown to alter drug responses. For example, a variant allele in the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene has been associated with statin-induced myalgia,[39] and a common promoter variant in the drug target of warfarin (*VKORC1*) is also strongly associated with interindividual dosing variability.[40] In an effort to organize and summarize data on these important pharmacogenetic genes and their variants, several organizations have curated pharmacogenetic gene lists based on relevant literature. Two examples include the PharmaADME "Core Gene List" (http://www.pharmaadme.org/) and the more thorough "Very Important Pharmacogene" summaries compiled by the Pharmacogenomics Knowledge Base (PharmGKB; http://www.pharmgkb.org; see Table 2), which are published regularly in the journal *Pharmacogenetics and Genomics*.

## Pharmacogenomics

The continued identification of relevant genes, sequence variants, and associated drug response phenotypes is evidenced by the paralleled increase in pharmacogenetics literature, particularly in relation to the completion of the Human Genome Project (Fig. 1). The availability of genome-wide sequence data at that time also helped launch the related field of "pharmacogenomics" (Fig. 1). Although frequently used interchangeably, pharmacogenetics is often considered the study of drug response in relation to specific genes, whereas pharmacogenomics is the study of drug response in relation to the genome. The tremendous advances in genotyping and sequencing technologies now allow for the rapid interrogation of genetic variation across the entire genome, which has been exploited for use in pharmacogenomic-directed GWAS in addition to the more common GWAS for complex diseases. Moreover, highly multiplexed genotyping assays enriched for important pharmacogenetic genes and functional variants have been commercially developed for both research and clinical use,[41] prompting the possibility of providing individuals with a predicted drug metabolism phenotype profile. However, which variant alleles included on these panels are actually clinically actionable is a continued source of debate.

Many GWAS for pharmacogenomic traits have been performed to identify genes that affect drug response or susceptibility to adverse drug reactions (for reviews, see Refs. 42–44). Similar to GWAS designs for common diseases, several important issues arise for pharmacogenomic GWAS, including the ability to achieve a sample size that allows for adequate statistical power, proper measurement of a drug response phenotype in the context of already diseased individuals, and the ability to interrogate potentially important genes that are often not included on commercial genotyping arrays due to homology and structural variation issues (e.g., *CYP450* and *HLA* loci).[45] Despite these challenges, successful GWAS on drug response have been reported and include, among others, the confirmation of *CYP2C9* and *VKORC1* and the additional role of *CYP4F2* in warfarin maintenance dosing,[46,47] *CYP2C19* and antiplatelet response to clopidogrel treatment,[30] *IL28B* and interferon-α response for hepatitis C infection,[48] and *SLCO1B1* and methotrexate response.[49]

Regarding adverse drug reactions, the aforementioned association between *SLCO1B1* and statin-induced myalgia was identified by a GWAS,[39] as were the recent associations

between *HLA-B\*5701* and flucloxacillin-induced liver injury[50] and *HLA-A\*3101* and carbamazepine-induced hypersensitivity reactions among individuals of European descent.[51] Despite the challenges of performing GWAS to identify pharmacogenomic loci implicated in drug responses and adverse reactions, both confirmatory and novel associations have already been discovered, which will likely increase in number as whole-exome and whole-genome sequencing strategies become more commonplace in pharmacogenomic studies. Clinical testing for several of the genes identified by these GWAS is now available, as are ongoing clinical trials to assess their clinical utility. For example, an early success was very recently reported for prospective *HLA-B\*1502* screening in Taiwan to avoid carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.[52]

## Race and pharmacoethnicity

Although their specific role in carbamazepine-induced hypersensitivity is not clear, different *HLA* alleles are associated with the adverse reaction among individuals of European and Han Chinese ancestry, *HLA-A\*3101* and *HLA-B\*1502*, respectively. Consistent with these data, one of the major findings in the pharmacogenetics field has been the discovery that drug effects not only vary among individuals but can also vary between racial and ethnic populations.[53] However, like most other complex traits, drug response phenotypes show greater variability among individuals within a particular ethnic population (10–40 fold) than between races or ethnicities (2–3 fold).[54] Although there are many environmental and demographic factors that can influence interethnic drug response variability, another reason is that pharmacogenetic allele frequencies can significantly differ between racial and ethnic populations. As such, clinical pharmacogenetic testing can have similar ethnic group "detectability" issues as observed with cystic fibrosis carrier screening depending on the specific variant alleles or mutations included in a particular clinical assay and the racial or ethnic population being tested.

Some examples of clinically relevant pharmacogenetic alleles that vary between populations include the *CYP2C19\*3* (p.W212X) loss-of-function and *CYP2D6\*10* (p.P34S; p.S486T) reduced function alleles prevalent among Asians; *CYP2C9\*8* (p.R150H), *CYP2D6\*17* (p.T107I; p.R296C); and *NAT2\*14* (p.R64Q) reduced function alleles prevalent among African-Americans; and the *VKORC1* p.D36Y allele associated with higher warfarin dose requirements common to the Ashkenazi Jewish population.[55,56] The associated clinical consequences can be further illustrated with the warfarin example, as studies have shown that current pharmacogenetic-based warfarin dosing algorithms perform less well for African-Americans than Caucasians.[57] This is explained, in part, by the significantly lower frequencies of the variant *CYP2C9* and *VKORC1* alleles commonly incorporated in most dosing algorithms among African-Americans compared with other populations (Fig. 2).[58] Online resources dedicated to summarizing multiethnic pharmacogenetic allele frequencies are available (e.g., FINDbase-PGx[36]) and are also summarized on the PharmGKB Web site (Table 2). Although population and genetic structure is beyond the scope of this review, racial and ethnic-specific pharmacogenetic alleles will likely continue to be of importance clinically, particularly for individual patients, as the degree of population admixture increases and the effectiveness of self-identified race and ethnic labels for complex trait risk decreases.[59]

# CLINICAL PHARMACOGENETICS AND IMPLEMENTATION

Not surprisingly, pharmacogenetic and pharmacogenomic discoveries are often followed by discussions on clinical implementation. However, identification of genetic markers associated with drug response does not always equate to clinically useful predictors of adverse outcomes, and independent replication of genotype-phenotype association is always required before pursuing clinical implementation.[60] Several personalized medicine programs

have invested in clinical pharmacogenetics and view its implementation as a logical first step toward incorporating genetics and genomics into more routine and individualized healthcare. Despite the enthusiasm, not everyone is as supportive, as evidenced by the relatively slow clinician uptake of available pharmacogenetic testing. Although a number of factors are likely responsible for this, general challenges and barriers to clinical implementation of pharmacogenetics are illustrated in Figure 3 and discussed below.

## Validity and utility

The criteria for evaluating genetic tests are summarized by the four components of the ACCE analytic framework: *A*nalytic validity, *C*linical validity, *C*linical utility, and associated *E*thical, legal, and social implications.[61] Although these concepts are imperative to genetic testing, some of their exact definitions with respect to pharmacogenetics and personalized medicine are not always clear.[62] Analytical validity refers to a test's ability to measure the genotype of interest accurately and reliably, which for constitutional pharmacogenetic variants is very robust. As mentioned earlier, more important is which gene variants to interrogate for a particular drug response phenotype and ethnic group to maximize clinical validity.

Clinical validity refers to a test's ability to detect or predict the clinical disorder or phenotype associated with the genotype. Because most drug response phenotypes are multifactorial, it is not always easy to achieve the high clinical validity for pharmacogenetic testing that is often observed with molecular testing for Mendelian disorders. Consequently, the positive predictive value of many pharmacogenetic assays can be low. For example, *CYP2C19*2* is a common variant allele (~15–25% allele frequency) associated with deficient clopidogrel pharmacodynamics and stent thrombosis, which is a rare clinical event (~0.5%) among clopidogrel-treated patients following percutaneous coronary intervention.[30,31] These disparate allele and phenotype frequencies result in a low positive predictive value for *CYP2C19* testing among these patients[63]; however, many argue that genetic testing in this scenario can still be useful and help coronary patients avoid serious life-threatening and unnecessary risks, particularly when taken into consideration with all other clinical factors. In this scenario, pharmacogenetic testing can be viewed analogous to other nongenetic clinical variables with imperfect prediction (e.g., age, concurrent medications, comorbidities, and liver function), yet still providing very useful and additive information.[4,64]

Clinical utility of a test is a widely used measure of its usefulness in the clinic and resulting changes in health outcomes. However, given the multidimensional nature of this kind of measurement, there is rarely consensus as to its precise definition or on how to adequately demonstrate it, particularly with regards to personalized medicine and pharmacogenetics.[62] Unfortunately, the common benchmark for interventional evidence in medicine is a randomized controlled trial, yet these are often resource prohibitive for testing pharmacogenetic hypotheses and may be unethical to conduct for strong associations of severe adverse effects associated with high-risk genotypes. As such, alternative evidence gathering mechanisms are required for pharmacogenetics, which include incorporating pharmacogenomics into premarket drug development and innovative clinical trial designs and continued postmarket observational and mechanistic studies.[65,66] Despite these challenges, successful clinical translation of pharmacogenetics has been reported for *HLA-B*5701* screening to reduce the potentially life-threatening hypersensitivity syndrome that occurs in ~5% of Caucasian HIV patients treated with the antiretroviral agent abacavir.[67]

## Professional education, evidence-based guidelines and recommendations

Clinician knowledge of pharmacogenetic testing also strongly influences the successful integration into clinical practice. A recent review on clinical genomics suggests that clinicians are generally not confident in providing genetic services because of insufficient training and knowledge.[68] Efforts are therefore needed to improve pharmacogenetic comprehension among clinicians, particularly by increasing its presence in medical school curriculums.[69] For general online resources regarding clinical pharmacogenetics, see Table 2. Moreover, the current significance of pharmacogenetics is not well understood by practicing clinicians and they may not understand how to manage a patient based on pharmacogenetic test results. Given the uniqueness to specific drug-gene clinical scenarios, there historically has been insufficient information or guidance available to help clinicians apply pharmacogenetic test results to individual patient management.

To address the current educational needs, clinical practice guidelines that describe the utility of pharmacogenetic testing in different clinical scenarios are warranted to assist health professionals to evaluate and determine test utility and facilitate the overall adoption of pharmacogenetic testing in actual clinical practice.[7] In addition to prescribing clinicians, it will also be important for clinical geneticists and genetic counselors to become knowledgeable about selected indications and the availability of pharmacogenetic testing, particularly with respect to interpretation of test results. Some of the first pharmacogenetic practice guidelines were developed by experts for *CYP2D6*- and *CYP2C19*-guided antidepressant dosing,[70,71] but since then, several other organizations have begun to prepare more formal documents. For a listing of currently published pharmacogenetic practice guidelines and recommendations, see Table 3. Although some guidelines seek to evaluate evidence and establish whether testing is warranted or not,[76,78] others take the approach not to make any recommendation for or against testing and more so provide evidence-based recommended clinical actions for when a patient's genotype is already known.[8–10] Notable examples include the thorough Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group guidelines that report on 53 drugs and 11 genes,[10] the expert-derived European Science Foundation guidelines,[8] and the Clinical Pharmacogenetics Implementation Consortium of the National Institutes of Health's Pharmacogenomics Research Network evidence- based, peer-reviewed gene/drug guidelines that are now published regularly in *Clinical Pharmacology and Therapeutics* and updated at the PharmGKB Web site based on new developments in the respective fields.[9]

Evidence-based practice recommendation statements for genetic testing, including some on pharmacogenetic testing, have also been generated by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (Table 3),[77] launched by the Centers for Disease Control and Prevention Office of Public Health Genomics. Although the EGAPP Working Group previously found insufficient evidence to support recommendations for or against CYP450 and *UGT1A1* genotyping in patients treated with selective serotonin reuptake inhibitors and those treated with irinotecan, respectively, their reports did identify important research gaps that could help facilitate future implementation.[76,78] Unfortunately, the level of evidence required for pharmacogenetic testing is not always clearly defined and is therefore often debated,[4,81–84] as some view pharmacogenetics as a unique entity from other elements of genomic medicine that in many cases is already warranted clinically, whereas others unwearyingly await additional evidence-based data. Regardless, it is very likely that in the future an increasing number of patients will already know their genotypes for certain genes and will therefore be expecting their physicians to be able to incorporate this information into their individualized clinical management.

## Regulation

The recent escalation of available DTC genetic testing has revived the interest of the FDA in overseeing genetic testing, which typically has been regulated by CLIA. As noted earlier, over the past several years, the FDA has revised a number of drug labels to now include relevant pharmacogenetic information; however, most do not require testing before initiating therapy. CLIA-regulated laboratory-developed pharmacogenetic tests and FDA-regulated tests without clinical claims do not necessarily have to provide full evidence of clinical validity and utility to be offered by a clinical laboratory. In an effort to enable further evidence of clinical utility in the postmarket period, the FDA Amendments Act of 2007 allows for systematic, ongoing efforts to continue developing evidence for safety and effectiveness after drug approval.[85] This postmarket time period is very important for pharmacogenetic discovery, and these data can be derived from parties other than the drug manufacturer, including academic researchers and test manufacturers. As this amendment is implemented over the upcoming years, it is possible that this new source of evidence and regulatory mechanism will facilitate and speed up the clinical translation of pharmacogenetics.

Although a number of important pharmacogenetic genes can be currently tested by CLIA-approved laboratories as laboratory-developed tests, there are only a small number of DNA-based pharmacogenetic tests that are actually FDA-approved for in vitro diagnostic testing at the present time, including assays for warfarin sensitivity (*CYP2C9* and *VKORC1*), *CYP2D6*, *CYP2C19*, and for *UGT1A1*. For quality assurance, clinical laboratories also have the option of participating in the pharmacogenetic proficiency testing program by the College of American Pathologists, which has provided graded and educational surveys for the past several years. To address the needs of quality control reference materials to cover alleles included by these and other assays, the Centers for Disease Control and Prevention Genetic Testing Reference Materials Coordination Program, in collaboration with members of the pharmacogenetic testing community and the Coriell Cell Repositories, have characterized a large panel of genomic DNA reference materials for genes commonly included in pharmacogenetic testing panels and proficiency testing surveys, which are commercially available through Coriell.[86]

## Costs and reimbursement

Insurance coverage for pharmacogenetic testing is currently sporadic, yet the healthcare reimbursement climate is constantly changing. As discussed earlier, genetic testing—including pharmacogenetic testing—should demonstrate clinical utility and/or effectiveness before widespread adoption, but for payers, it should also return on its investment. As such, it is of great importance for future pharmacogenomic clinical trials to include pharmacoeconomic studies that assess the impact of pharmacogenetic testing on the healthcare system. Several reports have attempted to systematically evaluate and review pharmacoeconomic examples; however, those relating to warfarin sensitivity testing have concluded with significant uncertainty in economic value, with high commercial genotyping expenses being a major determinant of cost ineffectiveness.[87,88] Although there has been much importance placed on demonstrating cost effectiveness, the rapid fall in genotyping costs makes many cost-effectiveness studies quickly outdated. Moreover, it is important to note that cost-effectiveness is certainly not the sole determinant when implementing new clinical tests, nor is it the only data assessed by insurers when making coverage decisions.

Unfortunately, in 2009, the Centers for Medicare and Medicaid Services determined that *CYP2C9* and *VKORC1* genetic testing to predict warfarin responsiveness was not reasonable or necessary, despite the availability of FDA-approved warfarin pharmacogenetic assays and product insert statements highlighting the importance of *CYP2C9* and *VKORC1* genetic

variants in warfarin dosing. Instead they announced a "coverage with evidence development" strategy where clinical testing would only be covered when a warfarin-naïve patient was enrolled in a carefully constructed prospective, randomized controlled clinical trial. Given that the direction Centers for Medicare and Medicaid Services takes on covering new technologies often influences how private payers respond, most insurers are also now awaiting the results of ongoing prospective warfarin pharmacogenetics clinical trials before implementing any *CYP2C9* and *VKORC1* genetic testing reimbursement policies.

Clearly, there is great potential for pharmacogenetics to improve the risk-benefit profile of new and existing medications and potentially even reduce healthcare costs by avoiding adverse drug reaction expenses. Further studies are therefore necessary to adequately measure the economics of pharmacogenetic testing implementation and hopefully facilitate a broader and more preemptive-based reimbursement system.

## CONCLUSION AND FUTURE PERSPECTIVE

In the past decade, the fields of pharmacogenetics and pharmacogenomics have grown exponentially and paralleled with that has been the burgeoning interest in implementing these discoveries to clinical practice. Important genetic associations that have been identified between variant genotypes and drug response phenotypes have prompted the FDA to revise drug labels to include relevant pharmacogenetic information and recommendations for certain drugs. However, despite the availability of pharmacogenetic testing from CLIA-approved laboratories, physician uptake of clinical pharmacogenetics has been underwhelming, in part due to a perceived lack of clinical utility, inadequate professional guidelines for pharmacogeneticbased management, and limited insurance reimbursement for testing. In the face of these challenges, selected pharmacogenetic examples have managed to achieve acceptance in clinical practice and a number of others are currently being evaluated by randomized controlled trials. The remarkable progress in genome sequencing technologies will undoubtedly identify additional important sequence variants and more sophisticated molecular models to predict drug responses, presumably in conjunction with personalized clinical variables. Of great importance for clinical laboratories, however, will be to have adequate computational and informatics support for these emerging genomic technologies as they become implemented for pharmacogenomic and/or Mendelian disease gene panels.

As such, there is again great potential for pharmacogenetics to facilitate improved and more effective pharmacotherapy. However, clinical implementation of these discoveries can only be realized with adequate assistance from the appropriate regulatory, professional, healthcare, and third-party payer organizations. Although not as quick as technology advancements, it seems that these agencies are at least making incremental strides to ultimately facilitate clinical pharmacogenetics into more routine patient care.

## Acknowledgments

## REFERENCES

1. Kan YW, Dozy AM. Antenatal diagnosis of sickle-cell anaemia by D.N.A. analysis of amniotic-fluid cells. Lancet. 1978; 2:910–912. [PubMed: 81926]

2. Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat. 2010; 31:1240–1250. [PubMed: 20672374]

3. Patrinos GP, Kollia P, Papadakis MN. Molecular diagnosis of inherited disorders: lessons from hemoglobinopathies. Hum Mutat. 2005; 26:399–412. [PubMed: 16138310]

4. Relling MV, Altman RB, Goetz MP, Evans WE. Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism. Lancet Oncol. 2010; 11:507–509. [PubMed: 20413348]

5. Motulsky AG. Drug reactions enzymes, and biochemical genetics. J AmMed Assoc. 1957; 165:835–837.

6. Valdes, R.; Payne, D.; Linder, MW., editors. Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice: National Academy of Clinical Biochemistry. 2010. Laboratory medicine practice guidelines.

7. Amstutz U, Carleton BC. Pharmacogenetic testing: time for clinical practice guidelines. Clin Pharmacol Ther. 2011; 89:924–927. [PubMed: 21508939]

8. Becquemont, L.; Alfirevic, A.; Amstutz, U., et al. Practical recommendations for pharmacogenomics-based prescription: 2010 ESF-UB Conference on Pharmacogenetics and Pharmacogenomics; Pharmacogenomics; 2011. p. 113-124.

9. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011; 89:464–467. [PubMed: 21270786]

10. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte—an update of guidelines. Clin Pharmacol Ther. 2011; 89:662–673. [PubMed: 21412232]

11. Issa AM. Personalized medicine and the practice of medicine in the 21st century. Mcgill J Med. 2007; 10:53–57. [PubMed: 18523593]

12. Ng PC, Murray SS, Levy S, Venter JC. An agenda for personalized medicine. Nature. 2009; 461:724–726. [PubMed: 19812653]

13. Shastry BS. Pharmacogenetics and the concept of individualized medicine. Pharmacogenomics J. 2006; 6:16–21. [PubMed: 16302022]

14. Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD. Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med Decis Making. 2010; 30:328–340. [PubMed: 20086232]

15. Manolopoulos VG, Dechairo B, Huriez A, et al. Pharmacogenomics and personalized medicine in clinical practice. Pharmacogenomics. 2011; 12:597–610. [PubMed: 21619425]

16. Frueh FW, Amur S, Mummaneni P, et al. Pharmacogenomic biomarker information in drug labels approved by the United States food and drug administration: prevalence of related drug use. Pharmacotherapy. 2008; 28:992–998. [PubMed: 18657016]

17. Lesko LJ, Zineh I. DNA, drugs and chariots: on a decade of pharmacogenomics at the US FDA. Pharmacogenomics. 2010; 11:507–512. [PubMed: 20350131]

18. Zineh I, Pacanowsi MA. Pharmacogenomics in the assessment of therapeutic risks versus benefits: inside the United States Food and Drug Administration. Pharmacotherapy. 2011; 31:729–735. [PubMed: 21923598]

19. Vogel F. Moderne problem der humangenetik. Ergeb Inn Med U Kinderheilk. 1959; 12:52–125.

20. Beutler E. Study of glucose-6-phosphate dehydrogenase: history and molecular biology. Am J Hematol. 1993; 42:53–58. [PubMed: 8416297]

21. Kalow W. Pharmacogenetics and anesthesia. Anesthesiology. 1964; 25:377–387. [PubMed: 14156579]

22. Blum M, Demierre A, Grant DM, Heim M, Meyer UA. Molecular mechanism of slow acetylation of drugs and carcinogens in humans. Proc Natl Acad Sci USA. 1991; 88:5237–5241. [PubMed: 1675794]

23. Motulsky AG. Drug reactions, enzymes, and biochemical genetics. JAMA. 1957; 165:835–837.

24. Kalow, W. Pharmacogenetics: heredity and the response to drugs. Philadelphia, PA: W.B. Saunders & Co.; 1962.

25. Mahgoub A, Idle JR, Dring LG, Lancaster R, Smith RL. Polymorphic hydroxylation of debrisoquine in man. Lancet. 1977; 2:584–586. [PubMed: 71400]

26. Sim SC, Ingelman-Sundberg M. The Human Cytochrome P450 (CYP) Allele Nomenclature Web site: a peer-reviewed database of CYP variants and their associated effects. Hum Genomics. 2010; 4:278–281. [PubMed: 20511141]

27. Owen RP, Sangkuhl K, Klein TE, Altman RB. Cytochrome P450 2D6. Pharmacogenet Genomics. 2009; 19:559–562. [PubMed: 19512959]

28. Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. Br J Clin Pharmacol. 2010; 69:222–230. [PubMed: 20233192]

29. de Morais SM, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of *S*-mephenytoin metabolism in humans. J Biol Chem. 1994; 269:15419–15422. [PubMed: 8195181]

30. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA. 2009; 302:849–857. [PubMed: 19706858]

31. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010; 304:1821–1830. [PubMed: 20978260]

32. Klein TE, Altman RB, Eriksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med. 2009; 360:753–764. [PubMed: 19228618]

33. Hein DW, Boukouvala S, Grant DM, Minchin RF, Sim E. Changes in consensus arylamine *N*-acetyltransferase gene nomenclature. Pharmacogenet Genomics. 2008; 18:367–368. [PubMed: 18334921]

34. Kroetz DL, Yee SW, Giacomini KM. The pharmacogenomics of membrane transporters project: research at the interface of genomics and transporter pharmacology. Clin Pharmacol Ther. 2010; 87:109–116. [PubMed: 19940846]

35. Mackenzie PI, Bock KW, Burchell B, et al. Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. Pharmacogenet Genomics. 2005; 15:677–685. [PubMed: 16141793]

36. Georgitsi M, Viennas E, Gkantouna V, et al. Population-specific documentation of pharmacogenomic markers and their allelic frequencies in FIND-base. Pharmacogenomics. 2011; 12:49–58. [PubMed: 21174622]

37. Sangkuhl K, Berlin DS, Altman RB, Klein TE. PharmGKB: understanding the effects of individual genetic variants. Drug Metab Rev. 2008; 40:539–551. [PubMed: 18949600]

38. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther. 2008; 84:326–331. [PubMed: 18305455]

39. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. N Engl J Med. 2008; 359:789–799. [PubMed: 18650507]

40. Limdi NA, Wadelius M, Cavallari L, et al. Warfarin pharmacogenetics: a single VKORC1 polymorphism is predictive of dose across 3 racial groups. Blood. 2010; 115:3827–3834. [PubMed: 20203262]

41. Burmester JK, Sedova M, Shapero MH, Mansfield E. DMET microarray technology for pharmacogenomics-based personalized medicine. Methods Mol Biol. 2010; 632:99–124. [PubMed: 20217574]

42. Crowley JJ, Sullivan PF, McLeod HL. Pharmacogenomic genome-wide association studies: lessons learned thus far. Pharmacogenomics. 2009; 10:161–163. [PubMed: 19207016]

43. Daly AK. Genome-wide association studies in pharmacogenomics. Nat Rev Genet. 2010; 11:241–246. [PubMed: 20300088]

44. Motsinger-Reif AA, Jorgenson E, Relling MV, et al. Genome-wide association studies in pharmacogenomics: successes and lessons. Pharmacogenet Genomics. [published online ahead of print July 15, 2010].

45. Peters EJ, McLeod HL. Ability of whole-genome SNP arrays to capture 'must have' pharmacogenomic variants. Pharmacogenomics. 2008; 9:1573–1577. [PubMed: 19018710]

46. Cooper GM, Johnson JA, Langaee TY, et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. Blood. 2008; 112:1022–1027. [PubMed: 18535201]

47. Takeuchi F, McGinnis R, Bourgeois S, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet. 2009; 5 e1000433.

48. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009; 461:399–401. [PubMed: 19684573]

49. Trevino LR, Shimasaki N, Yang W, et al. Germline genetic variation in an organic anion transporter polypeptide associated with methotrexate pharmacokinetics and clinical effects. J Clin Oncol. 2009; 27:5972–5978. [PubMed: 19901119]

50. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet. 2009; 41:816–819. [PubMed: 19483685]

51. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011; 364:1134–1143. [PubMed: 21428769]

52. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011; 364:1126–1133. [PubMed: 21428768]

53. Kalow W. Ethnic differences in drug metabolism. Clin Pharmacokinet. 1982; 7:373–400. [PubMed: 6754206]

54. Kalow W, Bertilsson L. Interethnic factors affecting drug response. Advanc Drug Res. 1994; 23:1–53.

55. Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol. 2001; 41:815–850. [PubMed: 11264478]

56. Scott SA, Edelmann L, Kornreich R, Desnick RJ. Warfarin pharmacogenetics: CYP2C9 and VKORC1 genotypes predict different sensitivity and resistance frequencies in the Ashkenazi and Sephardi Jewish populations. Am J Hum Genet. 2008; 82:495–500. [PubMed: 18252229]

57. Schelleman H, Chen J, Chen Z, et al. Dosing algorithms to predict warfarin maintenance dose in Caucasians and African Americans. Clin Pharmacol Ther. 2008; 84:332–339. [PubMed: 18596683]

58. Scott SA, Khasawneh R, Peter I, Kornreich R, Desnick RJ. Combined CYP2C9, VKORC1 and CYP4F2 frequencies among racial and ethnic groups. Pharmacogenomics. 2010; 11:781–791. [PubMed: 20504253]

59. Tayo BO, Teil M, Tong L, et al. Genetic background of patients from a university medical center in Manhattan: implications for personalized medicine. PLoS One. 2011; 6:e19166. [PubMed: 21573225]

60. Ryan SG. Regression to the truth: replication of association in pharmacogenetic studies. Pharmacogenomics. 2003; 4:201–207. [PubMed: 12605554]

61. Sanderson S, Zimmern R, Kroese M, Higgins J, Patch C, Emery J. How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. Genet Med. 2005; 7:495–500. [PubMed: 16170241]

62. Lesko LJ, Zineh I, Huang SM. What is clinical utility and why should we care? Clin Pharmacol Ther. 2010; 88:729–733. [PubMed: 21081937]

63. Hulot JS, Fuster V. Antiplatelet therapy: personalized medicine for clopidogrel resistance? Nat Rev Cardiol. 2009; 6:334–336. [PubMed: 19377495]

64. Green MJ, Botkin JR. "Genetic exceptionalism" in medicine: clarifying the differences between genetic and nongenetic tests. Ann Intern Med. 2003; 138:571–575. [PubMed: 12667027]

65. Zineh I, Lesko L. Pharmacogenetics in medicine: barriers, critical factors and a framework for dialogue. Pers Med. 2009; 6:359–361.

66. Burns DK. Developing pharmacogenetic evidence throughout clinical development. Clin Pharmacol Ther. 2010; 88:867–870. [PubMed: 20981004]

67. Phillips E, Mallal S. Successful translation of pharmacogenetics into the clinic: the abacavir example. Mol Diagn Ther. 2009; 13:1–9. [PubMed: 19351209]

68. Scheuner MT, Sieverding P, Shekelle PG. Delivery of genomic medicine for common chronic adult diseases: a systematic review. JAMA. 2008; 299:1320–1334. [PubMed: 18349093]

69. Green JS, O'Brien TJ, Chiappinelli VA, Harralson AF. Pharmacogenomics instruction in US and Canadian medical schools: implications for personalized medicine. Pharmacogenomics. 2010; 11:1331–1340. [PubMed: 20860470]

70. Kirchheiner J, Brosen K, Dahl ML, et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand. 2001; 104:173–192. [PubMed: 11531654]

71. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. Psychosomatics. 2006; 47:75–85. [PubMed: 16384813]

72. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Pharmacol Ther. 2011; 89:387–391. [PubMed: 21270794]

73. Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2010; 56:321–341. [PubMed: 20633831]

74. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450–2C19 (CYP2C19) Genotype and Clopidogrel Therapy. Clin Pharmacol Ther. 2011; 90:328–332. [PubMed: 21716271]

75. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450 2D6 (CYP2D6) genotype and codeine therapy. Clin Parmacol Ther. In press.

76. Recommendations from the EGAPP Working Group: can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? Genet Med. 2009; 11:15–20. [PubMed: 19125128]

77. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. Genet Med. 2009; 11:3–14. [PubMed: 18813139]

78. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med. 2007; 9:819–825. [PubMed: 18091431]

79. Flockhart DA, O'Kane D, Williams MS, et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. Genet Med. 2008; 10:139–150. [PubMed: 18281922]

80. Johnson JA, Gong L, Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clin Pharmacol Ther. 2011; 90:525–629.

81. Grosse SD, McBride CM, Evans JP, Khoury MJ. Personal utility and genomic information: look before you leap. Genet Med. 2009; 11:575–576. [PubMed: 19623080]

82. Khoury MJ. Dealing with the evidence dilemma in genomics and personalized medicine. Clin Pharmacol Ther. 2010; 87:635–638. [PubMed: 20485318]

83. Altman RB. Pharmacogenomics: "noninferiority" is sufficient for initial implementation. Clin Pharmacol Ther. 2011; 89:348–350. [PubMed: 21326263]

84. Khoury MJ, Gwinn M, Dotson WD, Bowen MS. Is there a need for PGxceptionalism? Genet Med. 2011; 13:866–867. [PubMed: 21799428]

85. Evans BJ. Establishing clinical utility of pharmacogenetic tests in the post-FDAAA era. Clin Pharmacol Ther. 2010; 88:749–751. [PubMed: 21081943]

86. Pratt VM, Zehnbauer B, Wilson JA, et al. Characterization of 107 genomic DNA reference materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and UGT1A1: a GeT-RM and Association for Molecular Pathology collaborative project. J Mol Diagn. 2010; 12:835–846. [PubMed: 20889555]

87. Verhoef TI, Redekop WK, Darba J, et al. A systematic review of cost-effectiveness analyses of pharmacogenetic-guided dosing in treatment with coumarin derivatives. Pharmacogenomics. 2010; 11:989–1002. [PubMed: 20602617]

88. You JH. Pharmacoeconomic evaluation of warfarin pharmacogenomics. Expert Opin Pharmacother. 2011; 12:435–441. [PubMed: 21231897]
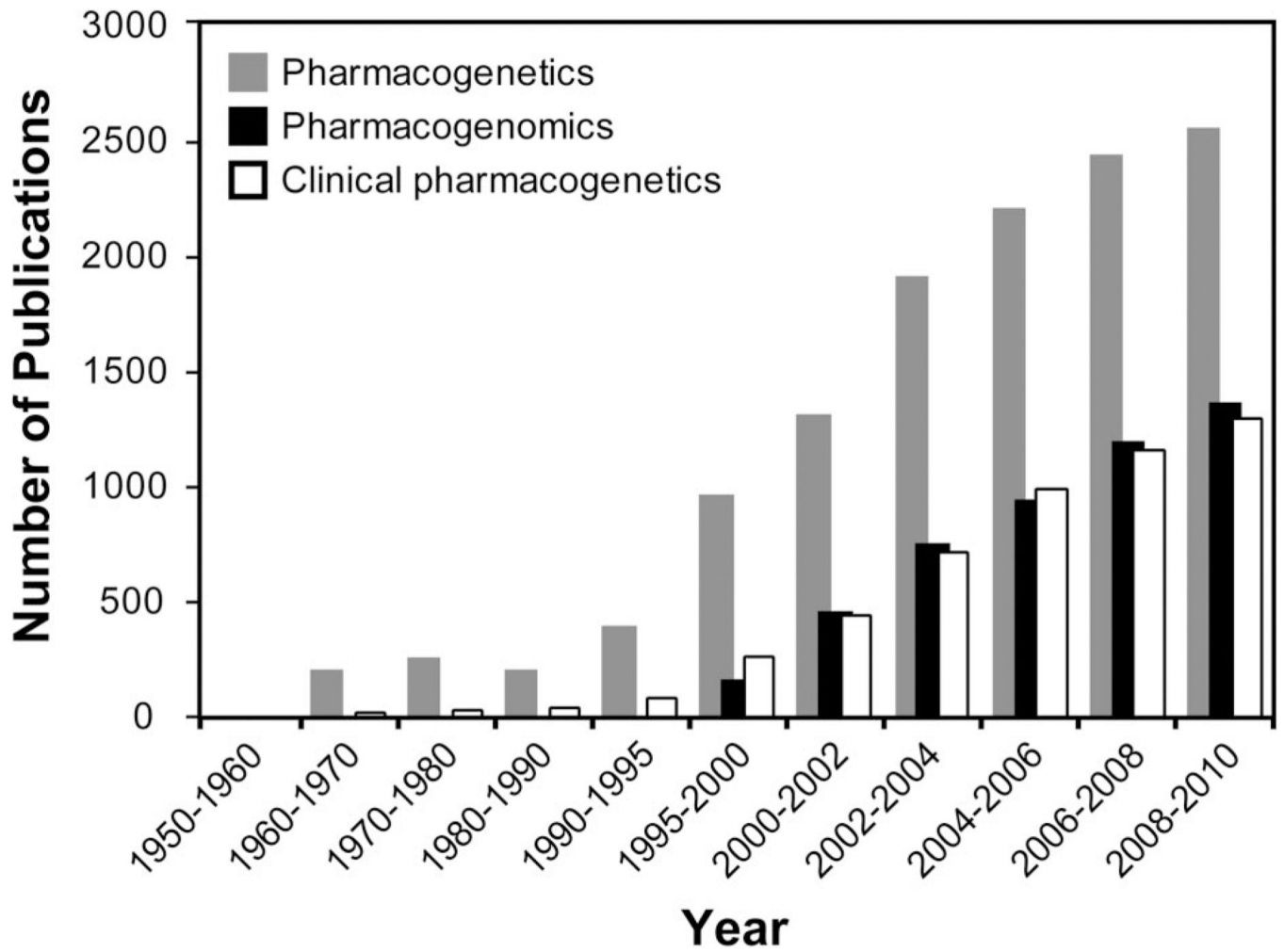
**Fig. 1.**
Number of PubMed citations (http://www.ncbi.nlm.nih.gov/pubmed) by date using the
keywords "pharmacogenetics," "pharmacogenomics," or "clinical pharmacogenetics."
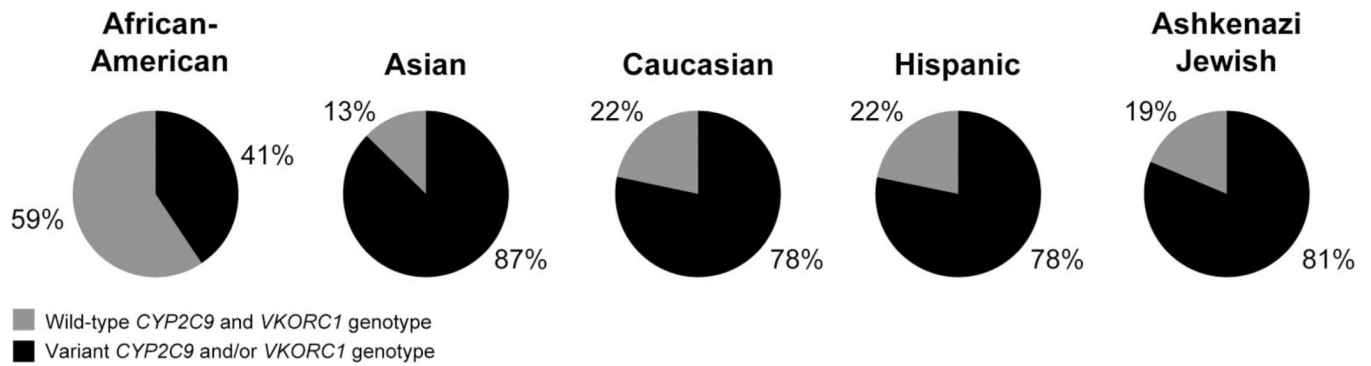
**Fig. 2.**
Population frequencies of wild-type *CYP2C9* (*1/*1*) and *VKORC1* (c.−1639G/G)
individuals (gray) and those carrying variant *CYP2C9* (*2*, *3*, *4*, *5*, *6*, *8*, and *11*) and/
or *VKORC1* (c.−1639G>A) alleles (black). Note the significantly higher frequency of
African-Americans who are wild-type for both *CYP2C9* and *VKORC1* (59%) compared with
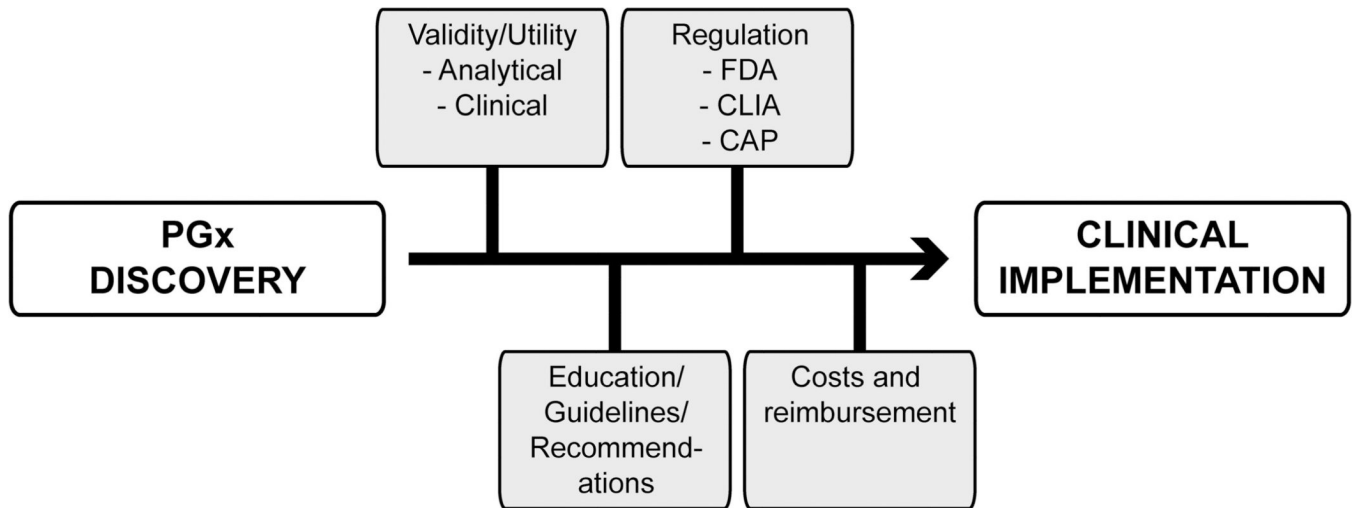other studied populations (13–22%; *P* < 0.0001). Adapted from Scott et al., 2010.[58]

**Fig. 3.**
Illustrated are some of the current challenges and barriers to clinical implementation of pharmacogenetics.

**TABLE 1**

Predicted metabolism phenotypes for CYP2D6, CYP2C19, and CYP2C9 based on example genotypes

| Predicted metabolism phenotype | CYP2D6[a,b] | CYP2C19[b,c] | CYP2C9[b] |
|---|---|---|---|
| Ultrarapid metabolizer (UM) | *1/*1xN, *1/*2xN | *1/*17, *17/*17 | — |
| Extensive metabolizer (EM) | *1/*1, *1/*4, *1/*5, *1/*10, *2/*41, *35/*41 | *1/*1 | *1/*1 |
| Intermediate metabolizer (IM) | *4/*10, *4/*41, *5/*41, *41/*41 | *1/*2, *1/*3, *1/*4, *1/*8 | *1/*2, *1/*3 |
| Poor metabolizer (PM) | *4/*4, *4/*5 | *2/*2, *2/*3, *3/*3 | *2/*2, *2/*3, *3/*3 |

[a]There are many known variant *CYP2D6* alleles that encode enzymes with increased, normal, reduced, or no activity. There are also a number of different classification schemes for *CYP2D6* genotype-predicted phenotypes. Shown here is the most commonly used,[27] whereby increased copy number of functional alleles predicts UM, any genotype that includes at least one fully functional allele (*1*, *2*, or *35*) predicts EM, one null allele and a reduced function allele or two reduced function alleles predicts IM, and two null alleles predicts PM. Although there is no discrepancy between UM and PM classification, other published methods of classification consider EMs as only those with two functional alleles.

[b]Many other variant alleles and possible genotypes exist for these genes. For more information on other variant alleles with references on their activity, see the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website (http://www.cypalleles.ki.se/).[26]

[c]*CYP2C19*17* is a gain-of-function increased activity allele, which can predict an UM phenotype; however, there is only limited data on *17* and loss-of-function alleles in compound heterozygosity. For example, the predicted phenotype of the *2/*17* genotype may be consistent with an EM or IM phenotype and may be substrate dependent.[28]

**TABLE 2**

Online resources and databases for clinical pharmacogenetics

| Name | Application | Website | Reference |
|---|---|---|---|
| Genes and Nomenclature | | | |
| Human Arylamine *N*-Acetyltransferase (NAT) Gene Nomenclature Committee | Catalog of *NAT1* and *NAT2* nucleotide variants, functional consequences, and links to relevant literature. | http://www.louisville.edu/medschool/pharmacology/NAT.html | Hein et al.[33] |
| Human Cytochrome P450 (CYP) Allele Nomenclature Committee | Catalog of *CYP450* genes, their nucleotide variants, functional consequences, and links to relevant literature. | http://www.cypalleles.ki.se/ | Sim et al.[26] |
| Pharmacogenetics of Membrane Transporters (PMT) Database | Catalog of nucleotide variants for solute carrier (SLC) and ATP binding cassette (ABC) transporters. | http://pharmacogenetics.ucsf.edu/ | Kroetz et al.[34] |
| UDP-Glucuronosyltranserase (UGT) Alleles Nomenclature Committee | Catalog of *UGT1A* and *UGT2B* nucleotide changes and haplotypes. | http://www.ugtalleles.ulaval.ca | Mackenzie et al.[35] |
| Pharmacogenetics and Pharmacology | | | |
| Cytochrome P450 Drug Interaction Table | A reference for known drug interactions that affect the human cytochrome P450 system. | http://medicine.iupui.edu/clinpharm/ddis/ | — |
| Pharmacogenetics and Pharmacogenomics | | | |
| FINDbase-PGx: Frequency of Inherited Disorders Pharmacogenomics Database | A database of pharmacogenomic allele frequencies in various racial and ethnic populations. | http://www.findbase.org/ | Georgitsi et al.[36] |
| PharmGKB: The Pharmacogenomics Knowledge Base | A comprehensive and central resource for pharmacogenomic data curation: genes, variants, drugs, diseases, and pathways. | http://www.pharmgkb.org/ | Sangkuhl et al.[37] |
| WarfarinDosing.org | An online tool to help clinicians estimate therapeutic warfarin doses using genetic information for patients initiating therapy. | http://www.warfarindosing.org | Gage et al.[38] |

**Table 3**

Clinical practice guidelines, recommendations, and statements on pharmacogenetic testing

| Drug(s) | Gene(s) | FDA drug label section with pharmacogenomic information | Reference | Organization |
|---|---|---|---|---|
| Abacavir | HLA-B*5701 | Boxed warning, contraindications, warnings and precautions, patient counseling information | Becquemont et al.[8] | ESF-UB |
| Azathioprine/6-mercaptopurine | TPMT | Dosage and administration, warnings and precautions, drug interactions, adverse reactions, clinical pharmacology | Becquemont et al.[8] | ESF-UB |
| | | | Relling et al.[72] | CPIC[9] |
| Clopidogrel | CYP2C19 | Boxed warning, dosage and administration, warnings and precautions, drug interactions, clinical pharmacology | Holmes et al.[73] | ACCF/AHA |
| | | | Becquemont et al.[8] | ESF-UB |
| | | | Scott et al.[74] | CPIC[9] |
| Codeine | CYP2D6 | Warnings and precautions, use in specific populations, clinical pharmacology | Crews et al.[75] | CPIC[9] |
| Flucloxacillin | HLA-B*5701 | — | Becquemont et al.[8] | ESF-UB |
| Irinotecan | UGT1A1 | Dosage and administration, warnings, clinical pharmacology | EGAPP Working Group[76] | EGAPP[77] |
| Selective serotonin reuptake inhibitors (SSRIs) | CYP2C19/CYP2D6 | For selected SSRIs, see FDA Biomarker Table[a] | EGAPP Working Group[78] | EGAPP[77] |
| Statins | SLCO1B1 | — | Becquemont et al.[8] | ESF-UB |
| Tacrolimus | CYP3A5 | — | Becquemont et al.[8] | ESF-UB |
| Tamoxifen | CYP2D6 | — | Becquemont et al.[8] | ESF-UB |
| Warfarin | CYP2C9/VKORC1 | Dosage and administration, precautions, clinical pharmacology | Flockhart et al.[79] | ACMG |
| | | | Becquemont et al.[8] | ESF-UB |
| | | | Johnson et al.[80] | CPIC[9] |
| Multiple (53 drugs) | Multiple (11 genes) | For selected drugs, see reference and FDA Biomarker Table[a] | Swen et al.[10] | KNMP-PWG |

[a]US Food and Drug Administration—Table of pharmacogenomic biomarkers in drug labels (http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm).

ACCF, American College of Cardiology Foundation; ACMG, American College of Medical Genetics; AHA, American Heart Association; CPIC, Clinical Pharmacogenetics Implementation Consortium; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; ESF-UB, European Science Foundation-University of Barcelona (Pharmacogenetics and Pharmacogenomics: Practical Applications in Routine Medical Practice Conference); KNMP-PWG, Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group.