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REVIEW

Implementation and utilization of genetic testing in personalized medicine

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Abstract: Clinical genetic testing began over 30 years ago with the availability of mutation detection for sickle cell disease diagnosis. Since then, the field has dramatically transformed to include gene sequencing, high-throughput targeted genotyping, prenatal mutation detection, preimplantation genetic diagnosis, population-based carrier screening, and now genome-wide analyses using microarrays and next-generation sequencing. Despite these significant advances in molecular technologies and testing capabilities, clinical genetics laboratories historically have been centered on mutation detection for Mendelian disorders. However, the ongoing identification of deoxyribonucleic acid (DNA) sequence variants associated with common diseases prompted the availability of testing for personal disease risk estimation, and created commercial opportunities for direct-to-consumer genetic testing companies that assay these variants. This germline genetic risk, in conjunction with other clinical, family, and demographic variables, are the key components of the personalized medicine paradigm, which aims to apply personal genomic and other relevant data into a patient's clinical assessment to more precisely guide medical management. However, genetic testing for disease risk estimation is an ongoing topic of debate, largely due to inconsistencies in the results, concerns over clinical validity and utility, and the variable mode of delivery when returning genetic results to patients in the absence of traditional counseling. A related class of genetic testing with analogous issues of clinical utility and acceptance is pharmacogenetic testing, which interrogates sequence variants implicated in interindividual drug response variability. Although clinical pharmacogenetic testing has not previously been widely adopted, advances in rapid turnaround time genetic testing technology and the recent implementation of preemptive genotyping programs at selected medical centers suggest that personalized medicine through pharmacogenetics is now a reality. This review aims to summarize the current state of implementing genetic testing for personalized medicine, with an emphasis on clinical pharmacogenetic testing.

Keywords: personalized medicine, pharmacogenetics, pharmacogenomics, direct-to-consumer genetic testing, point-of-care genetic testing, preemptive genetic testing, implementation

Introduction

Clinical genetic testing historically has been limited to germline mutation detection for Mendelian diseases; however, candidate gene and genome-wide association studies (GWAS) have identified polymorphic deoxyribonucleic acid (DNA) sequence variants that significantly contribute to common disease susceptibility, other complex traits, and a number of drug response phenotypes. This has created the potential for implementing genetic testing to estimate personalized disease risk and/or to help guide individual pharmacotherapy. However, despite initial enthusiasm for common disease variant testing, ongoing concerns over inconsistent results, lack of clinical validity,

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and return of results without counseling suggest that genetic testing for common disease risk estimation currently is not ready for widespread adoption.

Pharmacogenetics is the study of the genetic determinants of drug response variability, and increasing enthusiasm for implementing clinical pharmacogenetic testing is evidenced by the personalized medicine programs that are now preemptively genotyping germline pharmacogenetic variants[1] and the recent availability of clinical practice guidelines when pharmacogenetic test results are available.[2] Other developments supporting the implementation of pharmacogenetic testing include the recent availability of rapid sample-to-answer genotyping platforms that could potentially be used at the point-of-care[3] and the increasing use of clinical decision support (CDS) for health care providers deployed through electronic health records (EHRs).[4] This review aims to summarize the current state of the personalized medicine genetic testing field, with an emphasis on pharmacogenetic testing and clinical implementation.

Genetic testing: validity and utility

In the US, genetic tests are commonly evaluated in Clinical Laboratory Improvement Amendments of 1988 (CLIA)-certified laboratories by the Analytic validity, Clinical validity, Clinical utility, and associated Ethical, legal, and social implications (ACCE framework).[5] Analytical validity is the ability to measure the genotype of interest accurately and reliably, which is generally high for assays interrogating germline pharmacogenetic variants.[6,7] Clinical validity is the ability to detect or predict a phenotype associated with the genotype. Although it is a difficult metric to quantify for disease risk and pharmacogenetic testing, clinical utility is a measure of usefulness in the clinic and resulting changes in health outcomes.

The highest level of evidence to support clinical utility is derived from a prospective randomized controlled trial, yet these are often difficult to perform for pharmacogenetic hypotheses due to the challenges with achieving adequate power for low frequency adverse events and the potential ethical concerns with exposing individuals carrying at-risk genotypes.

Consequently, evidence to support clinical implementation of pharmacogenetic testing frequently has to be derived from alternative sources and study designs. Despite these challenges, the 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 the Caucasian human immunodeficiency virus patients treated with the antiretroviral agent abacavir.[8] Moreover, the incorporation of pharmacogenomics into early-phase drug development and clinical trial design has been proposed to facilitate variant discovery, clinical translation, and to help inform later-phase studies and potential clinical implementation.[9]

Personalized medicine: past and present

Although personalized medicine has only recently been acknowledged in medical practice, physicians and researchers have observed interindividual differences in clinical traits and therapy responses for centuries. Historical examples include the four humors theory used by Hippocrates to diagnose and to prescribe therapy for individual patients; AL Fox's observation of interindividual variability in phenylthiocarbamide taste perception; R Bonicke's, W Reif's, and HB Hughes's description of interpatient differences in unchanged isoniazid urinary excretion that was later found to be due to differences in metabolic acetylation activity; and the increased episodes of primaquine-induced acute hemolytic crises witnessed in African American soldiers compared to Caucasians during World War II.[10] Despite these and other more contemporary examples of interpatient variability in clinical course and therapy response, medicine of today is still largely based on the one-size-fits-all model where patients diagnosed with the same condition often are prescribed the same medication at the same dose. Although therapeutic successes have occurred with this model, for some medications this approach potentially can lead to preventable adverse drug reactions, reduced efficacy, noncompliance due to intolerance, and increased health care costs. For these reasons, a more patient-centric or personalized approach of medical practice has been proposed and is frequently debated.[11]

The completion of the Human Genome Project and the recent advances in genome sequencing technology have fueled translational research in genomics and the ongoing anticipation of medical practice that incorporates personal genomic data. Although understanding the genetic contribution to human disease is far from complete, polymorphic DNA sequence variants have been associated with common disorders and other complex traits by GWAS.[12] In addition to advancing our scientific understanding of disease mechanisms and providing starting points for the development of medical treatments, the identification of certain susceptibility variants with significant disease associations also allows for the estimation of personal disease risks. As such, the

personalized medicine paradigm now includes the utilization of individual genetic data in conjunction with other clinical, family, and demographic variables to inform decisions on disease prevention, diagnosis, treatment, and prognosis.

As noted in the "Clinical pharmacogenetic implementation programs" section, personalized medicine-based initiatives increasingly are being deployed by academic medical centers and other organizations. One resource for the personalized medicine community has been the Personalized Medicine Coalition, which was launched in 2004 in an effort to help advance the field.[13]

Common disease risk variants

Discovery of disease risk variants

The first reported GWAS identified a significant association between the complement factor H (*CFH*) gene and age-related macular degeneration (AMD) with an inspiring odds ratio of 4.6.[14] With more than 25 risk variants now identified, AMD remains one of the most genetically well-characterized complex disorders. Two of the most notable variants that contribute substantially to AMD risk, *CFH* and age-related maculopathy sensitivity 2 (*ARMS2*)[15] have shed light on disease pathogenesis and may have implications in treatment response.[16]

Type 1 diabetes (T1D) is another example of a prevalent complex disease for which genetic susceptibility has been the subject of intensive study. Human leukocyte antigen (HLA) associations with T1D were first observed in the 1970s,[17] and high-risk *HLA* class II variants remain the strongest genetic association with T1D, accounting for 30%–50% of the genetic risk and conferring up to a 20-fold increased risk for T1D.[18] Subsequent candidate-gene studies and GWAS have revealed more than 40 non-*HLA* risk variants for T1D,[19,20] which jointly confer only limited additional risk beyond the *HLA* variants, but nevertheless have provided important insights into the natural history and pathophysiology of the disease.[21] The most significant of these are variants in the insulin (*INS*) and protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) genes, with *PTPN22* variants also being independently associated with other autoimmune diseases.[22]

There are many other examples of common diseases for which GWAS have identified disease-variant associations;[12] however, the majority of these associations are of modest effect sizes, with a median odds ratio of only 1.33 – and few being >3.[23] Moreover, most identified disease risk variants can only explain a small proportion of the estimated genetic heritability of common diseases.[24] In addition, some common conditions, such as psychiatric diseases, have been more challenging to investigate by GWAS, requiring much larger sample sizes to identify significant associations. Despite the small amount of heritability explained by most reported common disease risk variants and the ongoing difficulties with risk prediction, these studies have illuminated new biology and previously unknown disease pathways.[25]

Genetic risk prediction

Traditional disease risk assessments incorporate environmental and clinical factors known to be associated with common diseases and are intended to help clinicians more accurately assess patient risk for the purpose of prevention, diagnosis, treatment, and prognosis. A widely used example of this is the Framingham risk score, which is a sex-specific algorithm that estimates 10-year cardiovascular disease risk.[26] While the importance of genetics in disease risk prediction has long been recognized by the presence or absence of a family history, genetic variables have only recently been incorporated into risk prediction models.

Genetic risk prediction began, with some success, using common variants of large effect size that were mostly discovered in the pre-GWAS era, such as the *HLA* effect in T1D.[21] To date, the most well-known genetic variables utilized in disease risk prediction are *BRCA1* and *BRCA2*, which were originally identified by linkage studies[27,28] to be associated with hereditary breast and ovarian cancer syndrome.[29] Genetic risk prediction models for other common diseases are beginning to surface, using various subsets of risk variants, sometimes in combination with clinical and environmental factors. In the case of AMD, a recent study showed a significant increase in disease predictability by incorporating six risk variants to an algorithm previously based on clinical and environmental factors.[30]

Direct-to-consumer genetic testing

Clinical genetic testing traditionally has been available through physicians and genetic counselors; however, the landscape of genetic testing has changed considerably with the emergence of direct-to-consumer (DTC) genetic testing. With DTC testing, consumers can order genetic tests directly, and results often are returned without health care provider involvement or genetic counseling. The modern era of DTC genetic testing began in 2007 with the launch of deCODE genetics, Navigenics, and 23andMe. By 2011, there were at least 27 reported companies offering DTC genetic testing

to US consumers.[31] Even though some of these companies are no longer in existence or offering DTC products, a broad range of DTC genetic tests remain available today.

An evolving aspect of DTC genetic testing has been the use of genetic risk prediction tools for a wide array of common diseases. Unfortunately, DTC genetic risk estimates typically have low-to-moderate predictive ability for common diseases, due to the small effect sizes of most disease risk variants. In addition, the reported effect sizes of these variants are dependent on the nature of the studied population, including ancestry. As such, an association detected in one population will not necessarily be transferable to another racial or ethnic group. Furthermore, for any given disease, there has been little concordance between DTC companies in their variant selection, effect sizes, average population risk, and algorithms used to calculate disease risk, which has resulted in substantial differences in individual risk prediction between the DTC companies.[32,33]

DTC pharmacogenetic testing is available for a variety of drug-gene pairs – including those with and without well-established guidelines.[34] Similar to the DTC disease risk estimates, DTC pharmacogenetic tests can differ in the genes and variants interrogated, which affects the interpretation of results and accuracy of predictions and is important when considering variants with allele frequencies that vary between racial and ethnic groups.[34]

Pharmacogenetic variants

The field of pharmacogenetics is generally believed to have originated in the late 1950s when the term "pharmacogenetics" was first published by F Vogel.[35] Many pharmacogenetic discoveries followed, including the 1977 identification of polymorphic debrisoquine hydroxylation inherited as an autosomal recessive trait.[36] The responsible enzyme was later identified as cytochrome P450-2D6 (CYP2D6) and is now believed to be involved in the metabolism of ~25% of all commonly used drugs.[37] Numerous *CYP2D6* genetic studies have been reported with more than 100 variant star (*) alleles now cataloged by the Human Cytochrome P450 (CYP) Allele Nomenclature Committee.[38]

In an effort to potentially utilize *CYP2D6* status to guide pharmacotherapy, some CLIA-certified genetic testing laboratories offer *CYP2D6* genotyping with an interpretation that categorizes patients into one of four metabolizer phenotypes: ultrarapid; extensive; intermediate; or poor.[37] Like other pharmacogenetic examples, the application of *CYP2D6* genotype results is dependent on the clinical context and specific medication for a given patient. Some known pharmacogenetic variants are associated with drug efficacy, while others are implicated in toxicity and/or adverse drug reactions.

There are more than 50 other known human cytochrome P450 enzymes and variant alleles in these genes are being discovered continuously in various populations. Two notable CYP2C subfamily enzymes with polymorphic genes that often are included in clinical pharmacogenetic genotyping panels are CYP2C9[39] and CYP2C19.[40] CYP2C9 metabolizes many clinically relevant drugs including phenytoin, warfarin, tolbutamide, and losartan. Among other associations, *CYP2C9* reduced-function alleles have been implicated in interindividual warfarin dosing variability and bleeding risk.[41] The vitamin K epoxide reductase complex 1 (*VKORC1*)[42] promoter variant (c.-1639G>A) is also strongly predictive of therapeutic warfarin dosing requirements[43] and variants from these two genes have been incorporated with other clinical variables into warfarin dosing algorithms.[44] Importantly, retrospective studies have shown that pharmacogenetic-guided warfarin dosing is more accurate than both fixed dosing and the dosing table in the warfarin label.[45] However, recent randomized clinical trials indicate that although pharmacogenetic-guided dosing is more accurate than typical fixed dosing,[46] an algorithm with only three *CYP2C9* and *VKORC1* variants common among Caucasians is not superior to a clinical variable dosing algorithm, particularly among individuals of African ancestry.[47] As such, a major issue behind the pharmacogenetic-guided warfarin dosing continues to be the appropriate selection of *CYP2C9* and *VKORC1* variants for a given ethnicity and the ongoing debate over clinical utility.[48] These important trials also suggest that more ethnic-specific dosing algorithms are needed.

The CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs and drug classes such as antidepressants, benzodiazepines, mephenytoin, proton pump inhibitors, and the antiplatelet prodrug clopidogrel. Importantly, the common *CYP2C19*2* allele has been associated with reduced active clopidogrel metabolites, higher on-treatment platelet aggregation, and adverse clinical outcomes compared to noncarriers among clopidogrel-treated patients with acute coronary syndromes and/or those undergoing percutaneous coronary intervention (PCI),[49,50] and practice guidelines on *CYP2C19*-directed antiplatelet therapy are available (Table 1).

Other notable enzymes and transporters with known variants and potential clinical utility include dihydropyrimidine dehydrogenase (*DPYD*) and fluorouracil response,[51] thiopurine S-methyltransferase (*TPMT*) and thiopurine toxicity,[52] UDP-

glucuronosyltransferase (*UGT1A1*) and irinotecan toxicity,[53] and the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene implicated in statin-induced myopathy.[54,55] Other genes and variants implicated in drug response variability are continually being discovered, most commonly now by genome-wide approaches.[56–58] With respect to drug efficacy, these include the identification of *IL28B* and interferon-α response for hepatitis C infection,[59] *SLCO1B1* and methotrexate response,[60] *GLCCI1* and glucocorticoid response,[61] and *CYP4F2* and its role in warfarin dosing.[62,63]

Examples involving drug toxicity or adverse drug reactions include *HLA-B*5701* and flucloxacillin-induced liver injury,[64] and *HLA-A*3101* and carbamazepine-induced hypersensitivity.[65] As noted previously, the frequencies of these variant alleles can significantly differ between racial and ethnic groups, which influence the variability in drug response observed between populations in addition to between individuals.[66,67] Online resources dedicated to summarizing multi-ethnic pharmacogenetic allele frequencies are available (eg, FINDbase-PGx),[68] and they are also summarized on the Pharmacogenomics Knowledge Base (PharmGKB) website (https://www.pharmgkb.org/).

Many of the genes and variants noted above currently are being considered for clinical implementation or are already implemented at several medical centers. However, despite this enthusiasm, routine clinician uptake of available pharmacogenetic testing has been low, likely due to a number of factors including concerns over clinical validity/utility and insufficient evidence, a lack of professional education and guidelines, and other logistic, regulatory, and reimbursement issues.[69] To specifically address the educational needs for pharmacogenetic testing implementation, clinical practice guidelines that detail therapeutic options based on pharmacogenetic test results are being developed by a number of organizations (Table 1). Although some guidelines evaluate the evidence and determine whether testing is warranted or not,[70,71] others simply provide evidence-based recommended clinical actions for when a patient's genotype is already known.[2,72,73] Examples include the Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group (KNMP-PWG) guidelines that report on 53 drugs and eleven genes[72] and the evidence-based gene/drug guidelines reported by the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network

Table 1 Candidate genes for pharmacogenetic implementation with available practice guidelines and recommendation statements

Gene(s)	Drug	Organization	Practice guidelines/ recommendation statements
CFTR	Ivacaftor	CPIC	Clancy et al; 2014[118]
CYP2C9/VKORC1	Warfarin	ACMG	Flockhart et al; 2008[119]
		CPIC	Johnson et al; 2011[120]
CYP2C19	Clopidogrel	CPIC	Scott et al; 2011,[121] 2013[122]
		ACCF/AHA	Holmes et al; 2010[123]
	TCAs	CPIC	Hicks et al; 2013[124]
CYP2D6	Codeine	CPIC	Crews et al; 2012[125]
	SSRIs	CPIC	In preparation; 2014[a]
		EGAPP	EGAPP Working Group; 2007[70]
	Tamoxifen	ACMG	Lyon et al; 2012[126]
	TCAs	CPIC	Hicks et al; 2013[124]
CYP3A	Tacrolimus	CPIC	In preparation; 2014[a]
DPYD	Fluoropyrimidine	CPIC	Caudle et al; 2013[127]
HLA-B	Abacavir	CPIC	Martin et al; 2012[128]
	Allopurinal	CPIC	Hershfield et al; 2013[129]
	Carbamazepine	CPIC	Leckband et al; 2013[130]
	Phenytoin	CPIC	In preparation; 2014[a]
IFNL3 (IL28B)	Interferon-α	CPIC	Muir et al; 2014[131]
SLCO1B1	Simvastatin	CPIC	Wilke et al; 2012[132]
TPMT	Azathioprine/6-mercaptopurine	CPIC	Relling et al; 2011,[133] 2013[134]
UGT1A1	Irinotecan	EGAPP	EGAPP Working Group; 2009[71]
Multiple (eleven genes)	Multiple (53 drugs)	KNMP-PWG	Swen et al; 2011[72]

Note: [a]Based on information available from Pharmacogenomics Knowledge Base website (http://www.pharmgkb.org/cpic/pairs), and K Caudle, CPIC Coordinator, personal communication.

Abbreviations: TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; ACCF, American College of Cardiology Foundation; ACMG, American College of Medical Genetics and Genomics; AHA, American Heart Association; CPIC, Clinical Pharmacogenetics Implementation Consortium; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; KNMP-PWG, Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group.

(PGRN) (Table 1).[2] In addition, evidence-based practice recommendation statements for pharmacogenetic testing have also been published by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,[74] launched by the Centers for Disease Control and Prevention Office of Public Health Genomics (Table 1).

Clinical pharmacogenetic testing and implementation

Clinical genetic testing regulation

In the US, CLIA regulations include federal standards applicable to all laboratories that test human specimens for health assessment or to diagnose, prevent, or treat disease. The CLIA program supports clinical laboratory quality by developing technical standards and laboratory practice guidelines, conducting laboratory quality improvement studies, monitoring proficiency testing practices, among other initiatives and resources. CLIA-certified laboratories can offer genetic tests using either validated laboratory-developed tests or commercially available products approved by the US Food and Drug Administration (FDA).

Table 2 summarizes the commercially available DNA-based pharmacogenetic tests that currently are US FDA-approved for in vitro diagnostic testing. Clinical laboratories can also participate in the pharmacogenetic proficiency testing programs offered by the College of American Pathologists, which provides graded and educational surveys for *CYP2C9* and *VKORC1*, *CYP2C19*, *CYP2D6*, and *UGT1A1*.[75] To address the need for quality control reference materials, the Coriell Cell Repositories and the Genetic Testing Reference Materials Coordination Program of the Centers for Disease Control and Prevention have characterized a panel of commercially available cell lines for genes and variants commonly interrogated by pharmacogenetic assays.[76] An expanded Genetic Testing Reference Materials Coordination Program pharmacogenomics reference material project is currently ongoing that is interrogating a much larger panel of genes and variants, using multiplexed targeted assays, genotyping microarrays, and next-generation sequencing gene panels.

Point-of-care genetic testing

A common challenge when implementing pharmacogenetic testing in a traditional health care environment is the frequent need for rapid return of results. In an effort to address this, biotechnology companies have been developing genotyping platforms that offer rapid sample-to-result assays for possible use at the point-of-care (POC).[6,77,78] For example, the reassessment of anti-platelet therapy using an individualized strategy based on genetic evaluation (RAPID GENE) trial successfully implemented POC *CYP2C19*2* genetic testing for cardiac patients initiating clopidogrel therapy following PCI.[3] Patients were randomized to either *CYP2C19*2* genotyping using a rapid POC cheek swab device or standard treatment with clopidogrel. Identified *CYP2C19*2* carriers in the genotyping arm were treated with prasugrel while

Table 2 Pharmacogenetic tests approved by the US FDA for IVD use[a]

Gene(s)	Assay	Alleles interrogated	Company	Date approved
CYP2C9 and VKORC1	Verigene® Warfarin Metabolism Test	*CYP2C9*2, *3, VKORC1* c.174-136C>T (1173C>T)	Nanosphere, Inc.	September 2007
	INFINITI® Warfarin Assay	*CYP2C9*2, *3, VKORC1* c.-1639G>A	AutoGenomics, Inc.	January 2008
	eSensor® Warfarin Sensitivity Test	*CYP2C9*2, *3, VKORC1* c.-1639G>A	GenMark Diagnostics, Inc.	July 2008; December 2011
	eQ-PCR™ LC Warfarin Genotyping Kit	*CYP2C9*2, *3, VKORC1* c.-1639G>A	TrimGen Corporation	February 2009
CYP2C19	AmpliChip® CYP450 Test	**2, *3*	Hoffmann-La Roche Ltd	January 2005
	INFINITI® CYP2C19 Assay	**2, *3, *17*	AutoGenomics, Inc.	October 2010
	Verigene® *CYP2C19* Test	**2, *3, *17*	Nanosphere, Inc.	November 2012
	Spartan RX CYP2C19 Assay	**2, *3, *17*	Spartan Bioscience Inc.	August 2013
	xTAG® CYP2C19 Kit v3	**2, *3, *17*	Luminex Molecular Diagnostics, Inc.	September 2013
CYP2D6	AmpliChip® CYP450 Test[b]	**2–*11, *15, *17, *19, *20, *29, *35, *36, *40, *41*, duplication	Hoffmann-La Roche Ltd	January 2005
	xTAG® CYP2D6 Kit v3	**2–*11, *15, *17, *29, *35, *41*, duplication	Luminex Molecular Diagnostics, Inc.	May 2013

Notes: [a]As listed on the US FDA IVD Product Database: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm; [b]the *CYP2D6* star (*) allele nomenclature for the AmpliChip® is based on the available nomenclature at the time of product release. The **41* allele reported by the AmpliChip® is not consistent with the current **41* haplotype nomenclature as it does not interrogate the 2988G>A variant that was discovered after the development of the Amplichip®.[135]
Abbreviations: FDA, Food and Drug Administration; IVD, in vitro diagnostic.

noncarriers were treated with clopidogrel. As a proof of concept trial, no carriers in the genotyping arm had high on-treatment platelet reactivity at day 7 compared with 30% of patients undergoing standard treatment.[3]

The success of RAPID GENE suggests that POC genetic testing can be performed effectively by nursing staff and that personalized antiplatelet therapy can reduce high on-treatment platelet reactivity in this patient population; however, this trial was not designed to test whether this strategy results in better clinical outcomes. A number of trials are underway to address this important question, including: the reassessment of antiplatelet therapy using an individualized strategy in patients with ST-segment elevation myocardial infarction (RAPID STEMI; ClinicalTrials.gov identifier, NCT01452139); the tailored antiplatelet therapy following PCI (TAILOR-PCI; NCT01742117), and the customized choice of P2Y12 oral receptor blocker based on phenotype assessment via point-of-care testing (PRU-MATRIX; NCT01477775).

Despite the support for POC genetic testing by the RAPID GENE trial, logistical and regulatory issues need to be considered when implementing POC genetic testing into actual routine clinical care. Although the genotyping platform used in RAPID GENE has recently been approved by the US FDA (Table 2), it currently is not supported as a true POC device since it does not qualify for a CLIA waiver. Furthermore, because any genetic testing is broadly categorized by CLIA as high complexity testing, all pharmacogenetic POC testing platforms will likely not be amenable to CLIA waivers. As such, a CLIA-certified genetics laboratory will be required to oversee POC testing by managing performance, interpretation, quality control/assurance, and proficiency, which ultimately may diminish the inherent advantages of a POC genetic testing device. Nevertheless, the dramatic reduction in turnaround times of these platforms is undoubtedly a major benefit when implementing pharmacogenetic testing for selected clinical scenarios.

Another challenge for POC pharmacogenetic testing is the content of the assays. Some of the most robust pharmacogenetic associations with large effect sizes involve the aforementioned *HLA* alleles and flucloxacillin-induced liver injury/abacavir hypersensitivity (*HLA-B*5701*)[79] and carbamazepine hypersensitivity (*HLA-B*1502*/*HLA-A*3101*).[65,80] Unfortunately, *HLA* genotyping is beyond the technical capacity of current POC platforms due to the extreme polymorphic nature of the *HLA* loci (including copy number variation) and the necessary requirement for highly multiplexed genotyping and/or sequencing. Additionally, other notable gene/drug examples will require the interrogation of multiple variant alleles for clinical validity in patient populations with diverse ancestries. As such, future POC genetic testing platforms ideally will need to be capable of multiplexed genotyping for alleles with clear clinical actionability and those that are prevalent in multiethnic patient populations.

Preemptive genetic testing

Another testing strategy that can circumvent some of the issues with both traditional external laboratory and POC pharmacogenetic testing is preemptive genotyping. Although this model also has inherent challenges for effective clinical implementation, preemptive pharmacogenetic testing recently has been deployed at selected academic medical centers (see the "Clinical pharmacogenetic implementation programs" section). This approach preemptively deposits genotype data into EHRs through prospective or biobank patient sampling and CLIA-certified genetic testing, and alerts prescribers at the POC through sophisticated electronic CDS when a drug is ordered for a patient with an at-risk genotype. The immediate knowledge of a pharmacogenetic interaction coupled with possible therapeutic options without significant disruption of routine clinical care is the clear advantage to this strategy. However, the necessary investments in infrastructure, informatics, health care provider participation and education, and preemptive testing in a CLIA-certified environment suggest that this mode of clinical pharmacogenetic delivery will be limited to large academic medical centers for the foreseeable future.

Information technology and clinical decision support

Genetic information is complex in nature, different to the other types of patient data that health care providers normally consider, and its significance to the individual patient changes frequently – all factors that today act as significant barriers to the widespread use of genetic information in clinical care.[81] In addition, the concept of genetic information having clinical utility outside of the clinical genetics domain is new and, as such, most practicing providers have no formal education in its use.[82]

Health care information technology offers a potential solution to these barriers. Almost in parallel with the rise of genomic data, US health care has seen a surge in digitized clinical data through the incentivization and subsequent widespread implementation of EHRs. As noted previously, one of the quality improvement mechanisms offered by EHRs is the potential for POC clinical decision support (CDS).

The CDS provides clinicians with knowledge presented at appropriate times, typically through computerized alerts and reminders.[83] To date, much of this has centered on drug–drug or drug–allergy interactions; however, with the emergence of disease-risk and drug response-associated genetic variants, the CDS has the potential to consolidate and translate genomic knowledge and integrate this knowledge into existing clinical workflows that will allow clinicians to make genome-informed decisions at the POC. Importantly, this will remove the significant burden from providers of remaining current in a rapidly changing field, where the potential permutations of clinical decision rules far exceed what could be expected of clinical providers to remember.

Clinical pharmacogenetic implementation programs

To identify and address barriers to implementing pharmacogenetics, the PGRN recently established the Translational Pharmacogenomics Program comprised of six diverse academic medical centers.[1] For this initiative, each implementation step is being systematically evaluated to develop a practical evidence-based toolbox of best practices for implementing pharmacogenetics across a variety of health care systems. Other instruments that will be developed for dissemination through publication include a best practices manual for clinical pharmacogenetic testing, and questionnaires and surveys to assess implementation metrics and effectiveness.

One of the first structured pharmacogenetics programs was a pharmacist-driven clinical service at St Jude Children's Research Hospital that initially offered *TPMT* and *UGT1A1* genotyping.[84] The expanded St Jude PG4KDS program is now migrating *CYP2C19*, *CYP2D6*, *SLCO1B1*, and *TPMT* genotype data from a microarray-based panel[85] into the EHR as prospective patients are enrolled, and deploying CDS when an intersection between a prescription and an at-risk genotype occurs.[86] The Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT) program at the Vanderbilt University Medical Center is preemptively genotyping *CYP2C19* in ~3,000 patients scheduled for cardiac catheterization, depositing data into the EHR, and providing POC CDS when clopidogrel is prescribed for patients with variant *CYP2C19* genotypes.[87] PREDICT is currently being expanded to include warfarin/*CYP2C9-VKORC1* and simvastatin/*SLCO1B1* drug/gene pairs. Similarly, the University of Florida and Shands Hospital's Personalized Medicine Program also is centered on clopidogrel and *CYP2C19* for a pharmacogenetics pilot program;[88] however, their multiplexed genotyping panel also includes a much larger number of genes and variants tested under research consent for storage in the EHR and possible use in future implementation efforts.[89] The 1,200 Patients Project at the University of Chicago is genotyping a large panel of germline pharmacogenetic variants among patients receiving outpatient medical care who are taking prespecified prescription medications.[90] Patient-specific results are then made available to the enrolling provider through an online genomic prescribing system.[91]

The Clinical Implementation of Personalized Medithrough Electronic Health Records and Genomics (CLIPMERGE)-Pharmacogenomics program at the Icahn School of Medicine at Mount Sinai is preemptively genotyping a panel of germline pharmacogenetic variants, storing data in an external data-management platform that interfaces with the EHR, and delivering CDS at the POC through the EHR. However, unlike some of the other implementation programs, patient recruitment is accomplished through the Mount Sinai's Bio*Me* Biobank Program, which currently includes ~30,000 multi-ethnic patients.[92] Patients for the pilot program are selected based on their regular attendance at Mount Sinai for their primary care and who are currently taking (or likely to take) clopidogrel, warfarin, simvastatin, tricyclic antidepressants, and/or selective serotonin reuptake inhibitors. As part of the CLIPMERGE program, enrolled physicians have been extensively surveyed regarding their views on genomic medicine and CDS.[93] These data have demonstrated that although physicians are generally familiar with and comfortable using CDS, there is a significant deficit in physician familiarity and comfort with interpreting and utilizing genomic information.[93] These insights suggest that to achieve the promise of personalized medicine, education on genomics must be a priority for clinical providers at all stages of their careers, and mechanisms that efficiently integrate personalized medicine into POC workflows via CDS and the EHR must continue to be developed and refined.

The Coriell Personalized Medicine Collaborative (CPMC©)[94] is a multi-institutional observational research study evaluating the utility of personalized genomic risk information in health care.[95] To interpret and report pharmacogenetic variants to study participants, the CPMC© has recently deployed the Pharmacogenomics Appraisal, Evidence Scoring and Interpretation System.[96] Guided by the expertise of an advisory group and thorough assessment of available evidence, drugs, and genes are identified for potential clinical utility, and selected drug/gene pairs are provided to CPMC© participants using risk reports containing genetic results, interpretation, educational summaries, detailed information

on genetic and nongenetic risk factors affecting drug response, and frequencies of drug response phenotypes in the population most relevant to the participant.

Personalized genetic testing results and patient behavior

Common concerns when implementing genetic testing for personalized medicine are often centered on the infrastructure, logistics, and other related issues noted previously; however, another important component that requires consideration is the perspective of the patient when receiving genetic test results.

Although an overview of genetic counseling is beyond the scope of this review, there are three key psychological questions to consider when implementing personalized medicine genetic testing:

1. Are patients open to and interested in receiving personalized genetic testing information?
2. What is the effect of personalized genetic testing information on psychological well-being?
3. Does personalized genetic testing information motivate patients to improve their health-related behaviors?

All of these questions are of importance both because they speak to important ethical considerations, and because they speak to aspects of the potential utility of genetic testing information for improving health-related outcomes.

Patient interest in receiving personal genetic results

Available evidence suggests that patients are more interested in receiving personal genetic results when the disease risk information has sufficient clinical utility to inform future preventative and/or therapeutic interventions that might mitigate any potential increased genetic risk.[97] Although the uptake of genetic testing for a given disease is influenced by multiple factors, patients appear to be influenced by the clinical validity of genetic tests as well as the severity of the diseases being tested. For example, while the uptake of the clinical genetic testing for hereditary colon cancer ranges from ~50%–80%,[98,99] the uptake of clinical genetic testing for Huntington's disease, which is a late-onset dominant disorder without any preventative intervention, is only ~15%–20%.[100,101] Similarly, patients are also generally less interested in receiving personal disease risk information on more severe neuropsychiatric conditions, such as Alzheimer's disease.[102] However, the observation that a minority of patients do opt for genetic risk information even when clinical utility is low indicates that some people derive personal utility from this information by enabling more educated future planning.[103]

Despite the ongoing research on the impact of DTC genetic testing on health care systems and patient behavior,[104–107] few studies have reported on patient interest in pharmacogenetic testing. However, recent data indicate that the general public generally has a high level of interest in receiving pharmacogenetic information,[108] suggestive of positive public attitudes toward the implementation of pharmacogenetics in clinical care. Although it is likely that patients will be reasonably comfortable with personal pharmacogenetic testing, the extent to which patients will be involved in the decision to actually receive pharmacogenetic information versus physicians making these decisions on their behalf is currently unclear. This is particularly relevant in the context of the preemptive genotyping strategies detailed previously where CDS is directed to the physician in the absence of a clinical geneticist or counselor. Given the inherent distinctions between pharmacogenetic testing and Mendelian disease genetic testing, formal genetic counseling for pharmacogenetic results is likely not going to be routine practice, underscoring the importance of continued education in pharmacogenetics for primary care and other providers so they are equipped to communicate these types of results.

Psychological outcomes

In the clinical genetics arena, the psychological harms from genetic testing information are generally uncommon,[97] which is likely due to the extensive genetic counseling received and through self-selection, where patients who feel they could not cope with adverse genetic test results are more likely to choose not to actually receive these results.[109] Similarly, available evidence suggests that the DTC genetic tests for common diseases and complex traits do not cause significant psychological harm.[105] Given the high benefit-to-risk ratio with pharmacogenetic testing, it is likely that there will also be minimal psychological harms from this mode of genetic testing; however, the lack of available data suggest that further study on psychological outcomes following pharmacogenetic testing is warranted, particularly as related to managing potential ancillary disease risk information.[110]

Behavioral outcomes

Studies on genetic testing for lung cancer risk suggest that personal genetic information does not independently have a significant impact on motivation to change behavior (eg, quit smoking).[111,112] Similarly, DTC genetic testing has not been shown to motivate people to make significant lifestyle

changes;[104,105] however, it is possible that genetic information may motivate people under certain circumstances. Psychological models of health behavior suggest that genetic information may motivate people to engage in healthier behaviors if the genetic information pertains to conditions or diseases that people feel threatened by, and when there is something they can do to reduce the disease risk. For example, in a study on Alzheimer's disease, 29% of *APOE* ε4 positive (higher risk) participants started to take dietary supplements in an effort to reduce their disease risk, compared to only 8% in the *APOE* ε4 negative (lower risk) group.[113] This increased genetic risk for Alzheimer's disease has also been associated with a higher likelihood of purchasing long-term care insurance.[114]

Although not well-studied, pharmacogenetic test results may have particular promise for influencing patient health behaviors. For example, recent data suggest that pharmacogenetic testing may improve medication adherence by increasing patient confidence in the efficacy of their prescribed medication and that their medication will work for them.[115] If a patient believes that pharmacogenetic testing provides personally relevant information about a disease that is threatening to them, and that the test results might effectively lead to increased efficacy and/or reduced likelihood of adverse side-effects from a prescribed medication, then it is plausible that pharmacogenetic testing could have a positive impact on medication adherence.

Conclusion and future direction

Although many agree that the concept of personalized medicine is important and an essential field to be developed, there have been few examples where the incorporation of personal genetic information has led to robust improvements in clinical care. The identification of common disease risk variants has undoubtedly revealed new biology and potential new avenues for therapeutic intervention; however, the modest effect sizes of most identified variants has resulted in personalized disease risk calculations with questionable clinical validity and utility. As such, testing for these variants is not common among clinical genetics laboratories and has largely been restricted to DTC genetic testing companies. Ongoing genome sequencing studies likely will identify rare variants that may improve the predictability for some diseases, but it is clear that further development of risk prediction algorithms is needed. In addition to genomic sequence data, these algorithms could include other forms of clinical, demographic, epigenomic and environmental data, and could potentially utilize more sophisticated network-based modeling approaches.[116,117]

The enthusiasm for pharmacogenetic testing and its potential utility has prompted a number of recent efforts to facilitate clinical implementation, including clinical practice guidelines for pharmacogenetic results, rapid turnaround time genotyping platforms, and institutional programs supporting preemptive pharmacogenetic genotyping with result returning and CDS at the POC. Together, these initiatives indicate that personalized medicine finally may be materializing at selected institutions through pharmacogenetics. However, these exciting advances for the field should be balanced by the clear needs for continued discovery research for variants and other factors that significantly influence drug response variability, particularly in populations from different racial groups and ethnicities, enhanced pharmacogenetics education for health care providers at all levels of their careers, and further development of information technology and other related mechanisms that can facilitate efficient implementation of result returning without interruption of routine clinical care. These exciting steps forward for personalized medicine are hopefully just the beginning of a future landscape where personal genomic information is routinely incorporated into health care for more informed and refined therapeutic decision making.

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OG is a co-inventor on patent applications related to personalized clinical decision support. The other authors report no conflicts of interest in this work.

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