Moving Pharmacogenetics Into Practice: It's All About the Evidence!

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The evidence for pharmacogenetics has grown rapidly in recent decades. However, the strength of evidence required for the clinical implementation of pharmacogenetics is highly debated. Therefore, the purpose of this review is to summarize different perspectives on the evidence required for the clinical implementation of pharmacogenetics. First, we present two patient cases that demonstrate how knowledge of pharmacogenetic evidence affected their care. Then we summarize resources that curate pharmacogenetic evidence, types of evidence (with an emphasis on randomized controlled trials [RCT]) and their limitations, and different perspectives from implementers, clinicians, and patients. We compare pharmacogenetics to a historical example (i.e., the evidence required for the clinical implementation of pharmacokinetics/therapeutic drug monitoring), and we provide future perspectives on the evidence for pharmacogenetic panels and the need for more education in addition to evidence. Although there are differences in the interpretation of pharmacogenetic evidence across resources, efforts for standardization are underway. Survey data illustrate the value of pharmacogenetic testing from the patient perspective, with their providers seen as key to ensuring maximum benefit from test results. However, clinicians and practice guidelines from medical societies often rely on RCT data to guide treatment decisions, which are not always feasible or ethical in pharmacogenetics. Thus, recognition of other types of evidence to support pharmacogenetic implementation is needed. Among pharmacogenetic implementers, consistent evidence of pharmacogenetic associations is deemed most critical. Ultimately, moving pharmacogenetics into practice will require consideration of multiple stakeholder perspectives, keeping particularly attuned to the voice of the ultimate stakeholder—the patient.

Some medical centers have adopted pharmacogenetic testing into routine clinical care,[1–6] but these examples of pharmacogenetic testing in practice remain limited. This is in large part because of varying opinions on the level of evidence needed to support clinical implementation.[7–28] Specifically, some argue for randomized controlled trial (RCT) data demonstrating that pharmacogenetic testing improves health outcomes over the standard, non-genotype guided care, before supporting testing as part of clinical practice.[7,24,25] Others counter that pharmacogenetics is held to a higher standard than required for other patient specific factors (e.g., renal and liver function) routinely incorporated into prescribing decisions without RCT evidence.[8,10,26] For example, many commonly used drugs, such as metformin, angiotensin-converting enzyme inhibitors, and direct oral anticoagulants, are avoided or dose-adjusted based on serum creatinine level without RCT evidence demonstrating that improves patient outcomes.[29] Importantly, the voice of the patient, the ultimate stakeholder, is often lost in conversations about what evidence is important for informing pharmacogenomic implementation.

These different perspectives on pharmacogenetic evidence can dramatically influence patient care. Therefore, we start this review by presenting two different patient cases that demonstrate how different perspectives on pharmacogenetic evidence influenced patient care. The first case focuses on a clinical molecular geneticist who was aware of evidence regarding cytochrome P450 (CYP)2D6 metabolic phenotype and tamoxifen efficacy, and she was aware of the controversy surrounding the evidence. Even though oncology clinical practice guidelines did not recommend *CYP2D6* testing,[30,31] she was aware of other literature (including Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines)[32] showing less favorable survival statistics for CYP2D6 intermediate and poor metabolizers. When she was diagnosed with breast cancer, she used her knowledge to advocate for *CYP2D6* testing and subsequent therapy change to avoid the possibility of unnecessary risk. Tamoxifen/*CYP2D6* is an example of differing stances on clinical actionability evidence between the CPIC, medical society guidelines, and, in this case, a well-informed patient.

The second patient case demonstrates how different providers have varying perspectives on pharmacogenetic evidence, which played a role in their management of the patient. Other common themes demonstrated in these cases is that the patients learned about pharmacogenetic evidence from other resources than their

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providers, and the patients became their own advocates for their pharmacogenetic testing. Therefore, it is critical that providers are also educated on pharmacogenetic evidence. Given the open question of the evidence required for the implementation of pharmacogenetics into clinical practice, after these patient cases, we provide a broad overview of the resources curating pharmacogenetic evidence, the types of available evidence and their limitations, and then highlight different perspectives on pharmacogenetic evidence: historical, practice guidelines, implementers, clinicians, patients, and the future.

Patient case 1

An ultrasound image of a tumor suddenly transformed a clinical molecular geneticist into a patient. The 55-year-old woman was subsequently prescribed tamoxifen for treatment of estrogen receptor positive, lymph node negative breast cancer (the patient had been taking oral contraceptives prior to her diagnosis and was therefore not known to be postmenopausal). As a geneticist, she was aware of the importance of CYP2D6 in metabolism of tamoxifen to its major active metabolite, endoxifen, and of clinical studies showing an association between the poor metabolizer (PM) and intermediate metabolizer (IM) phenotypes and increased risk of breast cancer recurrence.[33,34] After discussing relevant publications with her oncologist and sharing her concern about the possibility of unknowingly being in a genetically disadvantaged group regarding tamoxifen effectiveness, the clinician agreed to CYP2D6 testing. Testing was ordered through a commercial reference laboratory, with results revealing a *1/*4 genotype with gene duplication, and therefore the possibility of the IM phenotype. The oncologist agreed to switch treatment from tamoxifen to the aromatase inhibitor, anastrozole, which is not metabolized by CYP2D6 and has strong effectiveness for reducing the risk of recurrence and breast cancer mortality.[35] This therapy change is consistent with current CPIC guidelines for CYP2D6 and tamoxifen therapy.[32]

Patient case 2

A 45-year-old woman with hypertension, dyslipidemia, depression, and gastroesophageal reflux disease (GERD) had a history of intolerance or inadequate response to multiple medications for her depression and GERD requiring frequent medication changes. The patient learned about pharmacogenetic testing through a patient support group website and requested testing through her primary care physician (PCP). She specifically relayed her hope that the testing results would help explain her unsuccessful treatment odyssey to date and point toward treatment most likely to improve her symptoms without causing side effects. The PCP was familiar with testing, having ordered it through a commercial vendor for previous patients, and agreed that results would be useful for informing the patient's therapy. Thus, testing was ordered, and on receiving the report, the PCP found that the patient was a CYP2C19 ultrarapid metabolizer. Therefore, some of the patient's current medications for treating depression and GERD could have decreased efficacy, and adjustments to her drug therapy may improve her symptoms. However, on sharing the results with the providers specifically managing the patient's depression/anxiety and GERD, one provider placed the results in the medical chart without ever discussing them with the patient, and the other dismissed the report and its value all together. Therefore, the patient's pharmacogenetic test results were left unused, and their potential benefit was unexplored.

RESOURCES THAT CURATE PHARMACOGENETIC EVIDENCE

The US Food and Drug Administration (FDA) has incorporated genetic information into the labels for over 250 drugs, particularly when the impact of genotype on drug response is potentially serious or life-threatening.[36] In some cases, such as with clopidogrel, this information is in the form of a boxed warning, given the potentially serious implications of genotype for drug effectiveness.[37] For other drugs, this information may be included in other sections of the drug label, such as the clinical pharmacology, dosing and administration, or indications and usage. In early 2020, the FDA released a Table of Pharmacogenetic Associations,[38] listing medications and gene associations in 3 groups for which the data: (i) support therapeutic management recommendations; (ii) indicate a potential impact on safety and response; and (iii) demonstrate a potential impact on pharmacokinetic (PK) properties only. The agency encourages public input regarding the Table of Pharmacogenetic Associations and made some updates on March 18, 2021 and May 24, 2021.

Pharmacogenetic evidence has also informed the development of clinical guidelines from organizations such as the CPIC, the Dutch Pharmacogenomics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety, and other pharmacogenetic expert groups on interpretation and translation of genotype results into prescribing decisions for numerous gene-drug pairs.[39–41] The CPIC, DPWG, and the Pharmacogenomics Knowledgebase (PharmGKB) use rigorous systems to grade levels of evidence for clinical actionability of gene-drug pairs. CPIC guidelines are developed for gene-drug pairs with strong evidence,[42] and, as of early 2021, there were 25 CPIC guidelines. PharmGKB has clinically annotated over 160 gene-drug pairs to date with high levels of evidence.[43] In reference to case 1, the tamoxifen/*CYP2D6* association has the highest level of evidence per CPIC (level A), DPWG (level 4), and PharmGKB (level 1A). The evidence on the FDA-cleared tamoxifen label is considered actionable by PharmGKB. The FDA label states that CYP2D6 PMs, carrying two nonfunctional alleles, exhibit significantly lower endoxifen plasma concentrations compared with patients carrying one or more fully functional alleles,[44] but it also states that the impact on the efficacy of tamoxifen is not well-established.

There has been a push toward standardization in the field as a means to accelerate pharmacogenetic adoption,[45] and much progress has been made in this regard. This includes collaborative efforts by the CPIC and the DPWG to standardize terms for pharmacogenetic test results and efforts by the Association of Molecular Pathology (AMP) to recommend which alleles to include in pharmacogenetic tests.[46] The PharmGKB created a document cross-referencing the FDA Table of Pharmacogenetic Associations with CPIC gene-drug pairs and PharmGKB annotations to illuminate differences.[47] Along the same lines, the Personalized Medicine Coalition (PMC) Pharmacogenomics

Working Group is currently analyzing differences across these resources (personal communication). There are some gaps regarding pharmacogenetic information in FDA-approved prescribing information. For example, several drugs with CPIC level A gene drug designation have no pharmacogenetic information in their labeling. Differences in clinical pharmacogenetic recommendations among resources could be due to a variety reasons, including differences in the organizations' methods of evidence evaluation. For example, unlike CPIC, the FDA does not specifically define the phenotype (e.g., alleles defining a PM), nor does the FDA cite the evidence used to develop their recommendations. The American Society of Pharmacovigilance brought together a wide range of stakeholders, including patients, providers, industry, regulators, payers, and others to form the Standardizing Laboratory Practices in Pharmacogenomics (STRIPE) Collaborative Community in 2020. The goal of STRIPE is to harmonize pharmacogenetic testing-related standards, practices, and resources.[48] It is worth noting that differences among pharmacogenetic recommendations from different sources may never be resolved, especially because of differences in the organizations' mission and approach. However, a single standard of recommendations may not be necessary, as prescribers typically utilize a variety of information resources when making other types of prescribing decisions (e.g., UpToDate and Micromedex).

TYPES OF PHARMACOGENETIC EVIDENCE AND THEIR LIMITATIONS

RCTs are the gold standard for evaluating the clinical utility of new interventions. Many RCTs have assessed the clinical utility of pharmacogenetic testing, by comparing outcomes of genotype-guided drug therapy vs. the current standard of care (i.e., non-genotype guided drug therapy), and they are summarized in **Table S1**. Many of those pharmacogenetic RCTs have demonstrated improved outcomes with pharmacogenetic testing compared to usual care. RCTs have important limitations when applied specifically to pharmacogenetics. RCTs have been the gold standard for evaluating the clinical utility of new pharmacologic, surgical, or other interventions. However, they have not been typically used to evaluate the clinical utility of tailoring those interventions based on patient-specific factors, such as patient age, renal function, and other laboratory values, including plasma drug concentrations. Patient-specific factors, such as those, are routinely used to guide drug therapy in absence of RCT data showing that consideration of these factors improves outcomes. Rather, evidence that these variables influence the risk for adverse effects or likelihood of drug effectiveness is considered sufficient to support their consideration in practice. Moreover, only a subset of patients will carry the pharmacogenetic variant associated with an atypical drug response (i.e., reduced effectiveness or increased toxicity). Therefore, the RCT must be much larger than a typical drug trial (to account for the majority patients without the genetic variant), or a large number of patients must be screened in order to selectively enroll only those patients carrying the pharmacogenetic variant of interest. Sometimes the adverse event that the pharmacogenetic test is intended to prevent is rare, again requiring a very large sample size in order to provide sufficient power. RCTs in general cost millions of dollars and several years to complete, and thus adding those particular considerations for pharmacogenetic RCTs would increase the cost even more. The same limitations that apply to RCTs in general also apply to pharmacogenetic RCTs as well. For example, the generalizability of RCT results is usually limited, given the strict eligibility criteria for entry and lack of racial/ethnic diversity.[49]

In addition to limitations related to feasibility and generalizability, many argue that requiring an RCT for every gene-drug pair may also be unethical.[8–23,26] In cases where a pharmacogenetic variant is associated with a life-threatening adverse drug effect (e.g., carbamazepine-induced severe cutaneous reactions in patients with an *HLA*15:02* allele), it may be deemed unethical to randomize participants to the usual care arm. Because of these concerns, some advocate for alternative approaches to assessing outcomes with pharmacogenetic testing, such as pragmatic trials and observational studies or other types of evidence (e.g., PK data or case-control or cohort study designs), which may be supported by mechanistic or *in vitro* studies.[8–23,26]

Examples of alternative approaches to evidence generation include pragmatic trials and observational studies of patients receiving testing as part of clinical care. Similar to RCTs, many pragmatic and observational studies to date have demonstrated improved outcomes with a pharmacogenetic-guided approach.[50–55] Data from additional pragmatic trials are forthcoming from efforts, such as from the Implementing GeNomics In pracTicE (IGNITE) Pragmatic Trials Network (ClinicalTrials.gov Identifier: NCT04445792) and the Ubiquitous Pharmacogenomics Consortium.[4] Pragmatic studies are conducted in the context of clinical practice, and thus provide an advantage over RCTs in that they are more generalizable. They are also generally less costly and more efficient to conduct. However, data from nonrandomized studies are prone to selection bias and confounding that cannot be completely mitigated through statistical approaches.

DIFFERENT PERSPECTIVES ON PHARMACOGENETIC EVIDENCE

Historical perspective

Over 20 years ago, strikingly similar arguments over the level of evidence needed to support clinical implementation of pharmacogenetic testing occurred for the clinical implementation of PKs and therapeutic drug monitoring (TDM).[56–61] Like pharmacogenetics, PK/TDM was a budding "new" field of pharmacology, transitioning from research applications to clinical implementation. Also like pharmacogenetics, some held the view that RCTs were the required level of evidence for the clinical implementation of PK/TDM, whereas others did not.[57,58,60] Just like for pharmacogenetics, most of the evidence supporting the clinical implementation of PK/TDM derived from *in vitro* and observational clinical studies, and many of the clinical studies had surrogate end points instead of clinical outcomes.[56] Some RCTs of PK/TDM showed significant benefit, some did not show significant benefit, and some even showed a significant negative impact on patient outcomes.[56]

TDM of aminoglycosides is a good example of how varying levels of evidence still led to eventual clinical implementation.

Not all RCTs of TDM vs. non-TDM guided aminoglycoside therapy showed significant benefit as far as clinical outcomes nor cost savings.[56] Regardless, TDM for aminoglycoside therapy is now a routine part of clinical care. The routine clinical implementation of PK/TDM occurred in the absence of consistent RCT level of evidence for every drug. Authors at the time reported similar challenges as far as the limited feasibility and ethicalness of performing PK/TDM guided RCTs.[59] Ultimately, the enthusiasm for RCTs of PK/TDM waned. Eventually, sponsors were no longer interested in funding RCTs of PK/TDM, and clinicians lost interest in those RCTs, because institutions began implementing PK/TDM on their own.[59] A similar situation seems to be occurring for pharmacogenetics, in which several institutions have begun implementing pharmacogenetics in the absence of RCT data.[6] To avoid repeating history, perhaps it is time to put to rest the general requirement of RCTs for pharmacogenetics as well.

Practice guideline perspective

Clinicians rely on practice guidelines from expert consensus panels to guide prescribing decisions. Guideline writing committees are charged with weighing and ranking the evidence, and the highest ranking is provided to RCT data. Case 1 is a good example of when a tightly held standard of requiring an RCT to demonstrate improved outcomes with genotype-guided therapy may not be in the best interest of patients. *CYP2D6* testing in the context of tamoxifen is not currently recommended in the American Society of Clinical Oncology (ASCO) or National Comprehensive Cancer Network (NCCN) breast cancer guidelines,[30,31] and *CYP2D6* testing is not routinely offered by oncologists prior to tamoxifen prescribing. Negative findings from two secondary *CYP2D6* analyses of previous RCTs (BIG 1-98[62] and ATAC[63]) likely influenced the current ASCO and NCCN guidelines; however, these findings were found to be flawed. Multiple problems were identified in both studies, with serious genotyping errors in the BIG 1-98 study.[64,65] Both studies used formalin tumor tissue for *CYP2D6* genotyping, with erroneous genotype results due to loss of heterozygosity at the *CYP2D6* locus.[65] A more recent trial (CYPTAM),[66] has also been criticized.[67] The initial papers showing *CYP2D6* association with tamoxifen efficacy were in women with tamoxifen monotherapy,[68] whereas several negative studies have had treatment variability noise. When weighing evidence from studies, it is important to carefully evaluate the methodologies, patient populations, and treatments involved and focus on the appropriately designed studies.[64] A recent review reiterates that controversy continues in the oncology literature around *CYP2D6* testing to predict response to tamoxifen,[69] as does a recent study showing no difference in endoxifen or 40H-tamoxifen levels between patients who had recurrent breast cancer and those who did not in a low dose trial.[70] The low dose trial differs from previous studies of patients using a standard dose of tamoxifen.

The practice guidelines for the antiplatelet drug clopidogrel, a prodrug activated through metabolism by CYP2C19, are also controversial. The American Heart Association and the American College of Cardiology (AHA/ACC) joint practice guidelines for cardiovascular disease management categorize recommendations, which range from class I (recommended; benefit clearly outweighs risk) to class III (not recommended; potentially harmful), based on the evidence and expert consensus opinion. Again, RCT data is ranked as the highest level of evidence. Prior to availability of RCT data, but with substantial and consistent data that *CYP2C19* genotype is associated with risk for adverse cardiovascular outcomes after percutaneous coronary intervention (PCI), the guidelines provided a class IIb recommendation (benefit equal to or greater than risk) for genotyping in high-risk patients.[71] A class III recommendation was provided for routine genotyping of all patients undergoing PCI.

RCT data on outcomes with *CYP2C19*-guided antiplatelet therapy have since emerged. One RCT showed a significant reduction in risk for bleeding, without compromising the risk for atherothrombotic events, with a genotype-guided approach vs. universal use of potent $P2Y_{12}$ inhibitors (e.g., ticagrelor or prasugrel).[72] Subsequently published guidelines by the European Society of Cardiology note these RCT data, but they still provided a class IIb recommendation. The European guidelines specifically state that testing may be considered in select patients, especially those "deemed unsuitable for potent platelet inhibition" (e.g., those at high bleeding risk), even though the RCT did not limit eligibility to such patients.

In a subsequent RCT of genotype-guided therapy, the comparator arm was universal clopidogrel.[73] The trial found a 34% relative risk reduction in adverse cardiovascular events with the genotype-guided approach without reaching statistical significance ($P = 0.06$), likely because there were fewer cardiovascular events than anticipated. The trial also showed a significant reduction in prespecified sensitivity analyses of cumulative events and a post hoc analysis of events at 90 days in favor on genotype-guided therapy ($P = 0.001$). A meta-analysis of genotype-guided antiplatelet RCTs has recently been published.[74] The reduction of ischemic events in patients with coronary artery disease who predominantly underwent PCI by ticagrelor or prasugrel, in comparison with clopidogrel, was based primarily on the presence of *CYP2C19* loss-of-function carrier status.[74]

It remains to be determined how these RCT data will influence future AHA/ACC guidelines. Will the guideline writing committee consider the multiple observational studies showing improved outcomes with *CYP2C19*-guided antiplatelet therapy in practice,[50,51,53] leading to an upgrade in the recommendation for genetic testing? Or conversely, will they downgrade the recommendation because one of the major RCTs just barely missed the definition of statistical significance? How will they consider the recent meta-analysis of RCTs? These are important questions because how the AHA/ACC interprets this evidence may set the precedent for future pharmacogenetic recommendations in cardiology guidelines.

There are examples in which pharmacogenetic recommendations have been made in clinical practice guidelines based on lower levels of evidence than available for *CYP2C19* and clopidogrel. The 2020 NCCN guidelines for the treatment of adult acute lymphoblastic leukemia (ALL) state "Determination of patient TPMT (thiopurine methyltransferase) genotype using genomic DNA is recommended to optimize 6-MP

[6-mercaptopurine] dosing..."[75] The evidence supporting that recommendation is solely retrospective and observational.[76] To our knowledge, an RCT comparing genotype-guided thiopurine dosing vs. non-genotype guided in patients with ALL has not been performed. RCTs of genotype-guided thiopurine dosing in inflammatory conditions have been conducted, but none of them showed that genotype-guided thiopurine dosing significantly improved outcomes.[77] Regardless, the American College of Gastroenterology clinical guideline for the management of Crohn's disease in adults states "Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence)."[78] Another example is in the 2017 AHA/ACC/HRS guideline for the management of patients with syncope, which states "The response to beta-blockers depends on the genotype..."[79] The data supporting that statement comes solely from two observational registries.[80] Nearly half of drug-gene pairs have differences in their guideline recommendations,[81] which demonstrates variable interpretations of the available evidence in practice guidelines.

Implementer perspective

Implementers, such as from institutions that have already or are beginning to implement pharmacogenetic testing clinically, are faced with the challenge of finding the right amount and type of evidence needed to bring pharmacogenetics into clinical practice. This may mean going beyond medical society clinical guidelines and considering patient and provider needs. The National Human Genome Research Institute (NHGRI)-funded (IGNITE) and Electronic Medical Records and Genomics (eMERGE) networks both have pharmacogenetics working groups, and member institutions have experience in clinical implementation of pharmacogenetic testing.[3,82] We performed a survey to gather their perspectives on different types of pharmacogenetic evidence. Survey responses were solicited from February 20, 2020, to March 4, 2020, via REDCap electronic data capture tool, hosted at Vanderbilt University Medical Center, with anonymous responses stored in the secure REDCap database.[83] The survey was approved by the institutional review board at the University of Florida as an exempt study. A total of 47 individuals from 21 institutions were invited to participate. Fifteen individuals responded from 13 unique institutions (32% response rate). Characteristics of the individuals and institutions are displayed in **Table 1**.

In one set of questions, respondents were asked to rate, on a scale of 0–100, how essential, how easy to interpret, and how available 6 different types of evidence or guidance are: RCT data; real-world evidence or observational studies testing clinical outcomes with pharmacogenomic testing; real-world evidence or observational studies testing associations between genotype and drug response guidelines; pharmacogenetic guidelines (e.g., CPIC, DPWG); subspecialty guidelines and statements (e.g., American College of Obstetricians and Gynecologists, AHA/ACC); and the FDA or other regulatory communications and agency drug labels (e.g., FDA label). Results indicate diversity of opinion for each type of data for every question (**Figure 1**). Particularly for ratings of how essential data are, RCT data, specialty guidelines, and FDA label guidance demonstrated wide ranges (range 10–80, 20–100, and 20–90, respectively). Pharmacogenetic guidelines received the highest scores regarding ease of interpretation (range 80–100) and availability (range 50–100).

We also asked in the survey, "What are the factors you consider when determining whether or not to implement pharmacogenomic testing?" Availability of CPIC or other guidelines were the most consistently endorsed factor (100% of respondents), with other factors less unanimously indicated (**Figure 2**). Thus, among experts in the field, opinions on evidence and resources essential to support pharmacogenetic implementation are highly variable.

In addition to utilizing evidence to anchor their implementations in sound scientific data, implementers have an imperative to generate evidence for the use of pharmacogenetics in clinical practice, thereby ensuring the end-users of the implementation services, providers and patients, utilize pharmacogenetics in a responsible and prudent manner. Examining the patient and provider perspective of pharmacogenomic evidence illuminates the types of evidence implementers need to create.

Table 1 Characteristics of implementers of clinical pharmacogenetics (individuals and institutions) that completed the survey

Individuals (*n* = 15)	***n* (%)**
Type of training[a]	
PhD	2 (13%)
PharmD	13 (87%)
Master's degree	1 (7%)
Years since training completed	
0–5	6 (40%)
6–10	4 (27%)
11–15	3 (20%)
16 or more	2 (13%)
Pharmacogenetics training[a]	
None	2 (13%)
Fellowship	9 (60%)
Master's degree	1 (7%)
Residency	6 (40%)
Seminars, workshops, or CME	5 (33%)
Online training	2 (13%)
Certificate program	1 (7%)
Institutions (*n* = 13)	***n* (%)**
Type of institution[a]	
Academic	11 (85%)
Community	3 (23%)
Pharmacogenetic testing offered	
Broad	6 (46%)
Limited	7 (54%)
None	0 (0%)

CME, continuing medical education.
[a]More than one answer allowed.

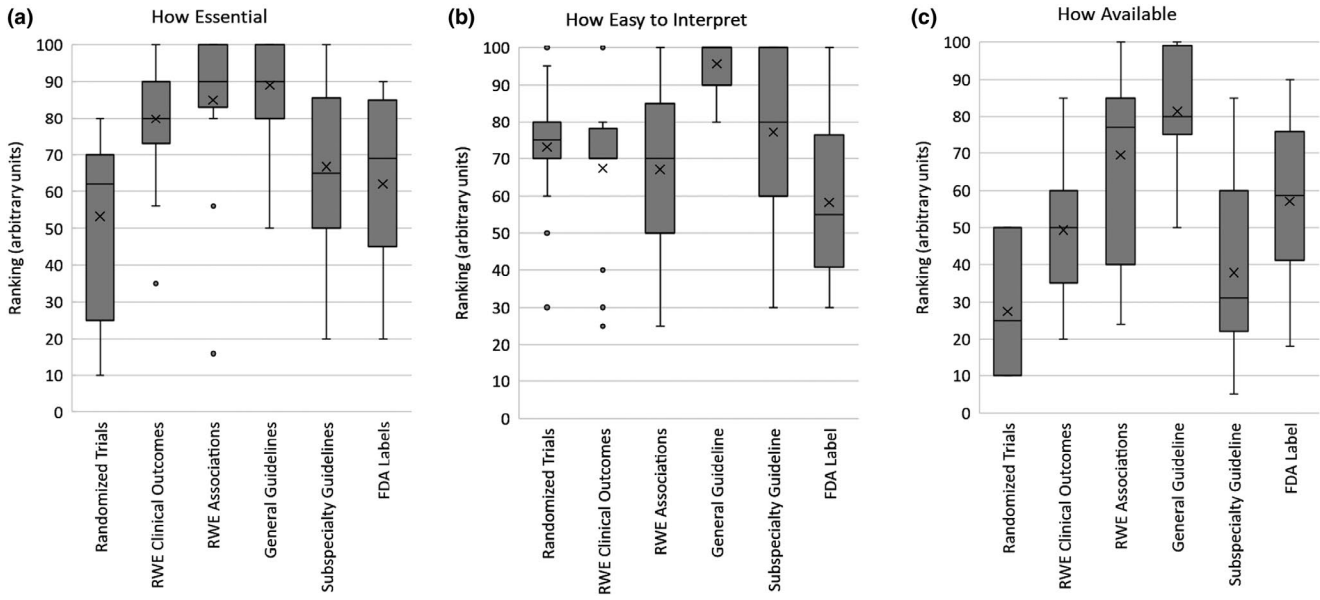

Figure 1 Survey respondent scores from implementers regarding pharmacogenomic evidence. For each of the six types of evidence listed on the *X*-axis, respondents were asked to rank how essential (**a**), how easy to interpret (**b**), and how available (**c**) that type of evidence is for clinical pharmacogenomic implementation on a scale from 0 to 100. The box and whisker plot shows the medians (horizontal lines within boxes), means (*X*), the interquartile ranges (boxes), the adjacent values (whiskers) and outliers (dots). FDA, US Food and Drug Administration; RWE, real-world evidence.

Clinician perspective

A problem with defining a single level of evidence for clinical implementation of pharmacogenetics is that every clinical scenario is unique, as demonstrated by the patient cases presented. The potential risks and benefits for pharmacogenetic-guided therapy vary greatly depending on the drug, the genomic signal, the alternative therapeutic strategies available, the indication for the drug, and many other variables, as displayed in **Table 2**. The balance of those risks and benefits should influence the level of evidence required for clinical pharmacogenetics, as has been argued by others.[10,27,28] All of these factors must be simultaneously considered and weighed in order to make rational, patient-centered decisions.

The clinical value of a test result drives the decision to test. The value is affected by many features, including cost, variant frequency, clinical impact of outcomes, and strength of evidence. For a patient with no previous pharmacogenetic testing, a clinician's first pharmacogenetic decision will be around whether to order testing. Two factors, actionability and cost, may contribute to a clinician's decision making. Here, actionability refers to whether the results of the test will alter the management of the patient. If the evidence for the pharmacogenetic association is very weak, the clinical difference between genotypic groups is very small, and the variant tested for is exceedingly rare in the population, there may be little impetus for the clinician to order the test. On the other hand, testing for a rare variant with robust evidence for a severe, life-threatening toxicity (e.g., *HLA* variants and hypersensitivity to abacavir and carbamazepine, or *TPMT/NUDT15* variants and myelosuppression from thiopurines) may be more quickly adopted into clinical practice. If there are two drugs with similar efficacy, but one has a higher cost (measured by financial cost, risk for toxicity, or need for ongoing monitoring), and a pharmacogenetic test can appropriately guide therapy, there may be higher uptake of the test.

Characteristics of the patient can also affect the acceptable level of evidence for a pharmacogenetic test for a provider. Lower levels of evidence may be required for patients with higher risk for the adverse clinical outcomes if not optimally treated because the potential benefit is greater. For example, lower levels of evidence for clopidogrel pharmacogenetic testing may be required for a patient who has multiple risk factors for adverse outcomes post-PCI (e.g., history of myocardial infarction, diabetes, and chronic kidney disease), compared with a patient with fewer risk factors (e.g., stable coronary disease, non-diabetic, and normal renal function). Clinicians may also seek context-specific evidence to support pharmacogenetic testing. For example, an interventional cardiologist who cares for patients in the cardiac catheterization laboratory and during their acute hospitalization may seek evidence for pharmacogenetic-guided antiplatelet therapy with end points relevant to time points when the patients are under his or her care (e.g., acute stent thrombosis). A general cardiologist managing patients' chronic antiplatelet therapy may be attentive to end points far beyond the acute hospitalization (e.g., bleeding or need for revascularization).

It also appears that the level of evidence for pharmacogenetics varies by the specialty within which the provider is practicing (e.g., cardiology, oncology, and pediatrics).[80] Cardiology clinical practice guidelines, for example, usually have not supported recommendations for pharmacogenetic testing in the absence of RCT data, whereas oncology clinical practice guidelines have.[80] Lower levels of evidence may be acceptable in specialties like pediatrics, where providers are accustomed to adjusting doses based on patient-specific

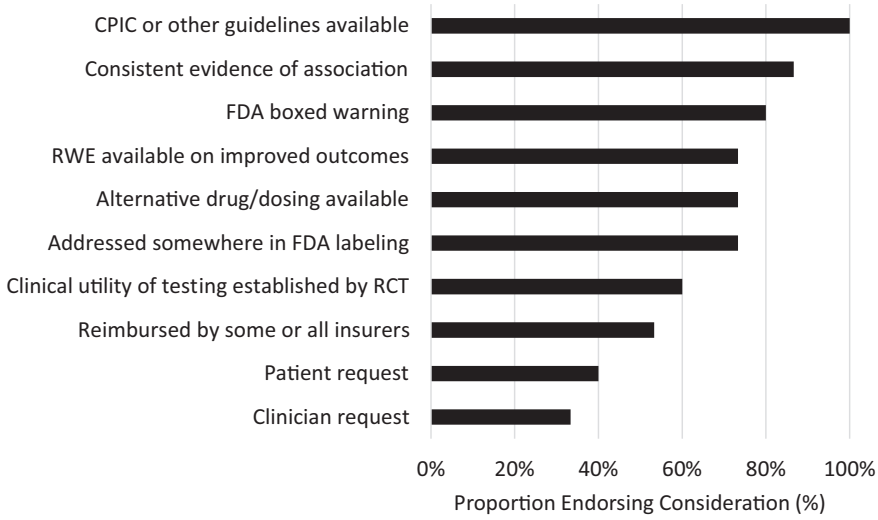

Figure 2 Factors considered by pharmacogenetic clinical implementers when determining whether or not to implement pharmacogenetic testing. Fifteen individuals from 13 different institutions were asked to rate their response on a scale from 0 to 100. CPIC, Clinical Pharmacogenetics Implementation Consortium; FDA, US Food and Drug Administration; RCT, randomized controlled trial; RWE, real-world evidence.

Table 2 Variables that may affect the level of evidence required for the clinical implementation of pharmacogenetics

	Level of evidence potentially required	
Variable	**Higher**	**Lower**
Genetic test	-Results not already available -Not available in-house -Slow return of results -High cost	-Results already available -Can be ordered in-house -Rapid return of results -Low cost
Genetic variant	-Rare -Low penetrance	-Common -High penetrance
Drug	-Cost of drug (or alternative) is low -Rarely used -Alternatives available	-Cost of drug (or alternative) is high -Commonly used -No alternatives available
Drug indication	-Mild -Rare	-Severe -Common
Adverse outcome	-Mild -Rare	-Severe -Common
Setting	-Inpatient	-Outpatient
Patient	-Low risk for adverse outcome -Risk-averse	-High risk for adverse outcome -Risk-taking
Provider	-Risk-averse	-Risk-taking
Specialty	-Cardiology	-Oncology -Pediatrics
Stakeholder	-Health system -Payers	-Patients -Providers

factors (including weight), using medications for off-label indications, and weighing evidence from a variety of study types, as large RCTs are uncommon for pediatric therapeutics. Thus, with all of these competing factors, it is difficult to define a single level of evidence for all clinical scenarios. A flexible standard for the required level of evidence for clinical implementation is rational.

Patient perspective

As the ultimate benefactor of testing, the patient will likely be a key driver of moving pharmacogenetic discoveries into practice. Understanding patient needs from pharmacogenetics evidence is important, and like providers, is varied based on a multitude of factors. Different patients have different concerns about specific risks, and this needs to be incorporated into the decision making. Patients consider their own personal experience and perceived risk in clinical decisions, and biomarkers providing information on the likelihood of toxicity may influence their willingness to proceed with certain treatment choices.[84] The patient in case 1 was uniquely well-informed on the evidence that CYP2D6 influences plasma concentrations of the active tamoxifen metabolite,

and that it may impact her risk for breast cancer recurrence. In her opinion, this evidence was impressive enough to warrant her request for testing. Unlike the patient in case 1 who had a genetic background, the patient in case 2 was less familiar with the evidence. Patients may hear about pharmacogenetic testing and request it from their providers. A thorough review of the patient's medical history, including responses to current and previous medications, and determination of pharmacogenetic relevance of the medications, may be necessary to determine if pharmacogenetic testing is indeed warranted. Patients should be educated accordingly in order to ensure shared decision making between patient and provider. Pharmacogenetic clinics are emerging at some institutions where providers can refer patients to determine if testing may be beneficial, and, if so, obtain consultation on how to best act on test results.[85] However, the possibility that pharmacogenetics could help explain the patient's responses to previous treatments, and identify the treatment regimen most likely to improve her symptoms with acceptable tolerability, was motivation enough for the patient to request testing.

Additional key insights into patient perspectives on pharmacogenetic evidence comes from focus groups and survey data. Cost is regularly cited as a barrier to patients completing pharmacogenomic testing.[86–89] Understanding the evidence behind the value and utility of pharmacogenomic testing is key to break through this barrier. A strong body of evidence is required to increase the insurance coverage of testing. In the last several years, there has been progress with reimbursement as United Healthcare and some Medicare local coverage determinations cover pharmacogenomic testing for patients meeting specific criteria.[90] Better reimbursement is expected to lead to reduced or no cost testing for patients, but it is still important for patients to understand the value and utility of testing in order to make informed decisions about whether to complete it. Patients have reported a wide range of value in pharmacogenetic evidence, including predicting effective therapy,[86] minimizing harm from wrong medications or doses,[91] increasing confidence in future medication decisions,[92] increasing compliance,[92,93] and increasing trust in the healthcare system.[91] Several of these are evident in the patient cases presented. An outstanding question is whether the perceived value by patients is rooted in clear scientific data or just pseudoscience. Are RCTs required to answer this question? Implementers must continue to cultivate evidence to support these claims of value if patients are going to continue to be encouraged to believe in them.

The full benefit of testing may not be realized unless patients understand their results and implications of results for drug response. Programs have used reports, portals, and integrated models of pharmacogenetic delivery, well-supported by a multidisciplinary team and pharmacogenetic experts[91,92,94] to help ensure that patients receive and understand their results. Studies evaluating pharmacogenetic reports and portals have consistently found that graphic displays are better than tables or text at conveying pharmacogenetic information, but they are not perfect.[91,94,95] Regardless of how patients access their test results (e.g., reports and patient portals), patients believe their providers are key to receiving the most benefit from their pharmacogenomic results.[92,94] More evidence is needed to determine the optimal method for returning results to patients and having them interact with the results through their lifetime. Patients are the ones who would ultimately benefit from pharmacogenetic testing. Therefore, although pharmacogenomic evidence from a patient perspective may be less about the drug-gene pairs, it is no less important to the future direction of the field.

THE FUTURE FOR PHARMACOGENETIC EVIDENCE

Evidence for reactive, individual pharmacogenetic tests vs. pre-emptive panels

Most of the currently available pharmacogenetic evidence focuses on individual drug-gene pairs (e.g., *CYP2C19*-clopidogrel and *CYP2D6*-tamoxifen). However, recently, there has been a shift in interest regarding implementation, from reactive testing for individual drug-gene pairs to pre-emptive panels that cover multiple drug-gene pairs.[96,97] Indeed, the cost of a dense pharmacogenetic genotyping array is now about the same as an individual pharmacogenetic test, and thus it is more cost efficient to order a pharmacogenetic panel instead of multiple individual pharmacogenetic tests.[26,98] Additionally, with the cost of the sequencing decreasing, pharmacogenetics is increasingly being included in germline hereditary disease or population screening panels. Evidence from clinical implementation of pre-emptive pharmacogenetic panels is already showing tremendous potential. When as few as five gene-drug pairs were considered, a pre-emptive genotyping panel yielded actionable variants in > 90% of patients at a single institution.[99] Implementation of the pre-emptive panel avoided the use of nearly 15,000 individual pharmacogenetic tests (if done reactively).[99] In 52,942 medical home patients in a single health system, it was estimated that nearly 400 adverse drug events could have been prevented by the implementation of that pre-emptive pharmacogenetic panel over the course of 5 years.[100] Recommendations based on the results of a pharmacogenetic panel resulted in an estimated US $621 in annual savings per patient across a patient population on 5 or more medications.[101] An RCT assessing the clinical utility of pre-emptive pharmacogenetic panels, called the PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study, is currently ongoing in Europe (as part of the Ubiquitous Pharmacogenomics Consortium (U-PGx)).[4] PREPARE is implementing pre-emptive genotyping of a panel of 50 variants in 13 pharmacogenes into clinical practice, in the context of a large prospective, international, block-randomized, controlled study (n = 8,100).

This cumulative evidence supporting all drug-gene pairs included on pharmacogenetic panels is developing, but it is important to note that the evidence supporting each individual gene-drug pair is still critical and the current barriers to panel testing. The content on pharmacogenetic panels varies widely (i.e., the specific genes and variants covered by the panel).[102] No 2 panels were the same in a comprehensive evaluation of several pharmacogenetic testing panels for 28 pharmacogenes.[103] Although out of the scope of this paper for discussion, reimbursement is a significant barrier for pharmacogenetic panels, in particular.[90] Some companies and laboratories are offering pharmacogenetic test panels that include genes and variants with weak evidence for an association with drug response.[104] Therefore, the evidence supporting each individual drug-gene pair informs many yet unanswered questions, such as

which genes and variants should be included on a pharmacogenetic panel? Which results should be reported to the electronic health record? And which results from the panel have sufficient evidence to be used to guide patient care? Answers to these questions will evolve from ongoing discussions in the pharmacogenetics community. A single, standardized pharmacogenetic panel may not be the goal, but at least the genes and variants included on a pharmacogenetic panel should be supported by strong evidence.

Evidence vs. education

The clinical implementation of pharmacogenetics may be slowed as much by a lack of education as by the perception of a lack of evidence.[8] Would advocates for RCT data still argue for such data if they found themselves or a family member in the position of being a patient, and they were armed with the knowledge that a genotype is strongly and consistently associated with drug effectiveness or risk for an adverse effect? For example, what if a provider required PCI for coronary disease management and is prescribed clopidogrel afterward? Knowing that 30% of the population carries a *CYP2C19* no function allele, and that having a no function allele significantly increases the risk for clopidogrel failure, would he or she ask to be genotyped? Or would he or she refuse to be genotyped because one RCT[73] just barely missed statistical significance?

The cases presented at the beginning demonstrate the educational barrier on the part of the provider. Currently, many providers are not confident about interpreting pharmacogenetic test results, and they are not aware of the resources for pharmacogenetic evidence described above.[105] Referring to case 1, the switch from tamoxifen to anastrozole occurred for two key reasons. First, as a geneticist, the patient was knowledgeable about pharmacogenetics, and second, her physician was willing to embrace the scientific evidence presented to him by the patient and change the treatment plan accordingly. In case 2, the patient found that her PCP was experienced in pharmacogenetic testing, but the providers prescribing her relevant medications was not. Thus, the pharmacogenetic test results went unused. Therefore, case 2 illustrates how even if pharmacogenetic tests results are readily available, eliminating the question about whether or not to order testing, there is significant diversity in the acceptance of pharmacogenetic evidence among physicians. Would the outcome of case 1 have been different had the patient not been knowledgeable about pharmacogenetics? Would the outcome of case 2 have been different had the providers been knowledgeable about the evidence supporting pharmacogenetic-guided prescribing decisions?

Data from a survey of ~ 10,000 US physicians suggest the answers to these questions is yes.[105] Specifically, the survey revealed that a large percentage of physicians (~ 98%) agreed that genetic variations may influence drug response, but few (~ 10%) felt adequately informed about pharmacogenetic testing. Only 29% reported receiving any pharmacogenetic education, and only 13% had ordered a test in the previous 6 months. Similarly, of 285 physicians surveyed across sites within the IGNITE Network, 70% believed that access to pharmacogenetic data would improve their ability to care for patients.[106] However, only 30% responded they were confident in their ability to use the results, and only 32% said they could find or use reliable sources of pharmacogenetic information while caring for patients. Clinicians may have concerns about liability of testing for genetic variants with implications for multiple drugs.

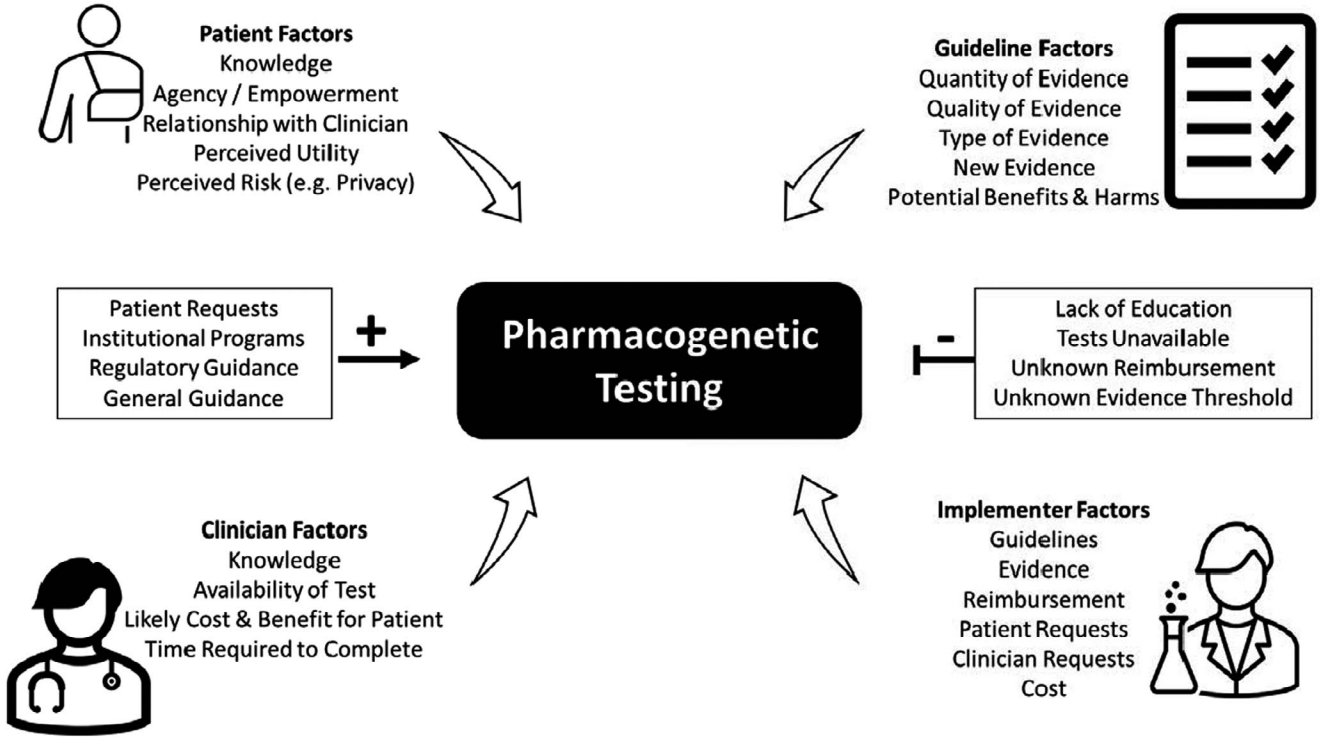

Figure 3 Factors to consider in the clinical implementation of pharmacogenetic testing. Plus sign indicates facilitators, and minus sign indicates barriers.

For example, a cardiologist may order a *CYP2C19* genetic test to guide antiplatelet therapy, but the patient's CYP2C19 phenotype may also affect responses to noncardiovascular medications, such as antidepressants and proton pump inhibitors.

If the lack of pharmacogenetic education is more of a barrier than limited RCT evidence, then we need to focus our resources on education instead of further investment in RCT data. Efforts to include pharmacogenetics in the US medical school curriculum are important and underway. The PGx Dissemination Working Group is involved in the collaborative development of pharmacogenetic continuing medical education (CME) materials with the Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC) and the American Academy of Family Physicians (AAFP).[107] The goal of the PGx Dissemination Working Group is to raise awareness and educate about resources available for pharmacogenetic implementation, such as CPIC guidelines, PharmGKB, the Pharmacogenomics Research Network (PGRN), and PharmVar, including also commentaries in journals, outreach to medical societies, letters to insurance companies, and through social media. Alignment of medical society practice guideline pharmacogenetic recommendations with these other resources is a critical step to enhance provider acceptance of the value of pharmacogenetic testing,[81] and to enhance the adoption into standard practice and availability for patients.

CONCLUSIONS

We reviewed multiple perspectives on the highly debated issue of the evidence required for the clinical implementation of pharmacogenetics. An overall summary of factors to consider in the clinical implementation of pharmacogenetic testing is presented in **Figure 3**. The perspective of the patient is often lost in this debate, and thus we presented two patient cases, in which the knowledge of pharmacogenetic evidence, on the part of both the provider and patient, affected their care. In our overview of the resources from organizations that curate pharmacogenetic evidence, such as the CPIC, the FDA, the DPWG, and PharmGKB, we point out that there are differences in the interpretation of the pharmacogenetic evidence across those resources. Efforts for standardization across these resources are underway. Our review of the types of pharmacogenetic evidence available included many RCTs of pharmacogenetic-guided therapy. However, the RCT design has many limitations when applied specifically to pharmacogenetics, and thus RCTs may not be necessary, appropriate, feasible, or ethical in pharmacogenetics. Similar arguments for RCT data for the clinical implementation of PK/TDM were reviewed in our historical perspective. However, similar to pharmacogenetics, institutions began routinely implementing PK/TDM in clinical practice in the absence of robust RCT data, and thus the arguments for RCT data supporting PK/TDM eventually waned.

Pharmacogenetic recommendations in clinical practice guidelines from medical societies are different and controversial. That may explain why practice guidelines from medical societies were not one of the most common determinants of clinical implementation of pharmacogenetic tests in our small survey of implementers. The three most common determinants for current implementers of pharmacogenetics were the availability of CPIC guidelines, consistent evidence of pharmacogenetic associations, and an FDA boxed warning. From the clinician perspective, they must weigh a multitude of variables when making clinical decisions regarding pharmacogenetics, as a single level of evidence cannot be applied to every unique scenario. Examples of the many variables that clinicians must weigh include the severity of the potential clinical outcome, the individual patient's risk factors, and the effect size and frequency of the genetic variant. Returning to the patient perspective, it is clear that patients also must weigh many variables in decisions on pharmacogenetic testing, especially the cost. Overall, patients believe that pharmacogenetic testing is valuable, and that their providers are key to receiving the most benefit from their pharmacogenomic results. Ultimately, the evidence for the pharmacogenetic tests described in the initially presented patient cases (i.e., tamoxifen and medications for treating depression and GERD) was not supported by the highest level of evidence (i.e., RCTs demonstrating clinical utility). Regardless, the evidence was sufficient for the patients to request pharmacogenetic testing from their providers.

Looking to the future of pharmacogenetics, it is important to recognize that clinical implementation of pharmacogenetics is shifting from individual, reactive tests to panel-based preemptive tests. Evidence for panels is showing early potential, and further efforts are underway to demonstrate the clinical utility of pharmacogenetic panels instead of just individual drug-gene pairs. The evidence for each individual gene-drug pair on a panel is still critical, as it will inform which genes and variants should be included in panels. In sum, to move pharmacogenetics into practice, a variety of stakeholders' perspectives need to be considered, particularly keeping attuned to the voice of the ultimate stakeholder—the patient.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTERESTS

A.K.T. is a Technical Director at Laboratory Corporation of America Holdings. All other authors declared no competing interests for this work.

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