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Challenges and Opportunities in Implementing Pharmacogenetic Testing in Clinical Settings

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Abstract

The clinical implementation of pharmacogenetic biomarkers continues to grow as new genetic variants associated with drug outcomes are discovered and validated. The number of drug labels that contain pharmacogenetic information also continues to expand. Published, peer-reviewed clinical practice guidelines have also been developed to support the implementation of pharmacogenetic tests. Incorporating pharmacogenetic information into health care benefits patients as well as clinicians by improving drug safety and reducing empiricism in drug selection. Barriers to the implementation of pharmacogenetic testing remain. This review explores current pharmacogenetic implementation initiatives with a focus on the challenges of pharmacogenetic implementation and potential opportunities to overcome these challenges.

1. BACKGROUND

PharmGKB: Pharmacogenomics Knowledge Base

CPIC: Clinical Pharmacogenetics Implementation Consortium

Pharmacogenetics, first introduced in the 1950s, is the concept of the role of inherited factors in drug response (1, 2). Pharmacogenomics was a term subsequently used to describe investigations of how genetic variants within the genome influence individuals' responses to drugs, affecting both efficacy and toxicity (3, 4). In this review, we use the term pharmacogenetics to describe the use of specific genes, genetic variants, or both to aid in clinical care. It is widely recognized that individual patients respond to drugs differently: Some patients may respond to a small dose, others may not respond even to a large dose, and some experience serious adverse effects at usual doses. This interindividual variability is a problem particularly when the prescribed dose is determined by age or body weight. The impact of pharmacogenetic variability is often overlooked in prescribing. Variability also increases empiricism in drug prescribing as clinicians and patients search for effective drugs and doses with minimal adverse effects.

This review presents two examples of translating pharmacogenetic data into clinical practice and summarizes current challenges and opportunities.

2. CURRENTLY AVAILABLE RESOURCES FOR THE IMPLEMENTATION OF PHARMACOGENETIC BIOMARKERS

Many resources are available to clinicians and health-care professionals to guide drug selection, predict therapeutic outcomes, and prevent drug-induced adverse events.

2.1. Pharmacogenomic Databases

The Pharmacogenomics Knowledge Base (PharmGKB) (**https://www.pharmgkb.org**) is a publicly available database hosted by Stanford University and funded by the National Human Genome Research Institute of the US National Institutes of Health. PharmGKB collects, curates, and disseminates updated pharmacogenomic information (5). It provides information by drug, pharmacology, biotransformation pathways, and pharmacogenetic markers (5). As of February 26, 2020, PharmGKB has information for 683 drugs, 147 drug biotransformation pathways, 139 clinical guideline annotations, and 750 drug label annotations for drug labels from the United States, Canada, Europe, and Japan.

The Pharmacogene Variation Consortium (**https://www.pharmvar.org**) is another online resource focused on the human cytochrome P450 (*CYP*) genes, which encode a class of enzymes frequently involved in drug metabolism (6). Other pharmacogenomic databases include the Human Leukocyte Antigen (HLA) and Adverse Drug Reaction (ADR) Database [a part of the Allele Frequencies Net Database (**http://www.allelefrequencies.net/hla-adr**)] (7), Clinical Genome Resource (**https://www.clinicalgenome.org**) (8), ClinVar (**https://www.ncbi.nlm.nih.gov/clinvar**) (9), and Ubiquitous Pharmacogenomics (**http://www.upgx.eu**) (10).

2.2. Pharmacogenetic Clinical Practice Guideline Development Groups

The Clinical Pharmacogenetics Implementation Consortium (CPIC) (**https://www.cpicpgx.org**) is an international project between PharmGKB and the US National Institutes of Health that provides peer-reviewed, evidence-based pharmacogenetic clinical practice guidelines (11). CPIC has issued 47 guidelines, many of which have been updated at least once (11, 12).

The Dutch Pharmacogenetics Working Group (DPWG), established by the Royal Dutch Pharmacists Association, is another multidisciplinary team developing therapeutic

recommendations based on the pharmacogenetic information (13). DPWG has published 93 guidelines (14, 15).

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) (**http://www.cpnds.ubc.ca**) is a pan-Canadian active ADR surveillance network that aims to reduce adverse reactions and improve drug safety and effectiveness. CPNDS has released eight guidelines (16). The CPNDS Clinical Practice Recommendation Group conducts systematic literature reviews followed by guideline development using the Appraisal of Guidelines Research and Evaluation Enterprise (AGREE) instrument (17). The method used for guideline development provides information on how evidence was reviewed (17). A new AGREE tool (AGREE II) has been developed to further assess the methodological rigor and transparency in which a practice guideline is developed and can be used to guide development (18, 19).

CPNDS: Canadian Pharmacogenomics Network for Drug Safety

ADR: adverse drug reaction

FDA: US Food and Drug Administration

6-MP: 6-mercaptopurine

TPMT: thiopurine methyltransferase

NUDT: nudix hydrolase

3. PHARMACOGENETIC BIOMARKERS IN DRUG LABELING

Drug label information and black box warnings are useful sources of information of pharmacogenetic biomarkers relevant to specific drugs. Clinical guidance on such markers often includes information on mandatory testing, recommendations for testing or information on pharmacogenetic biomarkers that may be helpful for clinicians in drug prescribing and monitoring (20). Genetic biomarker information of drugs by the US Food and Drug Administration (FDA), the European Medicines Agency, the Swiss Agency for Therapeutic Products, Health Canada, and the Pharmaceuticals and Medical Devices Agency of Japan is collected and updated in PharmGKB (21). The FDA also provides a list of pharmacogenetic biomarkers in drug labeling (22).

4. EXAMPLES OF IMPLEMENTING PHARMACOGENETIC TESTING IN CLINICAL SETTINGS

4.1. *TPMT* and *NUDT15* Variants in Patients Receiving 6-Mercaptopurine

6-Mercaptopurine (6-MP) is a chemotherapeutic drug for acute lymphoblastic leukemia (23, 24). One of the most common ADRs to 6-MP is myelosuppression (25, 26). Thiopurine methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*) are genes encoding enzymes involved in the metabolism of 6-MP (27–30). Loss-of-function variants of TPMT occur in human populations worldwide. For example, European allele frequencies of *TPMT*2* and *TPMT*3A* are 0.6% and 3%, respectively (31). Loss-of-function variants of NUDT15 are more common in East Asian patients. For example, *NUDT15*2* and *NUDT15*3* frequencies are 4% and 6%, respectively (31). Patients with loss-of-function variants in *TPMT* (e.g., *TPMT*2* or **3A*) and *NUDT15* (e.g., *NUDT15*2* or **3*) are more likely to experience 6-MP-induced myelosuppression (32, 33). Clinical practice guidelines have been developed to guide dose adjustments of 6-MP based on pharmacogenetic biomarkers (31). **Figure 1** summarizes the dose recommendation based on functional variants in *TPMT* and *NUDT15* by CPIC (31). Patients with one nonfunctional and one functional variant in *TPMT* should have their thiopurine dose reduced 30–80% (**Figure 1*a***). Patients with two nonfunctional variants should start thiopurines with a 90% dose reduction when the initial standard dose is 75 mg/m^2 or more (**Figure 1*a***). Similar dose recommendations apply to *NUDT15* variants (**Figure 1*b***). Of note, structurally similar drugs that utilize the same biotransformation pathways may share pharmacogenetic guidance. Structurally similar thiopurine drugs, including 6-MP and thioguanine, are metabolized by *TPMT* and *NUDT15*. Pharmacokinetic testing recommendations for *TPMT* and *NUDT15* apply to both agents (31, 34).

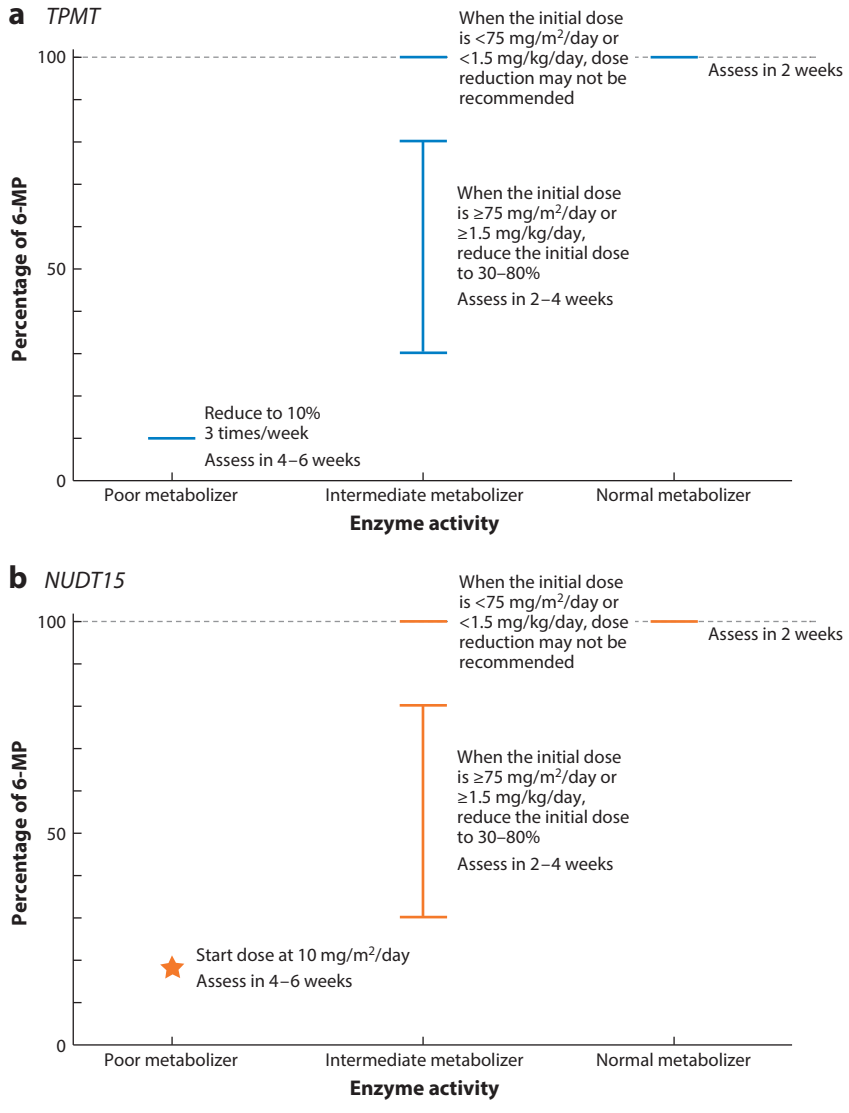


Figure 1

Dose adjustment of 6-mercaptopurine (6-MP) by genetic variants of thiopurine methyltransferase (*TPMT*) (*a*) and nudix hydrolase 15 (*NUDT15*) (*b*). Patients who are poor metabolizers of 6-MP due to low or intermediate activity *TPMT* or *NUDT15* variants require reduced doses. Panels *a* and *b* summarized from tables 2 and 3, respectively, of Reference 31.

HLA: human leukocyte antigen

4.2. *HLA-B*15:02* Testing in Carbamazepine-Induced Severe Cutaneous Adverse Reactions

*HLA-B*15:02* testing is another example of pharmacogenetic implementation that helps prevent idiosyncratic, nonpharmacological adverse reactions by using pretreatment screening. In 2004, Chung et al. (35) first reported the association between *HLA-B*15:02* and carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [odds ratio (OR), 2,504; 95% confidence interval (CI), 126–49,522; $P = 3.13 \times 10^{-27}$] in Han Chinese. The FDA subsequently

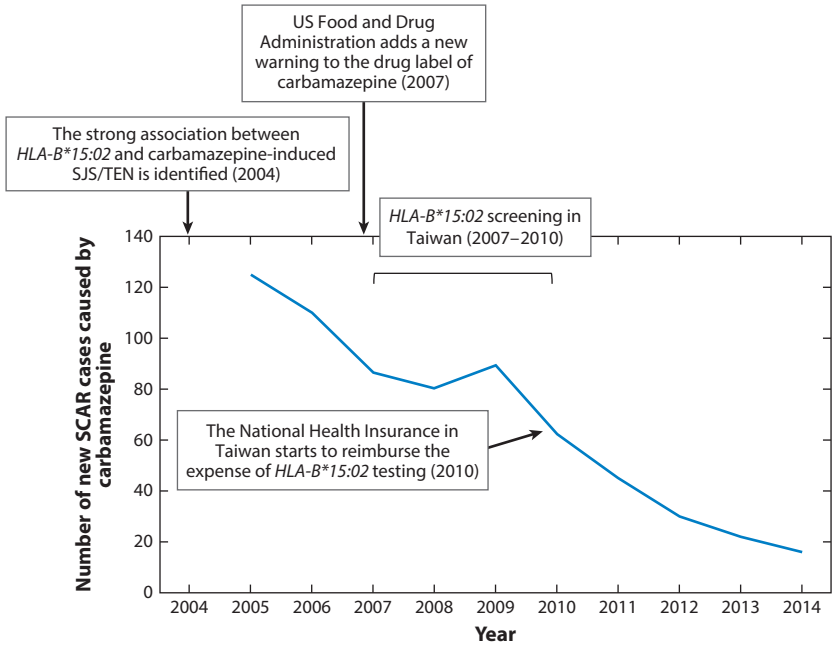


Figure 2

Pharmacogenetic implementation for human leukocyte antigen B allele *HLA-B*15:02* screening in Taiwan. The trend shows that pharmacogenetic testing of *HLA-B*15:02* implemented in Taiwan gradually reduced the number of carbamazepine-induced new severe cutaneous adverse reaction (SCAR) cases (40). This started with the identification of the association of this genotype with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (35) and continued through genotype screening in Taiwan (38).

recommended *HLA-B*15:02* genotyping before starting treatment with carbamazepine in patients of Asian ancestry to prevent the risk of developing life-threatening severe cutaneous adverse reactions (SCARs), including SJS/TEN (36). Regulatory authorities in Canada, Europe, Taiwan, Japan, Singapore, Hong Kong, Thailand, India, and elsewhere also made a similar labeling change to the drug safety information contained in the carbamazepine label (37). They stated that physicians should consider *HLA-B*15:02* genotyping as a screening tool in genetically at-risk populations (37). Subsequently, *HLA-B*15:02* screening became mandatory in certain parts of Southeast Asia, such as Taiwan, Hong Kong, Singapore, and Thailand (37–39). A 10-year, retrospective, nationwide study in Taiwan demonstrated that after the discovery of the pharmacogenetic marker, changes in the drug label, and dissemination of *HLA-B*15:02* pretreatment screening guidance, the number of new SCAR cases induced by carbamazepine was reduced by 87%, from 124 cases in 2005 to 16 cases in 2014 (40) (**Figure 2**).

The allele frequencies of *HLA-B*15:02* are approximately 5–10% in several Southeast Asian populations, 0.3% in Korea, 0.03% in Japan, and 0–0.2% in Europe (41). The CPIC and CPNDS guidelines further suggest that if a patient is carbamazepine naive or oxcarbazepine naive and *HLA-B*15:02* positive, carbamazepine and oxcarbazepine should be avoided (42, 43). Despite limited clinical evidence, for *HLA-B*15:02*-positive patients, other aromatic anticonvulsants with similar chemical structures, including lamotrigine and phenytoin, should be used, if necessary, with careful monitoring for SCARs, due to the possibility of cross-reactivity and the greater risk of SCARs (42, 43). Although *HLA-B*15:02* testing positively impacts the safe use of carbamazepine in patients with Southeast Asian ancestries, in populations in which

SJS: Stevens-Johnson syndrome

TEN: toxic epidermal necrolysis

OR: odds ratio

CI: confidence interval

SCAR: severe cutaneous adverse reaction

*HLA-B*15:02* is relatively rare, other *HLA* alleles contribute to the pathogenesis of carbamazepine-induced SCARs. For example, the *HLA-A*31:01* allele occurs in 2–5% of people with Northern European ancestry and 8% of people with Japanese ancestry (41) and increases susceptibility to carbamazepine-induced cutaneous adverse reactions, ranging from mild maculopapular exanthema to life-threatening SJS/TEN (44–46). Since the *HLA-A*31:01* allele is associated with a wider range of carbamazepine-induced cutaneous ADRs and the testing can apply to patients with various ancestries, the CPIC and CPNDS guidelines also suggest pharmacogenetic testing for *HLA-A*31:01* before carbamazepine initiation in patients of all ancestries (42, 43). Many patients have mixed ancestral backgrounds, making ancestry-specific recommendations difficult.

RCT: randomized controlled trial

5. MAJOR CHALLENGES IN THE CLINICAL IMPLEMENTATION OF PHARMACOGENETICS

Despite the substantial progress achieved using pharmacogenetic-guided biomarkers in clinical care, several implementation challenges remain.

5.1. Quality of Evidence and Clinical Relevance

Many pharmacogenetic biomarkers have marginal or controversial associations with drug outcomes. For example, patients who are homozygous or heterozygous for the long form of the serotonin transporter genes (*SLC6A4* and *HTTLPR*) in the promotor region may have a marginally better response to selective serotonin reuptake inhibitors over patients who are homozygous for the *HTTLPR* short form (47). Although a statistically significant *P* value was found ($P = 0.004$), the OR linking this variant to drug response holds only marginal clinical relevance (OR, 1.58; 95% CI, 1.16–2.16) (47). Randomized controlled trials (RCTs) are considered to be the highest-quality trials, but they are not always necessary for pharmacogenetic research. Some RCTs have been conducted, notably for warfarin (48) and abacavir (49). The life-threatening nature of copy-number duplications in *CYP2D6* makes RCTs unnecessary for codeine-induced infant respiratory depression and death due to maternal use; neither are RCTs needed for other drug trials in which the primary end point is to determine if a given genetic variant increases the risk of a life-threatening reaction (50). If the variant is known to be functionally related to the development of toxic in vivo concentrations of the drug, an observational case-control study would be a more ethical study design.

Many companies or clinical laboratories offer pharmacogenetic tests. These companies often test hundreds of gene variants and provide information on gene-drug associations. However, the evidence thresholds used for reporting the gene-drug associations are often not transparent. For example, reporting only the number of studies that found a gene-drug association but excluding important study details (e.g., number of patients, number of independent population replications, strength of association, 95% CI) limits the value of the testing. Additionally, reporting that studies have conflicting results without a quality assessment of each study also limits test value.

5.2. Rare but Life-Threatening Adverse Drug Reactions

The rarity of severe and life-threatening ADRs poses another challenge for clinical pharmacogenomic implementation. For example, the incidence of carbamazepine-induced SCARs is as low as 0.05‰ (51), and for infrequent ADRs, recruiting a sufficient number of patient ADR cases to identify biomarkers of clinical relevance can be difficult.

The variation in gene variant frequencies between different ancestries means that pharmacogenetics needs to account for these potential differences. In different countries, different variants within the same gene might be important for a particular drug. The difference in the frequency of such a pharmacogenetic risk variant may impact regulatory action. For example, in Taiwan, Hong Kong, Singapore, and Thailand, *HLA-B*15:02* testing is paid for by the government before carbamazepine is prescribed (37, 39). In Europe, the cost of *HLA-B*15:02* genotyping is not covered in most countries, likely due to the low incidence of this variant in patients who are of European ancestry (as noted above in Section 4.2).

5.3. Time Lag from Basic Science to Translation

The time lag between scientific findings and drug label annotations or clinical practice guidelines is also a challenge. It takes an average of 17 years for a research discovery to be implemented in medical practice (52). Knowledge translation from research to clinical care is a complex process that includes study design; funding; ethical approvals; publication; phase I, II, and III trials; regulatory licensing; postmarketing testing; and guideline preparation. Generally, only one-third of research evidence from basic science is successfully applied in clinical settings. To include pharmacogenomic information in a drug label or to write a clinical practice guideline, extensive discussion by expert teams is essential.

5.4. Time Lag from Test Order to Result

Another important technical and logistical challenge may exist if the time lag between the ordering of the test and the time necessary to receive the results is longer than is needed for appropriate clinical care. Not all care facilities or laboratories can quickly perform genotyping (53). Once the genotyping is performed, the results must be interpreted and resulting recommendations must be created. Because clinical care occurs on a relatively quick decision-making time line, improving and refining the reporting system for pharmacogenetic results to help maintain these preexisting time lines are important.

5.5. Insufficient Pharmacogenetics Education

The implementation of pharmacogenetics into clinical practice also requires the education of clinicians in both clinical pharmacology and pharmacogenomics. Neither subject is covered in detail in medical school curricula in the Unites States at present (54). Currently, most clinicians do not have sufficient knowledge to interpret pharmacogenetic results (55). According to two nationwide surveys in the United States, although almost all health-care providers acknowledge the potential benefit of pharmacogenetic testing, only a minority of physicians (10.3%) and pharmacists (14.1%) reported that they felt adequately informed about the availability of pharmacogenetic testing and its applicability to their patients' treatment (55, 56). Education that highlights the clinical utility of pharmacogenetics, thresholds of evidence for inclusion in clinical care, and its limitations in utility is critical. The increasing number of clinically actionable pharmacogenetic variants makes such educational programming essential.

5.6. The Complexity of Pharmacogenetic Results

The results of pharmacogenetic tests containing genetic information in individuals are, in general, complicated. Important pharmacogenetic biomarkers, such as *CYP2D6* or *CYP2C9*, are highly

polymorphic (6), which makes interpretation more difficult. Such interpretation, at a minimum, requires a detailed medication history of each patient's past drug use, including doses, durations, and reasons for discontinuation. This is necessary to arrive at specific clinical actions that should be taken based on the pharmacogenetic results.

Heterogeneous data from different testing sources also increase the difficulties associated with clinical implementation and decision making. Evidence thresholds for clinical action should be clearly stated. Evidence sufficiency should be based not only on the number of trials showing similar results but also on the quality of the data and the number of independent population replications. If trial results are conflicting, then instead of awaiting further trials to see if the results become more consistent, a quantitative analysis of relevant trials (e.g., systematic reviews and meta-analyses) is necessary.

5.7. Economic Impact of Pharmacogenetic Testing

A review of the economic evaluations of pharmacogenetic tests in FDA drug labels revealed that 57% of the tests were cost-effective. A total of 30% were cost-effective at acceptable additional cost, and 27% were cost-effective and cost-saving (57). Of course, cost-effectiveness also depends on the specific country, such as the health economy of the country in which it is implemented as well as the prevalence of the specific pharmacogenetic biomarkers within the population of the country. For implementation to be successful, an assessment of the cost-effectiveness in each country to find an optimal strategy is essential. Pharmacogenetic tests with robust evidence may be covered by health insurance agencies. For example, testing for genetic variants of *CYP2C9* and *VKORC1* is covered by Medicare in the United States (58). Pharmacogenomic testing of *CYP2C9* or *VKORC1* alleles to predict warfarin responsiveness is covered by Medicare only for patients who have not been previously tested for these alleles, have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered, and are enrolled in a prospective RCT that meets the standards specified in the decision memorandum (58). Economic evaluations most often consider cost-effectiveness on the basis of the number of patients with the relevant pharmacogenetic variant. However, in the case of serious, drug-induced harm, knowing a patient is not at an increased risk of such a reaction also provides additional value, and this should also be included in economic models.

Studies from several countries have demonstrated the economic viability of screening for high-risk *HLA* alleles, such as *HLA-B*57:01* for abacavir-induced hypersensitivity, *HLA-B*15:02* for carbamazepine-induced SJS/TEN, and *HLA-B*58:01* for allopurinol-induced SJS/TEN (**Table 1**). For populations with higher-risk allele frequencies, targeted *HLA* screening prior to medication initiation tends to be more cost-effective (59–75). However, some Asian countries such as Singapore and Malaysia are still evaluating whether to include testing in their jurisdictions (57, 76, 77). Chen et al. (78, 79) found that an extremely low incidence of SCARs, poor policy adherence, and a high cost of *HLA-B*15:02* screening for carbamazepine meant such screening was not cost-effective in Hong Kong. Similarly, a cost-effectiveness analysis from Malaysia demonstrated that *HLA-B*15:02* screening for carbamazepine is likely to worsen clinical and economic outcomes (80). This was because the alternatives to carbamazepine did not show similar clinical efficacy, resulting in worsened disease management and reduced quality of life (80). Treating seizure disorders successfully can be difficult regardless of the drugs used, and incorporating new approaches to treatment when patients are *HLA-B*15:02* positive was not successful. However, the prevention of even a single case of SJS/TEN has clinical benefits for a lifetime in patients who do not experience the lifelong implications of this syndrome. Similar limitations in cost-effectiveness have also been observed for *HLA-B*58:01* testing prior to allopurinol initiation in Singapore (76)

Table 1 Economic evaluations of *HLA* testing for prevention of specific drug-induced severe adverse reactions

HLA allele	Drug	ADR	Economic evaluations in different countries
*HLA-B*57:01*	Abacavir	Hypersensitivity	Cost-effectiveness evaluated from the health-care system perspective in the United Kingdom (59), Spain (60), the United States (61), and Germany (62) Cost-effective for partial ethnic populations (i.e., late-stage Malay and Indian patients) in Singapore (63)
*HLA-B*15:02*	Carbamazepine	SJS/TEN	Cost-effectiveness evaluated from the health-care system perspective in Thailand (64–66) and Australia (67) Cost-effective for Singaporean Chinese and Malays but not for Singaporean Indians in Singapore (68) Cost-effective for patients of Asian ancestry in the United States (69) Not cost-effective in Hong Kong (78, 79) and Malaysia (80)
*HLA-B*58:01*	Allopurinol	SJS/TEN	Cost-effectiveness evaluated from the health-care system perspective in Thailand (70), South Korea (71), and Taiwan (72) Cost-effective for at-risk populations (i.e., Asians and African Americans) but not for Caucasians or Hispanics in the United States (73) More likely to be cost-effective for patients with chronic renal insufficiency and populations with a higher *HLA-B*58:01* prevalence in the United Kingdom (74) Not cost-effective in Portugal (75), Singapore (76), and Malaysia (77)

Abbreviations: ADR, adverse drug reaction; HLA, human leukocyte antigen; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

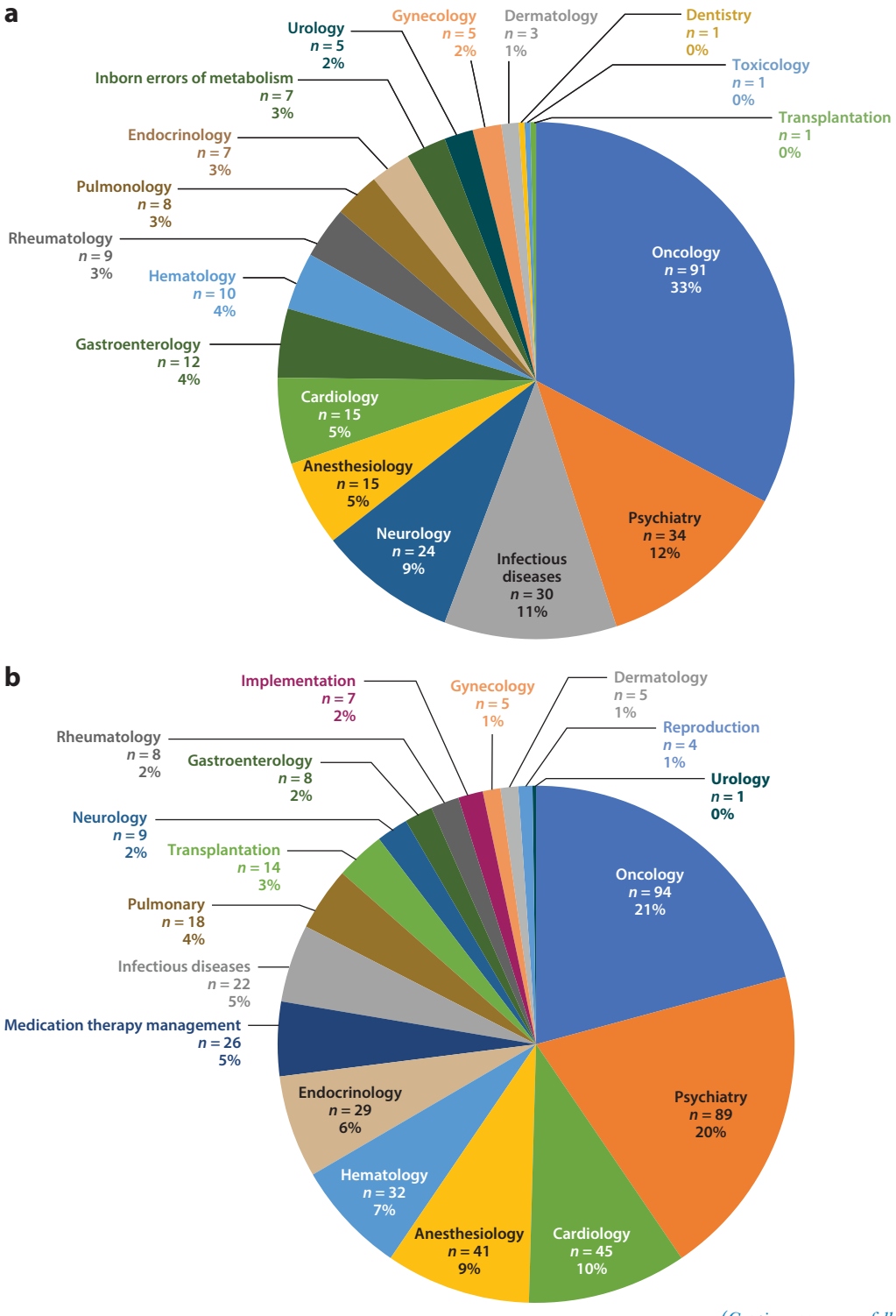
and Malaysia (77). One limitation of these cost analyses is that they calculate cost-effectiveness on the basis of the number of positive tests compared to the overall number of tests provided. Only positive tests are used in the determination of cost-effectiveness. Patient survivors of SJS/TEN and clinicians, however, would state that clinical value is obtained with negative test results; these provide reassurance to patients and their health-care providers that skin eruptions that occur subsequent to drug initiation are more likely to be self-limiting and not SCARs.

6. POTENTIAL OPPORTUNITIES TO ADDRESS CURRENT CHALLENGES

6.1. Building Capacity for Evidence-Based Pharmacogenetics

As the knowledge of pharmacogenetic biomarkers expands, many gene-drug associations have been identified and validated. As of March 2020, the FDA has included pharmacogenetic biomarkers in the drug labels of 278 therapeutic agents (22). These 278 medications involve 18 therapeutic areas, including oncology ($n = 91$, 33%), psychiatry ($n = 34$, 12%), and infectious diseases ($n = 30$, 11%) (**Figure 3*a***). Oncology medications account for the largest number of FDA drug safety labels. Of these 91 oncology biomarkers, 83 are somatic variants and the remaining 8 are germline. Importantly, these oncology biomarkers are commonly recognized and frequently described in clinical practice guidelines. **Table 2** summarizes the cancer pharmacogenetic testing recommended by CPIC (31, 81–83), DPWG (14, 15), and CPNDS (84–86). These FDA drug labels contain genetic information that provides physicians and other health-care providers the

DPWG: Dutch Pharmacogenetics Working Group



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Therapeutic areas for pharmacogenetic implementation. Panel *a* shows the number of US Food and Drug Administration–approved drug labels in each therapeutic area and the respective percentage of the total number of such labels ($n = 278$). Panel *b* shows the number of clinical trials studying pharmacogenomics or pharmacogenetics in each therapeutic area and the respective percentage of the total number of such trials ($n = 452$). Oncology and psychiatry are the medical disciplines that have implemented pharmacogenetic testing the most in clinical practice.

critical information they need to prescribe the medications, as well as specific actions to be taken prior to initiation, which are a key component for the effective utilization of pharmacogenetic tests.

Pharmacogenomic clinical trials help overcome the barrier of limited clinical information before and in the process of pharmacogenetic implementation. A search of the US federal government's clinical trials website (**https://www.clinicaltrials.gov**) on March 4, 2020, identified 452 studies categorized as pharmacogenomic(s)/pharmacogenetic(s) with an active, recruiting, or completed status. Of these 452 studies, 21% are oncology-related ($n = 94$) and 20% are psychiatry-related ($n = 89$), in line with these being the most common therapeutic areas in terms of numbers of drug labels but also because these two disciplines frequently incorporate genomic information and clinical data in routine patient health care. In addition, 26 trials (5%) are related to medication therapy management, such as primary care, communication, and economic impact. Seven clinical trials are studying the implementation of pharmacogenetics/pharmacogenomics. Clinical trials are also being conducted or have been completed in other therapeutic areas, including cardiology, anesthesiology, and hematology (**Figure 3*b***).

Table 2 Guideline-recommended pharmacogenomic information for oncology

Medication	Gene(s)	Adverse reaction(s)	Consortia giving clinical practice guidelines
Anthracyclines (daunorubicin or doxorubicin)	*RARG*, *UGT1A6*, and *SLC28A3*	Cardiotoxicity (e.g., fractional shortening by echocardiogram ≤26%)	CPNDS (84)
Cisplatin	*TPMT*	Ototoxicity [sensorineural hearing threshold of greater than 20 dB in the high frequencies at ≥6 kHz from a normal baseline (Grade 2)]	CPNDS (85)
Fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur)	*DPYD*	Gastrointestinal and hematological toxicity	CPIC (81) and DPWG (14, 15)
Irinotecan	*UGT1A1*	Myelosuppression and diarrhea	DPWG (14, 15)
Rasburicase	*G6PD*	Acute hemolytic anemia	CPIC (82)
Tamoxifen	*CYP2D6*	Increased risk of breast cancer relapse	CPIC (83), CPNDS (86), and DPWG (14, 15)
Thiopurines (azathioprine, 6-mercaptopurine, and thioguanine)	*TPMT*, *NUDT15*	Myelosuppression	CPIC (31) and DPWG (14, 15)

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; CPNDS, Canadian Pharmacogenomics Network for Drug Safety; CYP2D6, cytochrome P450 2D6; DPWG, Dutch Pharmacogenetics Working Group; DPYD, dihydropyrimidine dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; NUDT15, nucleoside diphosphate linked moiety X (nudix)-type motif 15; RARG, retinoic acid receptor gamma; SLC, solute carrier transporter; TPMT, thiopurine methyltransferase; UGT, uridine diphosphate-glucuronosyltransferase.

To improve the transparency of evidence on which pharmacogenetic tests are based, specific thresholds should be set to quantify the sufficiency of the evidence for clinical action. One recommended threshold is to report only the tests in which the pharmacogenetic testing information is included within the drug's label in the country where the clinical care is occurring. For smaller countries without the resources of the FDA, for example, this threshold may be too stringent. In smaller countries, a wider net of pharmacogenetic tests could be cast by sharing pharmacogenetic screening guidance among countries. A second recommended threshold of pharmacogenetic testing is to require clinical practice guidelines published by expert consortia. Since drug labeling and guideline development take significant time, we recommend a third threshold in which pharmacogenetic testing is reported for pharmacogenetic variants that have been replicated in at least three independent populations, each with a clinically significant OR of ≥ 3 for risk variants or ≤ 0.3 for protective variants.

6.2. Active Surveillance and International Collaborations

Despite the use of HLA testing in preventing certain drug-induced severe ADRs (e.g., *HLA-B*57:01* with abacavir-induced hypersensitivity in Europeans and *HLA-B*15:02* with carbamazepine-induced SCARs in Southeast Asian populations), the low incidence of serious ADRs in a given population and different frequencies of genetic variants in ancestries remain major barriers in the study of ADRs, especially rare adverse events. Active surveillance programs would help detect known ADRs of interest for pharmacogenomic studies. Well-trained clinical surveillors can provide rigorous data through characterizations of clinical phenotypes. High-quality phenotyping (e.g., clinical characterization of the ADR and assessment of causality) makes it more likely that clinically valid pharmacogenetic biomarkers can be identified from relatively small but well-characterized sample sizes. Moreover, the linking of national or international networks is an effective way to increase numbers of cases and well-matched controls for successful pharmacogenomic studies of rare ADRs. The CPNDS, for example, is a network of 14 pediatric and 18 adult academic health centers across Canada and internationally that uses active surveillance to identify patients who experience serious ADRs and matched controls, collect DNA, and conduct pharmacogenomic analyses (16). RegiSCAR, a multinational registry of SCARs to drugs, is another international network that brings together multidisciplinary scientists for the centralized collection of clinical data and biological samples (e.g., plasma, lymphocytes, DNA, and skin) from SCAR patients. These data and samples are used for pharmacogenetic studies and mechanistic investigations of drug reactions to improve the safety of medication use (51, 87). Leveraging international collaborators will also increase variations in ancestries to achieve adequate power to detect a meaningful difference and ensure generalizability.

6.3. Integrate Pharmacogenetics into Electronic Health Records

Since many pharmacogenetic markers can be useful across drug classes, pharmacogenetic information would optimally be shared with all of a patient's care providers. The integration of this information into electronic health records (EHRs) would facilitate this task (88, 89). Integrating laboratory and genetic test results into EHRs supports clinician decision making for individual patients and helps maximize awareness of pharmacogenetic results in real time. Clinical decision support systems are an efficient and effective tool to facilitate the translation from pharmacogenetic data to patient management (90–92). Health-care organizations may not use the same health information systems. But once the exchange of data becomes possible, through standardized data formatting, data integration can enhance pharmacogenetic implementation by improving the

quality of health care and reducing medical expenses (93, 94). A comprehensive EHR system will also enhance the rapid reporting and detection of patterns of adverse events over time (95).

NGS: next-generation sequencing

6.4. Advances in Genomic Technologies

Over the past two decades, the advancements in sequencing technologies have sped up the implementation of pharmacogenetic testing. Next-generation sequencing (NGS) has gradually replaced the traditional Sanger dideoxy terminator sequencing, which had been the gold standard for investigating genetic variants (96, 97). While Sanger sequencing is usually used to sequence relatively small fragments of DNA (up to 900 base pairs in length) in one gene at a time, NGS is a massively parallel, high-throughput approach used to sequence millions of fragments simultaneously (98). Despite NGS being much faster and comprehensive than traditional sequencing, current technologies remain limited by false-positive results in approximately 1% of cases, especially in complex genomic regions (e.g., HLA and G/C-rich regions). These regions, in particular, should be validated by Sanger sequencing (99).

However, the time it takes to genotype and provide clinical pharmacogenetic results has also been reduced from weeks to days. New technologies are being developed whereby NGS data may be available within hours. This method enables researchers to identify potential genetic variants throughout the entire human genome in a short period of time, which further facilitates genetic analyses in the early stages of pharmacogenetic implementation (100).

The rapid progress and development in sequencing technologies have led the price of sequencing a human genome to fall below $1,000 in 2019 (101, 102). As the number of tests increases, the cost per test is expected to drop further as sequencing costs are shared among a larger population of tested patients. At the same time, several biopharmaceutical companies are developing new testing panels of specific genetic variants, which could replace the existing traditional genotyping or sequencing methods. Targeted testing panels may provide an easier and faster way to implement pharmacogenetic results in routine clinical practice so that clinicians can treat patients based on specified clinical problems (103–105).

6.5. Machine Learning

Machine learning, a novel application of artificial intelligence, may be an efficient way to solve complex problems with large, diverse data sources (106–108). Several machine learning models have been developed to predict therapeutic outcomes, adverse events, or both by integrating existing large-scale pharmacogenomic datasets, such as a naive Bayesian model (a classification algorithm to rank and predict gene-drug adverse reactions) (109), HUME (a multiphase algorithm to identify causal pharmacogenomic relationships in gene and drug pathways) (110), and multi-omics late integration (MOLI) (a method to improve the accuracy of drug response prediction) (111). Although the use of machine learning is still in the early stages of development for pharmacogenetic analyses, these computational and statistical techniques are likely to provide new tools for the discovery of genetic variants through improved data mining techniques. Multidimensional analyses that predict therapeutic responses are the purpose of precision medicine (112, 113). Machine learning could help scientists explore the multidimensionality of drug outcomes more efficiently.

7. CONCLUSION AND FURTHER DIRECTIONS

In this review, we provide an overview of the current challenges for the clinical implementation of pharmacogenetic testing and discuss possible solutions (**Table 3**). Mounting research in

Table 3 Challenges on and possible solutions for the implementation of pharmacogenomics

Challenges	Possible solutions
Assuring the quality of evidence Marginal or controversial associations	Establish threshold of evidence. For example, clinically actionable biomarkers can be selected for at least one of the following three criteria: ■ Drug label recommendations by regulatory agencies ■ Clinical practice guidelines by expert consortia (e.g., CPIC, CPNDS, or DPWG) ■ Drug outcome–gene association in three populations with an odds ratio ≥3 for risk variants (≤0.3 for protective variants)
Low incidence of severe/life-threatening ADRs	High-quality phenotyping of ADRs Increase the sample size by national or international collaborations
Different incidences of genetic variants among ancestries	Active surveillance and international collaborations
Time lag between scientific findings and drug labels/guidelines	Establish threshold of evidence
Time lag from testing to receipt of results	Advance genotyping/sequencing techniques to save more time during the experimental process Improve reporting system by computer-based clinical decision support (e.g., electronic health record)
Expensive pharmacogenetic testing services	Assess the cost and effectiveness in each country to optimize available health-care resources Develop more cost-effective and time-efficient genotyping/sequencing techniques or commercial products (e.g., pharmacogenetic panels)

Abbreviations: ADR, adverse drug reaction; CPIC, Clinical Pharmacogenetics Implementation Consortium; CPNDS, Canadian Pharmacogenomics Network for Drug Safety; DPWG, Dutch Pharmacogenetics Working Group.

pharmacogenomics is beginning to fill knowledge gaps and increase our understanding of the association between genotypes and phenotypes for the individual patient. Evidence-based drug labeling and clinical practice guidelines are helping clinicians make more informed patient-specific clinical decisions. High-throughput, massively parallel genotyping is becoming cost-effective and time-efficient, which is further reducing the barriers of entry for patients and family members, but it still requires scale-up to see its cost-effectiveness maximized. Overall, the implementation of pharmacogenetic screening is gradually spreading. Based on the ongoing incremental advances in pharmacogenetic technology and knowledge, we can expect that pharmacogenetic testing will be utilized in more medical disciplines for the prevention of ADRs and more informed therapeutic interventions to achieve the goal of patient-specific precision medicine.

DISCLOSURE STATEMENT

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