REVIEW

Pharmacogenomics in Asian Subpopulations and Impacts on Commonly Prescribed Medications

Cody Lo[1], Samantha Nguyen[2], Christine Yang[3], Lana Witt[3], Alice Wen[3], T. Vivian Liao[2], Jennifer Nguyen[2], Bryant Lin[4], Russ B. Altman[5,6] and Latha Palaniappan[4,*]

Asians as a group comprise > 60% the world's population. There is an incredible amount of diversity in Asian and admixed populations that has not been addressed in a pharmacogenetic context. The known pharmacogenetic differences in Asian subgroups generally represent previously known variants that are present at much lower or higher frequencies in Asians compared with other populations. In this review we summarize the main drugs and known genes that appear to have differences in their pharmacogenetic properties in certain Asian populations. Evidence-based guidelines and summary statistics from the US Food and Drug Administration and the Clinical Pharmacogenetics Implementation Consortium were analyzed for ethnic differences in outcomes. Implicated drugs included commonly prescribed drugs such as warfarin, clopidogrel, carbamazepine, and allopurinol. The majority of these associations are due to Asians more commonly being poor metabolizers of cytochrome P450 (CYP) 2C19 and carriers of the human leukocyte antigen (HLA)-B*15:02 allele. The relative risk increase was shown to vary between genes and drugs, but could be > 100-fold higher in Asians. Specifically, there was a 172-fold increased risk of Stevens−Johnson syndrome and toxic epidermal necrolysis with carbamazepine use among HLA-B*15:02 carriers. The effects ranged from relatively benign reactions such as reduced drug efficacy to severe cutaneous skin reactions. These reactions are severe and prevalent enough to warrant pharmacogenetic testing and appropriate changes in dose and medication choice for at-risk populations. Further studies should be done on Asian cohorts to more fully understand pharmacogenetic variants in these populations and to clarify how such differences may influence drug response.

Pharmacogenetic differences in Asian populations represent an emerging area of research that stipulates certain adverse drug reactions (ADRs) or predictable alterations in drug metabolism due to genetic variation can be associated with Asian or other racial/ethnic backgrounds.[1-3] The known pharmacogenetic differences in Asians subgroups generally represent previously known variants that are present at much lower or higher frequencies in Asians as compared with other populations.[4-6] Although current literature suggests that there are important pharmacogenetic differences in Asian subgroups, these data are often not readily available, and healthcare practitioners treating diverse Asian populations lack specific prescribing guidelines.[7] The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the US Food and Drug Administration (FDA) offer some of the most evidence-based and rigorous recommendations on contraindications and dosing adjustments due to genetic variation. Some of these warnings, such as for carbamazepine[8] and clopidogrel,[9] specifically state that some of these ADRs are more prevalent in Asian populations.[6] However, most guidelines do not make race- or ethnicity-specific recommendations.

According to the United Nations, 61% (4.7 billion) of the world's population lives in Asia.[10] It is difficult to estimate the number of individuals who identify as "Asian" worldwide due to immigration and admixed populations. For example, "Asian Americans" are one of the fastest growing ethnic groups in the US and represent approximately 80% of foreign-born individuals in the country.[11,12] One's ethnicity may influence health and disease, as Asian American populations are at significantly higher risk of health conditions related to adverse outcomes such as cardiovascular disease and diabetes.[13,14] Asians are typically underrepresented in research studies, and studying Asian populations has historically been difficult. Participation by Asian Americans in clinical trial research is disproportionally low, with previous meta-analyses estimating only 1.4–5.0% of participants as being Asian. This lack of participation has been attributed in part due to lack of knowledge and negative attitudes toward this type of research.[15,16] The purpose of this review is to synthesize the currently available literature, FDA warnings, and CPIC guidelines to alert practitioners to important pharmacogenetic differences and prescribing considerations in Asian populations.

There are a total of 23 CPIC guidelines on management of well-studied pharmacogenetic drug interactions and these guidelines, including their supplemental summary statistics, were assessed for mention of potential ethnic differences in effect frequency and quantitative ethnic differences in phenotype frequency.[17] We also compiled all published FDA

[1]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]College of Pharmacy, Mercer University, Atlanta, Georgia, USA; [3]School of Medicine, Stanford University, Palo Alto, California, USA; [4]Division of Primary Care and Population Health, School of Medicine, Stanford University, Palo Alto, California, USA; [5]Department of Biomedical Data Science, Stanford University, Palo Alto, California, USA; [6]Department of Biomedical Engineering, Genetics and Medicine, Stanford University, Palo Alto, California, USA. *Correspondence: Latha Palaniappan (lathap@stanford.edu)

box warnings on drugs in which pharmacogenetic influence is mentioned and searched these guidelines for mention of specific differences in Asian populations. A scoping literature search of Google Scholar and PubMed was performed using the terms ["Asian" AND "pharmacogen*"] and titles were scanned for relevant articles. References for selected articles were also scanned for inclusion of additional relevant articles. Relevance of the primary literature was determined in the context of enriching the associations described in the CPIC or FDA guidelines. This was done intentionally to focus only on associations that have been well studied and have robust evidence. This review synthesizes the most well studied and established pharmacogenetic differences that are relevant to Asian populations as referenced in the CPIC guidelines, FDA warnings, and current literature (**Figure 1**). We identified the main disease classes and grouped drugs into the following categories: cardiology, oncology, neurology/psychiatry, rheumatology, and infectious disease. **Table 1** summarizes the key drug and gene interactions that will be discussed and the relative prevalence of these variants in individuals of Asian descent relative to populations of European descent.

It should be noted here that our analysis is restricted by the currently available summary statistics that have been published in this area. There are a number of ethnicities colloquially referred to as "Asian" with distinct genetic profiles and we recognize that grouping of such populations is problematic. A recent systemic review identified 49 different ethnic categories that were classified as "Asian" in pharmacogenetics studies and these criteria are often not standardized.[18] There have been a number of pharmacogenetic studies on very specific Asian subpopulations such as Han Chinese or Korean. This review relies heavily on summary statistics published by CPIC, which separates the global population into seven distinct subgroups.[19] Unless specified otherwise, "Asian" refers to the East and South Asian populations outlined by Huddart et al., as the majority of available literature is for these groups.[19] In addition, we aimed to provide the clinician with some knowledge of

reactions that may be important to look for in Asian populations—many patients will not know their exact genetic makeup, nor would a provider realistically be able to consult that information. Therefore, we still believe there is value in presenting a broad overview of risk alleles in what we subsequently refer to as "Asian" populations.

CARDIOLOGY
Clopidogrel

Clopidogrel is a preventive antiplatelet medication commonly prescribed after acute coronary syndrome and percutaneous coronary interventions, and there are > 21 million prescriptions given for this medication per year in the United States.[20] Clopidogrel acts by irreversible inhibition of the $P2RY_{12}$ receptor on platelets and is a prodrug that requires hepatic biotransformation by cytochrome P450 (CYP) 2C19 and other enzymes to produce its active form.[21] CYP2C19 is a prevalent hepatic enzyme and a member of the cytochrome P450 family that metabolizes at least 10% of all commonly prescribed drugs.[22] Knowledge of one's CYP2C19 metabolizer status may not only be useful in prescribing clopidogrel but also for other drugs (**Table 2**). Asian subgroups have substantially higher rates of being poor and intermediate CYP2C19 metabolizers (up to 15% and 47%, respectively) compared with African Americans (4% and 32%) and Caucasians (European and North American) (3% and 27%).[21] This pharmacogenetic difference results in reduced activity of clopidogrel, with Asians being at higher risk of adverse effects related to lack of platelet inhibition such as heart attack, unstable angina, stroke, and cardiovascular death.[21] The CPIC has published data on the frequency of the various CYP2C19 metabolizer–based ethnic subgroups (**Figure 2a**).

The FDA has added a box warning for clopidogrel that cautions against reduced activity in those who are poor metabolizers of CYP2C19 and informs providers about the number of genetic tests available to determine CYP2C19 status.[23] However, there is no specific guideline to check CYP2C19 status prior to prescribing clopidogrel, or other drugs metabolized by this enzyme. Universal CYP2C19
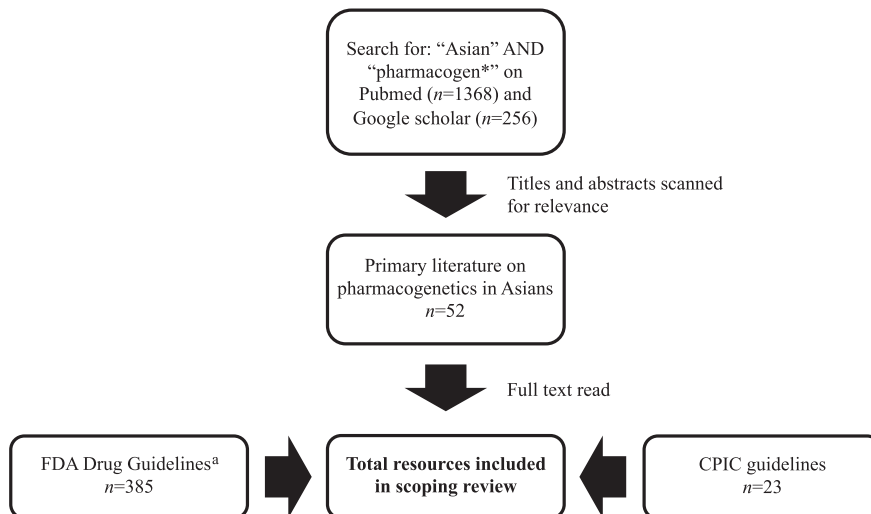
Figure 1 Flowchart. [a]taken from "FDA Table of Pharmacogenomic Biomarkers in Drug Labelling."[74]

Table 1 Important pharmacogenetic reactions with increased prevalence in Asian subpopulations[a]

Drug	Select gene and phenotype	Frequency in Asian subgroups	Increase in Asians having risk phenotype[b,c]	Side effect/toxicity	CPIC recommended action if found to have an at-risk genotype
Clopidogrel	CYP2C19 poor and intermediate metabolizer	0.62 (East Asians)	2.1×	Decreased antiplatelet activity (lack of efficacy)	Consider prescribing an alternative agent such as prasugrel or ticagrelor
Warfarin	VKORC rs9923231 SNP carrier	0.88 (East Asians)	2.1×	Excessive anticoagulation (supratherapeutic)	Lower dose to maintain target concentration
Tamoxifen	CYP2D6 intermediate or poor metabolizer	0.87 (East Asians)	1.2× for intermediate metabolizer	Lower drug concentrations; increased risk of cancer recurrence	Consider alternative hormonal therapy, such as aromatase inhibitor
Allopurinol	HLA-B*5801 carrier	0.05 (East and Central Asians)	6.7×	Significantly increased risk of SCARs, such as SJS and TENS	Do not use allopurinol; may consider an alternative agent, such as febuxostat
Carbamazepine	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use carbamazepine; may consider an alternative agent
Oxcarbazepine	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use oxcarbamazepine; may consider an alternative agent
Phenytoin	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use phenytoin; may consider an alternative agent
Selective Serotonin Reuptake inhibitors[d]	CYP2C19 poor metabolizer	0.62 (East Asians)	5.8×	Potential for arrhythmia at supratherapeutic doses (QT prolongation for citalopram)	Consider 50% dose reduction and monitor response; consider alternative agent
Tricyclic antidepressants	CYP2C19 poor metabolizer	0.62 (East Asians)	5.8x	Potential for suboptimal response	Consider alternative drug not metabolized by CYP2C19, such as secondary amines nortriptyline and desipramine, or 50% dose reduction
Thiopurines	NUDT15 intermediate or poor metabolizer	0.009	620× increase in East Asian for poor metabolizer	Increased risk of myelosuppression	Consider alternative drug class in nonmalignant conditions; use reduced dose of thiopurines in malignant conditions
Voriconazole	CYP2C19 poor metabolizer	0.15	5.8× increase in East Asians	Potential for hepatotoxicity, visual disturbances, and neurologic dysfunction	Consider alternative agent such as liposomal amphotericin B or posaconazole

CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, cytochrome P450; HLA, human leukocyte antigen; NUDT15, nucleoside diphosphate–linked moiety X-type motif 15; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; SNP, single-nucleotide polymorphism; SSRI, slective serotinin reuptake inhibitor; TEN, toxic epidermal necrolysis; VKORC, vitamin K epoxide reductase complex.
[a]Taken from supplemental data in the CPIC guidelines. Subgroups are as defined by the CPIC guidelines.[19]
[b]Relative to individuals of European descent.
[c]Ethnic frequencies calculated based on relevant CPIC guidelines.
[d]SSRIs mentioned in the CPIC guideline include citalopram, sertraline, escitalopram, paroxetine, fluvoxamine.

testing of all patients is not recommended prior to clopidogrel therapy, as the choice of using newer antiplatelet drugs, such as ticagrelor and prasugrel, is based primarily on clinical indications where demonstrable benefit has been observed.[24] The CPIC guideline for clopidogrel strongly recommends that alternative antiplatelets, such as prasugrel or ticagrelor, should be considered in those with poor CYP2C19 metabolism.[21] There is also a moderate recommendation for intermediate metabolizers, but this is relevant given the high frequency of this phenotype in Asian populations.[21] Treatment with prasugrel in a study of those with poor CYP2C19 metabolism did not show increased risk of cardiovascular death or any reduction of drug metabolite levels and inhibition of platelet aggregation.[25] This suggests that alternative drugs such as prasugrel may be superior to clopidogrel in poor metabolizers of CYP2C19 for certain indications. The impact of the CYP2C19 genotype on clopidogrel therapy is also dependent on the clinical situation in which it is given. Antiplatelet therapy for prevention of adverse cardiac and cerebrovascular events can be given both in the setting of stable angina and after acute myocardial infarction.[26] In their study on Asian populations, Kim Ho-Sook et al. found that CYP2C19 poor metabolizer status was only significantly associated with higher risk of adverse cardiac and cerebrovascular events after acute myocardial infarction, and this association was no longer significant when given in the context of stable angina. This suggests that, for clopidogrel, a clinician must consider the patient's CYP2C19 metabolizer status and the clinical context in which clopidogrel is given when deciding whether to alter therapy.

Warfarin
Warfarin is an anticoagulant that is known to have a narrow therapeutic window and there are a number of genetic, lifestyle, and clinical factors that may affect a patient's response.[27] A systematic review of ethnic differences in

Table 2 CYP2C19 drug interaction table[a]

Substrates	Inducers	Inhibitors
PPIs	*Antiepileptics*	*PPIs*
Esomeprazole	Carbamazepine	Esomeprazole
Lansoprazole	*Other*	Lansoprazole
Omeprazole	Efavirenz	Omeprazole
Pantoprazole	Enzalutamide	Pantoprazole
Antiepileptics	Norethindrone	*Other*
Diazepam → Nor	Prednisone	Chloramphenicol
Phenytoin(O)	Rifampicin	Cimetidine
S-mephenytoin	Ritonavir	Felbamate
Phenobarbitone	St. John's wort	Fluoxetine
Other		Fluvoxamine
Amitriptyline		Indomethacin
Carisoprodol		Isoniazid
Citalopram		Ketoconazole
Chloramphenicol		Modafinil
Clomipramine		Oral contraceptives
Clopidogrel		Oxcarbazepine
Cyclophosphamide		Probenicid
Hexobarbital		Ticlopidine
Imipramine *n*-deme		Topiramate
Indomethacin		Voriconazole
Labetalol		
R-mephobarbital		
Moclobemide		
Nelfinavir		
Nilutamide		
Primidone		
Progesterone		
Proguanil		
Propranolol		
Teniposide		
R-warfarin → 8-OH		
Voriconazole		

CYP, cytochrome P450; PPI, proton pump inhibitor.
[a]Adapted from the Flockhart table (University of Indiana).[75]

adverse events related to anticoagulants, including warfarin, showed that Asians were at increased risk of elevated international normalized ratio (odds ratio (OR), 3.8; 95% CI, 1.5–9.7), readmission for bleeding (OR, 4.0; 95% CI, 1.7–9.7), and intracranial hemorrhage (hazard ratio (HR), 4.06; 95% CI, 2.48–6.66) compared with Caucasians.[28] Previous work has shown that CYP2C9 and VKORC1 genotypes can predict 20% and 23% of a patient's response to warfarin, respectively.[27,29] The FDA has published dosing and administration recommendations for warfarin based on VKORC1, CYP4F2, and CYP2C9 genotypes.[30] VKORC1 is the main enzyme inhibited by warfarin and CYP2C9 is a major metabolizer of warfarin, so variation in these genes can result in a subtherapeutic warfarin response, increasing the risk of thromboembolism or a supratherapeutic response predisposing the patient to risk of bleeding.[31] The CPIC guideline recommends dosing adjustments for carriers of the vitamin K epoxide reductase complex (VKORC)1 rs9923231 single-nucleotide polymorphism (SNP) (also known as –1173 or 1639 G>A).[4] It has been reported that the VKORC rs9923231 SNP is present, on average, at a frequency of 88% in East Asians vs. 41% in Caucasians (European and North American) and 13% in African populations.[4] CPIC also recommends dose adjustments based on CYP2C9 intermediate or poor metabolizer status, but these phenotypes are not found at a substantially higher rate in Asians when compared with

other subpopulations (i.e., 33% for intermediate metabolizers in South/Central Asian vs. 32% in Caucasian).[4] CYP4F2 is an additional gene that has been shown to improve the accuracy of warfarin dose prediction models.[4] The CYP4F2*3 allele often requires an increase in warfarin dose and has been identified to vary markedly in frequency between ethnicities, with a frequency of 0.40 in Central Asian populations.[4,32] Warfarin is one of the most commonly used drugs in clinical practice with > 18 million prescriptions in the US in 2016, and it can result in potentially life-threatening adverse effects if not dosed properly.[33] The identification of adverse VKORC phenotypes with an increased prevalence in Asian populations that results in subtherapeutic warfarin response may be helpful in preventing adverse events.

ONCOLOGY
Irinotecan
Irinotecan is a topoisomerase I inhibitor and is approved as part of a combination therapy for the treatment of metastatic colorectal carcinoma.[34] There is also evidence of efficacy in the treatment of gastric, pancreatic, and some lung cancers.[35] Irinotecan is a prodrug metabolized by carboxylesterases to produce an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which is 100–1,000-fold more potent than the parent drug.[35] Irinotecan, in combination with folinic acid (leucovorin) and fluorouracil (FOLFIRI regimen), has been shown to prolong survival and has become a first-line treatment for metastatic colorectal cancer.[35] Glucuronidation of SN-38 theoretically decreases the irinotecan-induced side effects of severe delayed diarrhea and/or neutropenia, but variability in uridine diphosphate glucuronosyltransferases (UGTs), an enzyme that helps with irinotecan detoxification, can increase or decrease the side effects by changing the concentration of SN-38.[35] Estimating the frequency of poor metabolizers of UGT1A1 among various ethnic groups is challenging due to the numerous genotypes across various SNPs that produce the poor metabolizer phenotype. However, the UGT1A1*6 allele, which results in decreased enzyme activity, is > 18-fold more common in Asians (14.6%) compared with Caucasians (European and North American) (0.8%).[36] It should be noted that other alleles (*28, *37, or *80) that are associated with being a UGT1A1 poor metabolizer are also common in Asians, but the frequency is not markedly higher than in other ethnic populations.[36] The presence of the allele increases the risk of irinotecan-induced toxicities, such as severe diarrhea and neutropenia. The Dutch Pharmacogenetics Working Group recommends that poor metabolizers of UGT1A1 should start with 70% of the standard dose, and the dose can be increased based on neutrophil count if the patient tolerates the initial dose.[34]

Tamoxifen
Tamoxifen is a selective estrogen receptor modulator and an FDA-approved hormone therapy for metastatic breast cancer.[37] An estimated 90% of tamoxifen is demethylated by CYP3A4 to become *N*-desmethyltamoxifen and then oxidized by CYP2D6 to become an active metabolite, 4-hydroxy-*N*-desmethyl-tamoxifen (endoxifen), and a minor metabolic pathway involves the hydroxylation of
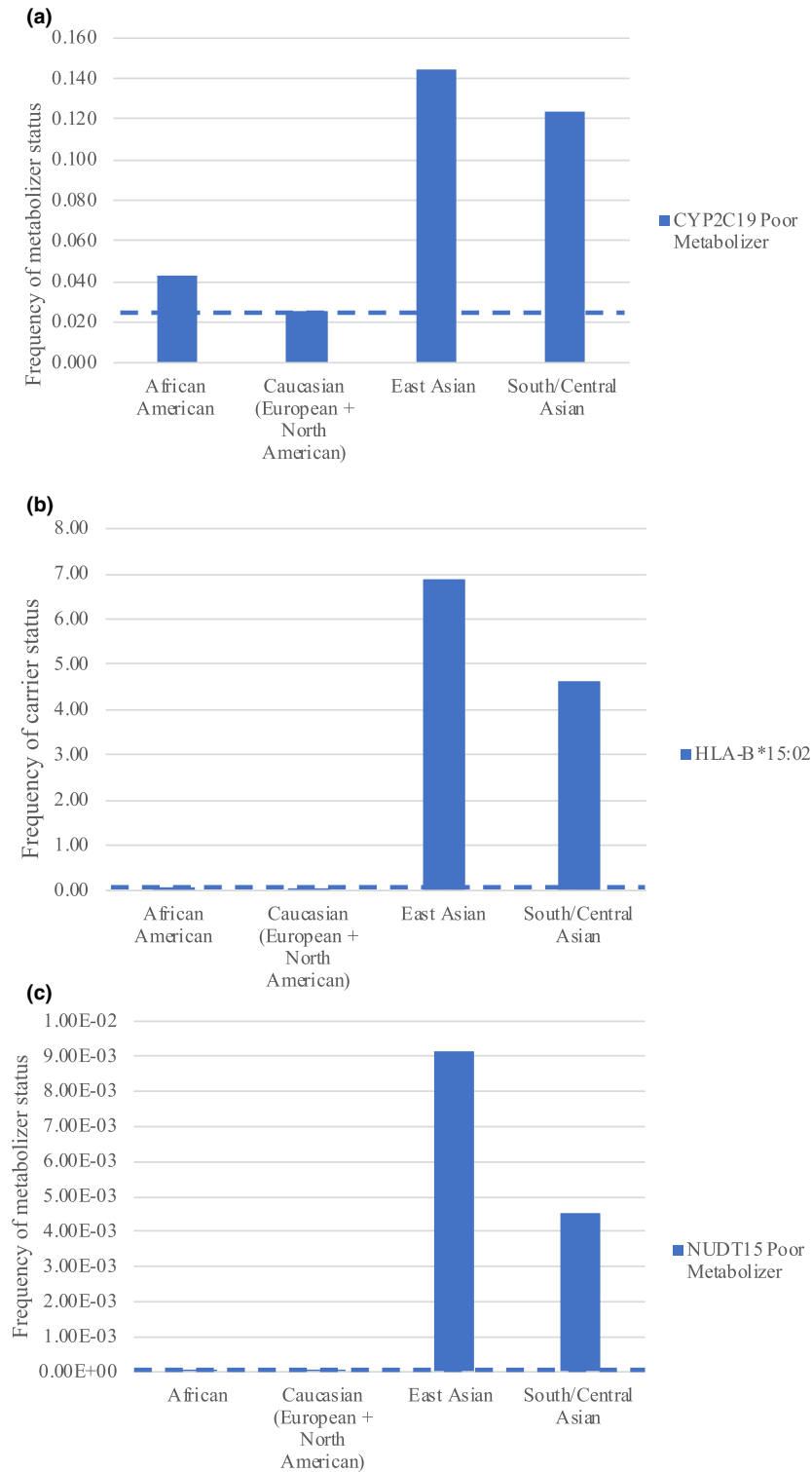
Figure 2 Frequency of adverse metabolizer status for various ethnic groups as reported by the CPIC guidelines. Dotted line represents baseline frequency in Caucasians (European and North American). (**a**) CYP2C19. Values found in the CPIC guideline for CYP2C19 and selective serotonin reuptake inhibitors, but this gene is also referenced in guidelines for clopidogrel, voriconazole, and tricyclic antidepressants (**b**) HLA-B. Values found in the CPIC guideline for HLA-B for carbamazepine and oxcarbazepine. (**c**) NUDT15. Values found in the CPIC guideline for TMPT, NUDT15, and thiopurines. CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, cytochrome P450; HLA, human leukocyte antigen; NUDT15, nucleoside diphosphate-linked moiety X-type motif15; TMPT, thiopurine *S*-methytransferase.

tamoxifen by CYP3A4, CYP2D6, and CYP2C19.[37] In the general population, East Asians consist of 1% of those with poor metabolism of CYP3A4 as compared with close to 0% in Caucasians (European and North American).[38] Also, East Asians consist of 0.8% of poor metabolizers of CYP2D6 and 19% of poor metabolizers of CYP2C19 as compared with Caucasians (European and North American) with 7% of poor metabolizers of CYP2D6 and 2% of poor metabolizers of CYP2C19.[38] Although the phenotypic differences for CYP2D6 do not vary greatly between ethnicities, it should be noted that there has been substantial work showing the increased prevalence of decreased function of CYP2D6*10 in Asian (42%) compared with Caucasian (3%) populations.[37,39] For poor and intermediate metabolizers of CYP2D6, other forms of hormonal therapy are recommended, such as aromatase inhibitors (anastrozole, letrozole, exemestane) for postmenopausal women or an aromatase inhibitor along with ovarian function suppression for premenopausal women.[37] Currently, the choice dosing regimen for poor metabolizers of CYP3A4 and CYP2C19 remains unclear.[37]

Allopurinol

Allopurinol is a xanthine oxidase inhibitor that is used for gout and hyperuricemia, and for the prevention of tumor lysis syndrome.[40,41] The medication is generally well tolerated but a common ADR related to allopurinol is severe cutaneous adverse reactions (SCARs), which is highly correlated with being a carrier of the HLA-B*58:01 allele.[40] SCARs comprise a spectrum of conditions, including Stevens-Johnson syndrome (SJS), severe toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms, and allopurinol hypersensitivity syndrome. The most common SCARs are SJS and TEN, which are life-threatening conditions that cause lesions of skin and mucous membranes.[40] HLA-B*58:01 is found most commonly in East Asian populations (6.1%) and has a fourfold (1.3%) greater risk of allopurinol-induced SCAR compared with Caucasians (European and North American).[6] The CPIC guidelines currently recommend that allopurinol should not be prescribed to patients who are carriers of HLA-B*58:01 and that an alternative therapy be used, such as febuxostat.[41-43] For individuals who are not HLA-B*58:01 carriers, the use of standard dosing of allopurinol is recommended.[41] A meta-analysis of 21 pharmacogenetic demonstrated that an allopurinol-induced SCAR is strongly associated with HLA-B*58:01 in matched (OR, 82.77; 95% confidence interval (CI), 41.63–164.58; $P < 10^{-5}$) and population-based (OR, 100.87; 95% CI, 63.91–159.21; $P < 10^{-5}$) studies. The same meta-analysis also showed that HLA-B*58:01 is a highly specific and effective genetic marker for the detection of allopurinol-induced SCAR, particularly in Asian populations.[44]

Thiopurines

Thiopurines are a class of drugs used as immunosuppressants in cancer and various rheumatologic conditions and include azathioprine, mercaptopurine, and thioguanine. Nucleoside diphosphate−linked moiety X-type motif 15 (NUDT15) is a gene that catalyzes the conversion of cytotoxic thioguanine triphosphate metabolites to a less toxic thioguanine monophosphate.[45] A loss-of-function mutation in NUDT15 reduces the degradation of toxic thiopurine metabolites and predisposes patients to myelosuppression.[45] Retrospective studies showed that patients with loss-of-function NUDT15 alleles were at an increased risk of thiopurine toxicity when the standard dose was administered.[45] According to the CPIC, NUDT15 poor metabolizers are approximately 620-fold more common in East Asians (0.9%) compared with Caucasians (European and North American) (0.0015%) (**Figure 2c**).[45] Although the absolute frequency of this phenotype is rare, it is very likely an oncologist will encounter an East Asian poor metabolizer of NUDT15, as approximately 1 of 100 East Asian patients will have this phenotype. This is in contrast to Europeans and Africans populations, where deficiencies related to the thiopurine *S*-methyltranferase gene are the primary cause of thiopurine intolerance.[45] In a study on NUDT15 polymorphism in relation to tolerance mercaptopurine, 404 Taiwanese children with acute lymphoblastic leukemia (ALL) and 100 adults with chronic immune thrombocytopenic purpura or localized lymphoma were tested for a NUDT15 poor metabolizer variant (rs116855232 C>T) associated with an intolerance to thioguanine and increased risk of hematopoietic toxicity.[46] Results showed that 11.6% of children with ALL and 15.5% of adults had the adverse NUDT15 rs116855232 allele—the frequency of this allele was estimated to be 9.6% in East Asian populations according to the CPIC.[45,46] Liang et al. suggested that this risk allele contributed to a reduced tolerance of mercaptopurine therapy, a backbone of ALL therapy.[46] In patients with the NUDT15 rs116855232 polymorphism, the maximal daily doses of mercaptopurine was lowest in homozygotes for the risk allele (TT) at 9.4 mg/m^2 and increasingly higher in heterozygotes (TC) (30.7 mg/m^2) and homozygotes for the wild-type allele (CC) (44.1 mg/m^2).[46] The NUDT15 gene plays a significant role in the metabolism of thiopurine drugs and, although the absolute frequency of poor metabolizer and loss-of-function alleles are rare, this phenotype shows a strong association with Asian descent and increased mercaptopurine toxicity.

NEUROLOGY AND PSYCHIATRY
Anticonvulsants

Anticonvulsant drugs are known to have serious cutaneous adverse effects influenced by pharmacogenetic variation, particularly in the human leukocyte antigen (HLA) family of genes. One of the initial studies looking for genetic markers of SJS in Han Chinese populations showed that the HLA-B*15:02 allele was present in 100% (44 of 44) of carbamazepine-SJS patients, but was only found in 3% (3 of 101) of carbamazepine-tolerant patients.[47] Previous studies have shown that, independent of genetic markers, Asians and African populations are at increased risk of SJS and TEN compared with other ethnicities.[48] The FDA now has a boxed warning with carbamazepine with regard to the risk of serious/fatal dermatologic reactions in HLA-B*15:02 carriers, and states the risk of a serious dermatologic adverse event in Asians is approximately 10-fold that of Caucasians (European and North American).[8] The phenytoin and carbamazepine CPIC guidelines state that HLA-B*15:02 carriers are more prevalent in Asian population and is associated

with increased risk of SJS and TEN.[6,49] The therapeutic recommendation is to not use carbamazepine, phenytoin, or fosphenytoin in HLA-B*15:02 carriers.[6,49] The CPIC guidelines report that East Asian and Oceanian populations have the highest frequency of HLA-B*15:02 carrier status at 6.88 and 4.64, respectively, in contrast to European populations, which have an HLA-B*15:02 carrier frequency of 0.04 (**Figure 2b**).[49] Another study also demonstrated an association between HLA-B*15:02 and oxcarbazepine−SJS ($P = 1.87 \times 10^{-10}$; OR, 27.90; 95% CI, 7.84−99.23) in Chinese populations.[50] Similar findings with the HLA-B*15:02 allele and carbamazepine have been reported in Asian populations for severe cutaneous reactions, such as SJS, TEN, and drug hypersensitivity syndrome.[2]

Antidepressants

Commonly used antidepressants include classes of drugs such as selective serotonin reuptake inhibitors and tricyclic antidepressants. The CPIC guideline for selective serotonin reuptake inhibitors recommends that doses of citalopram and sertraline be reduced by 50% in those who are poor metabolizers of CYP2C19.[51] Two of the most common star alleles producing poor metabolism of CYP2C19 are CYP2C19*2 and *3. Asian populations are more than twice as likely to have CYP2C19*2 and *3 compared with Caucasian (European and North American) or African populations.[51] For example, the rate of CYP2C19*2 in South Asians is 34% compared with 15% in Caucasians (European and North American).[51] CYP2C19 metabolizer status (**Figure 2a**) is also used in the CPIC guideline for tricyclic antidepressants, where individuals with poor metabolism are recommended secondary amines such as nortriptyline, which are not metabolized by the CYP2C19 pathway.[5] Development of pharmacogenetic guidelines is a useful way to provide clinicians with succinct recommendations on how to alter prescribing based on genetic data. In summary, the majority of pharmacogenetic adverse events in Asian populations using neuropsychiatric drugs are related to HLA and CYP genes, with the most well-studied being the increased risk of SJS/TEN in Asians using carbamazepine. Compared with other therapeutic classes, our understanding of the pharmacology of neuropsychiatric drugs is limited and, as our understanding improves, further interactions may likely be discovered.

INFECTIOUS DISEASE AND RHEUMATOLOGY
Voriconazole

Voriconazole is a triazole antifungal medication used to treat invasive fungal infections commonly seen in immunocompromised patients such as invasive candidiasis and invasive aspergillosis.[52] Voriconazole is metabolized predominantly by CYP2C19 (**Figure 2a and Table 2**) and the wide interpatient variability in voriconazole concentrations can be attributed in part due to activity of CYP2C19. ADRs with voriconazole include hepatotoxicity, neurotoxicity, photopsia, skin rash, photosensitivity, visual disturbances, and periostitis, as well as decreased clinical response to invasive fungal infections.[53]

CYP2C19 is highly polymorphic, with 35 defined variant alleles and, although decreased or no-function alleles are

relatively rare in the population—as mentioned previously in this review—CYP2C19*3, a poor metabolizer allele, is found to be more common in Asians.[54] Approximately 15% of East Asians are CYP2C19 poor metabolizers, which is 5.8-fold the rate in Caucasians (European and North American) (2.5%).[52] The CPIC recommendation for poor metabolizers is to choose an alternative agent that is not dependent on CYP2C19 metabolism.[54] Otherwise, voriconazole should be administered at a lower dose than standard, with therapeutic drug monitoring.[52] It should be noted that the evidence directly linking CYP2C19 phenotype to voriconazole toxicity is limited, but a strong association has been reported between poor metabolizers and increased voriconazole concentrations, resulting in ADRs such as hepatoxicity and neurologic disorders.[55] Alternative agents for treatment of invasive mold infections that use an alternative metabolic pathway and could be useful in those with poor metabolism of CYP2C19 include isavuconazole, lipid formulations of amphotericin B, and posaconazole.[52] CPIC acknowledges that there is a paucity of studies on those with intermediate metabolism (heterozygotes for a no-function allele such as *1 or *3), with inconsistent findings.[52] However, genotyping is not a replacement for therapeutic dose monitoring, and other factors, such as drug interactions, hepatic or renal function, and epigenetic phenomena, influence dose and use of voriconazole.[52]

Pegylated interferon-α

Pegylated interferon-α (PEG-IFN-α) is a cytokine that modifies biologic signaling and is commonly used to treat chronic hepatitis C (HCV) and various types of cancer.[56] It is commonly used in combination with ribavirin-based regimens to achieve sustained virologic response (SVR), defined as aviremia for 12–24 weeks, at end of therapy and results in lower morbidity and mortality.[57] However, SVR rate and associated side effects vary with ethnicity and it is hypothesized that is in part due to genetic predisposition.[57] Other viral and host factors affect the ability to achieve SVR, such as obesity, diabetes, and hepatic fibrosis or steatosis.[58]

The gene IFNL3, or IL28B, encodes for interferon-L3, which has antiviral activities and is critical in spontaneous or treatment-induced HCV clearance by inhibiting HCV replication.[59] The IFNL3 responder phenotype can be classified as either "favorable" or "unfavorable" with regard to promoting sustained SVR and has been shown to predict significant differences in monocyte, T-cell and natural killer–cell levels.[56] For previously untreated patients with HCV genotype 1, the IFNL3 genetic variation is a strong predictor for treatment response, particularly SNPs rs12979860 and rs8099917, which are associated with a twofold increase in achieving SVR in HCV genotype 1 patients.[56] The frequency of the IFNL3 favorable response based on the rs12979860 genotype is highest among East Asians (77%), approximately twofold that of Caucasian (European and North American) populations (38%).[56] Clinically, this is significant, as a poor IFNL3 response may warrant the addition of a protease inhibitor in combination with PEG-IFN-α and ribavirin therapy. In contrast to the other examples mentioned in this review, an IFNL3 favorable phenotype is more prevalent in Asian subpopulations, which may warrant increased use of

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PEG-IFN-α in these patients due to an increased likelihood of treatment success.

Atazanavir

Atazanavir is a highly selective HIV protease inhibitor and is often prescribed in combination with ritonavir, a pharmacokinetic enhancer, as it has been shown to have similar efficacy but a more favorable side-effect profile compared with other combination therapies.[60] However, there are many limitations and side effects, especially the unintended inhibition of UGT1A1. UGT1A1 is required for the conjugation of bilirubin, and its inhibition leads to buildup of unconjugated bilirubin, resulting in symptoms similar to those seen with Gilbert's syndrome, a typically asymptomatic liver condition. Extreme bilirubin elevation can cause systemic symptoms such as jaundice in adults and kernicterus in neonates.[36] Essentially all patients who take atazanavir have some elevation of bilirubin from baseline.[36] Asian Americans have the lowest rates of having never received HIV testing (66.5%), but they represent the only ethnic group with a continuous increase in HIV infection rate in recent years, despite the lower worldwide incidence of HIV infection.[61] UGT1A1*6, a decreased function allele, occurs almost exclusively in Asians (14.6%) compared with Caucasians (European and North American) (0.8%), and is associated with higher bilirubin level and Gilbert's syndrome.[36] The CPIC guidelines recommend that knowledge of the UGT1A1 genotype would be helpful before prescribing atazanavir, particularly for those who are homozygous for a reduced function allele, due to the high risk of developing jaundice.[36] Atazanavir can still be prescribed to poor metabolizers of UGT1A1, but may be discontinued if jaundice is a significant concern.[36] The association between UGT1A1 genotype and atazanavir side effects is an example of how pharmacogenetics can inform a tailored discussion of risks and benefits in a particular patient.

LIMITATIONS

A caveat of the frequency differences present in **Figure 2** is to consider that the absolute size of each population subtype in a given practice will vary widely and does not account for the possibility of admixed populations. However, it is important to consider these differences for providers who work with large groups of ethnic minorities. In addition, this review does not offer a comprehensive list of all drugs that may require special attention in Asian populations. As seen in **Table 2,** CYP2C19 is involved in the metabolism of many drugs, so the implications of CYP2C19 poor metabolizer status being more common in Asians may apply to these drugs as well. There are also many associations reported in the literature with various Asian subgroups, but this review is limited to a selection of the most well-studied studies and, consequently, those initially identified in individuals of European descent. For example, there is evidence to suggest that Loss Of Function variants in SLCO1B1 that are more common in Asians are associated with higher rates of statin-induced myopathy.[62] However, there was no clear ethnic trend seen in the summary statistics published in the CPIC guidelines for simvastatin and SLCO1B1.[63] There

is also increasing evidence for pharmacogenetic associations relevant to the Asian population in other common drugs such as metformin, which show genetic differences in membrane transporters impacting drug efficacy.[64,65] However, from the current evidence, it is difficult to quantify how much more likely these reactions are in Asian populations relative to other populations.[64,65] The role of ethnicity in pharmacogenetics is undoubtedly an evolving field, as heritability estimates of SNPs in pharmacogenetic studies of warfarin derived from primarily European cohorts have been found to be different in other ethnic groups.[66] This suggests that there may exist "hidden" associations in ethnic differences due to background genome or environmental effects that alter drug response. These points highlight the value of Asian-specific genomic databases, as the existing databases that include a variety of ethnicities such as GNOMAD typically have a relatively small number of Asians.[67] There are a number of projects, such as the South Asian Genomes and Exomes database and the GenomeAsia100k, that aim to produce ethnicity-specific resources in previously underrepresented populations.[68,69]

A common limitation of pharmacogenetic studies is the use of stringent inclusion criteria for adverse events and underreporting in observational studies that may underestimate the true prevalence of clinically relevant adverse events. For example, a 2006 systematic review of 37 studies from 12 countries estimated that > 90% of adverse drug reactions go unreported.[70] This landscape is complicated by the fact that the majority of research in the United States is informed by studies conducted using subjects who are primarily of European descent and male.[71] As mentioned earlier in this review, we were also limited by the availability of aggregated data and acknowledge that "Asians" are not a genetically homogeneous group. Some subgroups, such as Chinese, Japanese, and Korean, are mentioned more prevalently compared with others, such as Vietnamese and Filipino. Our review has also not addressed the impact of environment on genetics and genetic variances. For example, Asians living in the United States are exposed to different social and environmental parameters compared to those living in Asia which may impact their drug metabolism. The comparisons made throughout this study between Asian and Caucasian populations are further complicated by the fact that the CPIC includes North American populations as being Caucasian.[19] Increasingly, North America is becoming more genetically diverse, with a significant admixture of ethnicities. This may result in an underestimation of the ethnic differences in pharmacogenetic variants.

FUTURE IMPLICATIONS

Moving forward, individuals of Asian descent could be better served by conducting further pharmacogenetic studies on ethnically diverse cohorts and summary statistics for genetic studies that report these groups separately. A recent 2017 systematic review highlighted the increase in Asian-specific studies in recent years and noted a number of novel associations that emerged.[7] In addition, we are not advocating for all Asian patients to be screened for these variants—as with any screening test, the utility of a widely

implemented pharmacogenetic screening strategy should be assessed by criteria such as those set out by the World Health Organization: (i) "Is there a convenient and validated test of the risk factor? (ii) "Does testing provide clinically significant prognostic value above and beyond that provided by traditional risk factors?" (iii) "Do we know how to interpret the results of the test?" (iv) "Does the intervention that alters the risk factor lead to clinical benefit?" (v) "What are the direct and indirect risks of screening?"[72] Targeted screening for higher probability and actionable phenotypes in Asian populations specifically may provide increased justification for utilization of the test, particularly as the costs of genetic testing continue to decrease rapidly.

Many patients are now obtaining pharmacogenetic test results from direct-to-consumer (DTC) companies and as a clinical service. In fact, it could be argued that some DTC companies such as 23andme are developing a greater genetic understanding of specific populations when compared with academic efforts.[73] However, DTC companies still struggle with the same issues of making predictions based on European-descent cohorts and applying these interpretations to non-European customers. Given this influx of genetic information into health care, there is an imperative for providers to receive guidance on how to interpret these already existing results. As care providers, in addition to remembering some of the key interactions discussed here, there is also a need to understand the principles in which genetic variation may influence a patient's drug metabolism and how this could relate to their clinical outcome. Increasingly, we believe that knowledge of basic pharmacogenetic principles will become a larger part of clinical practice.

CONCLUSIONS

There are a number of well-studied pharmacogenomic-related adverse events and prescribing considerations that are more prevalent in Asians compared with other subpopulations. The majority of these associations are due to Asians more commonly being poor metabolizers of CYP2C19 and carriers of the HLA-B*15:02 allele. The resulting adverse events that are more prevalent in Asians range from reduced drug efficacy to severe cutaneous skin reactions. These reactions are severe and prevalent enough to warrant pharmacogenetic testing and appropriate changes in dosing and medication choice for at-risk populations. Our review has highlighted the complexity that comes with making generalizations about the ethnic differences in pharmacogenetic variants. Further work is needed in non-European populations to elucidate the differences in existing variants and to identify new variants that may be challenging to find in traditional pharmacogenetic cohorts. Such efforts will be crucial to translating pharmacogenetic knowledge to clinically useful recommendations that can be accurately applied in ethnically diverse populations around the world.

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