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The expanding role of gene-based prescribing for phase II drug-metabolizing enzymes

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ABSTRACT

Clinical pharmacogenomics has expanded rapidly with the ability to translate evidence from basic science findings into actionable decisions guiding pharmacotherapy in – various disease states. Most findings with potential clinical relevance have been in drug-metabolizing enzymes where variation could cause interindividual differences in response and efficacy. Conventionally, these metabolizing enzymes are classified as Phase I and Phase II enzymes. Although Phase II enzymes are responsible for the metabolism of many drugs, research has focused more on variation in Phase I enzymes. Our aim in this review was to discuss from a historical to present context, the research on key variants in major Phase II enzymes and to summarize clinical pharmacogenetic association studies that could help guide future translation into practice. We evaluated pivotal articles in PubMed (1980–2022) on human pharmacogenomic studies (preclinical and clinical) of N-acetyltransferases (NATs), methyltransferases, glutathione transferases, sulfotransferases, and glucuronosyltransferases for the evidence of clinical applicability and utility. Of the 5 Phase II enzyme superfamilies reviewed, there is presently evidence to support clinical utility for gene-based prescribing for two of them. A third family (NATs) is evaluated as having strong likelihood for future utility in the pharmacological treatment of acquired immunodeficiency syndrome-associated opportunistic infections, tuberculosis, and endemic diseases.

Keywords: Phase II variants, Genetic variations, Pharmacogenomics, Drug-metabolizing enzymes, Gene-based prescribing

INTRODUCTION

The efficacy and safety of a drug are often influenced by interpatient variability in pharmacokinetic (PK) processes such as absorption, distribution, biotransformation/metabolism, and elimination (ADME).[1] The physiologic processes involved in ADME reflect the actions of a variety of enzymes and transport proteins. Many of these enzyme systems expressed in the lungs, liver, intestines, and kidneys are especially critical to the processes of drug metabolism and subsequent elimination from the body.[2] Drug-metabolizing enzymes (DMEs) have historically been subdivided into phase I enzymes that catalyze oxidation, reduction and hydrolytic reactions, and phase II enzymes that catalyze conjugation reactions.

Many DMEs are genetically polymorphic in humans, a property that contributes to the interindividual variability in PK for many drugs. Historically, early reports on genetic variability in drug concentrations and response were for phase II DMEs, for example, N-acetyltransferases (NATs) and isoniazid.[3] Over time, greater focus has centered on cytochrome P450 enzymes,

which make up the bulk of phase I enzymes. This is not surprising considering that P450 enzymes contribute to the metabolism of approximately 75% of prescription drugs.[2] However, many phase II enzymes also play key roles in the metabolism of many clinically important drugs, and genetic differences affecting metabolism could lead to differential effects in drug response. In this review, we describe the current status of genetic variability in phase II DMEs followed by the potential clinical relevance of such variability.

GENETIC VARIABILITY IN PHASE II DMES

Phase II DMEs are called conjugation enzymes due to their role in facilitating the transfer of polar endogenous substrates onto readily available sites on drug molecules. As a result, they are called *transferases*. This section will cover genetic variations and its implications for major phase II enzymes: N-Acetyl transferases (NATs), methyltransferases (mainly thiopurine S-methyl transferase and catechol O-methyl transferase), glutathione S-transferases (GSTs), sulfotransferases (SULTs), and UDP-glucuronosyltransferases (UGTs).

NATs

Background

The human NAT gene locus comprises two genes, *NAT1* and *NAT2,* that encode 2 enzymes (NAT1 and NAT2), responsible for the transfer of acetyl groups (acetylation) to aromatic amines and hydrazines, as well as to heterocyclic amine groups present in many drugs and carcinogens.[4] These enzymes are responsible for the acetylation of a variety of drugs, but the highly polymorphic NAT2 is known for its role in the N-acetylation of several antituberculosis agents including isoniazid and pyrazinamide. It is also responsible for acetylating sulfonamide-containing antibiotics (sulfamethazine and sulfamethoxazole) and the antihypertensive agent, hydralazine. The correlation between *NAT2* genotype and acetylation phenotype is a classic in the field of pharmacogenomics and has been extensively reviewed.[5-9]

Results from early experiments with isoniazid identified a bimodal distribution in urinary acetylated metabolites and led to the assignment of "slow" and "rapid" acetylator phenotypes. These studies also showed that not all N-acetylated drugs exhibited this polymorphism, and for those that did, NAT2 was the enzyme responsible. Later studies suggested that the acetylator phenotype was more trimodal than bimodal incorporating the "intermediate" or "heterozygous rapid" acetylator phenotype.[10,11]

Genetic variation and testing

The reference allele for the *NAT2* gene is the *NAT2*4* allele. Phenotypic expression (acetylation) of this allele is described as rapid, intermediate, and slow for individuals with two, one, or zero copies of the **4* allele. The various haplotypes identified for *NAT2* are available online.[12] The most common single-nucleotide polymorphisms (SNPs) and nucleotide changes associated with acetylator phenotypes are rs1801279 (191G > A), rs1041983 (282C > T), rs1801280 (341T > C), rs1799929 (481C > T), rs1799930 (590G > A), rs1208 (803A > G), and rs1799931 (857G > A). Varying combinations of these yield the characterized *NAT2*5*, **6*, **7*, and **14* (slow acetylator) and the *NAT2*11*, **12,* and **13* (rapid acetylator) haplotypes. Each of these numbered alleles have several clusters of these SNPs assigned and are designated with an alphabet suffix for differentiation (e.g., the **5* haplogroup has the *NAT2*5A* to **5V* haplotypes). The 7 SNPs above serve as the basis for *NAT2* genotyping, although there is an extremely wide variation of allele frequencies between and within various ethnic groups.[13-15]

The marked variation in allele frequencies[14,16] has generated differing opinions on the usefulness of the seven SNP panels. In 2011, a tag SNP (rs1495741) was identified from genome-wide studies.[17,18] For economies of scale in genotyping, especially for resource-constrained areas, efficient SNP selection was advocated based on computational strategies[19] with 2-, 3-, and 4-SNP panels proposed and tested.[20] The ability of the tag SNP to infer acetylator phenotype has been compared with the 2, 3, 4, and 7 SNP panels; the 4-SNP panel is suggested to maximize sensitivity and specificity, particularly in populations of non-European ancestry in whom inference of *NAT2* phenotypes from SNP panels has been problematic.[21-24]

Methyltransferases

Methyltransferases are responsible for catalyzing the transfer of methyl groups to suitable donor atoms – (O, N, and S) on both endogenous and exogenous compounds, utilizing the methyl donor, S-adenosylmethionine. The 2 enzymes responsible for the majority of phase II drug methylation are the catechol-O-methyltransferases (COMT) and thiopurine S-methyltransferases (TPMT).

COMT

Background

COMTs are responsible for the O-methylation of biogenic catecholamines such as the neurotransmitters dopamine, epinephrine, and norepinephrine, as well as catechol-containing drugs such as the antihypertensive drug, methyldopa, and antiparkinsonian drug, L-dopa. It also methylates other endogenous catechol compounds such as the catechol estrogens formed *in vivo* from estrone and 17β-estradiol.[25] The pharmacogenetics of *COMT* has been reviewed by Weinshilboum *et al*.[25] and the distribution of

genotypes differs by ethnicity. With respect to genotype–phenotype correlations, functional polymorphisms leading to high and low activity forms of the soluble enzyme have been identified; these can be phenotyped by measuring erythrocyte *COMT* activity.[26]

Genetic variation and testing

The first *COMT* polymorphism, described by Lachman *et al*.,[26] was the functional polymorphism rs4680 322/472 G > A (Val108/158Met substitution in the soluble or membrane-bound forms of the enzyme, respectively). The major G (or Val) allele is expressed as the high *COMT* activity allele and the A (or Met) as the low activity allele. There are ethnic differences in prevalence; the frequency of the A allele ranges from 29% to 51% in Asian and European populations.[26] While rs4680 is a key *COMT* variant, 3 other SNPs, rs6269 A > G, rs4633 C > T, and rs4818 C > G, found in a tightly linked haploblock have been combined with it to yield high, intermediate, and low activity *COMT* haplotypes.[27] There is currently no defined star (*) allele nomenclature for *COMT*. In addition to the 4 SNPs mentioned, other studies have included rs737865 A > G, rs9332377 C > T, and rs165599 G > A SNPs.[28,29] To date, rs4680 remains the only functional *COMT* non-synonymous coding SNP, although a single association study identified another functional non-synonymous SNP rs6267 G > T (Ala72Ser substitution in the membrane bound form).[30] Other studies have reported functional haplotypes that include rs4680 and other synonymous coding SNPs (rs4633, rs4818).[31,32] Many of these *COMT* SNPs are represented on large-scale genome and exome-wide genotyping chips and rs4680 remains the most commonly referenced *COMT* SNP in commercial genotyping panels.[33]

TPMT

Background

TPMT catalyzes the S-methylation of thiopurine drugs such as azathioprine (AZA), 6-mercaptopurine (6-MP), and thioguanine (TG), as well as other heterocyclic sulfur-containing compounds.[34] TG and 6-MP are widely used for the treatment of lymphoid (6-MP) and myeloid malignancies,[35,36] and AZA and 6-MP are used to treat non-malignant conditions such as inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid disease. All three compounds are prodrugs that are activated to the same TG nucleotide (TGN) active metabolites; *TPMT* tempers this activation process by yielding inactive methyl 6-MP and methyl TG compounds.[37]

Thiopurines have a class effect of cytotoxicity, with a side effect profile that includes severe myelosuppression. The clinical implication is that individuals with low *TPMT* activity have higher blood levels of active TGN metabolites, and thus greater myelosuppression. The risk of developing life-threatening myelosuppression has been shown to be greatest in individuals with very low red cell *TPMT* activity treated with "standard" doses of thiopurines.[38] This relationship between *TPMT* activity and TGN levels was demonstrated in key studies reporting both trimodality[39] and a correlation between *TPMT* activity and TGN levels.[40,41] The pharmacogenetics of *TPMT* has been extensively studied and validated and a concise summary of the enzyme is available.[42] This summary along with information regarding its genetic architecture and relevant clinical annotations is also found on the Pharmacogenomics Knowledge Base (PharmGKB) website.[43,44]

Genetic variation and testing

TPMT genotypes are grouped into predicted phenotypes of normal or high activity, intermediate activity, and low or deficient activity based on the number of functional or variant alleles present. The reference allele for *TPMT* is the **1* or the high activity allele. Variant alleles representing low or deficient activity include **2* (rs1800462 C > G), **3A* (rs1142345 T > C and rs1800460 C > T), **3B* (rs1800460), **3C* (rs1142345), and **4* (rs1800584 C > T). The **3A* is a combination haplotype of the **3B* and *C* alleles and is the most common *TPMT* variation in Caucasians (frequency of approximately 5%).[45] The **3C* occurs more frequently in East Asian and African American populations, exemplifying the finding of major ethnic differences in allele frequency. *TPMT* phenotype was initially obtained from erythrocyte *TPMT* activity;[9,39] however, as with other DMEs, genotyping is now typically used to predict phenotype. There are over 40 variant alleles reported on PharmGKB and the *TPMT* allele nomenclature websites.[44,46] There are commercial and in-house Clinical Laboratory Improvement Amendments approved assays for *TPMT* genotyping with extremely high call rates, concordance, and accuracy.

GSTs

Background

The *GSTs* are a diverse group of enzymes responsible for conjugating reduced glutathione to electrophilic centers present on a variety of substrates, including endogenous and exogenous compounds. *GSTs* are implicated in drug metabolism as well as detoxification (and sometimes activation) of procarcinogenic agents.[2] They catalyze glutathione-conjugated inactivation of the anticancer agents, etoposide and busulfan, and the platinum-derived compounds; cisplatin, oxaliplatin, and carboplatin, in addition to drugs such as isoniazid, rifampicin, and pyrazinamide.

GSTs belong to a superfamily of soluble enzymes that have been further subdivided into different classes – alpha, delta, kappa, mu, omega, pi, theta, zeta, and microsomal proteins. Unlike many of the genes encoding other DMEs, each *GST* member has a unique chromosomal location.[47] Four of these, *GST* alpha (*GSTA*), *GST* theta (*GSTT*), *GST* mu (*GSTM*), and *GST* pi (*GSTP*), encoded by the *GSTA1*, *GSTT1*, *GSTM1,* and *GSTP1* genes, respectively, are implicated in phase II metabolism and are the most studied with respect to their pharmacogenetics.

Genetic variation and testing

GSTA1 is a major hepatic *GST* enzyme,[48] but has few genetic variations and those present are either of no known relevance or of minimal clinical importance.[49] *GSTM1*, *GSTP1,* and *GSTT1*, on the other hand, are more polymorphic, with *GSTM1* and *GSTT1* possessing common insertion/deletion (InDel) variants.[48]

In *GSTM1,* there is a common deletion expressed as a null allele or a non-null allele for the insertion variant, and a promoter SNP, rs3754446A > C, occurring with different ethnic frequencies (ranging from 1% to 6% in those of African ancestry to 67% in Asians). In *GSTT1,* there is also a deletion polymorphism characterized as the *null* or *GST*0* or *GST1 negative* allele as well as rs1007888C > T and rs4630> A SNPs.[50-53] *GSTP1* has no known deletion polymorphisms. Rather, there are two common non-synonymous SNPs, rs1695G > A (Ile105Val) and rs1138272C > T (Ala114Val), that appear to lower enzyme activity.[54,55]

All common *GSTT1*, *GSTM1,* and *GSTP1* polymorphisms are represented on many commercial genotyping panels and are part of core ADME gene lists.

SULTs

Background

Human *SULTs* are responsible for the sulfate conjugation of many important endogenous compounds and drugs. Substrate specificity differs for each *SULT* enzyme family of which the best characterized are *SULT1A, 1B, 1C, 2A, 2B,* and *4A* families.[54] The SULT1A family is composed of *SULT1A1*, *1A2,* and *1A3* enzymes that catalyze the sulfate conjugation of phenolic compounds, including simple phenols like nitrophenol, as well as catecholamines. Well-known substrates include drugs such as acetaminophen, dopamine, and minoxidil. Of all the *SULT* enzymes, *SULT1E1* has the highest substrate affinity and is responsible for the sulfation of both natural and synthetic estrogens, while other steroid hormones are sulfated mostly by the SULT1B and 2B families.[56-58] Genotype–phenotype correlation for *SULT* activity was initially conducted using biochemical assays for *SULT1A1* and subsequently *SULT1A2* enzymes.[59,60] These studies showed over 50-fold variation in phenotypic (biochemical) activity in human platelet *SULT* activity that correlated with low- and high-activity genotypes.

Genetic variation and testing

The *SULT* isoforms currently implicated in human phase II drug metabolism are *SULT1A1*, *1A2, 1A3,* and *1E1,* all encoded by highly polymorphic genes. *SULT1A1* is the most abundant and most important. This isoform has four haplotypes assigned – **1* the reference allele, **2* (rs9282861 G > A), **3* (rs1801030 G > A), and **5* (rs28374453 T > C). In addition, three SNPs in the coding region of the gene, *SULT1A1,* have copy number polymorphisms (X2 to X5, reflecting 2–5 copies of the gene) and two promoter SNPs rs3760091 G > C and rs750155 G > A that are of functional importance.[61]

SULT1A2 has three haplotypes assigned, **1* the reference allele, **2* (with two variants rs1136703 A > T, C, G and rs1059491 T > G), and **3* (rs10797300 C > G). All the above-listed *SULT1A* SNPs are non-synonymous coding polymorphisms that cause amino acid changes.

SULT1E1, encoding the only member in the 1E family, has four haplotypes assigned with the reference allele designated as **1* and 3 other polymorphic alleles differing in single nucleotide variations from the reference designated as **2* (rs11569705 C > A), **3* (rs34547148 G > A), and **4* (rs11569712 G > T). As with the *SULT1A* genes, these SNPs are non-synonymous coding polymorphisms. The *SULT1E1* variants occur at very low frequencies, ranging from 0.5 to 0.9% for the **2* and **4* alleles, and there is no well-defined minor allele frequency for the **3* variant. With respect to genotyping tests, only *SULT1A1* polymorphisms are represented (with varying degrees of SNP and copy number coverage) on some commercial genotyping platforms.

UGTs

Background

The superfamily of enzymes responsible for the conjugation of a glucuronic acid moiety onto suitable acceptors on a wide range of endogenous and exogenous substrate compounds are known as UDP-glucuronosyltransferases or uridine diphosphoglucuronosyl transferases (UGTs). The products of this conjugation are called glucuronides. Glucuronidation is an efficient metabolizing process contributing to over 30% of all phase II drug metabolism.[62] In addition to playing a role in the metabolic elimination of oral drugs, glucuronidation also serves a protective function through detoxification and elimination of carcinogens. Human UGTs are found in two main families – UGT1 and UGT2.

UGT1

The UGT1 gene family is composed of 12 *UGT1A* genes on a large and complex locus. The complexity occurs because each *UGT1A* gene has a unique exon 1 spliced to four common conserved exons (2–5).[63] Each gene is named *UGT1A1* to *UGT1A12* based on the proximity of the unique first exon to the shared ones. Although 12 distinct gene products exist in humans, four of these, *UGT1A2, UGT1A11, UGT1A12, and UGT1A13,* are pseudogenes. Genetic variations spanning the range of polymorphism mechanisms have been reported for all *UGT1A* active gene products and many have been characterized and studied in detail.[64-66] The pharmacogenetics of UGTs and their role in health, disease, and cancer have been extensively reviewed.[67-90]

UGT2

Enzymes in the UGT2 family fall into either 2A or 2B subfamilies. UGT2A members are mostly olfactory enzymes implicated in the detoxification of airborne xenobiotics and toxins. UGT2B enzymes, on the other hand, are responsible for the glucuronidation of both drugs and endogenous steroid hormones. Of the human UGT2 enzymes, UGT2B7, 2B15, and 2B17 are the most studied, although UGT2B7 seems to be the isoform with the greatest contribution to the glucuronidation of clinically useful entities.[72,91-94]

Genetic variation

The complexity of the *UGT1A* locus and its shared exons confers the advantage that many enzyme isoforms have overlapping substrate specificity. This could explain the fact that although several functional polymorphisms exist, effects are usually not large enough for meaningful clinical correlations. The one exception is *UGT1A1*, the sole enzyme responsible for bilirubin glucuronidation. A genetic difference in bilirubin clearance (leading to familial hyperbilirubinemia) has been ascribed to a key polymorphism (rs8175347 or $TA_{5/6/7/8}$) in the promoter region) resulting in variable enzyme expression and function. This variation, a short tandem TA repeat polymorphism, has the greatest clinical relevance among known *UGT1A* polymorphisms. Individuals with 6 TA repeats (*UGT1A1*1*) have normal *UGT1A1* protein expression (and activity), carriers of 7 (*UGT1A1*28*) and eight repeats (*UGT1A1*37*) have reduced enzyme activity, and those with 5 TA repeats (*UGT1A1*36*) have increased protein expression *in vitro*.[60-62] Reported allele frequencies for *UGT1A1*28* are between 0.26 and 0.31 in Caucasians and 0.42–0.56 in African Americans. *UGT1A1*36* and **37* are almost exclusive to African populations (allele frequencies between 0.02 and 0.1). The **28* allele is rarely found in Asian populations; rather, a functional SNP in exon 1 rs4148323G>A (*UGT1A1*6*) with allele frequencies of 0.16–0.22 is responsible for the reduced bilirubin conjugation phenotype.[95]

Associated haplotypes for all defined *UGT* SNPs are on the UGT allele nomenclature website.[96] In *UGT1A3*, two non-synonymous SNPs in the promoter region, rs2007584A > G and rs1983023T > C, constitute the **2* haplotype which has been linked to increased atorvastatin inactivation by lactonization both *in vitro* and *in vivo*.[79,97] In *UGT1A6*, similar to *UGT1A3*, two non-synonymous SNPs, rs1105879 A > C and rs2070959, are found in the **2* haplotype associated with high activity *in vitro*. *UGT1A6* polymorphisms have been implicated in aspirin metabolism and colorectal cancer risk.[77,98] For *UGT1A9*, one of the most studied polymorphisms is rs3832043T>-, a deletion polymorphism located in the promoter region (*UGT1A9*1b* formerly named *UGT1A9*22*).[76,99] This polymorphism has been implicated in the PKs and side effect profiles of irinotecan and mycophenolic acid.[73,80,100,101]

DISCUSSION – PHASE II DME GENE-BASED PRESCRIBING POTENTIAL AND PROGRESS

For a DME genetic variant to be clinically useful, certain fundamental criteria are required. First is the mapping, identification, and characterization of genes (and variants) involved in the drug's disposition. Next is the establishment of a reproducible and predictable association between the variants and a measurable phenotypic response. For many DMEs, the response is typically altered PKs. It is important, however, to consider that genetic variation is not the only cause of altered drug concentrations. Interactions with other drugs and food could also result in variable drug concentrations. Thus, functional variants may have little clinical relevance unless there is a genetic signal large enough to overcome the effects of other sources of variability.

The next step involves developing a standardized genotyping test. This is usually followed by a confirmation of the predictive value of genotyping, ideally under rigorous, well-defined conditions such as prospective clinical studies. On confirmation and validation of predictive value, adoption of genotyping in the clinic is usually dependent on the magnitude of effect and the clinical consequences conferred by the defined genetic variability. Figure 1 depicts a representative flow chart of the multiplicity of processes involved in determining the clinical utility of any identified DME variants with a potential for altering human drug responses.

Clinical studies – progress, implications, and recommendations

NATs

This class of enzymes is involved in the metabolism of many drugs and possesses genetic variants mostly implicated in

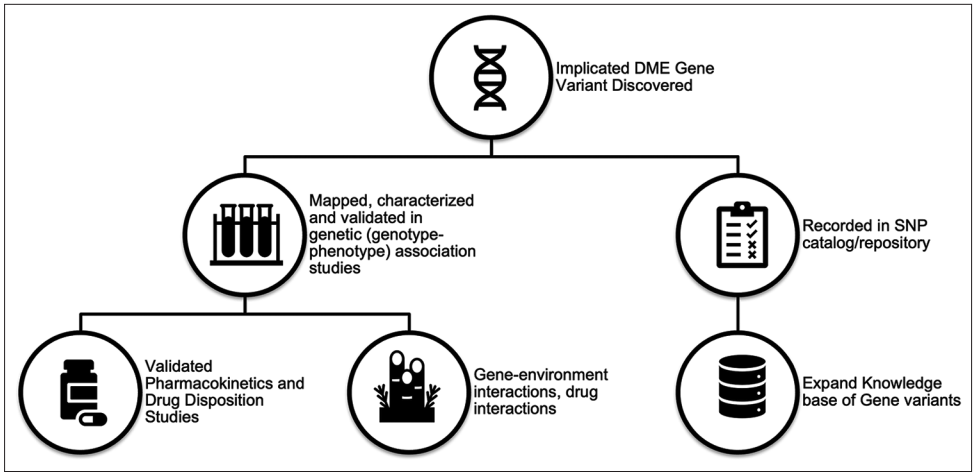

Figure 1: Simplified flowchart of criteria involved in determining clinical utility of any identified drug-metabolizing enzyme variants with the potential for altering drug response in humans.

Table 1: Key Phase II genes with clinical therapeutic consequences due to genetic variation.

Gene	Enzymatic reaction implicated	Drug and therapeutic use	Clinical consequences of impaired or decreased metabolism due to genetic variation
*TPMT**	*S*-Methylation	6-Thiopurines (anti-cancer)	Myelotoxicity.
*UGT1A1**	Glucuronidation	Irinotecan (anti-cancer)	Reduced clearance. Dose adjustment may be required to avoid toxicity (GI dysfunction, and immunosuppression).
GST	GSH Glutathione-conjugation	Busulfan (anti-cancer)	Impaired GSH conjugation due to gene deletion.
NAT2	*N*-Acetylation	Hydralazine (antihypertensive)	Lupus erythematosus-like syndrome.
	N-Acetylation	Isoniazid (antitubercular)	Peripheral neuropathy.

*Genes (and enzymes) with PGx-based therapeutic recommendations, TPMT: Thiopurine methyl transferases, UGT1A1: Uridine diphosphoglucuronosyl transferase, GST: Glutathione S-transferases, NAT2: N-acetyltransferase, GSH: Glutathione

clinical studies of acetylator phenotypes and isoniazid effects and toxicity. Other NAT pharmacogenetic areas of interest include adverse events such as skin reactions with sulfonamides and drug-induced lupus with hydralazine [Table 1].

Isoniazid remains a first-line drug for the treatment of latent and active tuberculosis, but problems include hepatic injury and treatment failure. Both problems have been associated with genetic differences in acetylation capacity, but the evidence is mixed with some studies reporting conclusive associations and others little or no association. Various meta-analyses of hepatic injury associated with antituberculosis drugs attributed an odds ratio between 1.59 and 4.7 to the slow acetylator genotype and risk of developing hepatic injury.[102-106] This association was more robust in individuals of Asian, Middle Eastern and Brazilian ancestry, with no significant associations for Caucasians, and very limited data in the African population.

As concerning isoniazid-associated hepatic injury, treatment failure for tuberculosis could have broader clinical and economic consequences since second-line drug regimens are usually more expensive and toxic. It has been hypothesized that rapid acetylators, due to extremely rapid inactivation of the parent isoniazid, do not attain adequate blood levels for optimal therapeutic response. The concept of using pharmacogenetics-guided isoniazid dosing to treat pulmonary tuberculosis using the WHO-recommended 6-month four-drug regimen was tested in a prospective randomized clinical trial.[107] Based on the results of PK dose-ranging studies, the isoniazid genotype-guided dose for slow and rapid acetylators was 0.5 and 1.5 times the standard dose used for intermediate acetylators, respectively. Despite the small sample size for slow ($n = 7$) and rapid ($n = 44$) acetylators in the pharmacogenetics guided arm and $n = 9$ and 48 in the standard treatment arm, the results were interesting. Hepatic injury occurred in 7 of 9 slow acetylators (78%) receiving standard dosing and in none of the seven who received pharmacogenetic-guided doses. In rapid acetylators, there was a significantly lower incidence of treatment failure in the test arm (15%) compared to standard treatment (38%). This study along with others modeled around it[108] illustrates the potential for *NAT2* genotype guided dosing, at least in the context of isoniazid.

Recommendation

Although there is no clear consensus regarding the clinical utility of *NAT2* genotyping, the potential of *NAT2* genotype-

guided regimens for isoniazid-based therapies bears consideration for use in treatment. This genotype-guided consideration may be most relevant for populations with a high TB burden and a prevalence of slow acetylators. The WHO over a decade ago recommended an increase in standard dosing for isoniazid from 5 to 10 mg/kg body weight for pediatric patients (Rapid advice: Treatment of Tuberculosis in Children, WHO, 2010). This higher dosing most likely favors increased efficacy in rapid acetylators while posing a greater risk of hepatotoxicity for slow acetylators. As a result, the potential utility of genotyping remains important, and more clinical studies clearly defining the relationship between acetylator status and isoniazid efficacy or toxicity will be helpful.

Methyltransferases

COMT

For *COMT*, the most relevant associations include those for exogenous levodopa used in the treatment of Parkinson's disease, and entacapone, the direct *COMT* inhibitor, used as an adjunct to boost effects of levodopa. There are studies on *COMT* genotypes and response to levodopa with some finding no association, and others showing the association between increased levodopa doses and greater functional activity *COMT* haplotypes.[26,109,110] A recent meta-analysis confirmed an association between the well-studied rs4680 and levodopa-induced dyskinesia.[111] The association between entacapone effects and *COMT* genotypes has also been inconsistent.[112,113]

Recommendations

Although a recent review on Parkinson's disease called for personalized treatments relying on pharmacogenetic procedures to optimize therapeutics in its management,[114] there is not enough evidence for using *COMT* pharmacogenomics profiles for gene-based prescribing.

TPMT

TPMT is one of the most successful examples of translating genetic variation in a DME into clinically relevant gene-based prescribing (for the purine-based analogs – azathioprine, 6-MP, and TG). The association between thiopurine use and risk of severe, potentially fatal myelosuppression, particularly in patients homozygous for *TPMT* low-activity variant alleles, has been long documented, especially in pediatric acute lymphoblastic leukemia.[115-118] For non-malignant conditions (e.g., inflammatory bowel disease) [Table 1], results are more mixed with earlier studies reporting associations and yet others reporting a lack of association between *TPMT* low-activity genotypes and azathioprine toxicity.[119-122] One plausible explanation for this discrepancy includes the lower doses used in non-malignant conditions compared to malignancy, and small sample sizes that may not include individuals at greatest risk of serious toxicity; the approximately 0.3% of patients are homozygous for *TPMT* low-activity alleles.

Recommendations

TPMT genotyping and dose adjustment recommendations are on FDA drug label information for thiopurine drugs. There are also guidelines published by the Clinical Pharmacogenetics Implementation Committee (CPIC)[36,123] on the use of genotyping for thiopurine drug therapy available for reference on both the CPIC and PharmGKB websites.[43,124] Suggested recommendations are stratified by thiopurine use in malignant and non-malignant conditions; information about genotype-based dosing by *TPMT* diplotype can be obtained from PharmGKB and from NCBI's Medical Genetics Summaries.[125]

GSTs

GSTs are involved in the disposition of alkylating agents such as busulfan and thiotepa, as well as the platinum-based compounds cisplatin, oxaliplatin, and carboplatin, the mainstay of chemotherapy for many cancers. The toxicities seen with many of the anticancer agents conjugated by glutathione have been attributed in part to the depletion of cellular glutathione, which leads to a buildup of toxic products and, subsequent, DNA damage. As a result, individuals with null variant genotypes may be predisposed to increased drug toxicity but better response due to greater intracellular drug accumulation.

Pharmacogenetic studies on drug response or toxicity and *GST* polymorphisms have produced inconsistent results. For *GSTM1* and *GSTT1*, most studies have focused on the null/non-null variants. Studies have reported an association between non-null *GST* genotypes and increased risk of ototoxicity in male testicular cancer survivors and in pediatric patients with solid tumors with odds ratios of 2.76 (1.35–5.64) and 10 (1.8–56.0), respectively.[126,127] The study on testicular cancer survivors had a haplotype consisting of the *GSTM1* and *GSTT1* null polymorphisms and the *GSTP1* rs1695 A > G SNP; the other study reported only an association with the *GSTT1* null genotype. The *GSTM1*/*GSTT1* double null haplotype has also been associated with lower clearance of intravenous busulfan in adult patients undergoing hematopoietic stem cell transplantation, although the association was no longer present when the effects of the individual *GST* null variations were modeled.[128] One study reported an association between a SNP (rs4630) in *GSTT1* and thalidomide-induced neuropathy in multiple myeloma.[129] This study reported that

23% of heterozygous carriers of the minor allele experienced toxicity compared to 60% of the homozygous patients; however, the cohort was small (28 patients), thus limiting interpretation of the findings.

GSTP1 has no null polymorphisms but has a well-studied functional SNP rs1695 (Ile105Val). Within the *GST* superfamily, this SNP probably has the most associations ascribed to it, and implicated in studies related to toxicity, response, and overall survival in colorectal cancer.[130,131] The minor G (Val) allele was associated with increased survival in patients receiving 5-FU/oxaliplatin therapy (median progression-free survival of 24.9, 13.3, and 7.9 months for patients bearing 2, 1, and 0 copies, respectively). This observation was subsequently validated in a second study.[132,133] Two other studies also confirmed a positive benefit on survival and response rate for patients bearing the G alleles.[134,135] However, in studies of ovarian and breast cancer, the opposite has also been observed with the major A allele being associated with increases in response rate and overall survival.[136-138] Some reasons for the differences in association trends could depend on the type of cancers studied as well as the regimens used. With respect to drug toxicity caused by platinum agents, an early pivotal study found an increased risk of neurotoxicity with the GG genotypes[139] while others reported an increase in neurotoxicity with the AA genotypes.[140,141]

Recommendations

Despite the numerous studies cited on pharmacogenomic studies of *GSTs* and pharmacotherapy with cytotoxic agents such as busulfan and platinum-containing agents, there is inadequate evidence to suggest that genotyping for *GST* polymorphisms would alter current standards of therapy.

SULTs

There are few clinical studies examining the pharmacogenetics of *SULT* enzymes and most have addressed cancer risk, which is beyond the scope of this review. *SULT1A1* pharmacogenetic associations have been studied for a role in the metabolism of tamoxifen, a mixed estrogen receptor agonist/antagonist, used as an adjuvant treatment for breast cancer. Results are mixed with better or worse outcomes associated with the *SULT1A1*2* allele.[142-145]

Recommendations

At present, there is inadequate evidence to support the clinical utility of *SULT* genotyping.

UGTs

Most clinical studies have focused on the TA repeat polymorphism and the disposition of the anticancer agent, irinotecan. The TA repeat polymorphism was reportedly associated with irinotecan side effects such as neutropenia and diarrhea due to the decreased ability of TA_7 carriers to clear the active metabolite SN-38 as the glucuronide.[74,82] However, not all studies have supported this finding with many studies finding no association between *UGT1A1**28 [Table 1] and irinotecan response or side effects and instead contending that pharmacogenetic findings are dependent more on a combination of haplotypes from *UGT1A* genes.[73,76] Different meta-analyses on associations between *UGT1A1* genotypes and irinotecan response and toxicity have effectively summed information about genetic associations with irinotecan dosing and side effects.[82,88,90] Dias *et al*.[88] examined the difference in objective response rate (ORR) between cancer patients with different *UGT1A1*28* genotypes (homozygous, heterozygous, and wild type variants) receiving irinotecan-based therapies and found no differences in ORR based on genotype. Another study carried out subgroup analyses with different irinotecan dose and combination regimens and found a greater than four-fold increased risk of neutropenia with the *UGT1A1*28* homozygous genotype compared to wild type. The risk of diarrhea was increased two-fold and limited to high dose irinotecan or combined use with 5-fluorouracil or its analogs.[90] The potential for individualization of irinotecan dose based on UGT genotype has been proven to improve clinical care in multiple PK and dose-optimization studies conducted from the time of initial reports.[146-150]

Recommendations

The TA repeat polymorphism (*UGT1A1*28* in the Caucasian population) was one of the earliest pharmacogenomic biomarkers approved by the United States FDA for reference on a drug label.[151] The agency-approved label for one irinotecan product has the following stated recommendation – "*when administered in combination with other agents or as a single agent, a reduction in the starting dose by at least one level should be considered for patients known to be homozygous for the UGT1A1*28 allele*" with no precise dose reduction provided. Another product, however, has a dose specification with a caveat to consider dose modifications based on individual tolerance to treatment (50 mg/m^2 administered by intravenous infusion over 90 min, with an increased dose to 70 mg/m^2 as tolerated in subsequent cycles).[152]

CONCLUSION

The implementation and clinical translation of phase II DME pharmacogenomics has advanced substantially from case reports and observations based on serendipity and small series of cases to the current state of using prospective well-designed trials to yield evidence for clinical utility. Genotyping for variants in 2 of the 5 major phase II DME superfamilies, *TPMT* and *UGT1A1*, is in clinical

use. However, for other phase II enzymes, the evidence supporting clinical utility is either weak or inconsistent. Further, characterization of *NAT2* pharmacogenomics is of great interest due to the potential to improve the treatment of tuberculosis, a serious endemic disease.

REVIEWERS' EXECUTIVE SUMMARY

Phase II enzymes are a major class of human DMEs that contribute to the metabolism of many drugs.

- They are responsible for drug detoxification through conjugation reactions
- The major phase II enzymes are NATs, methyltransferases, *GSTs*, *SULTs*, and glucuronosyltransferases.

Phase II enzymes are underrepresented in the clinical implementation of pharmacogenetic testing

- Historical to the current scope of studies exploring key pharmacogenomic variants with evidence for the utility of this information in clinical practice is presented.

Perspectives on recommendations for genotype-based prescribing based on available clinical evidence include

- *NAT2* genotyping may have potential utility in isoniazid-based regimens but additional studies are required
- There is not enough evidence to guide recommendations for *COMT* and *SULT* genotyping
- Evidence for the potential clinical utility of genotyping *GST* polymorphisms is conflicting
- *TPMT* genotype-guided therapy for thiopurine dosing is implementable in a variety of clinical settings
- *UGT1A1*28* genotype is associated with an increased risk of irinotecan toxicity and there is evidence for the use of a genotype-guided approach to irinotecan dosing in cancer.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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