

Pharmacogenomics and adverse drug reactions: Primetime and not ready for primetime tests



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1. To become familiar with pharmacogenetic associations of drug hypersensitivity.
2. To be able to recognize pharmacogenetic associations with immediate and delayed hypersensitivity drug reactions.
3. To identify US Food and Drug Administration (FDA)-issued alerts for pharmacogenetic screenings.

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Adverse drug reactions (ADRs) are a relatively common cause of morbidity and mortality. Many factors can contribute to ADRs, including genetics. The degree to which genetics contributes to ADRs is not entirely clear and varies by drug, as well as the type of ADR. Pharmacogenetics and, more recently, pharmacogenomics have been applied to the field of ADRs for both predictable ADRs and hypersensitivity drug reactions. Evaluations for glucose-6-phosphate dehydrogenase and thiopurine S-methyltransferase are commonplace clinical tests to reduce hematologic problems associated with drugs, such as dapsone and azathioprine, respectively. Numerous pharmacogenetic associations have been discovered for

immediate hypersensitivity reactions to β -lactams, aspirin, and nonsteroidal anti-inflammatory drugs; however, the clinical utility of testing for these genetic associations has not been established. In contrast, pharmacogenetic testing for *HLA-B*1502* before carbamazepine in patients of certain Asian ethnicities and testing for *HLA-B*5701* before abacavir treatment are recommended. This review will focus on pharmacogenetics and pharmacogenomics and their role in reducing ADRs, especially those caused by drug hypersensitivity reactions. (*J Allergy Clin Immunol* 2016;138:943-55.)

Key words: Pharmacogenetics, pharmacogenomics, drug allergy, adverse drug reactions, drug hypersensitivity, β -lactam, nonsteroidal anti-inflammatory drug, abacavir, carbamazepine

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Medications are a cornerstone of the therapeutic armamentarium for most clinicians. The goal of pharmacotherapy is to cure or control a specific condition or disease without causing adverse effects. Unfortunately, adverse drug effects are common and not always predictable. Adverse drug reactions (ADRs) have been defined as reactions that are noxious and unintended and occur at doses normally used in human subjects.¹ ADRs can be related to a number of factors, including known pharmacologic activity of a drug, drug interactions, drug toxicity,

Abbreviations used

ADR:	Adverse drug reaction
AERD:	Aspirin-exacerbated respiratory disease
ALL:	Acute lymphoblastic leukemia
CYSLTR:	Cysteinyl leukotriene receptor
DRESS:	Drug reaction with eosinophilia and systemic symptoms
G6PD:	Glucose-6-phosphate dehydrogenase
GWAS:	Genome-wide association study
LTC4S:	Leukotriene C ₄ synthase
NSAID:	Nonsteroidal anti-inflammatory drug
OR:	Odds ratio
SCAR:	Severe cutaneous adverse reaction
SJS:	Stevens-Johnson syndrome
SNP:	Single nucleotide polymorphism
TEN:	Toxic epidermal necrolysis
TPMT:	Thiopurine S-methyltransferase

and drug hypersensitivity. ADRs are a relatively common cause of morbidity and mortality.

In 1998, Lazarou et al² performed a meta-analysis of 39 prospective studies in the United States evaluating ADRs in hospitalized patients. They reported an overall incidence of serious ADRs of 6.7% and fatal ADRs of 0.32%. Based on data from 1994, they estimated that 106,000 fatalities occurred in the United States from ADRs, making these reactions between the 4th and 6th leading cause of death. A more recent review of 51 studies on ADRs in hospitalized patients from different countries found severe ADRs ranging from 10.9% to 74.5% of all ADRs.³

Although predictable type A reactions (eg, bleeding from warfarin) are the most common cause of ADRs, hypersensitivity reactions can represent up to one third of ADRs.⁴ In the aforementioned study by Lazarou et al,² the frequency of hypersensitivity reactions among all ADRs was reported for 8 studies, with a mean of 23.8%, but no studies reported the types of reactions among severe or fatal reactions. In a follow-up study of the Boston Collaborative Drug Surveillance Program, 2.2% of hospitalized patients were determined to have benign exanthems to drugs, with antibiotics being the most frequent culprit.⁵ Other studies from different countries and settings have shown very similar results.⁶

Although in the past ADRs were often viewed as unpredictable and unavoidable problems associated with pharmacotherapy, several strategies have now been used to reduce ADRs. Errors in dosing and nonadherence account for a substantial portion of medicine-related problems and can be minimized through a number of approaches. Genetics are another significant contributing factor in ADRs. Genetic factors can play a role in pharmacokinetics, pharmacodynamics, and susceptibility to hypersensitivity responses. The degree to which genetics contributes to ADRs is not entirely clear and varies by drug, as well as the type of ADR. One author has estimated that genotyping just for P450 would lead to a reduction in ADRs by 10% to 15%;⁷ however, this remains unproved. This review will focus on pharmacogenetics and pharmacogenomics and their role in reducing ADRs, especially those caused by drug hypersensitivity.

BACKGROUND ON PHARMACOGENETICS

At its most basic, the term pharmacogenetics describes any influence that genetics can have on drug therapy. The newer term

pharmacogenomics is often used interchangeably with pharmacogenetics, but there are some subtle differences. Pharmacogenetics mainly deals with single drug-gene interactions. In contrast, pharmacogenomics incorporates genomics and epigenetics to look at the effect of multiple genes on drug responses. Pharmacogenomics is considered the future of drug therapy and is a rapidly growing field in the area of precision (personalized) medicine. Fig 1 illustrates how pharmacogenomic approaches have been used in drug hypersensitivity.

Many factors can determine whether differences in genetic polymorphisms will be clinically relevant.⁸ The therapeutic index of a drug is one important factor. A polymorphism affecting the concentration of a drug that is safe over a wide range of concentrations is unlikely to have a clinically relevant effect. However, if a drug has a narrow therapeutic window (eg, warfarin), minor variations in concentrations from polymorphisms could be important. If the metabolite of a drug has a similar effect as the parent drug, polymorphisms in the enzyme creating the metabolite are unlikely to be important. If multiple metabolic or elimination pathways are present for a drug, the effect of a polymorphism affecting one pathway might also be negligible. Regarding drug hypersensitivity, polymorphisms must not only be associated with a significant risk but also have a degree of specificity that would not eliminate a large proportion of patients who would unlikely be harmed by taking the drug.

HISTORY OF PHARMACOGENETICS

One of the earliest examples of pharmacogenetic observations is from Pythagoras, who noted in 510 BC that some subjects would have an acute illness and even die after ingestion of fava beans.⁹ It was not until 1956 that we discovered that a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD) was the cause of hemolytic anemia from ingestion of fava beans or drugs such as primaquine.¹⁰ Shortly after this, pseudocholinesterase deficiency was discovered as a genetic cause for prolonged apnea from anesthesia with succinylcholine.¹¹ Fig 2 shows a timeline of some important discoveries of pharmacogenetics regarding ADRs.

One of the most well-known early examples of the genetics of drug metabolism is the acetylation polymorphism. Studies from the early 1950s observed that isoniazid, which was at the time a recently introduced treatment for tuberculosis, had marked differences in excretion among patients. These differences were discovered to be related to differences in a subject's ability to convert isoniazid to acetylisoniazid, and "slow acetylators" were more likely to have peripheral neuropathy.¹² These studies triggered many further epidemiologic, pharmacologic, and clinical studies in numerous countries, providing a model of how pharmacogenetic traits could be analyzed.¹³ This acetylation polymorphism also influenced the metabolism of other drugs, including sulfonamides, dapsone, hydralazine, procainamide, and many others. Many decades later, the molecular causes of these traits were discovered. Cloning of cDNA encoding the enzyme N-acetyltransferase led to identification of 2 common alleles, NAT2*5 and NAT*6, which account for more than 90% of slow-acetylator alleles.¹³

In 1957, Motulsky¹⁴ highlighted the genetic basis of adverse reactions to primaquine and succinylcholine in an article entitled

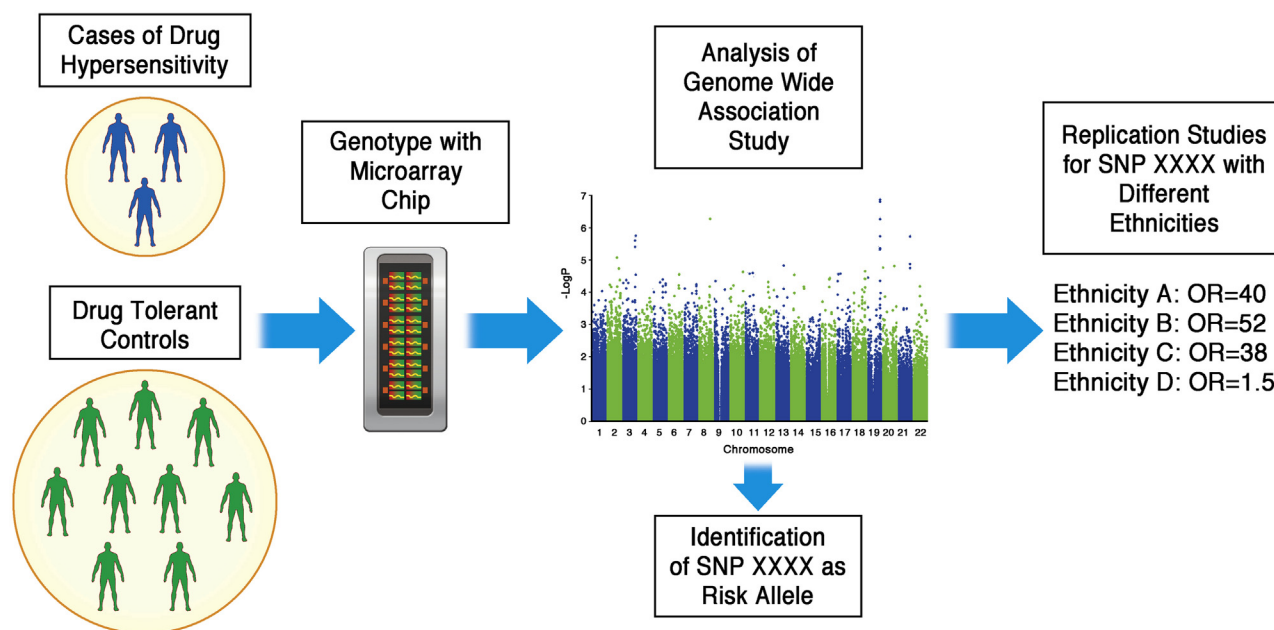


FIG 1. Application of pharmacogenomics to drug hypersensitivity and influence of ethnicity on genotype-associated risk.

“Drug reactions, enzymes and biochemical genetics.” He noted that “hereditary gene-controlled enzymatic factors determine why, with identical exposure, certain individuals become ‘sick,’ whereas others are not affected.” This article is thought to represent the beginning of pharmacogenetics as a discipline; the term “pharmacogenetics” was coined 2 years later by Vogel.¹⁵ Other seminal observations were made by Vesell and Page,¹⁶ who performed pharmacokinetic studies on twins and noted that differences in drug metabolism were genetically determined for several drugs, including phenylbutazone, antipyrine, and phenobarbital.¹⁶⁻¹⁸ The term pharmacogenomics was introduced in the 1990s with the emergence of the Human Genome Project. Fifty years after his seminal article on genetics and ADRs, Motulsky and Qi¹⁹ noted that “there is a tendency to over promise the future impact of pharmacogenetics or personalized medicine” and that considerably more research “is required before clinical applications of pharmacogenetics and pharmacogenomics will be realized.” Ten years later, this statement is still largely true.

PHARMACOGENETICS IN NONHYPERSENSITIVITY ADRs

A relatively common clinical use of pharmacogenetics involves ADRs that are not caused by hypersensitivity reactions. Prominent examples to be discussed include CYP isoenzymes, thiopurine S-methyltransferase (TPMT), and G6PD.

CYP isoenzymes

One of the most widely studied drug-metabolizing enzymes is the P450 enzyme CYP2D6. Studies from the 1970s found significant variability in metabolism of the antihypertensive drug debrisoquine and the antiarrhythmic drug sparteine, leading

to life-threatening side effects in susceptible subjects. By 1990, the gene for CYP2D6 was cloned, and a detailed sequence analysis led to identification of mutant alleles and a DNA-based genetic assay for identifying the poor metabolizer phenotype.²⁰ Well over 2500 articles have been published on the CYP2D6 enzyme since its discovery because it affects the metabolism of numerous common drugs, including codeine, antidepressants, statins, and antiplatelet therapies.¹³ Although genetic assays are available to identify many polymorphisms of CYP enzymes, routine genotyping is not considered standard practice because many have not been validated by prospective studies and others (eg, clopidogrel) have not been proved to reduce adverse effects in meta-analyses.²¹⁻²³

TPMT

TPMT is responsible for the metabolism of thiopurine drugs, such as azathioprine and 6-mercaptopurine. Polymorphisms in the *TPMT* gene can result in a marked decrease in enzymatic activity and increased risk for drug-induced leukopenia. The most common genotypes accounting for the vast majority of deficient TPMT activity are *TPMT**3A, *TPMT**2, and *TPMT**3C.²⁴ PCR-based methods for genotyping show excellent concordance between genotype and phenotype. However, less than 1% of the population has low to absent TPMT levels, and only approximately 25% of cases of leukopenia from azathioprine are caused by genetic polymorphisms. The American College of Gastroenterology indicates “many authorities” recommend a TPMT assay before azathioprine therapy and recommend the qualitative phenotypic assay over the genotype.²⁵ The British guidelines for inflammatory bowel disease recommend measuring TPMT levels before azathioprine but indicate that this is “still controversial.”²⁶

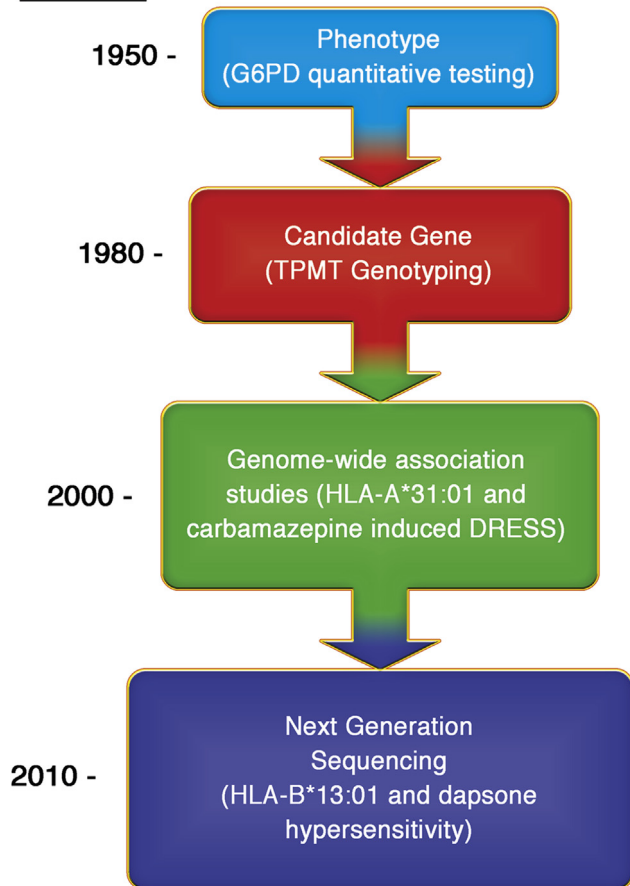
Timeline

FIG 2. Timeline of important pharmacogenetic discoveries and technologies used.

G6PD dehydrogenase

G6PD deficiency, an X-linked disorder, is the most common enzymatic disorder of red blood cells, affecting approximately 400 million people worldwide. Many drugs with oxidant potential can cause hemolysis in patients with G6PD deficiency, including dapsone, primaquine, rasburicase, and methylene blue. Screening before administration of some of these agents is recommended for nonurgent situations, such as before dapsone use in patients with chronic urticaria.²⁷

PHARMACOGENETICS/PHARMACOGENOMICS OF IMMEDIATE DRUG HYPERSENSITIVITY

Oussalah et al²⁸ have recently reported genetic associations with immediate drug reactions in a systematic review. They identified 42 studies reporting genetic predictors in association with immediate drug hypersensitivity. Nineteen were related to β -lactams, 12 to aspirin, 8 to other nonsteroidal anti-inflammatory drugs (NSAIDs), and 3 to other biologic agents.

Genetic associations with immediate β -lactam reactions

Based on prior associations of polymorphisms of T_H2 cytokines and IgE in patients with other allergic disorders, several studies have looked for associations of some of these

cytokines or receptors in patients with β -lactam allergy (Table I).²⁹⁻⁸⁵ Seven studies found associations with IL-4-related genes and β -lactam-induced immediate reactions,²⁹⁻³⁵ with 2 of these studies also finding associations with IL-13-related genes.^{30,31} Similarly, polymorphisms in the gene encoding for the Fc ϵ RI β subunit (*MS4A2*) have shown associations in 2 studies for both penicillin³⁶ and cephalosporin³⁷ allergy. A single study found a specific single nucleotide polymorphism (SNP) in signal transducer and activator of transcription 6 associated with penicillin allergy.³⁸ Associations of immediate reactions to β -lactams with polymorphisms in other inflammatory pathways (eg, IL-10, IL-18, TNF, *NOD2*, and IFN- γ) have also been reported.^{32,39-43} Many of these studies had significant limitations, including lack of clearly defined penicillin allergy, lack of confirmation of penicillin allergy, small populations, and use of healthy control subjects (not atopic control subjects without β -lactam allergy). Finally, none of these studies found any genetic associations that would be diagnostically predictive of β -lactam allergy.

To date, only one study using a pharmacogenomics approach has been conducted evaluating subjects with immediate reactions to β -lactams. Gueant et al⁴⁴ performed a genome-wide association study (GWAS) in 2 populations from Spain and Italy. The cohort from Spain included 436 subjects with immediate reactions to β -lactams (85% caused by amoxicillin) and 1124 control subjects paired for sex and age. The cohort from Italy consisted of 362 subjects with β -lactam allergy (47% caused by amoxicillin) and 299 age- and sex-matched control subjects. Control subjects for both cohorts had less atopy and lower total IgE levels. All subjects had β -lactam allergy identified based on history of an immediate reaction and either positive skin test results or positive drug provocation. Anaphylactic shock was reported in 51% of Spanish subjects and 79% of Italian subjects. SNPs in the HLA-DRA region were associated with a 1.6-fold reduction of β -lactam allergy in the Spanish cohort, specifically amoxicillin and penicillins but not cephalosporins. This was confirmed in the Italian cohort. Other SNPs were found in the Spanish cohort but either not confirmed or with a lower association in the Italian cohort.

Whether these findings can be extrapolated to other ethnicities or geographic locations is unclear. Furthermore, the clinical utility of these findings is unclear. Given the relatively modest reduction in risk, it seems unlikely that screening for any of the identified SNPs would have enough predictive power to make clinical recommendations based on the outcomes.

Aspirin/NSAID hypersensitivity

Aspirin-exacerbated respiratory disease. Korean investigators have performed the majority of studies evaluating genetic associations with the aspirin-exacerbated respiratory disease (AERD) phenotype of asthma. Initial studies were candidate gene association studies comparing the frequency of candidate gene polymorphisms between patients with AERD and control subjects with aspirin-tolerant asthma. Because dysregulation of the arachidonic acid metabolism pathway is important in the pathogenesis of AERD, initial studies focused on candidate genes in this area. A number of SNPs were reported to be associated with AERD from this pathway from several genes, including 5-lipoxygenase (*ALOX5*), COX2 (*COX2*), cysteinyl leukotriene receptors (*CYSLTR1/CYSLTR2*), leukotriene C_4

TABLE I. Pharmacogenetic associations and immediate hypersensitivity reactions

Medication	Genetic variant	Ethnicity	Type of evidence	References	Screening recommended
β -Lactams	<i>IL4, IL4R</i>	Chinese, European, United States	7 Case-control studies	29-35	No
	<i>IL13</i>	Chinese, European	2 Case-control studies	30,31	
	<i>FCER1</i>	Chinese, Korean	2 Case-control studies	36,37	
	<i>STAT6</i>	Chinese	1 Case-control study	38	
	<i>IL10</i>	European, Chinese	2 Case-control studies	32,39	
	<i>IL18</i>	Chinese	1 Case-control study	43	
	<i>TNF</i>	European	1 Case-control study	40	
	<i>IFNG</i>	Chinese	1 Case-control study	41	
	<i>NOD2</i>	European	1 Case-control study	42	
	<i>HLA-DRA</i>	European	1 GWAS study	44	
Aspirin/NSAIDs	Arachidonic acid metabolism				No
AERD	<i>ALOX5</i>	United States, Korean	2 Case-control studies	73,74	
	<i>COX2</i>	European	1 Case-control study	67	
	Cysteinyl leukotriene receptors	Korean	2 Case-control studies	76,77	
	<i>LTC4S</i> (positive association)	Eastern European	1 Case-control study	78	
	<i>LTC4S</i> (negative association)	United States, Japanese, Australian, Spanish, Korean	5 Case-control studies	45-49	
	Prostaglandin E ₂ receptor	Korean, Japanese	3 Case-control studies	79-81	
	Thromboxane A ₂ receptor	Korean, Japanese	2 Case-control studies	82,83	
	Other select genes				
	<i>CEP68</i> (centrosomal protein)	Korean	1 GWAS study	50	
	<i>HLA-DPB1</i>	Korean	1 GWAS study	51	
	<i>HLA-DQB1*0302</i>	Iranian	1 Case-control study	52	
Aspirin/NSAID-exacerbated chronic urticaria	<i>ALOX5</i>	Korean	1 Case-control study	53	
	<i>LTC4S</i>	Eastern European, Venezuelan	2 Case-control studies	54,84	No
	<i>FCER1</i>	Korean	2 Case-control studies	55,85	
	<i>TGFB1</i>	Korean	1 Case-control study	56	
	<i>TNFA</i>	Korean	1 Case-control study	57	
	Histamine N-methyltransferase	Korean	1 Case-control study	58	
	<i>IL18</i>	Korean	1 Case-control study	59	
	Prostaglandin E ₂ receptor	Korean	1 Case-control study	60	
	<i>HLA-B44</i>	European	1 Case-control study	61	
	No association	Spanish, Chinese	1 GWAS study	62	
Multiple NSAID/aspirin-induced acute urticaria	<i>ALOX5</i>	Spanish	2 Case-control studies	64,65	No
	Cysteinyl leukotriene receptors	Spanish	1 Case-control study	64	
	Prostaglandin D receptor	Spanish	1 Case-control study	64	
	Thromboxane A ₁ synthase	Spanish	1 Case-control study	65	
	<i>CEP68</i> (centrosomal protein)	Spanish	1 Case-control study	66	
	Diamine oxidase	Spanish	1 Case-control study	63	
Single NSAID-induced acute urticaria/anaphylaxis	<i>HLA-DR11</i>	Spanish	1 Case-control study	67	No
	No associations	Spanish	1 Case-control study	65	
Asparaginase	<i>GRIA1</i>	United States, European	1 GWAS study	68-70	No
	<i>HLA-DRB1*0701</i>	United States	1 GWAS study	71	
Infliximab	<i>FASL</i>	Danish	1 Case-control study	72	No

GRIA1, Glutamate receptor, ionotropic, AMPA 1; *NOD2*, nucleotide-binding oligomerization domain 2; *STAT6*, signal transducer and activator of transcription 6.

synthase (*LTC4S*), prostaglandin E₂ receptor (*PTGER/EP2*), thromboxane A₂ receptor (*TBXA2R*), and thromboxane A synthase (*TBXAS1*; Table I).⁸⁶ However, several other studies have not confirmed some of these associations in different populations, particularly for *LTC4S*.⁴⁵⁻⁴⁹ In subsequent years, SNPs involving numerous other genes involved in innate immunity (eg, *TAP2* and *TLR3*), dysfunction of epithelial cells (eg, *SPINK5*), biochemical signaling pathways in inflammatory

cells (eg, *ACE* and *PPARG*), T_H2 pathways (eg, *IL13* and *IL41*), and aspirin metabolism (eg, *NAT2* and *CYP2C19*) have also been associated with AERD and have been reviewed elsewhere.⁸⁶

In 2010, Korean investigators performed the first pharmacogenomics approach performing a GWAS study involving 80 patients with AERD (confirmed through aspirin challenge) and 100 patients with aspirin-tolerant asthma who were screened with

a chip assay for 109,365 SNPs.⁵⁰ Eleven SNPs with the most significant association signals were identified, and in a second phase of the study, 150 common SNPs from these 11 candidate genes were genotyped in 102 patients with AERD and 428 patients with aspirin-tolerant asthma. Multivariate logistic regression analysis led to discovery of the *CEP68* gene (a centrosomal protein) having the most significant association. This study had significant limitations in that it was underpowered given the sample size, the second-stage study included subjects in the first stage of the study, and it was limited to Korean subjects.

This group performed a second GWAS study using a different microbead assay with a slightly larger cohort (117 patients with AERD and 685 patients with aspirin-tolerant asthma) and this time found a different gene, *HLA-DPB1*, to have the most significant association with AERD.⁵¹ Neither of these SNPs had discriminative power to be used diagnostically.

Recently, these investigators have reported on 2 studies using these pharmacogenomics data and applying them to develop a diagnostic model for confirming a diagnosis of AERD. Their first study used a combination of 8 SNPs identified in their first GWAS study⁵⁰ and analyzed 195 samples from 96 patients with AERD and 99 patients with aspirin-tolerant asthma to determine the discriminative power of this approach.⁸⁷ The sensitivity was 78% and the specificity was 88% for detecting AERD in this 8-SNP model. Their second pharmacogenomic diagnostic study used a similar approach but with 14 SNPs from their second GWAS study.^{51,88} By using this 14-SNP model, the sensitivity was 65% and the specificity was 85%, with a positive predictive value of only 42% and a negative predictive value of 93%. Interestingly, none of the 14 SNPs used in this model relate to the arachidonic acid pathway. Whether this pharmacogenomics approach is better than history alone, which has fairly good specificity, is not clear.^{89,90}

Few studies have evaluated the role of pharmacogenetics in regard to treatment responses in patients with AERD. A study from Korea stratified 89 patients with AERD according to requirement for montelukast for asthma control and found an association with an SNP for *CYSLTR1*.⁹¹ A small study from Iran evaluated the predictive value of pharmacogenetics in relation to efficacy of aspirin therapy after aspirin desensitization in patients with AERD.⁵² The initial study evaluated the efficacy of aspirin desensitization, followed by 6 months of aspirin therapy in a randomized, double-blind, placebo-controlled study with 16 subjects in each arm.⁹² Significant improvements in lung function, quality of life, and symptoms were noted in the aspirin-treated versus placebo groups. Genotyping revealed that *HLA-DQB1*0302* expression was significantly lower in nonresponders than responders to aspirin therapy. The small number of patients (n = 16) involved in the genetic study and involvement of only Iranian patients make the generalizability of these findings unclear.

It is important to note that although there is general agreement on the phenotype of AERD, diagnostic testing for AERD varies. In the aforementioned studies from various centers and countries, diagnostic tests to confirm AERD varied significantly, ranging from inclusion of some patients based on history alone to use of lysine-aspirin bronchoprovocation to various oral aspirin challenge protocols. It is certainly possible that lack of a uniform

diagnostic criterion to classify a specific phenotype could influence the outcome of pharmacogenetic testing.

Aspirin/NSAID-related cutaneous diseases. Several different terminologies and acronyms have been developed to describe cutaneous hypersensitivity reactions to aspirin, NSAIDs, or both. Essentially there are 3 distinct phenotypes, 1 with underlying chronic urticaria and 2 without.

1. *Aspirin (or NSAID)-exacerbated chronic urticaria* is a phenotype to describe patients with underlying chronic urticaria who have a flare of their hives after ingesting aspirin or NSAIDs. Several candidate gene association studies (the majority from Korea) have found associations with SNPs for genes including *ALOX5*, *LTC4S*, *FCERIA*, *TGFB1*, *TNFA*, histamine N-methyltransferase (*HNMT*), *IL18*, prostaglandin E₂ receptor subtype EP4 (*PTGER4*), and *HLA-B44*.⁵³⁻⁶¹ The only pharmacogenomics approach using a GWAS analysis studied this phenotype in 2 separate populations involving 112 patients from Spain and 120 patients from Taiwan, both with acute urticaria to multiple NSAIDs/aspirin.⁶² Perhaps because of its relatively small sample size for a GWAS approach, no statistically significant genome-wide association was found. Although there were several SNP clusters that approached significance, they differed between populations.
2. *Acute urticaria to multiple NSAIDs or aspirin* (cross-reactive group) is another phenotype. Candidate gene association studies (mostly from Spain) for this phenotype of acute urticaria to multiple NSAIDs/aspirin have found associations with SNPs for genes, including the diamine oxidase gene (*DAO*), *CYSLTR1*, *ALOX15*, *PTGDR*, *TBXAS1*, and *CEP68*, the gene identified in one of the aforementioned Korean GWAS studies of AERD.⁶³⁻⁶⁶ Negative studies showing no association for this phenotype with histamine receptor genes have also been reported.⁹³
3. *Acute urticaria or anaphylaxis to a single NSAID* (drug-specific reactions) is the third phenotype. This phenotype has been less studied. A candidate gene association study for the phenotype of acute urticaria/anaphylaxis to specific NSAIDs found associations with SNPs for *HLA-DR11*.⁶⁷ In contrast, another study found no associated SNPs for this phenotype among 240 patients evaluated for 217 SNPs in 48 genes.⁶⁵

In contrast to AERD, no diagnostic studies using a pharmacogenomics approach have been performed for any of the aspirin/NSAID cutaneous reaction groups. Thus pharmacogenetic data generated thus far might have some relevance to understanding the pathogenesis of these reactions; however, no clinical utility to this information has been demonstrated.

Other immediate drug reactions

Asparaginase. Asparaginase is a commonly used drug in the treatment of acute lymphoblastic leukemia (ALL) and is associated with a relatively high rate of immediate reactions. A US study of 485 children with ALL treated with asparaginase used a GWAS approach to identify genetic variations contributing to the risk of asparaginase allergy.⁶⁸ One SNP

TABLE II. Pharmacogenetic associations and severe cutaneous adverse reactions

Drug reaction	Genotype	Ethnicity	No. of positive/total cases vs control subjects	OR	Type of evidence	Screening recommended by FDA	Reference
Carbamazepine-related SJS	<i>HLA-B*1502</i>	Han Chinese	102/109 40/384	115.3	Meta-analysis (5 studies)	Yes	97
		Thai	43/48 13/84	54.4	Meta-analysis (2 studies)		
		Malaysian	6/6 0/8	221	Single study		101
		Indian	6/8 0/10	70.4	Single study		102
		Korean	1/7 0/50	23.3	Single study		103
		Japanese	0/3 0/33	NA	Single study	No	104
Carbamazepine-related DRESS	<i>HLA-A*3101</i>	European	18/39 22/579	24.1	Meta-analysis (3 studies)	No	98
		Asians	40/80 69/712	10.3	Meta-analysis (5 studies)		
Carbamazepine-related SJS/TEN	<i>HLA-A*3101</i>	European	8/36 22/579	7.9	Meta-analysis (3 studies)	No	
		Asians	10/131 69/712	2.5	Meta-analysis (5 studies)		
Abacavir hypersensitivity syndrome	<i>HLA-B*5701</i>	Multiethnic	484/1223 57/2869 (broad clinical criteria)	32.1	Meta-analysis (11 studies)	Yes	99
		Multiethnic	180/315 21/1168 (strict clinical criteria)	177.7	Meta-analysis (4 studies)		
		Multiethnic	81/81 38/1378 (patch test criteria)	859.1	Meta-analysis (4 studies)		
Allopurinol-related SJS/TEN	<i>HLA-B*5801</i>	Asian	54/55 74/678 (matched control subjects)	96.6	Meta-analysis (4 studies)	No	105
		Asian and mixed	50/69 171/3378 (population controls)	79.3	Meta-analysis (5 studies)		
		European					
Dapsone hypersensitivity syndrome	<i>HLA-B*1301</i>	Han Chinese	65/76 148/1034	20.5	Single study	No	100

FDA, US Food and Drug Administration; NA, not applicable.

located in glutamate receptor, ionotropic, AMPA 1 (*GRIA1*), a gene located at 5q33 (a genetic locus associated with asthma and atopy), was associated with a higher risk of asparaginase allergy. Another smaller study from Slovenia confirmed the findings that SNPs in *GRIA1* were associated with asparaginase allergy in pediatric patients with ALL.⁶⁹ A larger study of 576 Hungarian children with ALL treated with asparaginase confirmed these findings and also found that the subtype of ALL (eg, T-ALL) had further influence on risk of the genetic association.⁷⁰ Finally, another US study evaluated the influence of HLA genes in patients with asparaginase allergy in a large cohort of 1870 children with ALL treated with different formulations of asparaginase (native and PEGylated).⁷¹ They identified a higher incidence of asparaginase allergy in patients with *HLA-DRB1*07:01* alleles and identified structural features of the binding pocket that might affect the interaction of asparaginase epitopes with the HLA-DRB1 protein.

Infliximab. Acute infusion reactions to TNF inhibitors, such as infliximab, are not uncommon. An observational retrospective study of 124 Danish patients with Crohn disease treated with infliximab explored the role of genetic variations in a limited number of SNPs involving the *TNFRSF* genes and *FAS* and *FASLG* genes.⁷² One of the outcomes analyzed was acute severe infusion

reactions that required immediate and permanent cessation of infliximab and treatment with antihistamines and/or hydrocortisone or epinephrine. Twenty (16%) of the 124 patients had acute severe infusion reactions, and the carriage of the minor allele of an SNP in *FASLG* was associated with an increased risk of reaction with an odds ratio (OR) of 4.0 (1.1-22.4).

PHARMACOGENETICS/PHARMACOGENOMICS OF DELAYED DRUG HYPERSENSITIVITY

In contrast to the pharmacogenetics of immediate drug reactions, studies involving delayed drug reactions have been more diverse and robust. In addition, prospective pharmacogenetic testing has been shown to reduce the incidence of severe cutaneous adverse reactions (SCARs) for a few drugs. Drugs that have been shown to have more robust pharmacogenetic data are discussed below.

Carbamazepine

Carbamazepine is a drug commonly used to treat a number of disorders, including seizures, bipolar disorder, trigeminal neuralgia, and chronic pain. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered to represent the varying spectrum of a single disease. SJS/TEN is a

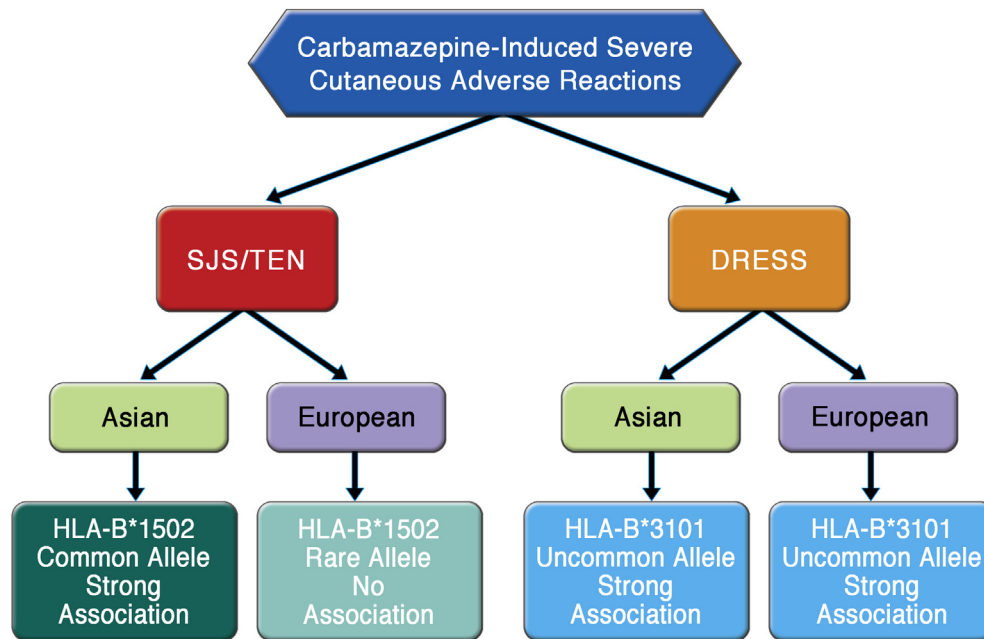


FIG 3. Risk of carbamazepine-induced severe cutaneous reactions varies by genotype, phenotype and ethnicity.

potentially life-threatening SCAR, with mortality being greater than 30% for the TEN spectrum. Carbamazepine is the most common cause of SJS/TEN in several Asian countries.^{94,95} In 2004, Chung et al⁹⁶ genotyped 44 patients with carbamazepine-induced SJS compared with 101 carbamazepine-tolerant patients and 93 healthy control subjects evaluating cytochrome-P450 and HLA genes. All patients were of Han Chinese descent in Taiwan. No association was found with cytochrome-P450 SNPs; however, a very high-risk HLA allele was discovered. The *HLA-B*1502* allele was present in 100% of the patients with carbamazepine-induced SJS but only 3% of carbamazepine-tolerant patients and 8.6% of healthy control subjects. The OR was an impressive 2504 (95% CI, 126-49,522), with a *P* value of 3.13×10^{-27} !

Several other studies in other Asian populations have confirmed this finding, and a recent meta-analysis confirmed a high risk of SJS/TEN in carbamazepine users with *HLA-B*1502*, with the risk varying by ethnicity (Table II).⁹⁷⁻¹⁰⁵ Respective risks of SJS/TEN for the *HLA-B*1502* allele are increased and vary by ethnicity as follows: 220-fold in Malaysians, 115-fold in Han Chinese, 60-fold in Thais, and 25-fold in Koreans. In 2007, the US Food and Drug Administration issued an alert regarding carbamazepine-induced SJS/TEN in Asians and recommended genetic screening for *HLA-B*1502* in patients with ancestry from areas in which the allele is present. In 2011, the same investigators from Taiwan who made the initial discovery performed a prospective screening study of Han Chinese subjects with 2 months of follow-up involving 4120 who took carbamazepine and were *HLA-B*1502* negative and 215 who were *HLA-B*1502* positive and treated with an alternative medication.¹⁰⁶ No cases of SJS/TEN occurred in any of the subjects. Based on the incidence of SJS-TEN, an estimated 10 cases of SJS-TEN would have been expected, and the difference between the observed cases (0) and expected cases (10) was significant (*P* < .001).

Although screening for *HLA-B*1502* is recommended for many with certain Asian ancestries, the frequency of this allele is rare in European cohorts, and studies have not found an association with *HLA-B*1502* in Europeans with carbamazepine-induced SJS/TEN.¹⁰⁷ Using a GWAS pharmacogenomics approach, investigators from the United Kingdom studied subjects with a spectrum of hypersensitivity reactions to carbamazepine, including 26 with drug reaction with eosinophilia and systemic symptoms (DRESS), 1 with acute generalized exanthematous pustulosis, 106 with maculopapular exanthems, and 12 with SJS/TEN.¹⁰⁸ They identified the *HLA-A*3101* allele as being associated with an increased risk for DRESS, maculopapular exanthems, and SJS/TEN. Another GWAS study of Japanese subjects confirmed associations with this allele and subjects with carbamazepine-induced DRESS and SJS/TEN.¹⁰⁹ However, a study involving a larger number of patients with SJS/TEN (20 from Europe and 53 from Taiwan) and 20 patients with DRESS (10 each from Europe and Taiwan) reached different conclusions.⁹⁸ They identified *HLA-A*3101* with carbamazepine-induced DRESS in both Europeans and Chinese but not with carbamazepine-associated SJS/TEN. They also performed a meta-analysis of studies of *HLA-A*3101* and carbamazepine-induced SCARs and confirmed a strong association with DRESS reactions but a much weaker association with SJS/TEN. Prospective studies to determine the utility of screening for *HLA-A*3101* are needed. Fig 3 illustrates how the impact of ethnicity and type of drug hypersensitivity reaction can influence the attributable risk associated with a specific genotype and administration of carbamazepine.

Abacavir

Abacavir is a nucleoside analogue with antiviral activity against HIV-1. Approximately 3% to 5% of patients treated

with abacavir have a hypersensitivity syndrome that typically appears within the first 6 weeks of therapy and rarely can be fatal.¹¹⁰ Multiorgan symptoms, including fever, rash, gastrointestinal symptoms, respiratory symptoms, and hypotension, can occur along with liver and renal involvement. In 2002, Mallal et al¹¹¹ used a candidate gene approach to identify associations between MHC alleles and abacavir hypersensitivity in the Western Australian HIV Cohort. The allele with the highest OR (OR = 117) for abacavir hypersensitivity was *HLA-B*5701*. Several studies, including a recent meta-analysis, have confirmed this observation in multiple ethnic groups, including whites, blacks, and Hispanics (Table II).⁹⁹

Based on this information, a landmark study was performed to determine whether screening patients with HIV-1 for *HLA-B*5701* before treatment with abacavir would reduce the incidence of the hypersensitivity reaction.¹¹² The Prospective Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) was a multicenter, prospective, randomized, double-blind study that evaluated 803 subjects screened by genotyping for *HLA-B*5701* and 847 nonscreened control subjects who were treated with abacavir. Initial screening identified 5.6% patients in the prospective screening group as being positive for *HLA-B*5701*, and these patients were not treated with abacavir. Clinically diagnosed hypersensitivity reactions occurred in 3.4% of the screened group and 7.8% of the control group (OR = 0.40, $P < .001$). The investigators also used patch testing with abacavir to identify hypersensitivity cases that were immunologically confirmed. When using this stricter criterion, none of the screened control group had a patch test–positive hypersensitivity reaction compared with 2.7% of the control group (OR = 0.03, $P < .001$). For these immunologically confirmed cases, the positive predictive value was 47.9% and the negative predictive value was 100%. This study was the first to show in a very rigorous manner the benefits of pharmacogenetic testing in reducing the risk of hypersensitivity reactions. In 2008, the US Food and Drug Administration issued an alert recommending that all patients should be screened for the *HLA-B*5701* allele before starting or restarting therapy with abacavir or abacavir-containing medications.

Allopurinol

Allopurinol is used to treat hyperuricemia-related diseases, especially gout, and is a common culprit in SCAR reactions. Hung et al,¹¹³ from Taiwan, performed a candidate gene analysis of 51 patients with allopurinol-related SCARs and used 135 allopurinol-tolerant control subjects. All patients and control subjects were of Han Chinese ancestry. They discovered a very strong association with *HLA-B*5801* and allopurinol-related SCARs (OR = 580, $P = 4.7 \times 10^{-24}$). Like the association of carbamazepine-induced SCARs and *HLA-B*1502*, ethnic differences have been seen, with strong associations in Thai populations with *HLA-B*5801* and allopurinol-related SCARs yet weaker but significant associations in European and Japanese populations.^{114–116} A study from Australia similarly found lower associations with *HLA-B*5801* and allopurinol-related SJS/TEN and minimal to no association with this allele and DRESS or maculopapular exanthems.¹¹⁷ To date, no prospective studies

have determined the utility of screening for the *HLA-B*1502* allele to reduce allopurinol hypersensitivity reactions. A decision analytic and Markov model predicted outcomes in a Thai population and suggested that genetic testing for *HLA-B*1502* would be cost-effective in Thailand.¹¹⁸

In contrast, an Australian group came to very different conclusions.¹¹⁷ They noted the high incidence of the *HLA-B*1502* allele (15% in South-East Asian populations) yet a very low rate of allopurinol-related SJS/TEN and calculated that for every 100,000 Han Chinese origin patients screened before allopurinol, only 1 to 2 would be prevented from having SJS/TEN yet 15,000 patients would be unnecessarily denied allopurinol. Clearly, prospective studies will be needed to determine the utility of screening for *HLA-B*1502* before allopurinol therapy.

Dapsone

Dapsone is an antimicrobial commonly used for the treatment and prevention of select diseases, including leprosy and *Pneumocystis jirovecii* pneumonia. Dapsone also has anti-inflammatory activity and is used to treat several dermatologic diseases, such as dermatitis herpetiformis. The dapsone hypersensitivity syndrome (likely a form of DRESS) is a multisystem hypersensitivity reaction characterized by fever, rash, lymphadenopathy, and hepatitis. It has an incidence of 1.4% and mortality of 9.9%.¹¹⁹ Zhang et al¹⁰⁰ performed a GWAS analysis in 833 subjects of Chinese descent who tolerated dapsone for treatment of leprosy and 39 patients with dapsone hypersensitivity syndrome. The strongest association was seen for *HLA-B*13:01*. To directly test for an association between *HLA-B*13:01* and the dapsone hypersensitivity syndrome, they performed replication analysis in a subset of cases ($n = 39$) and control subjects ($n = 78$) from the original cohort and an additional 38 cases and 206 control subjects using next-generation sequencing for HLA-B and HLA-C genotyping, which confirmed this association. Combining both analyses yielded a strong association of *HLA-B*13:01* and the dapsone hypersensitivity syndrome (OR = 20.5, $P = 6.84 \times 10^{-25}$). They calculated that *HLA-B*13:01* would have a poor positive predictive value (7.8%) but a high negative predictive value (99.8%) and that 84 patients would need to be screened to exclude 1 case of the syndrome. In a Chinese population screening would be predicted to reduce the risk of dapsone hypersensitivity syndrome from 1.4% to 0.2%. However, this allele is much more frequent in Asian populations, with rates of 0% in European and Africans. Dapsone hypersensitivity syndrome has been reported in other non-Asian populations, which suggests that other alleles might be a risk factor in these populations.

FUTURE CHALLENGES FOR IMPLEMENTING PHARMACOGENOMIC TESTING

Pharmacogenomic research will continue to identify potential genetic risk factors for ADRs. However, a number of challenges exist before implementing a screening test. An important barrier, as has been pointed out in this review, is that many genomic tests are based on retrospective analysis or observational case-control studies with limited statistical power and inconsistent results. Although prospective multicenter studies are ideal, these are expensive to do. The clinical

utility of a test regarding generalizability is another factor, as exemplified by carbamazepine and *HLA-B*1502*. Drug-test codevelopment has been suggested as a simpler method to demonstrate clinical utility, and abacavir has been called the poster child for postmarketing safety label updates in which a randomized trial proved the benefits of genetic testing.¹²⁰ However, because serious ADRs are rare and unpredictable, it would be challenging to discover a genetic risk during drug development. Other aspects needed before implementing a test include the genetic component of attributable risk (additional factors might also play a role), ease of interpretation of results, inclusion of testing in professional guidelines, the cost of the test, and reimbursement by payers. Finally, because the mechanisms of many drug hypersensitivity reactions still are unclear, focused candidate gene studies might not be realistic.

Interpretation of published literature on pharmacogenomics can also be a challenge. High ORs are typically heralded as an indicator of good predictive accuracy. However, because false-positive rates affect ORs, a high false-positive rate can still be associated with high ORs yet have a low accuracy. Some degree of false-positive results might be deemed acceptable if the ADR is serious and could still be cost-effective. Fortunately, resources are available to clinicians and researchers to help navigate the complex world of pharmacogenomics. In 2000, the National Institutes of Health Pharmacogenomic Research Network was developed with a mission “to lead discovery and advance translation in genomics in order to enable safer and more effective drug therapies.” As part of this network, a Pharmacogenetics Knowledge Base has been developed and a Clinical Pharmacogenetics Implementation Consortium was formed as a shared project between the National Institutes of Health knowledge base and the network. The Clinical Pharmacogenetics Implementation Consortium website (www.cpicgx.org) lists their guideline publications on pharmacogenetics and specific drugs, including guidelines on abacavir, allopurinol, and carbamazepine with links to online updates.

CONCLUSIONS

Although the field of pharmacogenetics is not entirely new, there has been a marked increase in the number of studies evaluating associations with various ADRs. Numerous genetic associations have been made for immediate drug reactions, but to date, none appear robust enough to make clinical recommendations based on pharmacogenetic data alone. In contrast, studies have been able to demonstrate that for carbamazepine and abacavir, screening for specific HLA alleles can reduce the risk of severe delayed drug reactions. With advances in genotyping technology, discovery of additional clinically important risk alleles for drug allergy are very likely. Pharmacogenomics will certainly play a role in the new era of precision medicine. Whether broad-based pharmacogenetic testing will be ready for “primetime” in most patients seems unlikely in the near future. Sir William Osler is noted to have said, “The first duties of the physician is to educate the masses not to take medicine.” Pharmacogenomics offers the hope of tailoring that message to identify those patients who are most vulnerable, whereby recommending avoidance of a specific medicine is truly in their best interest.

What do we know?

- Numerous pharmacogenetic associations have been identified for immediate reactions to β -lactams and NSAIDs.
- The US Food and Drug Administration recommends genetic screening for *HLA-B*1502* in patients with ancestry from areas in which the allele is present (eg, Chinese, Thai, Malaysian, and Korean) before carbamazepine therapy to reduce carbamazepine-related SJS/TEN.
- The US Food and Drug Administration recommends genetic screening for *HLA-B*5701* in all patients before abacavir therapy to reduce abacavir hypersensitivity syndrome.

What is still unknown?

- Will pharmacogenetic testing be able to exclude a diagnosis of AERD?
- Will pharmacogenetic testing be able to determine responsiveness to aspirin therapy in patients with AERD?
- Should testing for *HLA-A*3101* be recommended before carbamazepine to reduce DRESS?
- Should testing for *HLA-B*1502* before allopurinol be recommended?
- Would testing for *HLA-B*13:01* reduce the risk of dapsone hypersensitivity syndrome?
- Will pharmacogenetic testing to reduce ADRs ever become used on a broader scale for the majority of patients before pharmacotherapy?

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