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Therapeutic Actions and the Genetic Code: Examples of the Application of Pharmacogenetics

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Goal. The goal of this lesson is to provide information on how differences in genetics can affect patient response to drugs, causing both therapeutic effects and adverse reactions, to help pharmacists provide better medication therapy management.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate an understanding of pharmacogenetics and its application to pharmacy practice;
2. recognize variations in genes and the nomenclature used to identify variant alleles;
3. identify variation in alleles, diplotypes and metabolic phenotypes which can result in altered therapeutic response and adverse effects in patients; and
4. list examples of drug-gene interactions and interpret how these apply to patients in specific cases.

Introduction

The term pharmacogenetics (PGt) refers to differences in a given gene that can affect an individual's response to drugs. The variation in metabolism due to genetics can alter both the therapeutic effect of medications, as well as cause adverse effects. Drug-gene interactions are similar to drug-drug interactions, putting pharmacists in a unique position to apply their extensive drug knowledge and proficiently fill a new gap in medication management.

DNA is composed of a sequence of nucleotides (the triphosphates of adenine [*A*], cytosine [*C*], guanine [*G*], and thymine [*T*]), and serves as a "production manual" for the assembly of proteins. In relation to drugs, genes of interest ("pharmacogenetic genes") are the segments of DNA which code for receptors, transporters, and metabolizing enzymes. There are approximately 25,000 genes in the human genome, i.e., the entirety of DNA, with variations resulting in differences in pharmacodynamics (PD), or how individuals respond to a drug, and pharmacokinetics (PK), or how individuals "handle" a drug with respect to absorption, distribution, metabolism and excretion (ADME).

A variant form of a gene, called an *allele*, may result in altered drug response, due to altered PD or as a result of altered ADME. The most common variation in a gene is the single nucleotide polymorphism or SNP (pronounced "snip") which is the case where a single nucleotide is replaced in the gene DNA sequence by another nucleotide, such as *T* replacing *C*. For instance, the *C* in position 634 of a gene being replaced by *T* would be noted as 634C>T. As a SNP produces a variant allele, the variant form of the gene is given a specific designation to differentiate it from the "common" form. The variant form may result in altered protein function.

With reference to the cytochrome P450 (CYP) enzyme family, responsible for metabolizing many drugs, a "star" nomenclature has been adopted, where the most common form of a gene is typically termed the *1 form and variant forms are designated otherwise, such as *2, *3, and so on. It should be noted that a given "*" variant for one gene, such as *17, does not necessarily have the same meaning as a *17 variant for a different gene. For instance, the *17 form of the *CYP2C19* gene is a "gain-of-function" form resulting in increased drug metabolism by CYP2C19, whereas the *17 form of the *CYP2D6* gene is a "reduced-function" form resulting in decreased drug metabolism by CYP2D6.

Different alleles can affect protein function and, as in the case of the CYP enzyme family, this can lead to variability in drug metabolism. Some genetic effects are more drastic than others and, in the more extreme cases, genetic testing may make the difference between therapeutic failure and success, or safety and toxicity.

As data supporting the use of genetic testing in drug therapy decision-making accrues, more and more pharmacies are offering services that integrate pharmacogenetics into medication therapy management (MTM) programs. Currently, pharmacogenetic-based dosing guidelines have been pub-

lished for 10 gene-drug pairs: thiopurine methyltransferase (*TPMT*)-thiopurines; cytochrome P450 2C19 (*CYP2C19*)-clopidogrel; *CYP2C9* and vitamin k epoxide reductase subunit 1 (*VKORC1*)-warfarin; *CYP2D6*-codeine; human leukocyte antigen B (*HLA-B*)-abacavir; solute carrier organic anion transporter 1B1 (*SLCO1B1*)-simvastatin; *HLA-B*-allopurinol; *CYP2D6* and *CYP2C19*-tricyclic antidepressants (TCAs); *HLAB*-carbamazepine; and dihydropyrimidine dehydrogenase (*DPYD*)-5-fluorouracil and capecitabine. Additionally, another five guidelines are under development.

Guidelines are available on the pharmacogenomics knowledgebase website (www.pharmgkb.org) and are available as open access publications in *Clinical Pharmacology and Therapeutics*.

Relating a patient's drug response to genetics defines PGt. Genetic factors represent the underlying variability in response to a drug, notwithstanding environmental factors, diet, pathophysiology, concomitant drug use, and other factors that introduce variability. Table 1 provides examples of drug-gene interactions and the potential outcome of each interaction. Four specific case examples of the application of pharmacogenetics will be presented.

Table 1
Examples of drug-gene interactions and potential outcomes

Gene	Drug	Variant Allele (SNP)[a]	Effect on Protein[b]	Effect on PK/PD[c]	Potential Outcome
HLA-B	carbamazepine	15:02	HLA-B-altered protein structure	T-cell mediated immune response	Stevens-Johnson syndrome; toxic epidermal necrolysis
CYP2C19	clopidogrel	*17 (C>T) rs12248560[d]	increased CYP2C19 enzyme activity	increased clearance (conversion)[e]	increased clopidogrel effect; bleeding
CYP2D6	codeine	*3 A deleted rs35742686	nonfunctional CYP2D6 enzyme	decreased clearance (conversion)[f]	decreased codeine effect; lack of pain relief
CYP2C9	warfarin	*2 (C>T) rs1799853	decreased CYP2C9 enzyme activity	decreased clearance	increased warfarin effect; bleeding

[a]SNP = single nucleotide polymorphism where one DNA base (adenine (A), cytosine (C), guanine (G), and thymine (T)) replaces another (e.g., such as T replacing C; C>T). [b]Pharmacogenetic proteins include receptors, drug transporters, and drug metabolizing enzymes. [c]PK/PD = pharmacokinetics/pharmacodynamics. [d]rs number = a specific and consistent identifier of the SNP as found in the SNP database (dbSNP) of the National Center for Biotechnology Information. [e]The increased clearance of clopidogrel results in greater conversion to the active metabolite. [f]The decreased clearance of codeine results in less conversion to morphine, which is largely responsible for the analgesic effects of codeine.

CYP2D6-Codeine

Cytochrome P450 2D6 (*CYP2D6*) is a major drug metabolizing enzyme, responsible for metabolizing approximately 20 percent of drugs. There are more than 80 different alleles of the *CYP2D6* gene, which can result in a spectrum of CYP2D6 enzyme activity. As an individual receives genetic information from each parent, the combination of alleles (called a *diplotype*) will impart a certain level of enzyme activity relative to drug metabolism. Each allele inherited by an individual contributes to the phenotype of enzyme activity that is expressed and allows individuals to be classified by a "metabolism phenotype," such as *ultrarapid metabolizer* (UM) or *poor metabolizer* (PM). The classification of an individual by metabolism phenotype has shown to be of consequence when considering the use of codeine. **Case Example #1** describes one of the extremes of genetic influence on drug response.

This case example illustrates a lack of drug effectiveness. Neither JS nor his brother underwent simple pharmacogenetic testing relative to *CYP2D6* prior to receiving the codeine-containing product. Subsequent testing through a university medical center study showed that JS and his brother were in fact poor metabolizers,

Case Example #1

JS, a 19 y.o. healthy Caucasian male, is a body shop mechanic. JS visited the nearby university medical center emergency department (ED) after slicing his hand on a piece of sheet metal. Following suturing (18 stitches), the hand was bandaged and wrapped. JS was in pain and was complaining that his hand was "throbbing." He was given acetaminophen/codeine phosphate (300 mg/30 mg) in the ED and provided a prescription for a 72-hour period with the instructions to take 1 to 2 tablets every 4 to 6 hours as needed for pain. At the pharmacy, he asked if this was the same as Tylenol #3 because his younger brother had some prescribed for him after he had his tonsils removed. JS explained that the Tylenol #3 did not help his brother at all, so they "have plenty at home." The pharmacist explained that prescriptions are for specific individuals, and JS agreed to get the prescription filled for him and not use what was left from his brother's prescription. The pharmacist also told JS to monitor if the pain medication was working. At 36 hours, JS was still experiencing severe throbbing pain and called the pharmacy. The pharmacist discussed the situation with JS' family physician, who prescribed an alternative analgesic, which was used by JS with success. In discussion with JS' family physician, the pharmacist explained that the lack of efficacy of the acetaminophen/codeine combination may have a genetic basis, as neither JS nor his younger brother experienced pain relief with the codeine containing product.

each with a *3/*4 diplotype (combination of *CYP2D6* gene variants inherited from each parent). Having a diplotype that produced nonfunctional CYP2D6 enzymes, neither JS nor his brother had the metabolic capacity to convert codeine (a prodrug) to morphine (the active drug), which is largely responsible for the analgesia produced with acetaminophen/codeine use.

The other extreme of CYP2D6 enzyme activity, where excessive amounts of morphine are formed following codeine administration, is seen in individuals who are ultrarapid metabolizers. These individuals are at risk of morphine toxicity due to very efficient conversion of codeine. Additionally, infants who were breastfeeding have tragically died of morphine overdose because their mothers were UMs receiving codeine-containing products. Here, the infants received morphine that was passed onto them in the breast milk.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) pharmacogenetic-based dosing guidelines suggest avoiding codeine use in UM and PM individuals due to the potential for toxicity and lack of efficacy, respectively. Finally, in early 2013, the Food and Drug Administration issued a black box warning for the labeling of codeine-containing products, as well as a contraindication to the use of codeine-containing products in children following tonsillectomy and/or adenoidectomy. The aim of this labeling is to try and prevent opioid toxicity and death due to codeine use in children who may be UMs. The therapeutic action, based on an individual's genetics, would be to use an alternative opioid or a non-opioid analgesic.

HLA-B-Carbamazepine

The human leukocyte antigen (*HLA*) gene family is responsible for the coding of the *HLA* complex, a group of proteins which guide the immune system in identifying "foreign" cells. Individuals with the gene variant *HLA-B*15:02* are at increased risk of a T-cell-mediated immune response, resulting in the potentially life-threatening skin disease of Stevens-Johnson syndrome (SJS; also called erythema multiforme majus) or toxic epidermal necrolysis (TEN). SJS can be expressed as a mild form with the patient experiencing fever, itching, and malaise. Additionally, lesions (macular, papular, hive-like, with or without blisters) may be found symmetrically on the trunk and on upper and lower extremities. The severe form of SJS includes less than 10 percent of the patient's body surface area (BSA) being necrotic skin. When necrotic lesions extend beyond 30 percent of the BSA, the diagnosis of TEN is made. In addition to mucosa and skin involvement in SJS and TEN, vital organs can also be affected and severe forms result in mortality rates up to 40 percent, most often due to sepsis.

It is thought that carbamazepine hypersensitivity is the result of the drug's metabolites altering cellular proteins. The protein alteration results in the immune system identifying cells as "foreign" and elicits a T-cell mediated immune response, culminating in SJS or TEN. Individuals with the variant *HLA-B*15:02* are at increased risk of SJS and TEN when taking carbamazepine. **Case Example #2** illustrates the *HLA-B*-carbamazepine interaction.

Case Example #2

YL is a 17 y.o. Chinese male who is participating in a cultural exchange program with the United States. YL lives with his host family in Southwest Ohio. While attending a college baseball game, YL experiences a generalized tonic-clonic seizure. YL's airway and head are protected, and the seizure ends after approximately 90 seconds. YL is evaluated and transported by ambulance to the medical center emergency department. There is no documentation that YL has a seizure history, and it was never mentioned by YL or the exchange agency. In discussing treatment options, the pharmacist points out that the Asian population and, in particular, individuals of Han Chinese descent have been shown to have an increased risk of SJS and TEN related to the interaction of *HLA-B*15:02* with carbamazepine. With this in mind, alternative treatment options are considered.

The presence of one or two copies (one from each parent) of the variant *HLA-B*15:02* allele imparts an increased risk of developing SJS or TEN in patients who are to receive carbamazepine. Table 2 presents the frequencies of *HLA-B*15:02* in U.S. Asian populations. It should be noted that oxcarbazepine has also been shown to cause skin reactions in *HLA-B*15:02* positive individuals. The therapeutic action here, based on

Table 2
The frequency of occurrence of *HLA-B*15:02* in U.S. Asian populations compared to the reference population of Han Chinese[a]

Population	Frequency (%) of occurrence of *HLA-B*15:02*[b]	Total # of individuals tested for *HLA-B*15:02*	Approximate # of individuals testing "positive" for *HLA-B*15:02*
Han Chinese[c]	13	101	13
U.S. Asian population 1	5	358	18
U.S. Asian population 2	4	1772	71

[a]Adapted from allelefrequencies.net with the noted Han Chinese frequency for reference
[b]Rounded to approximate whole number
[c]Example Han population (Yunnan Province)

an individual's genetics, would be to use an alternative antiepileptic therapy that does not increase the risk of SJS or TEN in *HLA-B*15:02* positive individuals. The CPIC has recently published guidelines related to the *HLA-B*15:02*-carbamazepine interaction.

CYP2D6/CYP2C19-Tricyclic Antidepressants

Many drugs are metabolized by multiple cytochrome P450 enzymes such that specific isozyme (e.g., *CYP2D6*, *CYP2C19*) genotypes can influence the overall elimination (clearance) of a given substrate drug. Variant forms of the *CYP2D6* and *CYP2C19* genes produce increased enzyme function. Examples include multiple copies of functional variants as seen in *CYP2D6* UM; increased transcription (more RNA is transcribed from DNA, which results in increased production of the enzyme) as exhibited by the *CYP2C19*17* gene variant. Conversely, *CYP2D6* and *CYP2C19* alleles can also produce reduced-function or loss-of-function enzymes. For example, *CYP2D6*4* and *CYP2C19*2* are non-functional. The combinations of genetic variability relative to both *CYP2D6* and *CYP2C19* can influence the ADME and overall concentration versus time profile of substrate drugs and metabolites. Some examples of substrates for CYP2D6 and CYP2C19 include amitriptyline, nortriptyline, imipramine, and other tricyclic antidepressants.

Amitriptyline is metabolized to nortriptyline and imipramine is metabolized to desipramine via CYP2C19. Amitriptyline and nortriptyline are metabolized by CYP2D6 to their respective 10-hydroxy metabolites, whereas imipramine and desipramine, also via CYP2D6, are metabolized to their 2-hydroxy metabolites. The hydroxy metabolites are less active than their parent compounds. The overall metabolism of these drugs requires multiple steps, and at each step a different enzyme is introduced into the process. With multiple alleles existing for each enzyme, this adds a layer of complication and can allow for increased variation in drug metabolism.

As mentioned earlier, there are numerous variant alleles of the *CYP2D6* gene that contribute to various metabolism phenotypes. With respect to *CYP2C19*, there are 28 confirmed variant alleles, with the *2, *3, and *17 alleles being most commonly implicated in altered drug metabolism (Table 3). An individual with one "normal" copy of the gene and one copy of either the *2 or *3 alleles would be considered an intermediate metabolizer (IM), whereas an individual with two copies of the *2 or *3 alleles would be considered a PM. A *2/*3 individual would also be a PM, as both of the alleles are loss-of-function forms of the gene. The *17 form is considered a gain-of-function allele and individuals with the common form (*1) and the *17 allele, or two copies of the *17 allele, would be considered UM. Certainly the combination of *CYP2D6* and *CYP2C19* variant genes can be expected to impact drug metabolism, thus influencing an individual's response to tricyclic antidepressants including amitriptyline and imipramine. Consider **Case Example #3**.

Recall that amitriptyline is converted to nortriptyline via CYP2C19. In this case, the patient is an IM, which is likely the cause of elevated amitriptyline concentrations. Additionally, the patient is a CYP2D6 PM indicating decreased conversion of both amitriptyline and nortriptyline to their respective 10-hydroxy metabolites. The patient's genetic coding for decreased metabolism relative to the CYP2D6 and CYP2C19 pathways is likely responsible for the adverse effect noted in the above case. The interactions of CYP2D6 and CYP2C19 with tricyclic antidepressants have been evaluated and discussed. With two genes playing an important role in the metabolism of TCAs and both having many variants, predicting potential pharmacokinetic effects and the response to a given TCA can be difficult. The

Case Example #3

JD is a 51 y.o. African American male who presents to his family physician complaining of loss of appetite, fatigue, and apathy. He states he has been having difficulty at work and just "doesn't sleep well." He also states that he has been "irritable" and "quick to jump at people." JD adds that he has been feeling more and more frustrated with day to day life. He confides that he started feeling this way over the past two months after the death of his father, whom he was very close to. JD's physician makes an initial diagnosis of depression. Being older, the physician is most familiar with the use of the tricyclic antidepressant agents and starts JD on amitriptyline. JD receives 25 mg of amitriptyline BID. After two weeks, JD contacts his physician, complaining of confusion, lack of concentration and vomiting. JD is directed to be taken by his wife to the local hospital emergency department. At the ED, JD is examined, with the EKG showing a prolonged QRS complex with a right bundle branch block. While JD is receiving a relatively low dose of amitriptyline, the diagnosis of amitriptyline toxicity is made. As JD brought his vial of amitriptyline with him, a "pill count" indicates that JD has been following the administration directions. The ED physician calls the pharmacy to check on the generic form of the amitriptyline to see if it is the correct strength. A pharmacist confirms the strength of the tablets and suggests that pharmacogenetic testing be performed to identify the patient's metabolic phenotype relative to CYP2D6 and CYP2C19. JD provides a cheek swab sample for DNA analysis. The amitriptyline is held and JD is monitored. JD is discharged from the ED with instructions to see his family physician for follow-up. After five days the pharmacogenetic test results are available, indicating that JD is a CYP2D6 poor metabolizer with a *4/*4 diplotype and CYP2C19 intermediate metabolizer with a *1/*2 diplotype. These results explain the adverse reactions being related to amitriptyline overdose, here due to decreased metabolism as compared to the actual dose being considered too high. JD is switched to a selective serotonin reuptake inhibitor (SSRI) and responds well to treatment.

Table 3
Examples of *CYP2C19* alleles, diplotypes, and metabolic phenotypes

Functionality	Example Diplotype[a]	Metabolic Phenotype
Fully functional: *1 (wild type)	*1/*2	IM[b]
Loss-of-function: *2, *3, others	*2/*2	PM[c]
Gain-of-function: *17	*2/*17	IM
	*1/*1	EM[d]
	*1/*17	UM[e]

[a]Combination of alleles (*one from each parent*)
[b]Intermediate metabolizer
[c]Poor metabolizer
[d]Extensive metabolizer
[e]Ultrarapid metabolizer

recently published CPIC guidelines can help with the interpretation of such information. Based on the individual's genetics, the therapeutic action would be to use an alternative to a TCA for treatment of depression.

CYP2C19-Clopidogrel

As previously mentioned, CYP2C19 is a drug metabolizing enzyme which is responsible for metabolizing between 5 and 10 percent of drugs. The *CYP2C19* gene has been mostly discussed relative to the drug clopidogrel when considering conversion of this prodrug to its active form. The *1 form is related to normal metabolism, and is also commonly referred to as *extensive metabolism*. The *2 and *3 alleles, as present in heterozygous individuals (having two different alleles i.e., *1/*2, *1/*3) or homozygous individuals (having two of the same alleles i.e., *2/*2, *3/*3) result in decreased conversion of clopidogrel to its active form. This decreased conversion has been related to increased cardiovascular risk factors in patients having undergone coronary artery stent placement during percutaneous coronary intervention for treatment of acute coronary syndrome (ACS). In 2010, FDA issued a black box warning for clopidogrel stating that it may not be effective for patients with reduced CYP2C19 metabolizing capability. The *17 allele is associated with increased conversion of clopidogrel to its active metabolite, which puts the patient at increased risk for bleeding. **Case Example #4** presents an example of a *CYP2C19*-clopidogrel interaction.

Each *CYP2C19* gene can be categorized as a gain-of-function, normal function or loss-of-function allele. The combination of two alleles (one from each parent) results in the following expected "metabolizer" phenotypes: ultrarapid, extensive (normal), intermediate or poor (Table 4). The genotypes and expected metabolizer phenotypes have been evaluated relative to clopidogrel use as described by CPIC. The therapeutic action here,

Case Example #4

MR is a 52 y.o. Caucasian male. MR is an outpatient visiting the ambulatory care pharmacy to have his prescription for prasugrel filled. He explains that he is "very keen" about taking his prasugrel following the placement of two "tubes" in his "heart arteries." MR was previously diagnosed with ACS. He had gone to the ED after experiencing dizziness and chest pain. He had two stents placed to prevent coronary artery thrombosis and the consequences of a clot. MR was given a 60 mg loading dose of prasugrel and a prescription with the instructions to take one 10 mg tablet daily. His only other medication is atorvastatin 20 mg daily, being used for hyperlipidemia that was diagnosed five years ago. MR does not have prescription coverage as part of his healthcare insurance and is "shocked" at the price of prasugrel. He asks the pharmacist if there is an alternative drug he can take. The pharmacist suggests MR undergo pharmacogenetic testing, which is more expensive than a single prasugrel prescription, but in the long run will likely save MR a great deal of money. MR agrees to have a pharmacogenetic test done with the results indicating that he is an extensive metabolizer with a *CYP2C19* *1/*1 diplotype. The pharmacist contacts MR's family physician and the prasugrel is changed to clopidogrel 75 mg daily.

Table 4
***CYP2C19* alleles as related to expected metabolizer phenotypes**

Gene from second parent		Gene from first parent		
		gain-of-function allele	normal function allele	loss-of-function allele
	gain-of-function allele	UM[a]	UM	IM[b]
	normal function allele	UM	EM[c]	IM
	loss-of-function allele	IM	IM	PM[d]

[a]Ultrarapid metabolizer
[b]Intermediate metabolizer
[c]Extensive metabolizer
[d]Poor metabolizer

based on the individual's genetics, would be to use clopidogrel as a less expensive alternative to prasugrel.

Summary

Testing of an individual's pharmacogenetics is becoming more widely available and published dosing guidelines support its application in many pharmacy settings. Additionally, it is likely within the next five to 10 years that preemptive genetic testing, including partial or whole-genome (all genes) testing, will become a reality. Having the data available at the point of care will aid in the application of PGt.

Drug-gene interactions as described by the examples above can be thought of in a similar way to drug-drug interactions. The expertise of pharmacists calls for the profession to embrace PGt as an integral component of medication therapy management. Pharmacists need to be educated about PGt and should expect to educate other healthcare providers and patients regarding drug-gene interactions.

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This lesson is an application-based CE activity and is targeted to pharmacists in all practice settings.

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Therapeutic Actions and the Genetic Code: Examples of the Application of Pharmacogenetics

1. All of the following are components of DNA EXCEPT:
   a. adenine. c. thymine.
   b. cytosine. d. uracil.

2. The most common variation in a gene is the SNP ("snip") which refers to:
   a. single nucleotide polymorphism.
   b. single new protein.
   c. substituted nucleotide protein.
   d. slow new polymorphism.

3. With a gene variant that is a "gain-of-function" form, drug metabolism will:
   a. increase. c. remain the same.
   b. decrease.

4. Approximately what percent of drugs are metabolized by cytochrome P450 2D6 (CYP2D6)?
   a. 5 percent c. 20 percent
   b. 10 percent d. 75 percent

5. Codeine is a prodrug metabolized by what enzyme?
   a. CYP1A2 c. CYP3A4
   b. CYP2C19 d. CYP2D6

6. Individuals who are CYP2D6 poor metabolizers are at risk of morphine toxicity when taking codeine-containing products.
   a. True b. False

7. When a codeine-containing product is prescribed for a child following tonsillectomy, the therapeutic action is to:
   a. use the normal pediatric dose.
   b. use an alternative opioid or a non-opioid analgesic.
   c. increase the dose to achieve analgesia.
   d. decrease the dose to avoid toxicity.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b]	11. [a] [b] [c] [d]
2. [a] [b] [c] [d]	7. [a] [b] [c] [d]	12. [a] [b] [c]
3. [a] [b] [c]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c] [d]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c] [d]	10. [a] [b] [c] [d]	15. [a] [b]

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8. Following administration of carbamazepine, a patient with the *HLA-B*15:02* gene variant and necrotic lesions on more than 30% of his body would be diagnosed with:
   a. SJS. c. TEN.
   b. MPE. d. erythema.

9. Genetic testing could be considered when initiating carbamazepine to avoid what potentially life-threatening condition?
   a. Anaphylaxis c. Stevens-Johnson syndrome
   b. Heart attack d. Stroke

10. What ethnicity has a higher frequency of the *HLA-B*15:02* allele?
   a. Asian c. Native American
   b. African American d. Caucasian

11. Which guideline would you refer to for information about interpretation of genetic testing results?
   a. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)
   b. Infectious Disease Society of America (ISDA)
   c. Adult Treatment Panel III (ATPIII)
   d. Clinical Pharmacogenetics Implementation Consortium (CPIC)

12. Compared to their parent compound, how active are the hydroxy metabolites of tricyclic antidepressants?
   a. Same activity c. Less active
   b. More active

13. When considering conversion of the prodrug clopidogrel to its active form, which gene has been mostly discussed?
   a. *CYP2D6* c. *CYP3A4*
   b. *CYP1E2* d. *CYP2C19*

14. Which of the following is the expected metabolic phenotype for a patient with a normal function allele and a loss-of-function allele in regards to *CYP2C19*?
   a. Ultra metabolizer (UM) c. Intermediate metabolizer (IM)
   b. Poor metabolizer (PM) d. Extensive metabolizer (EM)

15. A patient with coronary artery stents who is an extensive metabolizer with a *CYP2C19*1/*1* diplotype can be effectively treated with clopidogrel 75 mg daily.
   a. True b. False

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