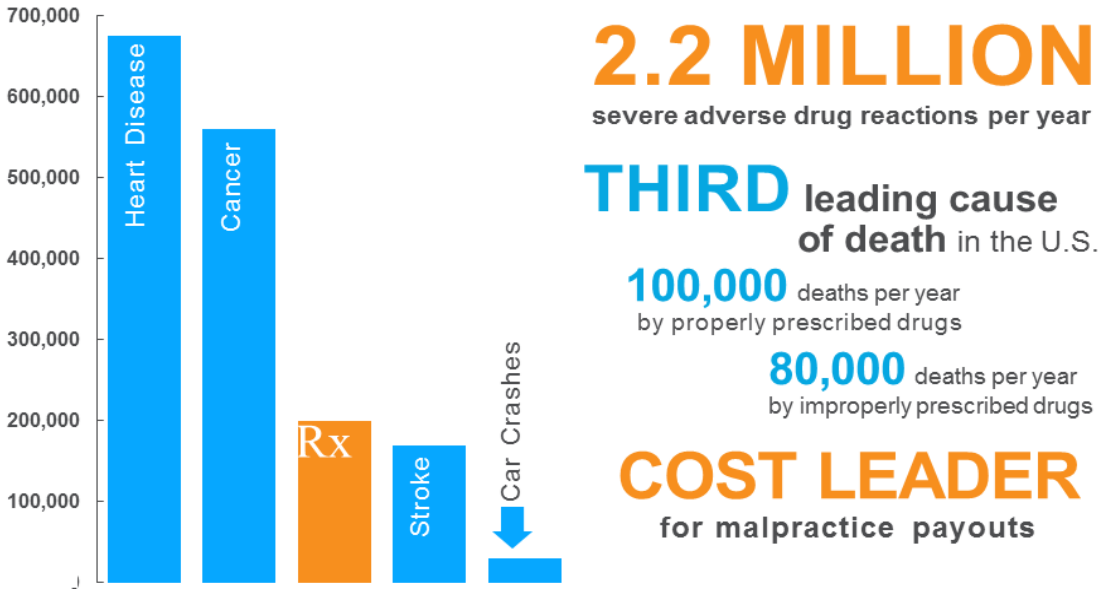
Application of Pharmacogenetics
Supplementary Worksheet

Section 1: Health care problem

Most people know that heart disease and cancer are leading causes of death, but few people are aware that one person dies every 5 minutes from adverse drug reactions to properly prescribed medications. That's the equivalent to a full 747 crashing every 34 hours.

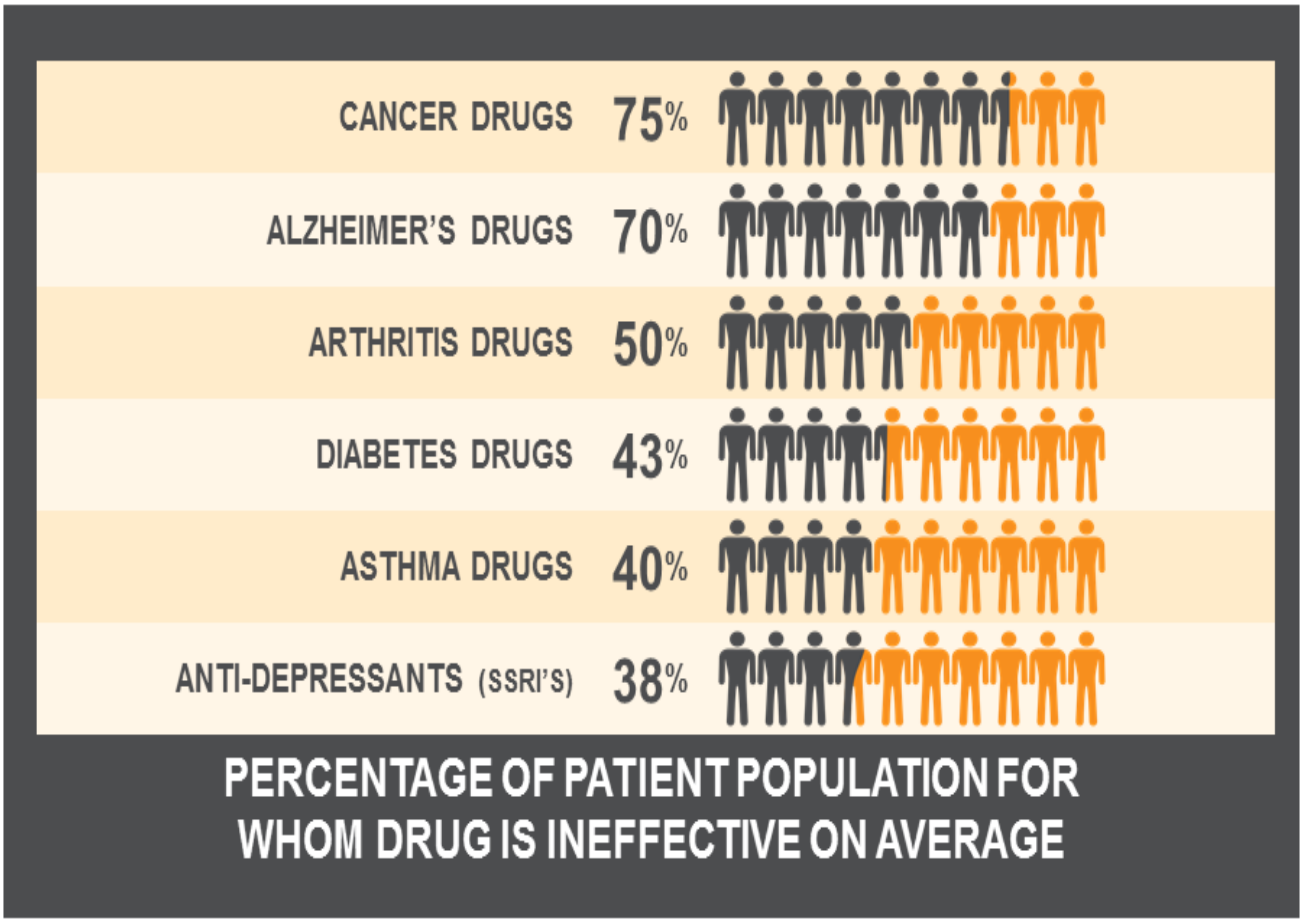
These are not medication errors; these are reactions to medication given according to the guidelines approved by the FDA. Its not just death, there are over 2 million severe adverse drug reactions every year[1]. This means that every day more than 5,000 Americans have an adverse drug reaction so serious that they must be admitted to the hospital.

This toll comes at a cost. In 2001 a study in the journal of the American Pharmacist Association estimated that adverse reactions costs $177 billion dollars in direct health care costs every year in the U.S.[2] This does not include the indirect cost of missed work and lower productivity or intangible cost such as pain and suffering. The FDA calls this a major but solvable health care problem.



[1] JAMA 279:1200 1998
[2] American Pharmacist Association

Treatment failures are another huge problem. An estimated 50% of medications do not work and are therefore wasted. We can't resolve all of the adverse reactions and all of the treatment failures, but with a better understanding of pharmacogenetics, we can dramatically reduce the problem, saving lives and health care dollars.



Check for understanding

1) Adverse Drug Reactions are one of the leading causes of death in the United States?
    a. True
    b. False

Section 2: Drug metabolism

One of the main drivers behind adverse reactions and treatment failures is drug metabolism. When we explain Cytochrome DNA testing, we compare CYP's to highways. Certain drugs only drive on certain highways. In Seattle, the main highways are I-5, I-90 and WA-99. Some drugs will drive only on I-90, some half on I-5 and half on WA-99 and some one-third through each.

Your genes determine your basic road map, how many lanes, and if you even have a highway. Other drugs, herbals and over the counter (OTC) medications can impact traffic on these highways by opening and closing lanes.

When we test patients for CYP 450 2D6, 2C9, and 2C19, we assign them to one of four phenotypes.

Extensive which we call "Normal" (NM) on our reports have 2 active genes. Back to the lanes analogy, they have 2 lanes for traffic to drive on.

Poor metabolizers (PM) have 2 inactive genes or no lanes. It is important to point out that this runs in families – so if you are a poor metabolizer your children cannot be normal metabolizers as you do not have an active gene to give.

Ultra Metabolizers (UM) have additional lanes, typically one, but they have seen up to 13 duplications in some patients.

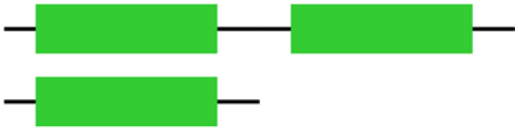
Intermediate metabolizers (IM) have one active and one inactive gene. This phenotype is very common and typically not an issue in patients taking few medications, but when multiple medications are being taken and one happens to shut down the other lane, you have a patient that will respond in a similar fashion as a poor metabolizer (we call this phenoconversion).

Phenotypes:

EM Extensive Metabolizer (Normal)
2 Active Genes

PM Poor Metabolizer
2 Inactive Genes

UM Ultra Metabolizer
More Than 2 Active Genes



IM Intermediate Metabolizer
1 Active/1 Inactive Gene

Check for understanding

2) Which of the following statements is **true?**
   a. Intermediate metabolizers can not present as a poor metabolizer. An IM will always respond to drugs like an IM.
   b. Intermediate metabolizers can be phenoconverted to a poor metabolizer by a drug that further inhibits that enzyme.
   c. Children of poor metabolizers can be normal metabolizers.
   d. An Extensive metabolizer is the same as a rapid metabolizer.

Section 3: Phase I and Phase II Metabolism

When drugs are administered orally, they are absorbed through the stomach wall into the portal vein where they are then transported to the liver. In the liver they are metabolized before entering the rest of the body.

Phase I metabolism is usually the first step in the process (though sometimes phase II occurs first). During phase I metabolism, drugs are made more hydrophilic by adding or exposing functional groups such as, –OH, -COOH, -NH2, and –SH. This change allows the drug to be more readily cleared by the kidneys and can activate or inactivate a drug. The cytochrome P450's or CYP450's are the most important enzymes involved in this process.

The second phase of metabolism, called phase II metabolism, occurs when enzymes such as the UGT's add endogenous substrate to the drug molecule to make a highly water soluble conjugate that is easily excreted from the body. Two examples of phase II metabolism include glucornidation and sulfation.

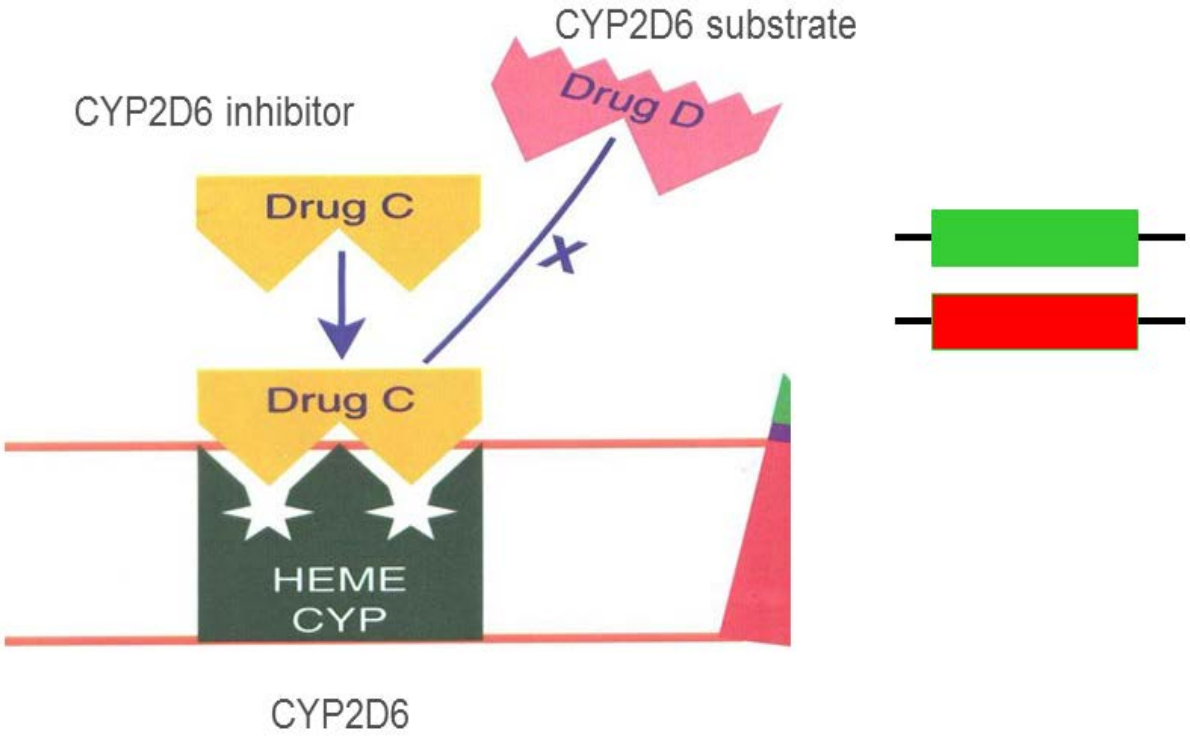
Check for understanding

3) The goal of both phase I and phase II metabolism is to make a drug molecule more lipophilic?
    a. True
    b. False

Section 4: Inhibitors and Inducers

Returning to the the lanes analogy, inhibitors are drugs, OTC's, herbals, or even foods that shut down a portion of a lane, full lanes, or even two lanes of the CYP highway. Inhibition occurs immediately.

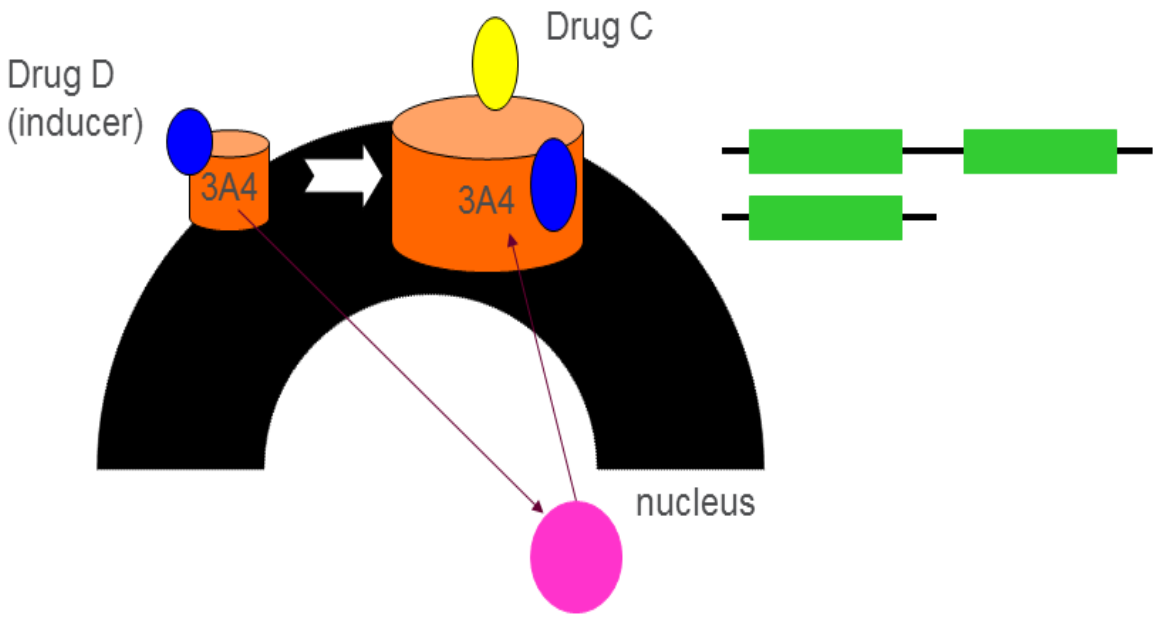
In this diagram, drug C blocks the CYP1A2 enzyme so that drug D can no longer be metabolized. There are two main types of inhibition, competitive and mechanism-based. For more information on these please see the recommended reading section. Compare the inhibitor image to the image on the right and consider its similarities to having one active gene copy (an intermediate metabolizer).



Inducers are drugs that do the opposite of inhibitors. They open another lane for traffic. Inducers take a week or longer of daily doses to take effect. Here, drug D sends a message to the nucleus of the cell, which

results in an increase in production of the CYP3A4 enzyme. Drug C as a result is metabolized more extensively. Again, notice to the right how drug induction is similar to having an extra gene copy (the ultra metabolizer phenotype).

*Drugs can be both inhibitors and inducers of multiple pathways.



Drug D sends message to nucleus to make more CYP protein---Induction of 3A4->lower concentration of Drug C

Check for Understanding:

4) A drug that prevents the metabolism of another drug is called
   a. Inhibitor
   b. Inducer
   c. Intermediate metabolizer
   d. Non-responder

Section 5: DNA and drug response

So just how important are pharmacogenetic polymorphisms? Most people are unaware that medicines most commonly associated with adverse drug reactions (ADRs) are 8-times more likely to be metabolized by an enzyme that is genetically variable. Over 75% of patients have variations in at least one of the 3 main CYPs that are commonly tested, which are 2D6, 2C9, and 2C19.

In an analysis of 9000 patients tested at Genelex, only 14% did not have a variation in at least one of the 3 main CYPS that are tested: 2D6, 2C9, and 2C19. These CYPs process about half of all medication, including antidepressants, heart medication, pain medication, diabetes medications, and many more. When patients are tested for 2D6, 2C9 and 2C19, they are assigned to one of 4 phenotypes. Refer back section 2 if you need a review. As previously mentioned, these variations run in families, so if you are a poor metabolizer, your children cannot be normal metabolizer, because you do not have an active gene to give them.

How common are the genetic variations? CYP2D6 processes about 25% of all medications and 10% of all patients are poor metabolizers, 7% ultra, and one-third intermediate. CYP2C9 acts on 15% of drugs, including warfarin. 2C19 works on about 10% of mediations – it is unique in that it has a wide ethnic variability in phenotypes. About 2-4% of Europeans ancestries are poor metabolizers, 10% of Africans and 20% of Asians. About 30% of all patients are ultra and about 25% to one-third are intermediate metabolizers.

Genetic variation frequency in Cytochromes P450s

	Normal	Intermediate	Poor	Ultra
CYP2D6	48%	35%	10%	7%
CYP2C9	~60%	>35%	2-4%	N/A
CYP2C19*	14-44%	24-36%	2-20%	30%

* There is wide variability among populations. People of Asian and African ancestry have a greatly increased prevalence of poor metabolizer status.

Check for Understanding

5) A family history of adverse drug reaction or treatment failure could help determine whether pharmacogenetics should be considered in tailoring drug therapy.

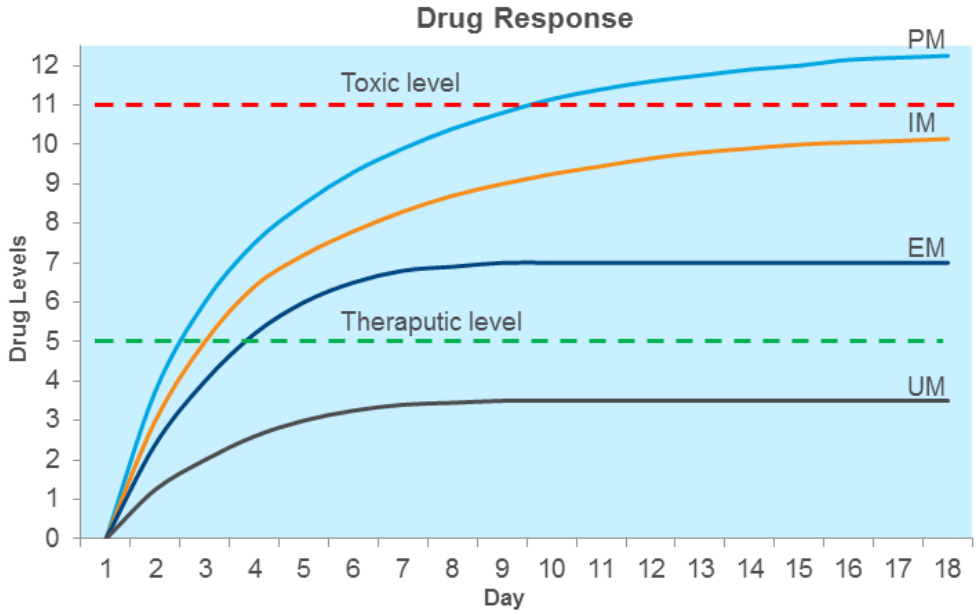
a. True
b. False

Section 6: Active drugs and prodrugs

The following diagrams illustrate how patients with a specific phenotype will respond to a drug. Ultra metabolizers, metabolize a drug so quickly that they may never reach therapeutic levels. Normal and intermediate metabolizers will likely be in range, and poor metabolizers are at risk of toxicity. The area between the therapeutic and toxic level varies by drug – so sometimes all phenotypes will be in range and sometimes even the intermediate metabolizers reach toxic levels.

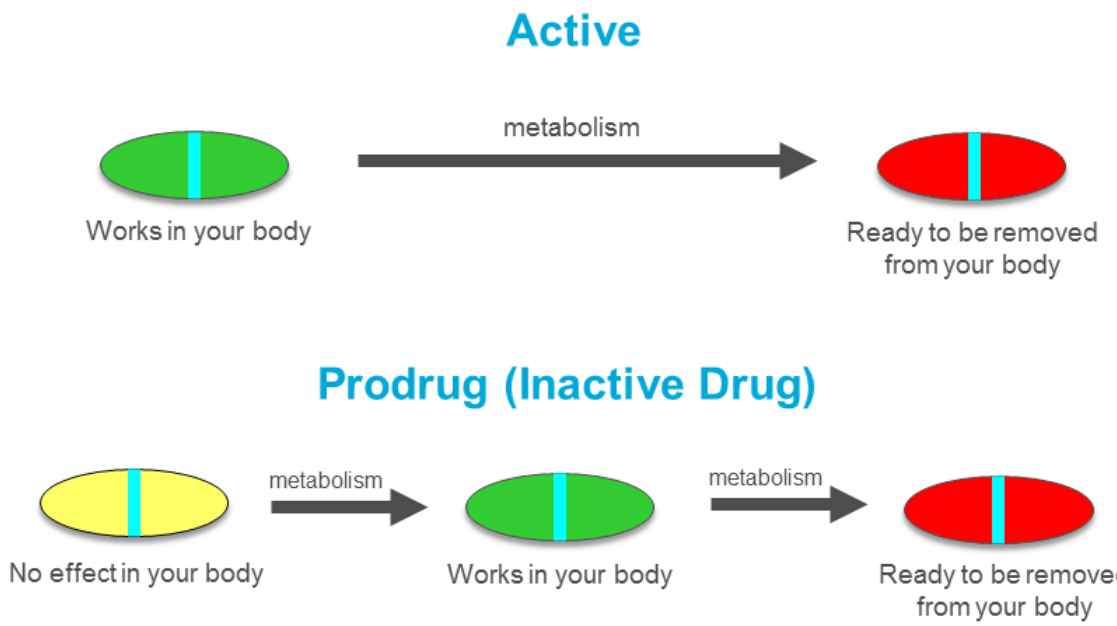
Drug response: Active drugs

Genetics affects drug clearance



PM: Poor Metabolizer IM: Intermediate Metabolizer EM: Extensive (normal) Metabolizer UM: Ultra Metabolizer

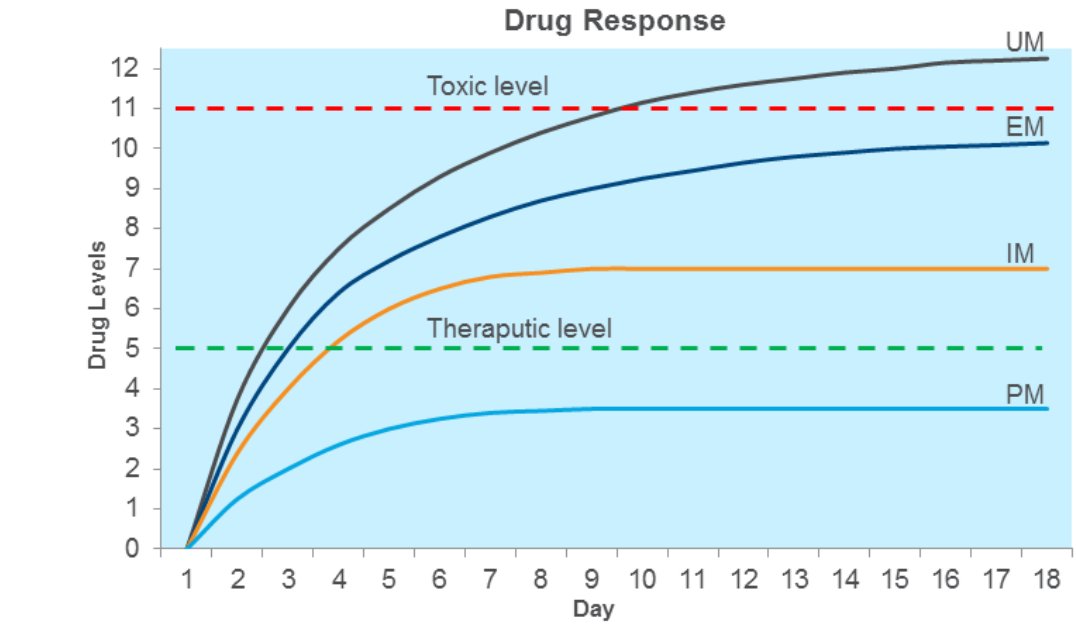
Many of the drugs that are impacted by pharmacogenetics are prodrugs. Prodrugs, like clopidogrel (Plavix) are taken in an inactive form, and have to be metabolized to work, and then metabolized again to be removed from the body. It is important to know if the drug being affected is a prodrug or active drug.



This diagram illustrates how a specific phenotype will respond to a prodrug.

Drug response: Prodrugs

Genetics affects drug clearance



PM: Poor Metabolizer IM: Intermediate Metabolizer EM: Extensive (normal) Metabolizer UM: Ultra Metabolizer

Here is the same information broken down in a different way.

Metabolizer Phenotype	Drug Type	
	Standard drugs	Prodrugs*
Poor Metabolizer (PM)	Reduced elimination Increased toxicity risk	Decreased effectiveness Decreased activation
Intermediate Metabolizer (IM)	Increased drug-to-gene and drug-to-drug interaction risk Possible increased toxicity risk	Increased drug-to-gene and drug-to-drug interaction risk Possible reduced effectiveness
Normal Metabolizer (NM)	Performs according to FDA label specifications	
Rapid or Ultra Rapid Metabolizer (RM, URM)	Reduced effectiveness Increased elimination	Increased activation Increased toxicity risk

Check for Understanding

6) For a prodrug, a patient that is a rapid metabolizer, may need a
   a. Reduced dose of the medication
   b. An increased dose of the medication
   c. An inhibitor to decrease metabolism

Section 7: Standard drug-metabolizing panel

You may be wondering why this review does not discuss some of the other important genes like TPMT and UGT1A1, used to screen for adverse drug reaction and sensitivity to specific medications like cancer drugs. The reason is, that while these enzymes are crucial in the treatment of their disease states, they are thankfully uncommon and most patients will never take them. CYP 2D6, 2C9, and 2C19 on the other hand are very common.

Think of 2D6, 2C9, and 2C19 as a standard drug-metabolizing panel. These 3 CYPs have wide genetic variation and impact over half of the most commonly prescribed medications for life. Although other enzymes may need to be tested on a case-by-case basis, these 3 will always be the most common and important from a genetic variability standpoint.

The list of medication with pharmacogenetics on the product label is constantly growing. Again, the majority are medications processed by 2D6, 2C9, and 2C19. It is important to note that while 3A4 is an important cytochrome that processes a large number of medications, not a single drug label has pharmacogenetics info on CYP3A4. Of the fifty 3A4 genetic variations that have been found, none have been proven to be clinically relevant.

Check for Understanding

7) CYP3A4 is not an important enzyme in drug metabolism.
   a) True
   b) False

Section 8: Resources and Tools for using pharmacogenetic information

1. FDA website
    a. Table of Pharmacogenetic Biomarkers in Product Labels: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
    b. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/default.htm
2. Genelex website
    a. http://youscript.com/healthcare-professionals/dna-learning/pharmacogenetic-resources/
3. Drug Interaction Book
    a. Clinical Manual of Drug Interaction Principles for Medical Practice. American Psychiatric Publishing, Inc.; 1 edition (October 30, 2008). Wynn, G., Oesterheld, J., Coza, K., Armstrong, S.
4. Ohio Northern University
    a. http://www.onu.edu/personalized_medicine

Check for understanding key

1) a
2) b
3) b
4) a
5) a
6) a
7) b