Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Pharmacogenomics in Pain Management

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Slide 1:
Hello, my name is Gwen McMillin. I am an Associate Professor of Pathology at the University of Utah, and a Medical Director for ARUP Laboratories, in Salt Lake City, Utah. Welcome to this Pearl of Laboratory Medicine on "Pharmacogenomics in Pain Management."

Slide 2:
The term "Pharmacogenomics" describes how genetics can predict or explain drug response. The FDA defines pharmacogenomics more specifically as "the science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effect." Each pharmacogenomic association relates to one of the two major processes that contribute to the drug response phenotype, specifically, pharmacokinetics or pharmacodynamics. In theory, all drugs could have a pharmacogenomic profile consisted of many genes that code for the proteins involved in the pharmacokinetics and pharmacodynamics of that drug. The drug response phenotype is also affected by expression of genes, which may be a consequence of endogenous factors such as clinical status, age, and gender, as well as exogenous factors such as drug-drug interactions, diet, or nicotine use.

Slide 3:
This slide shows examples of genes that may contribute to a pharmacokinetic or pharmacodynamic phenotype. The best-characterized genes that relate to pharmacokinetics, code for drug metabolizing enzymes. Cytochrome P450 enzymes, abbreviated CYPs, are responsible for the Phase I metabolism of most drugs, and are subject to wide inter-individual differences in expression and activity. Some of the inter-individual differences can be explained by variants in the corresponding CYP genes. Phase II metabolic enzymes such as thiopurine s-methyltransferase, abbreviated TPMT, are also known to exhibit inter-individual differences. TPMT is among the first pharmacogenomic targets described, and is used clinically to qualify patients for 6-mecaptopurine therapy, and optimize dose, based on genotype and/or phenotype testing. When considering the processes involved in pharmacodynamics, we recognize variant genes that code for effector molecules such as receptors, ion channels, or enzymes. Predictive algorithms and guidelines that incorporate pharmacogenomics of pharmacokinetics and pharmacodynamics with clinical and other factors have been proposed. For example, *CYP2C9* and *VKORC1* genotypes, used in combination with known endogenous and exogenous covariates, may be

used to estimate a loading dose, therapeutic maintenance dose, and dosing strategy for warfarin, for an individual patient. While pharmacogenomic testing does not replace the need for clinical or therapeutic drug monitoring, results may help reduce some of the 'trial and error' that is common to dose optimization for many drugs.

Slide 4

Drug therapy is commonly used to manage pain, whether the pain is acute or chronic. It is not unusual for chronic pain management patients to be prescribed several drugs, some targeting the source of pain, and other drugs intending to manage factors that exacerbate pain, such as inflammation, muscle tension, mood, and insomnia. Unfortunately, prescription drugs, particularly opioids and benzodiazepines, are associated with therapeutic failure and have become a common contributor to accidental death. One reason for the risk of therapeutic failure or accidental death is a failure to recognize and respond to individual variation in drug metabolism and response, and failure to understand the differences in potency.

Slide 5:

This slide, which is not all-inclusive, illustrates the approximate analgesic potency for several prescription opioids, as compared to codeine. Very potent drug are likely to exhibit higher risk of unintentional overdose. Also of concern are drugs that rely on metabolism for activation. A drug that requires metabolic activation is called a prodrug. Prodrugs may put a patient who has either inherited or acquired variant metabolism, at substantial risk for therapeutic failure or unintentional overdose. Variant metabolism is one of the factors that can explain the wide range of plasma half-life observed for many of these drugs. Pharmacogenomics can help predict or explain patient variation in drug response and associated dose requirements for opioids and other drugs, and could become an important tool for pain management providers. That said, there is little consensus regarding what, how, and who to test, for most drugs. Codeine is one exception.

Slide 6:

The Clinical Pharmacogenomics Implementation Consortium (CPIC) has published a guideline for the association of *CYP2D6* genotype and analgesic response to the opioid drug codeine. Codeine is a prodrug and thereby requires metabolic activation to exert the intended analgesic response. As shown on this slide, codeine is converted to morphine by a reaction mediated primarily by *CYP2D6*. The amount of codeine that is converted to morphine, and the rate of codeine elimination, is influenced by the enzymatic phenotype of *CYP2D6*. The metabolic phenotype can be predicted or explained by *CYP2D6* genotyping. As such, pre-therapeutic *CYP2D6* genotyping could help qualify a patient as a candidate for analgesic therapy with codeine.

Slide 7:

This slide illustrates the major categories of phenotypes that are described for *CYP2D6*. The extremes of phenotype include no activity, known as the poor metabolizer phenotype, and excess activity, known as the ultra-rapid metabolizer phenotype. Between the extremes exists a continuum of enzymatic phenotypes that range from intermediate to normal. Normal metabolism is classically described as extensive metabolism. These phenotypes are commonly abbreviated as PM, IM, EM, and UM. Genotypes for *CYP2D6* can sometimes predict the *CYP2D6* phenotype. Because we as humans are

diploid, the clinical phenotype for an individual is predicted from the combination of both alleles. However, the *CYP2D6* gene is very complicated and is associated with over 100 variant alleles. Most clinical genotyping assays detect only a few common variants, and may not detect the number of gene copies that a person has inherited. The ultra rapid metabolizer phenotype frequently presents as a consequence of inheriting more than two copies of non-variant alleles, leading to excess amplification of functional *CYP2D6* enzyme. In addition, when multiple variants are identified, it may not be possible for the laboratory to determine whether those variants are in cis or trans. Due to the inherently limited sensitivity and specificity of *CYP2D6* genotyping methods, the *CYP2D6* phenotype cannot always be accurately predicted from a genotype test. Phenotype testing, such as through determining metabolic ratios after administration of a probe drug, is well-described, but is not widely available. If the *CYP2D6* phenotype is known, or if the *CYP2D6* phenotype is predicted based on *CYP2D6* genotype, one can use the CPIC guideline to make decisions about whether a patient is a good candidate for use of codeine to manage pain.

Slide 8:

The CPIC guideline for codeine supports use of codeine in extensive and intermediate metabolizer phenotypes, but has published STRONG consensus recommendations for the extremes of *CYP2D6* phenotype. A *CYP2D6* poor metabolizer, whether predicted from genotype or as a result of drug-drug interactions, is unlikely to activate codeine, and as such, is unlikely to realize the therapeutic potential of codeine, regardless of dose. As such, poor metabolizers should avoid codeine, and other drugs that require metabolic transformation mediated primarily by *CYP2D6*.

Slide 9:

CYP2D6 ultra rapid metabolizer phenotypes should also avoid codeine, but for a different reason. Because codeine is a pro-drug, the ultra-rapid metabolizer phenotype will activate an unpredictable amount of codeine to morphine, and could lead to an unintentional opioid overdose, that could be responsible for life-threatening consequences. Populations at unique risk include opiate-naïve children and breast-fed infants born to mothers who are *CYP2D6* ultra rapid metabolizers. As a result, the FDA has issued public health advisory statements about codeine and several professional organizations have advocated against the use of codeine for patients with unknown *CYP2D6* phenotype. Pre-therapeutic *CYP2D6* genotyping, performed using a test that is designed to detect alleles associated with the poor and ultra rapid metabolizer phenotypes, could qualify a patient for use of codeine.

Slide 10:

CYP2D6 phenotype can also be applied to a wide variety of other drug substrates that are either activated or inactivated by reactions mediated primarily by *CYP2D6*. Examples of such drugs are shown on this slide. As has been discussed here for codeine, *CYP2D6* will catalyze production of active metabolites for other opioid analgesics, including tramadol, oxycodone, and hydrocodone. Note also that some *CYP2D6* substrates, such as fluoxetine and paroxetine, are also *CYP2D6* inhibitors. Strong inhibitors, as defined by the FDA, will increase the area under the curve of a substrate by more than 5-fold, and could create an acquired poor metabolizer phenotype, regardless of *CYP2D6* genotype. Moderate inhibitors will, as you might expect, exert a more moderate inhibitory effect on *CYP2D6* and may or may not change the patient phenotype.

Slide 11:
This slide summarizes the involvement of four cytochrome P450 drug metabolizing enzymes in the activation or inactivation of several analgesics. All of the corresponding genes exhibit variant genotypes that could impact the phenotype and corresponding sensitivity to these drugs. If making drug and dosing decisions for a patient predicted to exhibit an extreme *CYP2D6* phenotype, we might avoid the drugs that are known to be associated with *CYP2D6*, and instead, pick a drug like hydromorphone, which is not described to undergo metabolism by any of these enzymes. Likewise, if the *CYP2D6* phenotype is normal but the *CYP3A4* phenotype is expected to be impaired, then codeine may be a good choice of drug use. As stated previously, however, this information is but one tool used to guide patient care decisions, and should not be assumed to be completely accurate or appropriate, considering the many other factors that could impact response to therapy for an individual patient.

Slide 12:
In conclusion, pharmacogenomics has great potential to optimize therapy in pain management and other complicated pharmacotherapy scenarios, but most applications require further characterization. Pharmacogenomics is most useful when it can predict a defined aspect of pharmacokinetics and/or pharmacodynamics, and is used in combination with other important covariates when making decisions about whether to use a specific drug, or dose of drug for an individual. Application of the predicted *CYP2D6* phenotype to codeine represents one example of a well-characterized pharmacogenomics association that could be applied clinically today.

Slide 13: References
I encourage you to consult the current peer-reviewed literature and electronic references such as those shown on this slide, to further understand the utility of pharmacogenomics in selecting and optimizing drug therapy for pain, and other clinical indications.

Slide 14: Disclosures

Slide 15: Thank You from www.TraineeCouncil.org
Thank you for joining me on this Pearl of Laboratory Medicine on "Pharmacogenomics in Pain Management." I am Gwen McMillin. These Pearls of Laboratory Medicine are part of the *Clinical Chemistry* Trainee Council.