Clinical Update: Month 2020

Introduction to PGx for Pain Management

Aegis offers pharmacogenetic testing focusing on medication/gene pairs that are supported by clinical guidelines, FDA-approved labeling, or clinical studies and must be graded as level A or B by the Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC is one of the most widely recognized expert groups providing genetic testing information, examining scientific literature, and drafting evidence-based guidelines. Currently, the genes encoding for cytochrome P450 (CYP) enzymes with the highest levels of evidence involved in the metabolism of drugs used to treat pain include CYP2D6 and CYP2C9.[1,2,3] Therefore, Aegis' current pharmacogenetic (PGx) offerings for pain management are focused on these two pathways.

Many in the healthcare industry agree that personalized medicine, which is based on the premise that medical treatment should be tailored to patients' unique needs, is one way to improve patient care. Ideally, by identifying the best medication regimen for each patient at initiation of therapy, this approach will streamline therapy and reduce therapeutic failures and adverse effects. Discussions surrounding personalized medicine often focus on genetic testing. Pharmacogenetics refers to the study of specific genes and their impact on patient response to medication. The terms "pharmacogenetics" and "pharmacogenomics" are often used interchangeably, although they technically differ. Pharmacogenomics is a broader term that refers to the impact of genes on medication response. Pharmacogenetics generally refers to the study of specific genetic alterations and their effect on medications.[4]

Please see the PGx Tip "Introduction to PGx for Behavioral Health" for a general explanation of pharmacogenetic testing.

Many medications used to treat acute and chronic pain are metabolized by CYP enzymes. Codeine, hydrocodone, oxycodone, and tramadol are metabolized by both CYP3A4 and CYP2D6 into norcodeine, norhydrocodone, noroxycodone, and nortramadol and into morphine, hydromorphone, oxymorphone, and O-desmethyltramadol, respectively. The "nor"-metabolites of CYP3A4 do not provide analgesia, but the accelerated or slowed rate of CYP3A4 metabolism can affect the amount of parent drug metabolized by the CYP2D6 pathway.[5] Currently, the CYP3A4 enzyme lacks enough supporting evidence for identifying frequencies of known variants in alleles. Therefore, Aegis does not currently test for the CYP3A4 enzyme. However, a significant amount of evidence supports that CYP2D6 polymorphisms impact the effectiveness of prescription opioids; therefore, CYP2D6 testing is part of the Aegis' PGx test offering.[1,2,5] The CYP2D6 pathway metabolizes codeine, hydrocodone, and oxycodone into more pharmacologically active metabolites than the parent drug itself. Therefore, poor CYP2D6 metabolizers (PM) of these drugs produce low plasma concentrations of the active metabolite, and thus are less likely to achieve the accepted level of pain control. Conversely, ultrarapid metabolizers (UM) of CYP2D6 run the risk of reaching supratherapeutic levels of the metabolite, potentially causing toxicity for these drugs.[5] Lastly, variants of CYP2C9 have been shown to reduce the inactivation of celocoxib by up to 50%.[1,2,5] This slowed metabolism results in prolonged action of the active parent drug, and thus a higher potential for side effects such as GI bleeding.[6]

Understanding the value of pharmacogenetic testing can streamline therapy and reduce therapeutic failures and adverse effects by identifying the best medication regimen for each patient at initiation of therapy.[4] Aegis' pharmacogenetic offering focuses on providing actionable information based on CPIC recommendations, which are backed by rigorous clinical evidence. This offering is not inclusive of all pain management medications as some are metabolized outside of the CYP pathways that are incorporated into our test offering and don't have sufficient scientific evidence for inclusion in testing (OPRM1, phase II glucuronidation, etc.).[1]

Aegis current PGx offerings in pain management are as follows:

Pain Management	
◯ CYP2C9	Celecoxib (Celebrex)
◯ CYP2D6	Codeine (Tylenol III, Tylenol IV)
◯ CYP2D6	Oxycodone (OxyContin, Percocet)
◯ CYP2D6	Tramadol (Ultram)

CPIC gene/drug pairs (pain management)[1]

Gene	Drug	CPIC Level*	PharmGKB Level†	PGx on FDA Label[x]
CYP2C9	**Celecoxib**	**B**	**2A**	**Actionable PGx**
CYP2D6	**Codeine**	**A**	**1A**	**Actionable PGx**
ABCB1	Fentanyl	C/D	2B	-
OPRM1	Fentanyl	C/D	3	-
CYP2B6	Methadone	B	2A	-
ABCB1	Methadone	C/D	2B	-
OPRM1	Methadone	C/D	3	-
OPRM1	Naloxone	C/D	2B	-
OPRM1	Naltrexone	C/D	3	-
CYP2D6	**Oxycodone**	**A**	**2A**	**-**
ABCB1	Oxycodone	C/D	2B	-
CYD2D6	**Tramadol**	**A**	**1B**	**Actionable PGx**
ABCB1	Tramadol	C/D	2B	-
OPRMI	Tramadol	C/D	3	-

Items in bold denote Aegis offerings in pain management.

*CPIC Level: CPIC assigns CPIC levels to gene/drug pairs. Definitive CPIC level assignments (A, B, C, and D) are only designated to gene/drug pairs that have been the subject of guidelines with sufficient in-depth review of evidence. Only CPIC level A and B gene/drug pairs have sufficient evidence for at least one prescribing action to be

recommended. CPIC level C and D gene/drug pairs are not considered to have adequate evidence or actionability to have prescribing recommendations.[1]

[†]PharmGKB Level: PharmGKB is an NIH-funded resource that provides information about how human genetic variation affects response to medications. PharmGKB collects, curates and disseminates knowledge about clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB Clinical Annotation Levels of Evidence include 1A, 1B, 2A and 2B, 3, and 4, with level 1 meeting the highest level of evidence criteria. PharmGKB clinical annotation levels are derived from variant annotations. A variant annotation is single genetic variant and a drug response, as reported in a single publication. Clinical annotations are all the variant annotations that discuss the same genetic variant and the same medication response with genotype-based summaries that describe the phenotypic impact of the variant.[2]

[x]PGx on Food and Drug Administration (FDA) Label: PharmGKB gathers information from the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" and from FDA-approved labels which include specific actions to be taken based on the gene information:[3]

1. Testing required
2. Testing recommended
3. Actionable PGx: The label may contain information about changes in efficacy, dosage, metabolism or toxicity due to gene/protein/chromosomal variants or phenotypes (e.g. "poor metabolizers").
4. Informative PGx

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

References:

1. CPIC Clinical Pharmacogenetics Implementation Consortium. Retrieved from https://cpicpgx.org/.
2. PharmGKB. Retrieved from https://www.pharmgkb.org/.
3. US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. Retrieved from https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
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5. Kaye AD, Garcia AJ, Hall OM, et al. Update on the pharmacogenomics of pain management. Pharmgenomics Pers Med. 2019 Jul 3;12:125-143. doi: 10.2147/PGPM.S179152. eCollection 2019.
6. Kapur BM, Lala PK, Shaw JLV. Pharmacogenetics of chronic pain management. Clin Biochem. 2014;47(13–14):1169–1187. doi:10.1016/j.clinbiochem.2014.05.065