Clinical Pharmacology & Toxicology Pearl of the Week

Interpreting pharmacogenomic test results

- ✓ Mutations in enzymes responsible for drug metabolism can lead to increased or decreased clearance of a drug from the body, or increased or decreased bioactivation of prodrugs.
- ✓ Mutations can also lead to increased risk of toxicity, or risk of non-response to medications.
- ✓ Phenotypes of drug metabolism are categorized as poor metabolizers, intermediate metabolizers, extensive metabolizers (normal), or ultra-rapid metabolizers.
- ✓ Knowing a patient's phenotype prior to drug choice and drug prescription can lead to changes in dosage or medication selection to improve patient response and decrease the risk of adverse events.

I have the pharmacogenomics test result, what does it mean?

- ✓ Genetic testing will provide information on which alleles a patient has.
  - Every patient has two alleles, called a diplotype, where one allele comes from each parent.
  - Occasionally, patients can have an increase in their gene copy number. This can increase the enzymatic activity of the gene product if the duplicated gene is functional, by increasing the quantity of enzyme produced. Alternatively, the increase in copy number may have no effect if the duplicated gene is non-functional
- ✓ Functional studies *in vivo* and *in vitro* are done that determine the function of each allele.
  - Does the allele increase or decrease enzymatic activity? Does it make the enzyme non-functional?
- ✓ A patient's diplotype along with functional studies will determine their *phenotype*, which is the observable end result of a patient's genetics or genotype.

Phenotype	What this means
Ultra-rapid metabolizer	They metabolize drug targets of this gene much faster than most patients. This can lead to increased bioactivation of pro-drugs, or increased clearance of active drugs
Extensive metabolizer	They metabolize drug targets of this gene at the expected rate
Intermediate metabolizer	They metabolize drug targets of this gene at a reduced rate. This can lead to decreased bioactivation of pro-drugs or decreased clearance of active drugs
Poor metabolizer	They do not metabolize drug targets of this gene. This can lead to an inability to bioactivate pro-drugs, or a very reduced clearance of active drugs

Examples of Clinical Applications

Gene Product	Phenotype (% of population)	Drug of Interest	Clinical Implication
CYP 2D6	Poor Metabolizer (1-6%)	Codeine	Patient unable to convert codeine to morphine. No analgesic effect from codeine. Use alternative agent.
	Poor Metabolizer (1-6%)	Tramadol	Patient unable to convert tramadol to opioid metabolite. Decreased analgesic effect from tramadol and increased SNRI effect from higher concentration of parent compound
	Ultra-rapid Metabolizer (1-20%)	Codeine	Patient converts codeine efficiently to morphine. Higher risk of respiratory depression, overdose, and addiction.
	Ultra-rapid Metabolizer (1-20%)	Tramadol	Patient converts tramadol efficiently to opioid metabolite. Increased risk of opioid adverse effects and addiction.
CYP 2C19	Intermediate and Poor Metabolizers (24-47%; 2-46%)	Clopidogrel	Patient unable to activate clopidogrel. Increased risk of thrombosis. Consider alternative agent.
	Ultra-rapid Metabolizer	Citalopram/ Escitalopram	Increased clearance and decreased drug efficacy. Consider alternative SSRI.
CYP 2C9	Intermediate and Poor Metabolizers (7-41%)	Warfarin	Impaired clearance of warfarin. May require reduced dose compared to wild-type patients.
		Ibuprofen	Decreased clearance of ibuprofen, consider 25-50% dose reduction to decrease risk of adverse effects
DPYD	Poor Metabolizer (1-4%)	Fluoropyrimidines (5-FU, capecitabine)	Impaired clearance and risk of toxicity. Choose alternative chemotherapeutic agent.

TMPT	Poor Metabolizer (3-7%)	Azathioprine, mercaptopurine	Impaired clearance and risk of toxicity. Consider alternative chemotherapeutic or start with drastically reduced dose

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References:

1. Brunton L, Hilal-Dandan R, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Medical; c2018
2. Peck RW. Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient. Annu Rev Pharmacol Toxicol. 2018;58:105-122. doi:10.1146/annurev-pharmtox-010617-052446
3. https://cpicpgx.org/guidelines/