Clinical Pharmacology & Toxicology Pearl of the Week

~ Interpreting Pharmacogenomic Test Results ~

- ✓ Genetic variants 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.
- ✓ Genetic variants in enzymes responsible for drug metabolism can lead to increased risk of toxicity, or risk of non-response to medications.
- ✓ Phenotypes of drug metabolism are categorized as poor metabolizers, intermediate metabolizers, normal metabolizers, rapid metabolizers, 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. For example: CYP2D6 *1/*4 means a patient has two alleles, the *1 and *4 allele. *1 represents the 'wild type' allele. The *1 allele is assigned when the genetic test does not find any of the alleles it was designed to detect. The *1 is assumed to have 'normal' function.
    - 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, increasing the function of the enzyme product by increasing the quantity of enzyme produced.
- ✓ Functional studies *in vivo* and *in vitro* are done that determine if a new genetic variant changes the functional ability of the gene product (e.g., enzyme).
- ✓ A patient's diplotype and functional studies will determine phenotype
    - A phenotype 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
Rapid Metabolizer	They metabolize drug targets of this gene slightly faster than normal metabolizers. This can lead to increased bioactivation of pro-drugs, or increased clearance of active drugs
Normal 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 Alberta population)	Drug of Interest	Clinical Implication
CYP2D6	Poor Metabolizer (5%)	Codeine	Patient unable to convert codeine to morphine. No analgesic effect from codeine. Use alternative agent.
		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 (3%)	Codeine	Patient converts codeine efficiently to morphine. Higher risk of respiratory depression, overdose, and addiction.
		Tramadol	Patient converts tramadol efficiently to opioid metabolite. Increased risk of opioid adverse effects and addiction.
CYP2C19	Intermediate and Poor Metabolizers (34%)	Clopidogrel	Patient unable to activate clopidogrel. Increased risk of thrombosis. Consider alternative agent.
	Ultra-rapid Metabolizer (5%)	Citalopram/ Escitalopram	Increased clearance and decreased drug efficacy. Consider alternative SSRI.
CYP2C9	Intermediate and Poor Metabolizers (35%)	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	Intermediate and Poor Metabolizer (5%)	Fluoro-pyrimidines (5-FU, capecitabine)	Impaired clearance and risk of toxicity. Choose alternative chemotherapeutic agent.
TMPT	Intermediate and Poor Metabolizer (8%)	Azathioprine, mercaptopurine	Impaired clearance and risk of toxicity. Consider alternative chemotherapeutic or start with drastically reduced dose

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/

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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