SCHOOL OF MEDICINE
INDIANA UNIVERSITY

PGX CYP2C19 Genotyping

For detection of CYP2C19 *variants affecting drug metabolism*

Clinical Background

- CYP2C19 isan isoenzyme of the CYP450 superfamily that metabolizes and eliminates common prescription drugs, including anti-convulsants, anti-depressants, proton pump inhibitors, and antithrombotics (clopidogrel/Plavix®), as well as anti-malaria and anti-ulcer drugs.
- Metabolizer phenotypes can be predicted by the *CYP2C19* genotype
- The clinical impact of the *CYP2C19* genotype is influenced by whether a drug is activated or inactivated by CYP2C19, involvement of other metabolic pathways, and other non-genetic factors (eg, other medications)

Epidemiology

- *CYP2C19* variant frequency is ethnicity dependent.
- The poor metabolizer phenotype (caused by two non-functional *CYP2C19* alleles) is present in 4% of Caucasians, 5% of African Americans, and up to 25% of Asians.

Genetics

- The *CYP2C19* gene has nine exons and is located on chromosome 10q23.33.
- Inheritance is autosomal recessive.
- Penetrance is drug-dependent.

Indications for Ordering

- Pre-therapeutic testing to identify individuals who should avoid, or may require unconventional doses of medications metabolized by CYP2C19.

Interpretation

- If no *CYP2C19* variants are detected, this suggests *1 allele and normal enzymatic activity.
- If one decreased functional or non-functional *CYP2C19* variant is detected, intermediate-to-normal CYP2C19 enzymatic activity is predicted.
- If two non-functional variants are present on opposite alleles, this predicts low CYP2C19 enzymatic activity and a poor metabolizer phenotype.

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- Genotype results should be interpreted in context of the individual clinical situation. Consultation with a clinical pharmacy professional is recommended.

CPIC Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS patients undergoing PCI:

Likely phenotype	Genotypes	Examples of genotypes	Implications for clopidogrel	Therapeutic recommendations
Ultrarapid metabolizer (UM) (~5-30% of patients)	An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased activity allele (*17)	*1/*17, *17/*17	Increased platelet inhibition; decreased residual platelet aggregation [1]	Clopidogrel - label recommended dosage and administration
Extensive metabolizer (EM) (~35-50% of patients)	An individual carrying two functional (*1) alleles	*1/*1	Normal platelet inhibition; normal residual platelet aggregation	Clopidogrel - label recommended dosage and administration
Intermediate metabolizer (IM) (~18-45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2-*8) or one loss-of-function allele (*2-*8) plus one increased activity allele (*17) [2]	*1/*2, *1/*3, *2/*17	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor
Poor metabolizer (PM) (~2-15% of patients)	An individual carrying two loss-of-function alleles (*2-*8)	*2/*2, *2/*3, *3/*3	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication); e.g., prasugrel, ticagrelor

Methodology

- Realtime Polymerase chain reaction (PCR) and microarray analysis

Variants in *CYP2C19* Assay

Allele	variant	dbSNP	Predicted enzyme activity
*1	Assumed when no variant detected		normal
*2	c.681G>A	rs4244285	Non-functional
*3	c.636G>A	rs4986893	Non-functional
*4	c.1A>G	rs28399504	Non-functional
*6	c.395G>A	rs72552267	Non-functional
*8	c.358T>C	rs41291556	Non-functional /decreased function
*17 (also *4 haplotype [*4B])	c.-806C>T	rs12248560	Increased function