What are the limitations of *CYP2C19* genotyping screening?

This test examines the most common alleles and variants of *CYP2C19* gene. Other unknown variants in the gene may change the way Clopidogrel is processed in the body. Genetic variation is one of the factors that can affect how someone may respond to Clopidogrel. However other pharmacodynamic or pharmacokinetic factors such as having Type 2 Diabetes, kidney failure or taking certain other drugs at the same time as Clopidogrel can also change how well the drug will work.

Our appointed distributor:

About Us

At LifeStrands Genomics we believe that everyone should have access to better healthcare through the advancement of clinical genomics. Within our accredited laboratories, our dedicated team of medical professionals and scientists work together to deliver high quality and reliable genomic solutions to researchers, clinicians and patients.

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LifeStrands

Is your patient taking Clopidogrel (Plavix®)?

Find out how *CYP2C19* genotyping screening can optimize therapeutic outcomes.

CYP2C19 Genotyping

Genetic Screening to Guide Clopidogrel Use

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What is pharmacogenomics and genotyping?

Pharmacogenomics is the science of how a patient's genetic makeup influences the way they respond to medications. With pharmacogenomics, clinicians can tailor-make medication plans specifically for their patients based on their genetic profile. This in turn may prevent potentially dangerous adverse drug reactions and re-hospitalizations.

Genotyping is the process of determining the DNA sequence, called a genotype, at specific positions within the genome of an individual. It is used in pharmacogenomics to determine how an individual is able to process or metabolize drugs.

What is clopidogrel and *CYP2C19*?

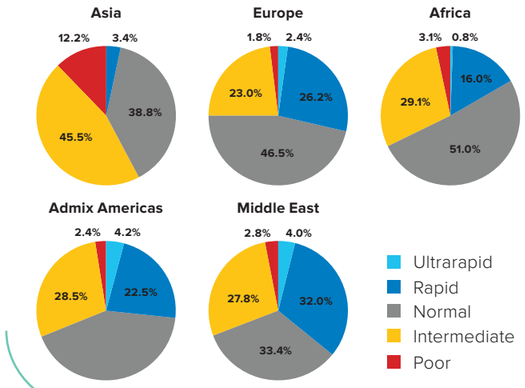
Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor such as clopidogrel remains the standard-of-care following percutaneous coronary interventions (PCI) to prevent major adverse cardiovascular events (MACEs), including cardiovascular death, myocardial infarction, and stent thrombosis.

Clopidogrel is a thienopyridine prodrug that requires hepatic biotransformation via the hepatic enzyme *CYP2C19* to form an active metabolite that selectively and irreversibly inhibits the P2RY12 receptor and thus, inhibiting platelet aggregation. However, genetics can determine if the patient treated with clopidogrel is a poor or intermediate metabolizer. The effects may result in the active metabolite not reaching therapeutic levels and the subsequent risk of clotting events occurring.

CYP2C19 contributes to the metabolism of a large number of clinically relevant drugs such as antidepressants, benzodiazepines, proton pump inhibitors, mephenytoin and especially clopidogrel. It is highly polymorphic, with >25 known variant alleles associated with functional drug metabolism. With respect to clopidogrel pharmacodynamics, loss-of function (LOF) alleles are inherited as autosomal traits because platelet responsiveness to clopidogrel can lie between homozygous wild type (i.e. *1/*1) and a LOF allele homozygote or compound heterozygotes (e.g. (*2/*3). On this basis, individuals are categorized as intermediate metabolizers (IM e.g. *1/*2 and *1/3) or poor metabolizers (PM, e.g., *2/*2 and *2/*3).[1] (Refer to Table 1)

Why is *CYP2C19* genotyping important?

Below are population frequency estimates of *CYP2C19* metabolizer phenotypes by geographic region. Estimates were derived from a meta-analysis of 52,181 healthy volunteers from 138 original research articles.[8]



Approximately 12-13% of people of Asian descent are *CYP2C19* poor metabolizers, while > 40% are intermediate metabolizers.[1,8] As a result, there may be a higher risk of MACE when prescribed Clopidogrel.

FDA recommendation included on Clopidogrel (Plavix) labelling:[1,3]

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE *CYP2C19* GENE

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

How does genotyping of *CYP2C19* guide clopidogrel use?

Able to determine whether the patient is a poor, intermediate, normal or ultra-rapid metabolizer.

Assist the doctor to decide which medication and dose is most appropriate.

Offers the potential to improve precision of antiplatelet therapy selection for cerebrovascular indications.

In the Implementing Genomics in Practice study (IGNITE), pooled data from patients genotyped across sites examined outcomes of genotype-guided antiplatelet therapy. Of 1,815 subjects, 572 (31.5%) were found to have a *CYP2C19* LOF allele. Of those, 346 (60.5%) were prescribed alternative therapy. This resulted in a significantly lower incidence of MACE, equivalent to that of patients without a LOF allele. This was similar in both intermediate and poor metabolizers.[9] This is concordant among other meta-analyses with genotyping performed.[2,4]

How to order a *CYP2C19* genotyping test for a patient?

1. Either buccal swabs or a simple blood draw is required.
2. Endorsed & tested in our dual accredited laboratory.
3. Comprehensive report with CPIC recommendations within 3-5 business days upon sample reception.

Contact our sales representative or your appointed local distributor for more information.

Summary of *CYP2C19* genotyping and current recommendations

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy summarised recommendations are as follows:[1]

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregationb	Clopidogrel:label-recommended dosage and administration	Strong
Intermediate metabolizer (*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	Moderate
Poor metabolizer (*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	Strong

Table 1 - *Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for acute coronary syndrome (ACS)/PCI patients*[1]