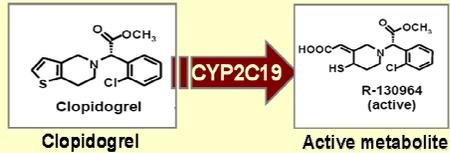


TECHNICAL INFORMATION

DNA-Guided Clopidogrel Management CYP2C19 Variants Predict Clopidogrel Effectiveness



ProDrug, Inactive
Requires metabolism by
CYP2C19 for anti-platelet
activity

Metabolite, Active
More potent as P2Y12
blocker than clopidogrel

The CLOPIDOGREL DNA Typing System performs high-resolution DNA Typing to individualize clopidogrel management. The System determines an individual's capacity to activate clopidogrel by DNA Typing the *CYP2C19* gene at 7 variable sites that harbor loss of function alleles. DNA Typing results and recommended dosage guidelines are reported.

DNA Typing is performed at the Laboratory of Personalized Health (LPH), a division of Genomas Inc. (Hartford CT). LPH is a high-complexity clinical DNA testing center licensed by the Connecticut Department of Health (CL-0644) and certified by the Centers for Medicare and Medicaid Services (ID# 07D1036625) under CLIA (Clinical Laboratory Improvement Amendments). The CLOPIDOGREL DNA Typing system is available through Clinical Laboratory Partners with Patient Service Centers throughout CT.

DNA FOR CLOPIDOGREL PER FDA

The FDA has identified DNA Typing as a powerful tool to enhance drug safety for pharmaceuticals in the market now. DNA Typing is being added to supplement other precautionary measures to assure safe dosage and to avoid drug interactions.

The FDA issued a Public Health Advisory in 2009 that clopidogrel was less effective in patients with impaired CYP2C19 function. In March 2010 the FDA revised the clopidogrel (*Plavix*[®]) label to include DNA Typing of *CYP2C19* based on evidence that patients with certain gene variants are poor metabolizers. Healthcare is being revolutionized by the introduction of DNA-guided medicine into clinical practice.

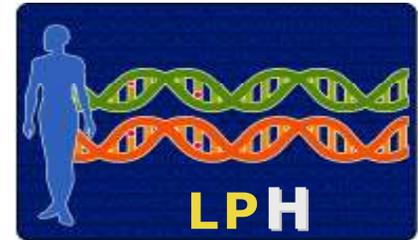
ORDERING CLOPIDOGREL DNA Typing

- Order forms are available from the website of the Laboratory of Personalized Health (LPH) at www.genomas.com/LPH
- The test is available through **Clinical Laboratory Partners (CLP)**. A listing of the CLP Patient Service Centers is on the LPH website or at www.clpct.com. CLP can be reached at 800-286-9800. (Contact LPH for referral if there is no nearby CLP Center.)

Further Questions?

Call the LPH @ 860-545-4589 or
e-mail to LPH@genomas.net or
visit www.genomas.com/LPH

LABORATORY OF PERSONALIZED HEALTH



**Clopidogrel
(Plavix[®])
DNA Typing
System for
DNA-Guided
Antiplatelet
Management**

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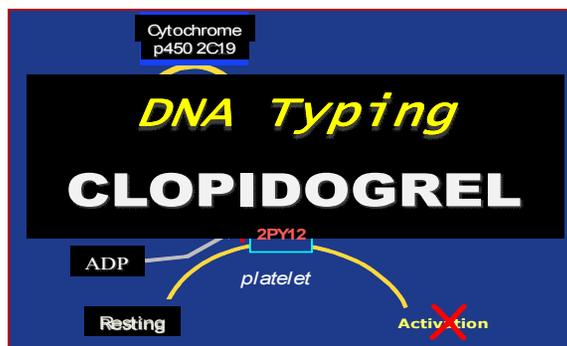
CLOPIDOGREL MANAGEMENT

Clopidogrel (*Plavix*[®]) is prescribed frequently for the treatment of acute coronary syndrome and prevention of thromboembolism. More than 25 million prescriptions were written in this country in 2009 and two million doses are administered daily. Clopidogrel is an antiplatelet drug with a documented history of safety. Bleeding complications occur at a relatively low rate. However for about 30% of patients who are poor metabolizers, clopidogrel efficacy is compromised. These patients are carriers of *CYP2C19* *2 or *3 allele variants. The variants result in null enzyme activity, and slow or failed activation of the drug. *CYP2C19* genotype status is a new and important consideration to add to clinical variables such as age, weight, presence of diabetes, and drug interactions that determine the dose and indeed the efficacy of clopidogrel therapy.

For the physician, safe and effective antiplatelet therapy represents a challenge. Every patient in the population does not obtain the same benefit from the standard maintenance dose of clopidogrel. Major adverse cardiovascular events are more frequent in carriers of null alleles and can be fatal. They lead to great risk to the patient.

For patients, not knowing whether personal carrier status includes a null allele represents an added burden to the diseases they already have and which are supposed to be treated, resulting in frustration and poor compliance.

DNA-GUIDED MEDICINE



Clopidogrel effectiveness is based to some degree on the patient's own inherited metabolic traits. DNA Typing identifies the major inherited factor from the patient's DNA to predict effectiveness. What is revolutionary for clinical practice is that by means of DNA Typing, the innate metabolic capacity of the patient relevant to a drug treatment can be predicted simply from a blood sample. With the CLOPIDOGREL DNA Typing system, patients who are unable to activate clopidogrel can be identified to avoid reduced therapeutic effects.

The standard of care protocol for antiplatelet therapy considers body size, presence/absence of diabetes, age (greater or less than 75 yr.), and risk of bleeding for dose adjustment or drug selection. In accordance with the Black Box placed on the clopidogrel label in March 2010, the *CYP2C19* genotype test to detect poor metabolizers can be added to the list.

DNA-GUIDED ANTIPLATELET THERAPY

Clopidogrel is metabolized to an active metabolite by the CYP2C19 isoenzyme of the Cytochrome P450 system. About 27% of the population is a carrier of one functionally null *CYP2C19* gene variant and 3% are carriers of two. Clopidogrel exerts its anticoagulant effect through its inhibition of the P2Y₁₂ receptor found on the platelet. When inhibited, the receptors do not respond to adenosine diphosphate (ADP), a stimulator of platelet aggregation, and platelet reactivity is decreased.

Null *CYP2C19* variants lead to high residual platelet activity and increased risk of major adverse cardiovascular events.

Black Box placed on the clopidogrel (*Plavix*[®]) label by FDA in March 2010

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)