

Genetic Testing for CYP450 Polymorphisms to Predict Response to Clopidogrel: current evidence and test availability

Application: Pharmacogenomics

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Abstract

The anti-platelet agent clopidogrel bisulfate (sold under the trade name Plavix in the United States) is a widely prescribed medication for the prevention of blood clots in patients with acute coronary syndrome, in those who have suffered other cardiovascular disease-related events such as ischemic stroke, and in patients who are undergoing percutaneous coronary intervention. Response to clopidogrel varies substantially due to genetic and acquired factors. Patients who experience recurrent cardiovascular ischemic or thrombotic events while taking clopidogrel are typically described as non-responsive or resistant.

The drug's oxidation is mainly dependent on the cytochrome P450 enzyme 2C19 (CYP2C19). Patients with certain genetic variants in CYP2C19 have been found to have lower levels of the active metabolite, less platelet inhibition, and greater risk of major adverse cardiovascular events such as heart attack, stroke, and death. Testing for CYP2C19 polymorphisms may identify patients who will not respond adequately to the standard clopidogrel regimen and who should, consequently, be given an alternate treatment strategy. This article outlines the evidence concerning pharmacogenetic testing for clopidogrel response, including data on clinical validity and clinical utility, and summarizes the currently available tests marketed for this purpose.

Clinical Scenario

Pharmacogenetic testing to identify patients at risk of an inadequate response to the standard clopidogrel regimen so that alternate treatment strategies can be initiated, with the goal of preventing adverse cardiovascular events such as stent thromboses, recurrent ischemic events, and death.

Test Description

Genetic polymorphisms in several genes (e.g., *CYP1A2*, *CYP3A4*, and *CYP3A5*) have been studied for an association with antiplatelet response and clinical outcomes in those taking clopidogrel. However, despite the many enzymes known to be involved in the metabolism of clopidogrel, only genetic variation in *CYP2C19* has been consistently and significantly associated with clopidogrel response in multiple populations [1][2][3].

The numerous commercial pharmacogenetic tests that are available genotype variants in *CYP2C19* for the purpose of predicting response to clopidogrel (see Table 1). These tests differ in genotyping methodology, sample type required, and availability (direct-to-consumer or physician-ordered). However, all tests include, at a minimum, the most common alleles (*1, and loss-of-function alleles *2 and *3), which have been shown to account for most of the variability in response to clopidogrel [1][2]. Some tests also include other identified reduced-function variants (named *4, *5, *6, *7, *8, *9, and *10). A newer allele, *CYP2C19*17*, has been described that is associated with increased enzymatic activity and ultra-rapid drug metabolism [4][5], which in turn is predicted to result in higher levels of the active metabolite of clopidogrel.

Each test includes:

- Analysis of multiple single nucleotide polymorphisms in CYP2C19.
- Genotype-based prediction of CYP2C19 enzymatic activity to categorize patients as:
 - Extensive metabolizers [carrying two "normal" alleles (i.e., *1/*1)].
 - Intermediate metabolizers [carrying one reduced-function allele (e.g., *1/*2)].
 - Poor metabolizers [carrying two reduced-function alleles (e.g., *2/*2 or *2/*3)].
 - Ultra-rapid metabolizers [carrying one or two increased-function alleles (i.e., *1/*17 or *17/*17), though it is not clear

whether *1/*17 carriers have a different phenotype than *1/*1 carriers].

Table 1. Pharmacogenetic Tests for Clopidogrel Response

Test	Company	CYP2C19 Variants Included	Sample Type	Available to Consumer (Yes/No)
AccuType™ CP testing for Clopidogrel CYP2C19 Genotype (*1, *2, *3, *4, *5)	Quest Diagnostics	*1, *2, *3, *4, *5	Whole blood or saliva	No
Clopidogrel P450 Genotype	Quest Diagnostics	*1, *2, *3 (also includes 26 variants in CYP2D6)	Whole blood	No
Plavitest for Clopidogrel Resistance (CYP 2C19)	Genelex Corporation	*1, *2, *3, *4, *5, *6, *7, *8	Whole blood or buccal (cheek) swab	No
Comprehensive DNA Drug Sensitivity Test	Genelex Corporation	Unspecified	Whole blood or buccal (cheek) swab	No
Medications Panel [part of the "Health Compass"]	Navigenics, Inc.	"Two of the most common genetic variants in CYP2C19"	Saliva	No
Clopidogrel Efficacy [part of the "Health Edition" test]	23andMe	*1, *2, *3, *4, *8, and *17	Saliva	Yes
Drug Response (Medication) [part of the "Total Health Insight" test]	Pathway Genomics	Unspecified	Saliva	Yes, except York state
Clopidogrel Activation	Matrix Genomics	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *17	Buccal (cheek) swab	Yes
Cytochrome P450 2C19 (CYP2C19) 7 Mutations	ARUP Laboratories	*1, *2, *3, *4, *5, *6, *7, *8	Whole blood	No
CYP450 2C19 Gene Test / Genetic Physician Consult	MyMedLab, Inc.	Unspecified	Buccal (cheek) swab	Yes, though must be approved by a MyMedLab physician
Clopidogrel Genetic Test	Theranostics Lab	Unspecified	Buccal (cheek) swab	Yes

Note: These tests were found through Google searches combining terms such as "clopidogrel", "genetic test" and "CYP2C19" and by searching individual websites of known commercial genetics companies (such as Pathway Genomics). Attempts were made to make this table comprehensive. However, there are tests that genotype variants in CYP2C19 that either do not specify that the test is for pharmacogenetic purposes, or do not specifically mention that the test can be used in determining response to clopidogrel. Such tests have not been included in this table.

Disclaimer:

Inclusion of tests in this table does not constitute an endorsement of any test by the Centers for Disease Control and Prevention (CDC) nor the Department of Health and Human Services (DHHS) of the U.S. government. No endorsement should be inferred.

Public Health Importance

Clopidogrel is the second highest top-selling drug in the world [6] ; approximately 29 million prescriptions were dispensed in 2008 in the United States alone [7] .

Estimates of the prevalence of laboratory-defined clopidogrel non-responsiveness vary widely, but have been estimated at 21-26% overall [8][9][10] .

An inadequate response to clopidogrel can cause stent thromboses, recurrent ischemic events, and death [8][9][10] . Approximately 9% of patients taking clopidogrel have a major adverse cardiovascular event such as myocardial infarction, stroke, or cardiovascular death [11][12] . Alternately, an enhanced response to clopidogrel may cause major bleeding [13] , which typically occurs in ~1.5% of patients (though much higher rates have been reported) [11][12][13][14] .

Sizeable proportions of some populations possess at least one loss-of-function *CYP2C19* allele (typically *2 or *3) that could affect clopidogrel response: ~ 30-50% of Asians, 11-16% of Caucasians, and 14-25% of African-Americans [1][15][16] . It is estimated that the *CYP2C19* “poor metabolizer” phenotype is exhibited by 10-25% of Asians, 2-3% of Caucasians, and 4% of African-Americans [1][15][16] . *CYP2C19**2 and *3 account for more than 95% of cases of the “poor metabolizer” phenotype [1] . The allele frequency of *CYP2C19**17 is estimated as 18-27% among Caucasians, 17-18% among Africans/African-Americans, and 0.5 – 4% among Asians [4]

Recently, the U.S. Food and Drug Administration (FDA) issued a black box warning for clopidogrel due to the reduced effectiveness of the drug in poor metabolizers [17][18] .

Published Reviews, Recommendations and Guidelines

Systematic evidence reviews

None.

Recommendations by independent group

None.

Guidelines by professional groups

In July 2010, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published a Clinical Alert in response to the FDA's black box warning on clopidogrel [19] . The report stated that:

- The evidence base is insufficient to recommend routine genetic testing at the present time.
- “Clinical judgment is required to assess clinical risk and variability in patients considered to be at increased risk. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism (“poor metabolizers”) may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. This might include, among others, patients undergoing elective high-risk PCI procedures (e.g., treatment of extensive and/or very complex disease).”

Other guidelines

The U.S. Food and Drug Administration (FDA) determined in 2009 that the available data have “provided compelling evidence that genetic variation in *CYP2C19* is a significant and independent predictor of clopidogrel pharmacokinetics, pharmacodynamics and clinical response”, which prompted the FDA to change clopidogrel's prescribing information [3][20][21] . More recently (March 12, 2010), the FDA issued a black box warning for clopidogrel [17][18] due to the reduced effectiveness of the drug in poor metabolizers. The FDA recommended that health professionals be aware that some patients may be poor metabolizers of clopidogrel because of low *CYP2C19* activity and to also “be aware that tests are available to determine patients' *CYP2C19* status” [17] . **The FDA neither mandated nor explicitly recommended *CYP2C19* genetic testing in patients prescribed clopidogrel** , and the agency did not offer any specific guidance on drug dosing in *CYP2C19* variant allele carriers [17] . The November 2009 label update did recommend that doctors avoid use of clopidogrel “in patients with impaired *CYP2C19* function due to known genetic variation or due to drugs that inhibit *CYP2C19* activity” [21] , while the more recent warning no longer specifically advises against use of clopidogrel in *CYP2C19* poor metabolizers [17] .

Evidence Overview

Analytic Validity: Test accuracy and reliability in identifying *CYP2C19* genotypes (analytic sensitivity and specificity).

- When reported, accuracy of the various genotyping methods/platforms used in commercial tests is noted as = 99% [22][23][24][25][26][27]. However, no information on analytic sensitivity or specificity can be found for the tests offered by Pathway Genomics [28], Matrix Genomics [29], or MyMedLab [30], or for some tests offered by Quest Diagnostics [31] or Genelex Corporation [32].
- Cross validation of the techniques used in *CYP2C19* genotyping assays, along with their reliability, specificity, and reproducibility, is extremely limited [19].

Clinical Validity: Test accuracy and reliability in predicting response to clopidogrel (predictive value).

- Numerous published studies have examined the relationship of *CYP2C19* alleles to clopidogrel response [33].
 - HuGE Navigator : query “clopidogrel and *CYP2C19*”
- At least 22 studies have examined pharmacokinetic and/or pharmacodynamic responses by *CYP2C19* genotype; these studies differed in the populations tested and the specific pharmacokinetic or pharmacodynamic measure(s) that were employed (most studies reviewed in [1][34]). Twenty studies examined reduced-function variants (mostly *2 alone or in combination with other variants) [2][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53]. All studies except one [37] reported statistically significant differences in clopidogrel response in reduced-function allele carriers. In these 19 studies, p values ranged from 4.3×10^{-11} to <0.05 .
- Seven studies have examined the association of the *17 variant with pharmacokinetic or pharmacodynamic responses specifically to clopidogrel, with inconsistent results [2][39][44][48][53][54][55]. Only one of these studies measured plasma levels of the clopidogrel active metabolite. However, *17 allele carriers were grouped with *1/*1 extensive metabolizers; and so individual effects of the *17 allele on clopidogrel metabolism cannot be determined [44].
- Only one clinical trial explicitly reported measures of clinical validity. In the EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate) trial, the sensitivity and specificity of *CYP2C19**2 carrier status for detecting high on-clopidogrel residual platelet aggregation (RPA) was 45.1% and 75.0%, respectively [35]. Measures of sensitivity and specificity can be calculated from data reported in some of the other published studies.
- No investigators explicitly included estimates of positive predictive value (PPV) or negative predictive value (NPV) for clopidogrel response in their original published reports. Using data from the EXCELSIOR report [35], estimates of PPV and NPV are 41.6% and 77.6%, respectively.

Clinical Utility: Net benefit of test in improving health outcomes.

- A recent meta-analysis of seven prospective cohort studies was published that examined the *CYP2C19**2 variant and cardiovascular recurrences in 8,043 coronary artery disease patients taking clopidogrel. The authors found a statistically significant increased risk of major adverse cardiovascular events in *CYP2C19**2 carriers (RR = 1.96) and an even greater risk when stent thrombosis was analyzed separately using four studies that included 4,975 patients (RR = 3.82) [56].
- A more recent meta-analysis that was not restricted to prospective cohort studies examined the *CYP2C19**2 variant and the incidence of major adverse cardiovascular events (MACE) and mortality in patients taking clopidogrel [57]. The pooled data showed that *CYP2C19**2 carriers had a statistically significant increased risk of MACE (OR = 1.29) using data from ten studies (11,959 patients). Carriers of *2 also had statistically significant increases in risk for stent thrombosis (OR = 3.45 using data from 4 studies including 4,905 patients) and death (OR = 1.79 using data from 5 studies including 6,225 patients). Four studies including 5,694 patients allowed the separate assessment of heterozygotes and homozygotes of the *2 allele. Increased risks for MACE and stent thrombosis were noted for both groups, though the odds ratio for MACE was significant only for homozygotes [57].
- Hulot and Fuster [58] calculated the PPV for clinical outcomes of *CYP2C19* loss-of-function variants using data from two studies. They estimate the PPV for a cardiovascular event is between 12% [36] and 20% [59].
- Most studies have examined *CYP2C19* genotypes only among patients taking clopidogrel. In the only published study to date that included a placebo-controlled group, neither *CYP2C19**2 or *3 allele carriage nor metabolizer phenotype influenced the effect of clopidogrel on cardiovascular disease-related outcomes compared to the placebo group [60].
- Tests that assay *CYP2C19**17 may also identify individuals at increased risk for bleeding events [13][14] or those who may derive a larger benefit (reduction in cardiovascular events) with clopidogrel treatment compared to placebo [60].
- There are no published clinical trial data evaluating the net benefit of *CYP2C19* testing prior to administration of clopidogrel in improving health outcomes.
- It is unknown if the risk from a given individual's genomic profile changes over time, depending on the specific clinical

scenario (for example, acute coronary syndrome versus stable angina pectoris)[19] . However, a meta-analysis demonstrated that the increased occurrence of major adverse cardiovascular events and of mortality in CYP2C19*2 carriers was independent of patients' baseline cardiovascular risk[57] .

- Any benefits of DNA testing may be hampered by the following considerations:
 - The response to clopidogrel is unclear for some CYP2C19 genotypes, such as reduced-function alleles in the presence of *17. The only study to directly assess the combined effect of *17 and reduced-function alleles (in this case, *2) found a gradient of effect on pharmacodynamic response to clopidogrel[53] .
 - Genotyping only for CYP2C19 alleles does not capture all of the genetic variability in pharmacodynamic, pharmacokinetic, or clinical responses to clopidogrel. Variants in the ABCB1 gene also seem to be potentially important to the interindividual variability in these phenotypes [3][14][61][62] .
 - Currently, there are no standardized clinical guidelines to manage patients with an inadequate response to clopidogrel. Typically, one or more alternatives are tried: higher loading or maintenance doses of clopidogrel, dual therapy with aspirin if this has not already been initiated, or treatment with another antiplatelet medication[19] .

Links

- Human Cytochrome P450 (CYP) Allele Nomenclature Committee, CYP2C19 allele nomenclature (<http://www.cypalleles.ki.se/cyp2c19.htm>), last accessed: March 17, 2010.
- HuGE Navigator: query “clopidogrel and CYP2C19”
- U.S. Food and Drug Administration:Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels
- ClinicalTrials.gov:Clopidogrel and CYP2C19 . Note: not all clinical trials list a pharmacogenetic component to their study, even if one exists. For instance, some studies have been found to include genetic analyses only after publication of those data. Consequently, searching for “clopidogrel and CYP2C19” or a similar search will not return all relevant studies.
- PharmGKB:clopidogrel , clinical PGx for clopidogrel

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Competing interests

The author declares that no competing interests exist.

Disclaimer

The CDC does not offer medical advice to individuals. If you have specific concerns about your health or genetic testing, we suggest that you discuss them with your health care provider.

References

1. Verstuyft C, Simon T, Kim RB. Personalized medicine and antiplatelet therapy: ready for prime time? *Eur Heart J*. 2009 Aug;30(16):1943-63. Epub 2009 Jul 28. PubMed PMID: 19638479.
2. Shuldiner AR, O'Connell JR, Bliden KP, Gandhi A, Ryan K, Horenstein RB, Damcott CM, Pakyz R, Tantry US, Gibson Q, Pollin TI, Post W, Parsa A, Mitchell BD, Faraday N, Herzog W, Gurbel PA. Association of cytochrome P450 2C19 genotype with

- the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009 Aug 26;302(8):849-57. PubMed PMID: 19706858.
3. Ellis KJ, Stouffer GA, McLeod HL, Lee CR. Clopidogrel pharmacogenomics and risk of inadequate platelet inhibition: US FDA recommendations. *Pharmacogenomics*. 2009 Nov;10(11):1799-817. Review. PubMed PMID: 19891556.
 4. Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. *Br J Clin Pharmacol*. 2010 Mar;69(3):222-30. PubMed PMID: 20233192; PubMed Central PMCID: PMC2829691.
 5. Sim SC, Risinger C, Dahl ML, Aklillu E, Christensen M, Bertilsson L, Ingelman-Sundberg M. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006 Jan;79(1):103-13. PubMed PMID: 16413245.
 6. IMS Health. Top-line Industry Data: 2009 Global Prescription Sales Information. IMS Health Web site. Accessed July 2, 2010. REFERENCE LINK
 7. Top 200 Drugs of 2008. Accessed March 15, 2010. REFERENCE LINK
 8. Snoep JD, Hovens MM, Eikenboom JC, van der Born JG, Jukema JW, Huisman MV. Clopidogrel nonresponsiveness in patients undergoing percutaneous coronary intervention with stenting: a systematic review and meta-analysis. *Am Heart J*. 2007 Aug;154(2):221-31. Review. PubMed PMID: 17643570.
 9. Combescure C, Fontana P, Mallouk N, Berdague P, Labruyere C, Barazer I, Gris JC, Laporte S, Fabbro-Peray P, Reny JL; CLOpidogrel and Vascular ISchemic Events Meta-analysis Study Group. Clinical implications of clopidogrel non-response in cardiovascular patients: a systematic review and meta-analysis. *J Thromb Haemost*. 2010 May;8(5):923-33. Epub 2010 Feb 12. PubMed PMID: 20156305.
 10. Sofi F, Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF. Clopidogrel non-responsiveness and risk of cardiovascular morbidity. An updated meta-analysis. *Thromb Haemost*. 2010 Mar 31;103(4):841-8. Epub 2010 Feb 2. PubMed PMID: 20135063.
 11. Helton TJ, Bavry AA, Kumbhani DJ, Duggal S, Roukoz H, Bhatt DL. Incremental effect of clopidogrel on important outcomes in patients with cardiovascular disease: a meta-analysis of randomized trials. *Am J Cardiovasc Drugs*. 2007;7(4):289-97. PubMed PMID: 17696569.
 12. Berger JS, Bhatt DL, Cannon CP, Chen Z, Jiang L, Jones JB, Mehta SR, Sabatine MS, Steinhubl SR, Topol EJ, Berger PB. The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis. *J Am Coll Cardiol*. 2009 Nov 17;54(21):1935-45. Review. PubMed PMID: 19909874.
 13. Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, Schömig A, von Beckerath N, Kastrati A. Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. *J Thromb Haemost*. 2010 Feb;8(2):250-6. Epub 2009 Nov 28. PubMed PMID: 19943882.
 14. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, Becker RC; for the PLATO investigators. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010 Aug 27. [Epub ahead of print] PubMed PMID: 20801498.
 15. Rosemary J, Adithan C. The pharmacogenetics of CYP2C9 and CYP2C19: ethnic variation and clinical significance. *Curr Clin Pharmacol*. 2007 Jan;2(1):93-109. Review. PubMed PMID: 18690857.
 16. Myrand SP, Sekiguchi K, Man MZ, Lin X, Tzeng RY, Teng CH, Hee B, Garrett M, Kikkawa H, Lin CY, Eddy SM, Dostalík J, Mount J, Azuma J, Fujio Y, Jang IJ, Shin SG, Bleavins MR, Williams JA, Paulauskis JD, Wilner KD. Pharmacokinetics/genotype associations for major cytochrome P450 enzymes in native and first- and third-generation Japanese populations: comparison with Korean, Chinese, and Caucasian populations. *Clin Pharmacol Ther*. 2008 Sep;84(3):347-61. Epub 2008 Mar 19. PubMed PMID: 18231117.
 17. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. Accessed March 12, 2010. REFERENCE LINK
 18. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Plavix (clopidogrel bisulfate). Prescribing Information. Bridgewater, NJ; Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; revised March 2010. Accessed on March 18, 2010. REFERENCE LINK
 19. Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning" A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *J Am Coll Cardiol*. 2010 Jul 20;56(4):321-41. PubMed PMID:

20633831.

20. U.S. Food and Drug Administration (FDA). Plavix (clopidogrel bisulfate) 75 mg tablets: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) -- May 2009. Accessed March 19, 2010.

21. U.S. Food and Drug Administration (FDA). Plavix (clopidogrel bisulfate) 75 mg tablet: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) - November 2009. Accessed March 19, 2010.
REFERENCE LINK

22. Roche Diagnostics. About the AmpliChip CYP450 Test. Accessed May 11, 2010.
REFERENCE LINK

23. Genelex: Plavitest Technical Information. Accessed March 22, 2010.
REFERENCE LINK

24. Navigenics, Inc. Applying Preventive Genomic Medicine in Clinical Practice. Available at http://www.navigenics.com/visitor/for_physicians/.

25. ARUP Laboratories. Technical Bulletin-- Cytochrome P450 2C19 (CYP2C19) 7 Mutations: for detection of CYP2C19 mutations affecting drug metabolism. Last updated February 2009. Available at <http://www.aruplab.com/Testing-Information/technicalbulletins.jsp>.

26. 23andMe, Inc. How accurate is the genetic data you provide? Accessed April 8, 2010.
REFERENCE LINK

27. Theranostics Lab. FAQs. Accessed April 8, 2010.
REFERENCE LINK

28. Pathway Genomics. Drug Response (Medication). Accessed June 14, 2010.
REFERENCE LINK

29. Matrix Genomics. Drug Metabolism- Clopidogrel (Plavix) Activation. Accessed April 6, 2010
REFERENCE LINK

30. MyMedLab, Inc. CYP450 2C19 (PlavixTM) Gene Test / Genetic Physician Consult. Accessed June 30, 2010.
REFERENCE LINK

31. Quest Diagnostics. AccuTypeTM CP testing for Clopidogrel CYP2C19 Genotype (*1, *2, *3, *4, *5). Accessed May 11, 2010.
REFERENCE LINK

32. Genelex Corporation. DNA Drug Sensitivity Testing. Accessed March 22, 2010
REFERENCE LINK

33. HuGE Navigator
REFERENCE LINK

34. Ma TK, Lam YY, Tan VP, Kiernan TJ, Yan BP. Impact of genetic and acquired alteration in cytochrome P450 system on pharmacologic and clinical response to clopidogrel. *Pharmacol Ther.* 2010 Feb;125(2):249-59. Epub 2009 Nov 14. Review. PubMed PMID: 19919843.

35. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol.* 2010 Jun 1;55(22):2427-34. PubMed PMID: 20510210.

36. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009 Jan 22;360(4):354-62. Epub 2008 Dec 22. PubMed PMID: 19106084.

37. Fontana P, Senouf D, Mach F. Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome P450 2C19*2 allele on clopidogrel responsiveness. *Thromb Res.* 2008;121(4):463-8. Epub 2007 Aug 2. PubMed PMID: 17681590.

38. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, Lachno DR, Salazar D, Winters KJ. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J Thromb Haemost.* 2007 Dec;5(12):2429-36. Epub 2007 Sep 26. PubMed PMID: 17900275.

39. Gladding P, Webster M, Zeng I, Farrell H, Stewart J, Ruygrok P, Ormiston J, El-Jack S, Armstrong G, Kay P, Scott D, Gunes A, Dahl ML. The pharmacogenetics and pharmacodynamics of clopidogrel response: an analysis from the PRINC (Plavix Response in Coronary Intervention) trial. *JACC Cardiovasc Interv.* 2008 Dec;1(6):620-7. PubMed PMID: 19463375.

40. Hulot JS, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, Aiach M, Lechat P, Gaussem P. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood.* 2006 Oct

1;108(7):2244-7. Epub 2006 Jun 13. PubMed PMID: 16772608.

41. Hulot JS, Wuerzner G, Bachelot-Loza C, Azizi M, Blanchard A, Peyrard S, Funck-Brentano C, Gaussem P. Effect of an increased clopidogrel maintenance dose or lansoprazole co-administration on the antiplatelet response to clopidogrel in CYP2C19-genotyped healthy subjects. *J Thromb Haemost.* 2010 Mar;8(3):610-3. Epub 2009 Dec 21. PubMed PMID: 20040040.
42. Kim KA, Park PW, Hong SJ, Park JY. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin Pharmacol Ther.* 2008 Aug;84(2):236-42. Epub 2008 Mar 5. PubMed PMID: 18323861.
43. Umemura K, Furuta T, Kondo K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. *J Thromb Haemost.* 2008 Aug;6(8):1439-41. Epub 2008 Jun 4. PubMed PMID: 18532997.
44. Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, Siegbahn A, Walker J, Wallentin L, Winters KJ, Close SL. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur Heart J.* 2009 Jul;30(14):1744-52. Epub 2009 May 9. PubMed PMID: 19429918; PubMed Central PMCID: PMC2709885.
45. Frere C, Cuisset T, Morange PE, Quilici J, Camoin-Jau L, Saut N, Faille D, Lambert M, Juhan-Vague I, Bonnet JL, Alessi MC. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am J Cardiol.* 2008 Apr 15;101(8):1088-93. Epub 2008 Feb 6. PubMed PMID: 18394438.
46. Giusti B, Gori AM, Marcucci R, Saracini C, Sestini I, Paniccia R, Valente S, Antonucci D, Abbate R, Gensini GF. Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients. *Pharmacogenet Genomics.* 2007 Dec;17(12):1057-64. PubMed PMID: 18004210.
47. Fontana P, Hulot JS, De Moerloose P, Gaussem P. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J Thromb Haemost.* 2007 Oct;5(10):2153-5. Epub 2007 Aug 3. PubMed PMID: 17697139.
48. Geisler T, Schaeffeler E, Dippon J, Winter S, Buse V, Bischofs C, Zuern C, Moerike K, Gawaz M, Schwab M. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. *Pharmacogenomics.* 2008 Sep;9(9):1251-9. PubMed PMID: 18781853.
49. Kim IS, Choi BR, Jeong YH, Kwak CH, Kim S. The CYP2C19*2 and CYP2C19*3 polymorphisms are associated with high post-treatment platelet reactivity in Asian patients with acute coronary syndrome. *J Thromb Haemost.* 2009 May;7(5):897-9. Epub 2009 Feb 12. PubMed PMID: 19220726.
50. Aleil B, Léon C, Cazenave JP, Gachet C. CYP2C19*2 polymorphism is not the sole determinant of the response to clopidogrel: implications for its monitoring. *J Thromb Haemost.* 2009 Oct;7(10):1747-9. Epub 2009 Jul 17. PubMed PMID: 19624462.
51. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Büttner HJ, Neumann FJ. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J Am Coll Cardiol.* 2008 May 20;51(20):1925-34. PubMed PMID: 18482659.
52. Jeong YH, Kim IS, Park Y, Kang MK, Koh JS, Hwang SJ, Kwak CH, Hwang JY. Carriage of cytochrome 2C19 polymorphism is associated with risk of high post-treatment platelet reactivity on high maintenance-dose clopidogrel of 150 mg/day: results of the ACCEL-DOUBLE (Accelerated Platelet Inhibition by a Double Dose of Clopidogrel According to Gene Polymorphism) study. *JACC Cardiovasc Interv.* 2010 Jul;3(7):731-41. PubMed PMID: 20650435.
53. Sibbing D, Gebhard D, Koch W, Braun S, Stegherr J, Morath T, von Beckerath N, Mehilli J, Schömig A, Schuster T, Kastrati A. Isolated and interactive impact of common CYP2C19 genetic variants on the antiplatelet effect of chronic clopidogrel therapy. *J Thromb Haemost.* 2010 May 21. [Epub ahead of print] PubMed PMID: 20492469.
54. Frère C, Cuisset T, Gaborit B, Alessi MC, Hulot JS. The CYP2C19*17 allele is associated with better platelet response to clopidogrel in patients admitted for non-ST acute coronary syndrome. *J Thromb Haemost.* 2009 Aug;7(8):1409-11. Epub 2009 May 30. PubMed PMID: 19496924.
55. Sibbing D, Koch W, Gebhard D, Schuster T, Braun S, Stegherr J, Morath T, Schömig A, von Beckerath N, Kastrati A. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation.* 2010 Feb 2;121(4):512-8. Epub 2010 Jan 18. PubMed PMID: 20083681.
56. Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome P450 2C19(*)2 polymorphism and cardiovascular

recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J*. 2010 Mar 30. [Epub ahead of print] PubMed PMID: 20351750.

57. Hulot JS, Collet JP, Silvain J, Pena A, Bellemain-Appaix A, Barthélémy O, Cayla G, Beygui F, Montalescot G. Cardiovascular risk in clopidogrel-treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis. *J Am Coll Cardiol*. 2010 Jul 6;56(2):134-43. PubMed PMID: 20620727.

58. Hulot JS, Fuster V. Antiplatelet therapy: Personalized medicine for clopidogrel resistance? *Nat Rev Cardiol*. 2009 May;6(5):334-6. PubMed PMID: 19377495.

59. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G, Beygui F, Bensimon G, Funck-Brentano C, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009 Jan 24;373(9660):309-17. Epub 2008 Dec 26. PubMed PMID: 19108880.

60. Paré G, M.D. SRM, Yusuf S, Anand SS, Connolly SJ, Hirsh J, Simonsen K, Bhatt DL, Fox KAA, Eikelboom JW: Effects of CYP2C19 Genotype on Outcomes of Clopidogrel Treatment. *NEJM*. 2010 Aug 29; online. PMID: pending.

61. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet*. 2010 Aug 27. [Epub ahead of print] PubMed PMID: 20801494.

62. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009 Jan 22;360(4):363-75. Epub 2008 Dec 22. PubMed PMID: 19106083.