

Dear Health Care Provider,

This CYP2C19 Plavix (clopidogrel) resistance information package contains the following:

- **Research Summary with Bibliography** - A brief summary of the relevant research pointing out the utility of Plavix (clopidogrel) resistance testing in improving patient care and outcomes.
- **FDA Black Box Warning Information**
- **Frequently Asked Questions**
- **Sample Letter to Mail to All Patients taking Plavix**
- **Prescription Form** - A prescription form is included that is simply completed and provided to the patient. We know you are busy, so we handle the rest.
- **CYP2C19 Testing Declination Form** to maintain in the chart of any patient's deciding against testing.

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## Research Summary with Bibliography

A series of recent studies (see below) has demonstrated the importance of patient cytochrome P450 2C19 (CYP2C19) genotypes to outcomes in clopidogrel treated patients. DNA testing of CYP2C19 identifies the 30% or more of patients at up to 3.56 increased risk of MI, stroke, or stent thrombosis because of reduced ability to activate the prodrug clopidogrel. Patients with variant CYP2C19 genotypes have:

- Decreased serum levels of the active metabolite.
- Decreased platelet inhibition.
- Double the risk for major adverse cardiovascular events.

Simon et al. 2009. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. *New Engl J Med* 360(4):363-75.

**Conclusion:** Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying *CYP2C19* loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention. Patients carrying any two *CYP2C19* loss-of-function alleles (\*2, \*3, \*4, or \*5) had a higher event rate than patients with none (21.5% vs. 13.3%; adjusted hazard ratio, 1.98; 95% CI, 1.10 to 3.58). Among the 1535 patients who underwent percutaneous coronary intervention during hospitalization, the rate of cardiovascular events among patients with two *CYP2C19* loss-of-function alleles was 3.58 times the rate among those with none (95% CI, 1.71 to 7.51).

Collet et al. 2009. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *The Lancet* 373(9660):309 – 317.

**Conclusion:** After multivariable analysis, the *CYP2C19*\*2 genetic variant was the only independent predictor of cardiovascular events (HR 4.04 [1.81—9.02],  $p=0.0006$ ). Median clopidogrel exposure time was 1.07 years (IQR 0.28—3.0). Baseline characteristics were balanced between carriers (heterozygous \*1/\*2,  $n=64$ ; homozygous \*2/\*2,  $n=9$ ) and non-carriers ( $n=186$ ) of *CYP2C19*\*2 variant. The primary endpoint occurred more frequently in carriers than in non-carriers (15 vs 11 events; hazard ratio [HR] 3.69 [95% CI 1.69—8.05],  $p=0.0005$ ), as did stent thrombosis (eight vs four events; HR 6.02 [1.81—20.04],  $p=0.0009$ ). The detrimental effect of the *CYP2C19*\*2 genetic variant persisted from 6 months after clopidogrel initiation up to the end of follow-up (HR 3.00 [1.27—7.10],  $p=0.009$ ).

Mega et al. 2009. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. *New Engl J Med* 360(4):354-362.

**Conclusion:** Among persons treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers. Among clopidogrel-treated subjects in TRITON-TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with noncarriers (12.1% vs. 8.0%; hazard ratio for carriers, 1.53; 95% confidence interval [CI], 1.07 to 2.19;  $P = 0.01$ ) and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00;  $P = 0.02$ ).

Gladding et al. 2009. Pharmacogenetic Testing for Clopidogrel Using the Rapid INFINITI Analyzer: A Dose-Escalation Study. *JACC* 2(11):1095-1011.

**Conclusion:** Increasing the dose of clopidogrel in patients with nonresponder polymorphisms can increase antiplatelet response. Personalizing clopidogrel dosing using pharmacogenomics may be an effective method of optimizing treatment. Carriers of the *CYP2C19*\*2 allele had significantly reduced platelet inhibition at baseline (median 18%, range 0% to 72%) compared with wildtype (*wt*) (median 59%, range 11% to 95%,  $p = 0.01$ ) and at 1 week ( $p = 0.03$ ). *CYP2C19*\*2 allele carriers had an increase in platelet inhibition of (mean -9 \_ 11%,  $p = 0.03$ ) and reduction in platelet reactivity (mean -26 ± 38 platelet response unit,  $p = 0.04$ ) with a higher dose.

## Additional References

Gladding P et al. 2009. Pharmacogenetic Testing for Clopidogrel Using the Rapid INFINIT Analyzer – A Dose Escalation Study. *JACC* 2:1095-1101.

Sibbing D et al. 2009. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. *Eu Heart J* 30:916-922.

Simon T et al. 2008. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. *N Engl J Med* 360:363-375.

Mega JL et al. 2008. Cytochrome P-450 Ploymorphisms and Response to Clopidogrel. *N Engl J Med* 360:354-362.

## FDA Black Box Warning

The U.S. Food and Drug Administration (FDA) has added a *Boxed Warning* to the label for Plavix, the anti-blood clotting medication. The *Boxed Warning* is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The *Boxed Warning* in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Plavix is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Plavix works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots.

For Plavix to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert Plavix to its active form. In these patients, Plavix has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. It is estimated that 2 to 14% of the population are poor metabolizers; the rate varies based on racial background.

**Healthcare professionals** should be aware that a subgroup of patients are poor metabolizers and do not metabolize Plavix effectively; this can result in reduced effectiveness of Plavix. Healthcare professionals should consider use of other anti-platelet medications or alternative dosing strategies for Plavix in these patients.



Accredited DNA Testing Pioneers Since 1987

## Frequently Asked Questions

### Who Should Be Tested

The CYP2C19 test for Plavix (clopidogrel) resistance is considered appropriate for any patient taking or considering taking Plavix (clopidogrel).

### Does Medicare cover the testing?

According to the Noridian Medicare policy on therapy-directing testing available at <http://bit.ly/940EIz>, “Noridian will allow payment for such tests, either those currently available or those to be brought into use in the future, based on applicable FDA approval and labeling (if such exists) and appropriate standards of medical reasonableness and necessity.” CYP2C19 testing for Plavix meets these requirements.

### Does private insurance cover the testing?

Most major insurers cover CYP2C19 testing when ordered by a physician as long as genetic testing is a covered benefit. Please see the Physician Referral Prescription form for optional preauthorization instructions; cash pay rates, and financial assistance options.

### How do I order testing?

Buccal swab or blood collection kits with return shipping can be supplied on request at 800 TEST-DNA (800-837-8362). Alternatively, you can complete the required prescription information on the enclosed Physician Referral Prescription form, and fax the form to 206-219-4000 with the patient's insurance information, mailing address, and phone number, and we will handle the rest.

### How do I interpret test results?

For every test ordered, we provide 90-days access to GeneMedRx Drug and Gene Interaction software with the patient's genotypes already entered so you can determine the impact of genetics in the context of their overall medication regimen. GeneMedRx was primarily authored by Dr. Jessica Oesterheld, a recognized expert in drug interactions and coauthor of the top selling book, *Clinical Manual of Drug Interaction Principles for Medical Practice*. A short demo of the software and a free 30-day trial is available at [www.GeneMedRx.com/demo](http://www.GeneMedRx.com/demo).

### How long does testing take?

Results are typically available within 6 business days.

### Is FDA-approval required for this test?

Laboratory-developed DNA tests (LDT) are regulated by the Center for Medicare Services (CMS) under the authority of the Clinical Laboratory Improvement Act of 1988 (CLIA '88). Elizabeth Mansfield, Director of Personalized Medicine at the FDA, confirmed that FDA-approval is not required for cytochrome P450 DNA testing.

Analytical specificity and sensitivity for Genelex's cytochrome P450 and other pharmacogenetic tests, sold as DNA Drug Sensitivity Testing™, is greater than 99% as determined by internal and inter-laboratory testing and performance on College of American Pathologists proficiency tests. Detailed technical information can be found at [www.HealthandDNA.com](http://www.HealthandDNA.com) or requested via email at [info@genelex.com](mailto:info@genelex.com).

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[www.HealthandDNA.com](http://www.HealthandDNA.com)

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Genelex spoke with Rick Nauman, Senior V.P. of Underwriting and Marketing at Physicians Insurance, a malpractice insurance company. He stated that physicians prescribing Plavix have a medical duty to their patients to explain the recent black box warning. They need a clear protocol and need to document the protocol and the patient encounter. The following forms and letters were created to help your practice easily achieve this.

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**If you have any questions or would like to make arrangements, please contact a Genelex DNA Testing Consultant at 800-837-8362.**

Date: XXXX 2010

Dear {Patient},

Our records indicate that you are currently on Plavix. If you are not on this medication please disregard this letter.

Plavix is a medication that we believe will help prevent a heart attack given your medical condition. We have just received a warning from the manufacturer that Plavix may not be effective in some patients. A test is available to identify individuals who are 'poor responders.' It is currently recommended by the FDA that we identify patients who may not be good candidates for Plavix so that alternative treatment can be prescribed.

Attached is a prescription form for this test. Please follow the instructions provided. A Genelex representative will assist you and provide you with the cheek swab testing kit. Call 800-837-8362 to order the kit which Genelex will then mail to your home. Medicare and approximately 70% of private insurance carriers usually cover the cost of the test. Patients can also opt for our patient safeguard program if they have a high deductible or know genetic testing is not covered. The cost for the test is \$235. This option allows the patient to submit for reimbursement directly to their own insurance company. Genelex will provide a detailed invoice to the patient and will not submit a claim. Information is also included to assist you in obtaining authorization from your insurance company.

You may also not elect to have the test done, but there is a chance that Plavix may not be an effective drug in preventing heart attacks in your case. We ask that you contact our office with your decision regarding this recommended testing so that we may update your chart accordingly. A declination form is also enclosed.

Signed,

**{Physician}**

## Physician Referral Prescription CYP2C19 Plavix (clopidogrel) Resistance DNA Test

Your physician thinks that you will benefit from having a test for Plavix resistance and has included a prescription for this below. The test examines a gene called 2C19 which produces the liver enzyme CYP2C19. This enzyme is necessary for the body to metabolize a number of drugs, including Plavix (clopidogrel). Different people have different variations of this gene. Some variations metabolize 2C19 drugs very quickly, while others don't metabolize them as well. Still others don't metabolize them at all.

According to two recent landmark studies, an estimated 30 percent of patients taking Plavix are at a 3.58 times greater risk of having a stroke, heart attack, or other serious cardiac event because they have a 2C19 variation that reduces the effectiveness of Plavix.

Please call a DNA Testing Consultant at 800 TEST-DNA (800-837-8362) with this prescription in hand to obtain the cheek swab collection kit for Plavix resistance. The consultant can also answer any questions you may have at that time. Alternatively, you can fax this form with a copy of both sides of your insurance card, and your mailing address and phone number to 206-219-4000 and your kit will be mailed.

**Patient's Name:** \_\_\_\_\_

Date of Prescription: \_\_\_\_\_ Phone: \_\_\_\_\_ DOB: \_\_\_\_\_

To: Genelex Corporation  
3000 First Ave., Suite One  
Seattle, WA 98121  
Phone: 800-523-3080 **Fax: 206-219-4000**

**From (Referring Physician):**

Name: \_\_\_\_\_

Address: \_\_\_\_\_

City, State, Zip: \_\_\_\_\_

Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

Email: \_\_\_\_\_

**TESTING IS MEDICALLY NECESSARY.** Please perform the following pharmacogenetic tests for the diagnosis codes noted below.

CYP2C19 (10% of meds including Plavix)  CYP2D6 (25% of meds)  CYP2C9 & VKOR (10% of meds)

Physician Signature: \_\_\_\_\_

License #: \_\_\_\_\_ UPIN: \_\_\_\_\_

**Diagnosis Codes (use the same codes used to indicate the need for Plavix or other meds.):**

## Is the testing covered by Medicare?

According to the Noridian Medicare policy on therapy-directing testing available at <http://bit.ly/940Elz>, “Noridian will allow payment for such tests, either those currently available or those to be brought into use in the future, based on applicable FDA approval and labeling (if such exists) and appropriate standards of medical reasonableness and necessity.” CYP2C19 testing for Plavix meets these requirements.

## Is the testing covered by private insurance?

Genelex has seen pharmacogenetic testing coverage by the insurers listed below however coverage benefits can vary by plan. To confirm coverage prior to submitting a sample, see preauthorization instructions at the bottom of this page. Alternatively, we have a patient safeguard program that limits patient out of pocket expense to \$235.00. This option allows the patient to submit for reimbursement directly to their own insurance company. Genelex will provide a detailed invoice to the patient and will not submit a claim. This is also the option available for patients with no insurance or who do not want their insurance to be billed. For patients with financial hardship, please call 800 TEST-DNA (800-837-8362) to request a financial consideration form.

HMO	Blue Cross	Aetna	Cigna
Humana	United Healthcare	DWI Holding	Group Health
Farm Bureau	Tricare	Oxford	

### Optional Preauthorization Instructions

Call the number on your insurance card and provide them with:

1. The CPT codes for requested testing:  
1 x 83891, 2 x 83892, 1 x 83900, 3 x 83901, 8 x 83914, 1 x 83909, 1 x 83912, 1 and 83912-26
2. The ICD-9 diagnosis codes provided by your physician.
3. Your physician’s name and other requested information.

Record the following information about your insurance company call(s):

1. Date of phone call \_\_\_\_\_ Phone number with extension \_\_\_\_\_
2. Name of person you spoke with \_\_\_\_\_
3. Preauthorization number \_\_\_\_\_ Valid dates: \_\_\_\_\_

If preauthorization is denied, Genelex encourages patients to appeal. Contact Jennifer Rustan at [jennifer@genelex.com](mailto:jennifer@genelex.com) or call 800 TEST-DNA (800 837-8362) for help with this process. We have successfully handled appeals before and have materials we can provide on your behalf.

**CYP2C19 Plavix Resistance Testing Declination**

I have discussed the potential risk of Plavix treatment failure due to genetic factors, and have chosen to decline CYP2C19 testing for Plavix Resistance at this time.

Patient Signature \_\_\_\_\_ Date \_\_\_\_\_

Print Full Name \_\_\_\_\_