Known CYP2D6 Inhibitors[22,23,24]		
amiodarone	escitalopram	paroxetine
bupropion	flecainide acetate	perphenazine
celecoxib	fluoxetine	primaquine phosphate
chloroquine phosphate	fluphenazine	propafenone
chlorpheniramine	fluvoxamine maleate	propoxyphene
chlorpromazine	halofantrine	quinacrine
cimetidine	haloperidol	quinidine
cinacalcet	histamine H1 receptor antagonists	ranitidine
citalopram	hydroxychloroquine	reduced haloperidol
clemastine	hydroxyzine	ritonavir
clomipramine	labetalol	sertraline
cocaine	levomepromazine	terbinafine
codeine	lomustine	thioridazine
darifenacin hydrobromide	lumefantrine	ticlopidine
delavirdine mesylate	methadone	tripelennamine
desipramine	metoclopramide	valdecoxib
diphenhydramine	mibefradil	vinblastine sulfate
doxepin	midodrine	vincristine sulfate
doxorubicin	moclobemide	vinorelbine tartrate
dronedarone	norfluoxetine	yohimbine
duloxetine		

Known CYP2D6 Substrates[22,24,25]		
alprenolol	fenfluramine	oxycodone
amitriptyline	fentanyl	paliperidone
amoxapine	flecainide	paroxetine
amphetamine	fluoxetine	penbutolol sulfate
aripiprazole	fluphenazine	pentazocine lactate
atomoxetine	fluvoxamine	perhexiline
betaxolol	formoterol	perphenazine
bisoprolol	galantamine	phenacetin
bufuralol	haloperidol	phenformin
captopril	hydrocodone	pindolol
carvedilol	hydrocortisone	promethazine
cevimeline	hydroxyamphetamine hydrobromide	propafenone
chlorpheniramine	iloperidone	propoxyphene
chlorpromazine	imipramine	propranolol
chlorpropamide	labetalol	protriptyline
cinacalcet	lidocaine	quetiapine
clomipramine	loratadine	ranolazine
clonidine	maprotiline	risperidone
clozapine	meperidine	ropivacaine
codeine	methadone	selegiline
cyclobenzaprine	methamphetamine	S-metoprolol
cyclophosphamide	methoxyamphetamine	sparteine
darifenacin hydrobromide	metoclopramide	tamoxifen
debrisoquine	metoprolol	tamsulosin
delavirdine mesylate	mexiletine	thioridazine
desipramine	minaprine	tiagabine
dexfenfluramine	mirtazapine	timolol
dextromethorphan	molindone	tolterodine
diphenhydramine	morphine	tramadol
dolasetron	nebivolol	trazodone
donepezil	nortriptyline	trimipramine maleate
doxazosin mesylate	olanzapine	venlafaxine
doxepin	ondansetron	yohimbine
duloxetine	orphenadrine citrate	zuclopenthixol
encainide		

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V58.83 Encounter for therapeutic drug monitoring

References

1. Johnson JA, Cavallari LH, Beitelshees AL, et al. Pharmacogenomics: application to the management of cardiovascular disease. *Clinical pharmacology and therapeutics.* 2011;90:519-31.
2. Metoprolol. DrugBank web site. http://www.drugbank.ca/drugs/DB00264. Updated February 2012. Accessed July 20, 2012.
3. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clinical pharmacology and therapeutics.* 2009;85:45-50.
4. Goryachkina K, Burbello A, Boldueva S, et al. CYP2D6 is a major determinant of metoprolol disposition and effects in hospitalized Russian patients treated for acute myocardial infarction. *European journal of clinical pharmacology.* 2008;64:1163-73.
5. Wuttke H, Rau T, Heide R, et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clinical pharmacology and therapeutics.* 2002;72:429-37.
6. Rau T, Wuttke H, Michels LM, et al. Impact of the CYP2D6 genotype on the clinical effects of metoprolol: a prospective longitudinal study. *Clinical pharmacology and therapeutics.* 2009;85:269-72.
7. Fux R, Mörike K, Pröhmer AM, et al. Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clinical pharmacology and therapeutics.* 2005;78:378-87.
8. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *Journal of clinical pharmacy and therapeutics.* 2006;31:99-109.
9. Lennard MS, Silas JH, Freestone S, et al. Oxidation phenotype--a major determinant of metoprolol metabolism and response. *The New England journal of medicine.* 1982;307:1558-60.
10. Rau T, Heide R, Bergmann K, et al. Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. *Pharmacogenetics.* 2002;12:465-72.
11. Sharp CF, Gardiner SJ, Jensen BP, et al. CYP2D6 genotype and its relationship with metoprolol dose, concentrations and effect in patients with systolic heart failure. *The pharmacogenomics journal.* 2009;9:175-84.
12. Lopressor [package insert]. Novartis Pharmaceuticals Corporation, Sufferin, NY; February 2008. http://www.pharma.us.novartis.com/product/pi/pdf/lopressor.pdf. Accessed June 19, 2012.
13. Toprol [package insert]. AstraZeneca, Wilmington, DE; 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019962s038lbl.pdf. Accessed August 3, 2012.
14. Yuan H, Huang Z, Yang G, et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. *The Journal of international medical research.* 2008;36:1354-62.
15. McGourty JC, Silas JH, Lennard MS, Tucker GT, Woods HF. Metoprolol metabolism and debrisoquine oxidation polymorphism--population and family studies. *British journal of clinical pharmacology.* 1985;20:555-66.
16. Kirchheiner J, Heesch C, Bauer S, et al. Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clinical pharmacology and therapeutics.* 2004;76:302-12.
17. Silas JH, McGourty JC, Lennard MS, Tucker GT, Woods HF. Polymorphic metabolism of metoprolol: clinical studies. *European journal of clinical pharmacology.* 1985;28 Suppl:85-8.

18. Dayer P, Mérier G, Perrenoud JJ, Marmy A, Leemann T. Interindividual pharmacokinetic and pharmacodynamic variability of different beta blockers. *Journal of cardiovascular pharmacology.* 1986;8 Suppl 6:S20-4.
19. Zineh I, Beitelshees AL, Gaedigk A, et al. Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clinical pharmacology and therapeutics.* 2004;76:536-44.
20. Clark DW, Morgan AK, Waal-Manning H. Adverse effects from metoprolol are not generally associated with oxidation status. *British journal of clinical pharmacology.* 1984;18:965-7.
21. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clinical pharmacology and therapeutics.* 2011;89:662-73.
22. P450 Drug Interaction Table. Indiana University School of Medicine Division of Clinical Pharmacology web site. http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Updated January 2012. Accessed September 20, 2012.
23. CYP2D6-inhibitors. MedSort web site. http://drugs.medsort.com/Drugs/ClassProfile.aspx?ClassID=43. Accessed September 20, 2012.
24. Cytochrome P450 Drug Interactions. ILD Care web site. http://www.ildcare.eu/downloads/artseninfo/cyp450_drug_interactions.pdf. Updated May 2003. Accessed September 20, 2012.
25. CYP2D6-substrates. MedSort web site. http://drugs.medsort.com/Drugs/ClassProfile.aspx?ClassID=49. Accessed September 20, 2012.

Interferon-alpha/ribavirin

(DC:TB-0218.001 06DEC2012)

Report Type: Pharmacogenetics

About: Hepatitis C virus (HCV) infection is the most common chronic, blood-borne infection in the US and affects 170 million worldwide.[1] The standard treatment for HCV infection, particularly in resource-limited settings, is a combination of pegylated (polyethylene glycol) IFN-alpha (PEG-IFN-alpha) and ribavirin (RBV).[2] IFN-alpha stimulates the natural defense against the viral infection, and pegylation enhances its antiviral potency.[2] Ribavirin is a nucleoside antimetabolite that inhibits replication of the virus.[3] Telaprevir and boceprevir are HCV NS3/4A protease inhibitors that require co-administration with PEG-IFN-alpha/RBV.[4,5]

IFN-based therapies are expensive and can induce severe side effects; therefore, it would be beneficial to distinguish responders from non responders prior to treatment screening.[6,7]

Genetics: A variant in the rs12979860 marker near the IL28B gene is a strong predictor of response to PEG-IFN-alpha/RBV.[4,5] The IL28B gene encodes a cytokine called interleukin 28B (IL28B), also known as IFN-lambda-3.

A meta-analysis of seven studies containing a total of approximately 4,700 patients found that variants at rs12979860 near the IL28B gene could be used as a predictor of treatment response,[8] as measured by sustained virological response (SVR). SVR is defined as an absence of hepatitis C viral RNA six months after therapy. SVR was higher in patients who were homozygous for the C allele of rs12979860 compared to patients who were heterozygous. Additionally, rs12979860 can explain some of the variability in the response rate between different ethnic groups.[8] Individuals of European ancestry have a higher chance of successful treatment than African Americans,[9] consistent with higher C allele frequency in European Americans (70%) compared to African Americans (40%) (see “Allele Frequency” table below).[9] Moreover, East Asians have a higher C allele frequency and higher SVR rate than European patients.[10]

Patients who are homozygous for the C allele also have higher rates of clearing HCV without treatment[11] and may have an increased SVR rate after liver transplantation.[12] Conversely, carriers of the T allele are at an increased risk of therapeutic failure,[13] and being homozygous for the T allele is associated with a more severe recurrence of hepatitis after transplantation.[14]

Precisely how rs12979860 variation affects response to PEG-IFN-alpha/RBV is not well understood.[15] Other variants near the IL28B gene have been shown to alter the expression, stability or receptor binding of IL28B.[15] Rs12979860 is located in a DNA methylation site, and it has been speculated that the C variant may decrease expression of IL28B.[16]

The association of IL28B variants with treatment response varies with the strain of the HCV virus. The association is strongest for patients infected with the HCV-1 virus, the viral strain most commonly found worldwide. In patients infected

with HCV-2, -3 or -6, however, IL28B variants are weakly associated with response to PEG-IFN-alpha/RBV.[15,17,18] For patients infected with HCV-5 virus, IL28B variants have not been shown to be associated with response to PEG-IFN alpha/RBV.

Telaprevir and boceprevir are newly approved drugs for treatment of Hepatitis C. They are inhibitors of the viral NS3/4A protease and are indicated for patients with a null or partial response to PEG-IFN-alpha/RBV treatment.[4,5] These drugs require co-administration with PEG-IFN-alpha/RBV. In addition, many candidate drugs for treating hepatitis C are in various phases of clinical trials.[2] Thus, genotyping may help determine the best treatment strategy for HCV-infected patients.[7]

Recommendations: NA

Possible Outcomes: Poor Responder, Responder

Markers or Alleles Tested: IL28B [rs12979860]

Ethnic Distribution of Tested Alleles:

Population	C allele frequency (rs12979860)[1]
Biaka Pygmies	23.5%
Zaramo	37.2%
Yoruba	31.2%
Hungarians	65.1%
Irish	73.9%
European-American	67.4%
Druze	77.6%
Yemenite Jews	69.5%
Indians	65.5%
Laotians	93.6%
Chinese, San Francisco	97.5%
Koreans	93.5%
Micronesians	98.6%
Pima, Mexico	55.5%
Mayans	37.5%
Ticuna	20.2%
Karitiana	82.4%

Limitations and Warnings: In patients infected with HCV-2, -3 or -6 strains, the IL28B variants are weakly associated with treatment response.[15,17,18]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

1. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature.* 2009;461:798-801.
2. Pawlotsky JM. New antiviral agents for hepatitis C. *F1000 biology reports.* 2012;4:5.
3. Ribavirin. DrugBank web site. http://www.drugbank.ca/drugs/DB00811. Updated February 2012. Accessed November 6, 2012.
4. Incivek [package insert]. Vertex Pharmaceuticals Incorporated, Cambridge, MA; October 2012. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ed0e4f33-cf21-4fe3-918d-1d5b3a23eee4. Accessed November 6, 2012.
5. Victrelis [package insert]. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ; July 2012. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ae879ebe-b620-4829-b6f8-74b58da1c771. Accessed November 6, 2012.
6. Kobayashi M, Suzuki F, Akuta N, et al. Association of two polymorphisms of the IL28B gene with viral factors and treatment response in 1,518 patients infected with hepatitis C virus. *Journal of gastroenterology.* 2012;47:596-605.
7. McCarthy JJ, Li JH, Thompson A, et al. Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. *Gastroenterology.* 2010;138:2307-14.
8. Li S, Hu P, Zhang QQ, et al. Single nucleotide polymorphisms of the IL28B and sustained virologic response of patients with chronic hepatitis C to PEG-interferon/ribavirin therapy: A meta-analysis: Meta-analysis of IL28B. *Hepatitis monthly.* 2011;11:163-72.
9. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009;461:399-401.
10. Liapakis A, Jacobson I. Pharmacogenetics of hepatitis C therapy. *Pharmacogenomics.* 2010;11:135-9.
11. Wapner J. Pharmacogenomics. Gene variants affect hepatitis C treatment, but link is elusive. *Science (New York, N.Y.).* 2010;330:579.

12. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology (Baltimore, Md.).* 2011;53:317-24.
13. Cavalcante LN, Abe-Sandes K, Angelo AL, et al. IL28B polymorphisms are markers of therapy response and are influenced by genetic ancestry in chronic hepatitis C patients from an admixed population. *Liver international : official journal of the International Association for the Study of the Liver.* 2012;32:476-86.
14. Lange CM, Moradpour D, Doehring A, et al. Impact of donor and recipient IL28B rs12979860 genotypes on hepatitis C virus liver graft reinfection. *Journal of hepatology.* 2011;55:322-7.
15. Lange CM, Zeuzem S. IL28B single nucleotide polymorphisms in the treatment of hepatitis C. *Journal of hepatology.* 2011;55:692-701.
16. Fischer J, Böhm S, Scholz M, et al. Combined effects of different interleukin-28B gene variants on the outcome of dual combination therapy in chronic hepatitis C virus type 1 infection. *Hepatology (Baltimore, Md.).* 2012;55:1700-10.
17. Antaki N, Bibert S, Kebbewar K, et al. IL28B polymorphisms do not predict response to therapy in chronic hepatitis C with HCV genotype 5. *Gut.* 2012;61:1640-1.
18. Seto WK, Tanaka Y, Liu K, Lai CL, Yuen MF. The Effects of IL-28B and ITPA polymorphisms on treatment of hepatitis C virus genotype 6. *The American journal of gastroenterology.* 2011;106:1007-8.

Beta-blockers, LVEF response

(DC:TB-0208.002 07MAY2013)

Report Type: Pharmacogenetics

About: Beta-blockers (carvedilol, metoprolol, etc.) are used as a standard therapy for heart failure.[1] This class of drugs antagonizes beta-adrenergic receptors and down-regulates the effects of catecholamine hormones (epinephrine and norepinephrine). Genetic variants that affect beta-adrenergic signaling may influence outcomes in heart failure patients treated with beta-blockers.

Genetics: In heart failure patients, the benefits of treatment with beta-blockers for left ventricular ejection fraction (LVEF) are associated with variants in the ADRB1 gene, which encodes the beta(1)-adrenergic receptor.[2] A meta-analysis of three pharmacogenetic studies in heart failure patients found that individuals who are homozygous for the Arg389 allele have a greater increase in LVEF in response to beta-blockers (carvedilol, metoprolol or bisoprolol) compared to individuals who carry the Gly389 allele.[2] This genetic effect was also reported in a study involving patients who underwent 1.5 years of carvedilol treatment.[3]

In a number of small studies, the Arg389 allele has been studied in relation to other phenotypes, including exercise heart rate, response to rate-control therapy in atrial fibrillation, changes in heart rate and blood pressure in patients with essential hypertension and LV hypertrophy, and transplant-free survival in heart failure patients.[4,5,6,7] However, it is still controversial whether Arg389 modifies the outcomes of beta-blocker therapy. Some studies showed no association, while others reported significant associations but do not always agree on the direction of the genetic effect.

Recommendations: NA

Possible Outcomes: Enhanced Benefit, Beneficial

Markers or Alleles Tested: ADRB1 [rs1801253]

Ethnic Distribution of Tested Alleles:

Ethnicity	Arg389 allele (C allele) frequency[8]
Caucasian	~70%
East Asians	75-85%
Africans	~60%

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,

nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

1. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nature medicine.* 2008;14:510-7.
2. Muthumala A, Drenos F, Elliott PM, Humphries SE. Role of beta adrenergic receptor polymorphisms in heart failure: systematic review and meta-analysis. *European journal of heart failure.* 2008;10:3-13.
3. Chen L, Meyers D, Javorsky G, et al. Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol. *Pharmacogenetics and genomics.* 2007;17:941-9.
4. Kurnik D, Li C, Sofowora GG, et al. Beta-1-adrenoceptor genetic variants and ethnicity independently affect response to beta-blockade. *Pharmacogenetics and genomics.* 2008;18:895-902.
5. Parvez B, Chopra N, Rowan S, et al. A common β1-adrenergic receptor polymorphism predicts favorable response to rate-control therapy in atrial fibrillation. *Journal of the American College of Cardiology.* 2012;59:49-56.
6. Karlsson J, Lind L, Hallberg P, et al. Beta1-adrenergic receptor gene polymorphisms and response to beta1-adrenergic receptor blockade in patients with essential hypertension. *Clinical cardiology.* 2004;27:347-50.
7. Sehnert AJ, Daniels SE, Elashoff M, et al. Lack of association between adrenergic receptor genotypes and survival in heart failure patients treated with carvedilol or metoprolol. *Journal of the American College of Cardiology.* 2008;52:644-51.
8. International HapMap Project. International HapMap Project web site. http://hapmap.ncbi.nlm.nih.gov. Accessed October 23, 2012.

Methotrexate toxicity

(DC:TB-0226.001 06DEC2012)

Report Type: Pharmacogenetics

About: Methotrexate (MTX) is a chemotherapeutic agent used in the treatment of lymphoma and leukemia, as well as uterine, breast, skin, ovarian and other cancers. MTX is also used to treat very severe and disabling psoriasis or in hematopoetic stem cell transplantation to prevent graft-versus-host disease. Some patients taking MTX may experience many and/or severe side effects, which are often referred to as MTX toxicity.[1]

Genetics: The T allele of the rs1801133 marker (C677T variant) in the MTHFR (5,10-methylenetetrahydrofolate reductase) gene, which is important for folate metabolism, was shown to be associated with MTX toxicity in patients with rheumatoid arthritis. The T allele results in an amino acid change that leads to reduced enzyme activity. Homozygotes for the T allele have approximately 30% of the expected MTHFR enzyme activity, and heterozygotes have approximately 65% activity, compared to the most common genotype, C allele homozygotes. Reduced MTHFR enzyme activity may result in reduced elimination of MTX, thus resulting in higher than expected MTX plasma concentrations and increasing the likelihood of MTX toxicity.[2]

While other MTHFR mutations are associated with MTHFR deficiency, only the C677T variant has shown significant association with methotrexate toxicity. In a meta-analysis of eight small studies, individuals with a T allele were shown to have a 1.7-fold increased risk for MTX-induced side effects.[3] These studies included patients from India, Japan, South Korea, Israel and the Netherlands. Additionally, a meta-analysis of 14 studies demonstrated that the T allele was associated with an increased risk of MTX-induced toxicity (liver toxicity, myelosuppression, oral mucositis, gastrointestinal toxicity and skin toxicity) in patients with acute lymphoblastic leukemia (ALL).[4]

Most studies with statistically significant data indicate an association between the T allele with MTX-induced side effects in patients with rheumatoid arthritis and ALL. It should be noted, however, that a 2011 meta-analysis did not identify a significant association between the C677T variant and MTX toxicity in patients with rheumatoid arthritis.[5] Association of the T allele with MTX toxicity has also been observed in patients undergoing hematopoetic cell transplantation and in patients with high-grade non-Hodgkin's lymphoma, acute leukemia, ovarian cancer, breast cancer, or juvenile idiopathic arthritis.[2] However, these studies are relatively small and controversial. In addition to MTX toxicity, the T allele has been associated with lowered efficacy of MTX, such as reduced anti-tumor activity or reduced survival in some studies but not others. The T allele has also been shown to be associated with therapeutic response to a different chemotherapy, fluorouracil (5-FU), in some studies but not others.[6,7,8,9]

Recommendations: Varying the MTX dose or supplementing with folic or folinic acid (leucovorin) has been shown to reduce the risk of toxicity-related discontinuation of MTX treatment in patients with and without the T allele.[10,11,12]

Please also see the related tests: MTHFR deficiency and Genetic risk for decreased folate.

Possible Outcomes: Increased Risk, Typical Risk

Markers or Alleles Tested: MTHFR [rs1801133]

Ethnic Distribution of Tested Alleles: The minor allele frequency was approximately 29.4% to 33.5% in Caucasians.[5]

Limitations and Warnings: Some variants not reported in the test also result in altered MTHFR activity. Therefore, a negative result for the reported MTHFR variant does not rule out the presence of additional variants that can cause altered MTHFR activity related adverse effects upon MTX treatment.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

1. Methotrexate. PubMed Health web site. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000547/. Updated April 2009. Accessed July 20, 2012.
2. De Mattia E, Toffoli G. C677T and A1298C MTHFR polymorphisms, a challenge for antifolate and fluoropyrimidine-based therapy personalisation. *European journal of cancer (Oxford, England : 1990).* 2009;45:1333-51.
3. Fisher MC, Cronstein BN. Metaanalysis of methylenetetrahydrofolate reductase (MTHFR) polymorphisms affecting methotrexate toxicity. *The Journal of rheumatology.* 2009;36:539-45.
4. Yang L, Hu X, Xu L. Impact of methylenetetrahydrofolate reductase (MTHFR) polymorphisms on methotrexate-induced toxicities in acute lymphoblastic leukemia: a meta-analysis [published online ahead of print April 20, 2012]. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2012. Accessed August 28, 2012.
5. Owen SA, Lunt M, Bowes J, et al. MTHFR gene polymorphisms and outcome of methotrexate treatment in patients with rheumatoid arthritis: analysis of key polymorphisms and meta-analysis of C677T and A1298C polymorphisms. *The pharmacogenomics journal.* 2013;13:137-47.
6. Cohen V, Panet-Raymond V, Sabbaghian N, et al. Methylenetetrahydrofolate reductase polymorphism in advanced colorectal cancer: a novel genomic predictor of clinical response to fluoropyrimidine-based chemotherapy. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2003;9:1611-5.

7. Jakobsen A, Nielsen JN, Gyldenkerne N, Lindeberg J. Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphism in normal tissue as predictors of fluorouracil sensitivity. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23:1365-9.
8. Etienne MC, Formento JL, Chazal M, et al. Methylenetetrahydrofolate reductase gene polymorphisms and response to fluorouracil-based treatment in advanced colorectal cancer patients. *Pharmacogenetics.* 2004;14:785-92.
9. Marcuello E, Altés A, Menoyo A, Rio ED, Baiget M. Methylenetetrahydrofolate reductase gene polymorphisms: genomic predictors of clinical response to fluoropyrimidine-based chemotherapy? *Cancer chemotherapy and pharmacology.* 2006;57:835-40.
10. Ortiz Z, Shea B, Suarez Almazor M, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *The Cochrane database of systematic reviews.* 2000;CD000951.
11. van Ede AE, Laan RF, Blom HJ, et al. The C677T mutation in the methylenetetrahydrofolate reductase gene: a genetic risk factor for methotrexate-related elevation of liver enzymes in rheumatoid arthritis patients. *Arthritis and rheumatism.* 2001;44:2525-30.
12. Hoekstra M, van Ede AE, Haagsma CJ, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Annals of the rheumatic diseases.* 2003;62:423-6.

Phenytoin hypersensitivity

(DC:TB-0221.001 06DEC2012)

Report Type: Pharmacogenetics

About: Phenytoin is used to treat epilepsy, accounting for approximately 52% of all prescriptions for antiepileptic drugs.[1] It acts by blocking voltage-sensitive sodium channels in neurons.[2] Monitoring phenytoin levels is often necessary due to the drug's narrow therapeutic range and large individual variability in clearance.[1] Use of phenytoin can lead to cutaneous adverse reactions that vary from mild maculopapular eruption with increasing severity to hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN are rare but life-threatening.[3]

Genetics: The HLA-B*1502 allele of the HLA-B gene has been shown to be associated with phenytoin-induced cutaneous adverse reactions in Asians. The association between HLA-B*1502 and phenytoin-induced SJS/TEN has been found in both Thai and Chinese populations.[4,5,6] The HLA-B gene encodes a human leukocyte antigen protein that is involved in immune response. The HLA-B*1502 allele has also been shown to be associated with increased risk of SJS/TEN for antiepileptic drugs that are related to phenytoin, such as carbamazepine and oxcarbazepine.[4,5,6,7]

Recommendations: FDA advises that alternative therapies should be considered for HLA-B*1502-positive patients, who are at an increased risk of phenytoin-induced adverse reactions.[8]

Possible Outcomes: Hypersensitive, Typical, Unknown

Markers or Alleles Tested: HLA-B [HLA-B*1502]

This test includes rs3909184 and rs2844682, which together tag the HLA-B*1502 allele in Han Chinese.[9] Patients with one or two HLA-B*1502 alleles are assigned a "Hypersensitive" result. Patients with no HLA-B*1502 alleles are assigned a "Typical" result.

For patients with a particular genotype (rs3909184 (G/C), rs2844682 (C/T)), the HLA-B*1502 status cannot be determined, and thus these patients are assigned an "Unknown" result. These patients may require further evaluation.

Ethnic Distribution of Tested Alleles: The HLA-B*1502 allele is more prevalent in individuals of Asian ancestry.[10] The HLA-B*1502 allele has been observed in about 10% to 15% of patients in parts of China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan. The frequency of this allele in South Asian individuals, such as Indians, is about 2% to 4%, but the frequency may be higher in some groups. The frequency of HLA-B*1502 is much lower (less than 1%) in Japan and Korea.[11] The HLA-B*1502 allele is also less frequently found (less than 1%) in those of African, European, Hispanic or Native American descent.[10]

Limitations and Warnings: The markers tested for HLA-B*1502 are most applicable to patients of Han Chinese descent.[9] If clinically indicated, patients of other Asian ethnicities could be advised to undergo HLA sequencing to assess their risk of

phenytoin hypersensitivity. There are insufficient data to associate HLA-B*1502 with phenytoin hypersensitivity in other non-Asian ethnicities. Many HLA-B*1502-positive Asian patients treated with phenytoin will not develop SJS/TEN. Conversely, these reactions can still occur infrequently in HLA-B*1502-negative patients of any ethnicity. Therefore, healthcare professionals are advised to watch for symptoms in all patients.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E936.1 Hydantoin derivatives causing adverse effects in therapeutic use Applies to: • Phenytoin	N/A

References

1. Chaudhry AS, Urban TJ, Lamba JK, et al. CYP2C9*1B promoter polymorphisms, in linkage with CYP2C19*2, affect phenytoin autoinduction of clearance and maintenance dose. *The Journal of pharmacology and experimental therapeutics.* 2010;332:599-611.
2. Tate SK, Depondt C, Sisodiya SM, et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proceedings of the National Academy of Sciences of the United States of America.* 2005;102:5507-12.
3. Min FL, Shi YW, Liu XR, Liao WP. HLA-B*1502 genotyping in two Chinese patients with phenytoin-induced Stevens-Johnson syndrome. *Epilepsy & behavior : E&B.* 2011;20:390-1.
4. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia.* 2008;49:2087-91.
5. Hung SI, Chung WH, Liu ZS, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics.* 2010;11:349-56.
6. Neuman MG, Cohen L, Nanau RM, Hwang PA. Genetic and immune predictors for hypersensitivity syndrome to antiepileptic drugs. *Translational research : the journal of laboratory and clinical medicine.* 2012;159:397-406.
7. Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. *Expert opinion on drug safety.* 2010;9:15-21.
8. Dilantin [package insert]. Remedy Repack, Inc., Indiana, PA; July 2011. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=0c2e0671-bb5e-4704-a242-83c5b9a0bbb0. Accessed November 6, 2012.
9. de Bakker PI, McVean G, Sabeti PC, et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. *Nature genetics.* 2006;38:1166-72.
10. Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics.* 2008;9:1543-6.

11. Franciotta D, Kwan P, Perucca E. Genetic basis for idiosyncratic reactions to antiepileptic drugs. *Current opinion in neurology.* 2009;22:144-9.

Phenytoin metabolism

(DC:TB-0222.001 06DEC2012)

Report Type: Pharmacogenetics

About: Phenytoin is used to treat epilepsy, accounting for approximately 52% of all prescriptions for antiepileptic drugs.[1] Monitoring phenytoin levels is often necessary due to the drug's narrow therapeutic range and large individual variability in clearance.[1] Phenytoin acts by blocking voltage-sensitive sodium channels in neurons[2] and is primarily metabolized to hydroxyphenytoin (p-HPPH)[3] by the CYP2C9 enzyme, which accounts for up to 90% of the drug's metabolism.[4] p-HPPH has no anticonvulsant properties but is associated with some side effects, such as gingival hyperplasia, somnolence, dry month and fatigue.[5]

Genetics: The most common reduced function CYP2C9 variants are the CYP2C9*2 and CYP2C9*3 alleles. *In vitro* studies have shown that CYP2C9*2 and CYP2C9*3 are associated with approximately 29% and 95% reductions in phenytoin clearance, respectively, as compared to the wild-type allele, CYP2C9*1[2]. The CYP2C9*6 allele is a rare loss-of-function variant found in African populations.[6,7] Different combinations of CYP2C9 alleles give rise to different levels of CYP2C9 enzyme activity. For example, individuals with two wild-type alleles (e.g., CYP2C9*1/ CYP2C9*1) are extensive metabolizers. Individuals with one wild-type and one reduced function allele (e.g., CYP2C9*1/ CYP2C9*2) are intermediate metabolizers. Individuals with two reduced function alleles (e.g., CYP2C9*2/ CYP2C9*2 or CYP2C9*2/ CYP2C9*3) are poor metabolizers. These genetically determined differences in phenytoin metabolism can lead to toxicity and variable efficacy.[8,9]

CYP2C9 intermediate and poor metabolizers have increased plasma concentrations of phenytoin[10,11,12,13,14] and increased risk of phenytoin-induced neurological toxicity.[4,8,15,16,17,18,19] Symptoms of neurological toxicity may include dizziness, nystagmus (lateral and vertical), ataxia, slurred speech, lethargy and mental confusion.[8]

Recommendations: The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy recommends a 25% dose decrease of phenytoin for CYP2C9*1/CYP2C9*2 and CYP2C9*1/CYP2C9*3 individuals and a 50% dose decrease of phenytoin for CYP2C9*2/CYP2C9*2, CYP2C9*3/CYP2C9*3 and CYP2C9*2/ CYP2C9*3 individuals.[20] The German AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) strongly recommends therapeutic drug monitoring (TDM) of plasma phenytoin in all patients, regardless of CYP2C9 genotype, in their Consensus Guidelines for Therapeutic Drug Monitoring.[21] According to the Guidelines, the therapeutic reference range for phenytoin is 10 to 20 µg/ml and the alert level is 25 µg/ml, indicating a narrow therapeutic range.[21]

CYP2C9 metabolizer status may affect response to other drugs, such as warfarin, tolbutamide, glipizide, celecoxib and fluvastatin.[22,23]

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer

Markers or Alleles Tested: CYP2C9 [CYP2C9*2, CYP2C9*3, CYP2C9*6]

Ethnic Distribution of Alleles:[24]

Gene	Allele	African	Caucasian	Japanese	Chinese
CYP2C9	*1	80.6	77.9	96.5	95.8
CYP2C9	*2	1.2	15.9	0	0.1
CYP2C9	*3	0	5.7	3.4	4.1
CYP2C9	*6	1.2	0	0	0

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

1. Chaudhry AS, Urban TJ, Lamba JK, et al. CYP2C9*1B promoter polymorphisms, in linkage with CYP2C19*2, affect phenytoin autoinduction of clearance and maintenance dose. *The Journal of pharmacology and experimental therapeutics.* 2010;332:599-611.
2. Tate SK, Depondt C, Sisodiya SM, et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proceedings of the National Academy of Sciences of the United States of America.* 2005;102:5507-12.
3. Leeder JS. Mechanisms of idiosyncratic hypersensitivity reactions to antiepileptic drugs. *Epilepsia.* 1998;39 Suppl 7:S8-16.
4. Depondt C, Godard P, Espel RS, et al. A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. *European journal of neurology.* 2011;18:1159-64.
5. He SM, Zhou ZW, Li XT, Zhou SF. Clinical drugs undergoing polymorphic metabolism by human cytochrome P450 2C9 and the implication in drug development. *Current medicinal chemistry.* 2011;18:667-713.

6. Allabi AC, Gala JL, Horsmans Y. CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population. *Pharmacogenetics and genomics.* 2005;15:779-86.
7. Allabi AC, Gala JL, Horsmans Y, et al. Functional impact of CYP2C95, CYP2C96, CYP2C98, and CYP2C911 in vivo among black Africans. *Clinical pharmacology and therapeutics.* 2004;76:113-8.
8. Kesavan R, Narayan SK, Adithan C. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. *European journal of clinical pharmacology.* 2010;66:689-96.
9. Soga Y, Nishimura F, Ohtsuka Y, et al. CYP2C polymorphisms, phenytoin metabolism and gingival overgrowth in epileptic subjects. *Life sciences.* 2004;74:827-34.
10. Odani A, Hashimoto Y, Otsuki Y, et al. Genetic polymorphism of the CYP2C subfamily and its effect on the pharmacokinetics of phenytoin in Japanese patients with epilepsy. *Clinical pharmacology and therapeutics.* 1997;62:287-92.
11. van der Weide J, Steijns LS, van Weelden MJ, de Haan K. The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement. *Pharmacogenetics.* 2001;11:287-91.
12. Mamiya K, Ieiri I, Shimamoto J, et al. The effects of genetic polymorphisms of CYP2C9 and CYP2C19 on phenytoin metabolism in Japanese adult patients with epilepsy: studies in stereoselective hydroxylation and population pharmacokinetics. *Epilepsia.* 1998;39:1317-23.
13. Hung CC, Lin CJ, Chen CC, Chang CJ, Liou HH. Dosage recommendation of phenytoin for patients with epilepsy with different CYP2C9/CYP2C19 polymorphisms. *Therapeutic drug monitoring.* 2004;26:534-40.
14. Kidd RS, Curry TB, Gallagher S, et al. Identification of a null allele of CYP2C9 in an African-American exhibiting toxicity to phenytoin. *Pharmacogenetics.* 2001;11:803-8.
15. Brandolese R, Scordo MG, Spina E, Gusella M, Padrini R. Severe phenytoin intoxication in a subject homozygous for CYP2C9*3. *Clinical pharmacology and therapeutics.* 2001;70:391-4.
16. Ramasamy K, Narayan SK, Chanolean S, Chandrasekaran A. Severe phenytoin toxicity in a CYP2C9*3*3 homozygous mutant from India. *Neurology India.* 2007;55:408-9.
17. McCluggage LK, Voils SA, Bullock MR. Phenytoin toxicity due to genetic polymorphism. *Neurocritical care.* 2009;10:222-4.
18. Dorado P, López-Torres E, Peñas-Lledó EM, Martínez-Antón J, Llerena A. Neurological toxicity after phenytoin infusion in a pediatric patient with epilepsy: influence of CYP2C9, CYP2C19 and ABCB1 genetic polymorphisms. *The pharmacogenomics journal.* 2013;13:359-61.
19. Ramasamy K, Narayan SK, Shewade DG, Chandrasekaran A. Influence of CYP2C9 genetic polymorphism and undernourishment on plasma-free phenytoin concentrations in epileptic patients. *Therapeutic drug monitoring.* 2010;32:762-6.
20. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clinical pharmacology and therapeutics.* 2011;89:662-73.
21. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. *Pharmacopsychiatry.* 2011;44:195-235.
22. Kirchheiner J, Brockmöller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clinical pharmacology and therapeutics.* 2005;77:1-16.
23. P450 Drug Interaction Table. Indiana University School of Medicine Division of Clinical Pharmacology web site. http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Updated January 2012. Accessed November 6, 2012.

24. Man M, Farmen M, Dumaual C, et al. Genetic variation in metabolizing enzyme and transporter genes: comprehensive assessment in 3 major East Asian subpopulations with comparison to Caucasians and Africans. *Journal of clinical pharmacology.* 2010;50:929-40.

Proton pump inhibitors

(DC:TB-0219.001 06DEC2012)

Report Type: Pharmacogenetics

About: Proton pump inhibitors (PPIs), such as omeprazole, esomeprazole (S-isomer of omeprazole), lansoprazole, rabeprazole and pantoprazole, are potent gastric acid inhibitors that are used to treat gastroesophageal reflux disease, duodenal and gastric ulcers, erosive esophagitis, and pathological hypersecretory conditions, such as Zollinger-Ellison syndrome.[1] PPIs are converted to sulfenamides by the acidic environment of the stomach. The sulfenamide is the active form of the drug and inhibits gastric acid secretion by forming a disulfide bond with the gastric acid pump H K -ATPase enzyme.[2] PPIs, with the exception of rabeprazole, are primarily metabolized by the CYP2C19 enzyme in the liver prior to elimination from the body.[2]

Genetics: The CYP2C19 genotype is the most important genetic determinant for PPI treatment.[1] Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).[3]

CYP2C19 PMs and IMs have lower clearance rates and higher plasma concentrations of PPIs than CYP2C19 EMs. Therefore, they are likely to benefit more from the PPI treatment and may experience stronger suppression of gastric acid secretion, an improved eradication rate of *Helicobacter pylori* infection, and improved cure rates of gastroesophageal reflux disease, esophagitis or ulcers.[1,2,4] PPIs are very safe drugs, even in CYP2C19 PMs, who are expected to have elevated plasma concentrations of PPIs.[1,4] In CYP2C19 EMs, the clearance of omeprazole, lansoprazole and pantoprazole is significantly increased, resulting in lower plasma concentrations, compared to PMs.[1] Thus, EMs may experience insufficient suppression of gastric acid secretion and a decreased therapeutic effect in some cases.[1,2,4] CYP2C19 UMs have decreased drug exposure and are at increased risk of therapeutic failure.[5,6]

For *H. pylori* eradication, PPIs are typically used in dual and triple therapies together with the antibiotics amoxicillin and/or clarithromycin;[1,7,8] the PPIs make the antibiotics more stable by reducing intragastric acidity.[2] Genetic testing for CYP2C19 has been shown to predict efficacy of *H. pylori* eradication treatment. For example, one study reported that the cure rates for *H. pylori* infection were 29%, 60% and 100%, respectively, for CYP2C19 EM, IM and PM individuals.[9] However, the success of eradication depends on additional critical factors, including patient compliance, the choice of PPI regimen, type of therapy (i.e., dual or triple) and antibiotic resistance of *H. pylori*.[1] Thus, the choice of PPI and regimen is considered to be the most practical approach for *H. pylori* eradication.[1]

Recommendations: The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy recommends dose increases for CYP2C19 UM individuals using omeprazole, esomeprazole, lansoprazole or pantoprazole for *H. pylori* eradication treatment.[10]

The FDA-approved label for Plavix warns against concurrent use of omeprazole or esomeprazole with clopidogrel because omeprazole can inhibit CYP2C19 activity and reduce the effectiveness of clopidogrel.[11] Thus, patients who are at risk for heart attack or stroke will not receive the full anti-clotting effect of clopidogrel if they are also using omeprazole.[12]

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers or Alleles Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles

The CYP2C19 panel detects alleles that have a combined frequency of over 99% in major ethnic groups.[3]

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND[a]	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

Other critical factors that may influence the therapeutic effect of PPIs include the following: patient compliance, choice of PPI regimen, type of therapy (i.e., dual, triple) and antibiotic used, age, sex, nutritional status, liver and kidney function, concomitant diseases and medications, pharmacogenetics of CYP3A4, and IL-1 beta polymorphisms.[1,13,14,15,16,17]

Though the CYP2C19 genotype is associated with therapeutic efficacy for omeprazole, lansoprazole and pantoprazole, it is considered to have little or no effect on the therapeutic efficacy of rabeprazole, which is mainly metabolized by a nonenzymatic reduction.[1,18]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

1. Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics.* 2011;12:873-88.
2. Yang JC, Lin CJ. CYP2C19 genotypes in the pharmacokinetics/pharmacodynamics of proton pump inhibitor-based therapy of Helicobacter pylori infection. *Expert opinion on drug metabolism & toxicology.* 2010;6:29-41.
3. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clinical pharmacology and therapeutics.* 2011;90:328-32.
4. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *European journal of clinical pharmacology.* 2008;64:935-51.
5. Sim SC, Risinger C, Dahl ML, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clinical pharmacology and therapeutics.* 2006;79:103-13.
6. Baldwin RM, Ohlsson S, Pedersen RS, et al. Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy volunteers. *British journal of clinical pharmacology.* 2008;65:767-74.
7. Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *The American journal of gastroenterology.* 2006;101:1467-75.
8. Kang JM, Kim N, Lee DH, et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. *Journal of gastroenterology and hepatology.* 2008;23:1287-91.
9. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for Helicobacter pylori infection and peptic ulcer. *Annals of internal medicine.* 1998;129:1027-30.
10. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clinical pharmacology and therapeutics.* 2011;89:662-73.
11. Plavix [package insert]. sanofi-aventis, Bridgewater, NJ; December 2011. http://products.sanofi.us/plavix/plavix.pdf. Accessed November 6, 2012.
12. Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec) - Drug Interaction. U.S. Food and Drug Administration web site. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm190848.htm. Updated November 2009. Accessed November 6, 2012.
13. Tamura T, Kurata M, Inoue S, et al. Improvements in Helicobacter pylori eradication rates through clinical CYP2C19 genotyping. *Nagoya journal of medical science.* 2011;73:25-31.

14. Furuta T, Sugimoto M, Kodaira C, et al. CYP2C19 genotype is associated with symptomatic recurrence of GERD during maintenance therapy with low-dose lansoprazole. *European journal of clinical pharmacology.* 2009;65:693-8.
15. Furuta T, Shirai N, Kodaira M, et al. Pharmacogenomics-based tailored versus standard therapeutic regimen for eradication of H. pylori. *Clinical pharmacology and therapeutics.* 2007;81:521-8.
16. Furuta T, Shirai N, Xiao F, Ohashi K, Ishizaki T. Effect of high-dose lansoprazole on intragastic pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19. *Clinical pharmacology and therapeutics.* 2001;70:484-92.
17. Chaudhry AS, Kochhar R, Kohli KK. Genetic polymorphism of CYP2C19 & therapeutic response to proton pump inhibitors. *The Indian journal of medical research.* 2008;127:521-30.
18. Shirai N, Furuta T, Moriyama Y, et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Alimentary pharmacology & therapeutics.* 2001;15:1929-37.

Simvastatin-induced myopathy

(DC:TB-0229.001 06DEC2012)

Report Type: Pharmacogenetics

About: Simvastatin is a member of the statins, a class of cholesterol-lowering drugs whose major adverse effect is skeletal muscle toxicity. Approximately 5% to 10% of patients taking statins experience muscle pain (myalgia).[1] A small portion of patients, (1.5% to 5.0%) may develop more severe symptoms indicating muscle degradation (myopathy).[1] In rare cases (0.1 to 0.2 cases per 1,000 person-years), severe muscle damage leads to acute, potentially lethal kidney failure (rhabdomyolysis).[1,2]

Genetics: Simvastatin-induced myopathy has been shown to be influenced by variation in the SLCO1B1 gene.[3] Approximately 60% of myopathy cases in a simvastatin (80 mg/day) clinical trial were attributed to the C allele of the rs4149056 marker in the SLCO1B1 gene.[3] SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1, also known as OATP-C or OATP2), which regulates the hepatic uptake of statins and other drugs. The C allele at rs4149056 reduces the activity of the OATP1B1 transporter,[4] leading to increased blood simvastatin levels and the potential for increased toxicity to the muscles. However, available clinical data are insufficient to show whether the SLCO1B1 variant also alters myopathy risk associated with the use of statins other than simvastatin.[5]

The risk of myopathy varies with the type of statin and is dose-related. Some statins are associated with lower risk of myopathy compared with others,[1] and the pharmacokinetic effects of variants of rs4149056 are not uniform for different statins.[6,7] The incidences of myopathy and rhabdomyolysis while taking 80 mg simvastatin daily are disproportionally higher than those with lower doses.[8]

Genetic variation in SLCO1B1 also affects pharmacokinetics of other drugs, such as methotrexate and HIV protease inhibitors.[9]

Recommendations: The NIH Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for SLCO1B1 genotyping and simvastatin-induced myopathy, recommending reduced dose or alternative statins for patients with the C allele at rs4149056. The CPIC also recommends routine surveillance of serum creatine kinase levels for those patients.[5]

Possible Outcomes: Increased Risk, Typical Risk

Markers and Alleles Tested: SLCO1B1 [rs4149056]

Ethnic Distribution of Tested Allele

Frequency of C allele of the rs4149056 marker in major ethnic groups.[5]

Ethnicity	C allele frequency (rs4149056)
Caucasian	15%
African	3%
Middle Eastern	20%
Asian	13%

Limitations and Warnings: Although the tested SLCO1B1 variant has the most significant genetic effect on the risk of simvastatin-induced myopathy in clinical studies, rarer mutations in SLCO1B1 that may also affect the function of the encoded protein are not screened in this test. Current knowledge is limited on the involvement of other genes in the metabolism and clinical effects of simvastatin. In addition to genetic effects, the risk of simvastatin-induced myopathy varies with the patient's age, gender, body mass index, ethnicity and other clinical factors.[5]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
359.4 Toxic myopathy	N/A

References

1. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Annals of internal medicine.* 2009;150:858-68.
2. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003;289:1681-90.
3. SEARCH Collaborative Group., Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. *The New England journal of medicine.* 2008;359:789-99.
4. Kameyama Y, Yamashita K, Kobayashi K, Hosokawa M, Chiba K. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. *Pharmacogenetics and genomics.* 2005;15:513-22.
5. Wilke RA, Ramsey LB, Johnson SG, et al. The clinical pharmacogenomics implementation consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clinical pharmacology and therapeutics.* 2012;92:112-7.
6. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clinical pharmacology and therapeutics.* 2007;82:726-33.
7. Niemi M, Pasanen MK, Neuvonen PJ. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. *Clinical pharmacology and therapeutics.* 2006;80:356-66.
8. Zocor [package insert]. Merck and Co., Inc, Whitehouse Station, NJ; March 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019766s080lbl.pdf. Accessed August 3, 2012.
9. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacological reviews.* 2011;63:157-81.

Voriconazole metabolism

(DC:TB-0220.002 29JAN2013)

Report Type: Pharmacogenetics

About: Voriconazole is a triazole antifungal drug that is used to treat a wide variety of fungal infections, such as *Candida*, *Cryptococcus*, *Aspergillus*, most dimorphic fungi and other yeasts and hyaline molds.[1] Therapeutic drug monitoring is recommended for optimizing voriconazole therapy and preventing toxicity due to the drug's high interpatient variability and nonlinear pharmacokinetic properties in adults.[1,1,2,3] Voriconazole serum concentrations less than 1 mg/L are associated with therapeutic failure, whereas levels greater than 5.5 mg/L have been linked to encephalopathy without improvement of therapeutic efficacy.[4]

Though the metabolic pathways of voriconazole are not completely understood, voriconazole is mainly metabolized to N-oxide,[5] which has low antifungal activity.[3] Metabolism to N-oxide is primarily mediated by enzymes encoded by CYP2C19 and CYP3A4, and to a lesser extent by CYP2C9,[6,7] though voriconazole has the highest affinity for CYP2C19.[8]

Genetics: Variants in the CYP2C19 gene have been associated with variability in voriconazole metabolism and exposure.[3] Individuals can be classified based on their CYP2C19 enzyme activity into four metabolizer groups: Ultrarapid Metabolizer (UM, higher than normal enzyme activity), Extensive Metabolizer (EM, normal enzyme activity), Intermediate Metabolizer (IM, intermediate enzyme activity) and Poor Metabolizer (PM, low or no enzyme activity).[9]

Variants of the CYP2C19 gene account for approximately half of the variability in oral clearance.[10,11] UMs have decreased plasma concentrations of voriconazole with exposure reduced by up to approximately 50% compared to EMs.[10,12,13] CYP2C19 PMs display decreased metabolism of voriconazole, increased plasma concentrations and approximately four-fold higher voriconazole exposure than EMs. Pharmacokinetic effects in IMs are between those of PMs and EMs.[3,5,10,11,13,14,15]

There is not yet sufficient evidence for an association of CYP2C19 genotype and pharmacodynamic effects such as treatment efficacy or adverse events in patients treated with voriconazole.[16,17] However, there are data linking VOR plasma concentrations to treatment failure or risk of adverse events. Low plasma concentrations of voriconazole, as found in some UMs, are associated with an increased risk of treatment failure and mortality in some non-genetic studies.[18,19,20,21] In a 2011 study, the UM genotype was found to be more prevalent in patients with extremely low plasma concentrations of voriconazole (0.03 mg/mL).[12] In another study, 5 patients with persistently low VOR concentrations (<0.35 mg/mL) died from invasive fungal infection.[18] In another study, 1 patient who had low plasma concentrations of voriconazole experienced therapeutic failure, which was reversed with a higher dose.[19]

In addition, high plasma concentrations of voriconazole have been shown to be associated with liver toxicity,[18,21,22,23] although a recent study indicates no association of plasma VOR levels with liver toxicity.[24]

Recommendations: The Royal Dutch Association for the Advancement of Pharmacy's Pharmacogenomics Working Group recommends therapeutic drug monitoring (TDM) for voriconazole treatment of CYP2C19 PMs and IMs.[25]

The FDA-approved label indicates that when CYP2C19 is inhibited, dose adjustment or monitoring for adverse events or lack of efficacy may be needed.

Co-administration of inhibitors of CYP2C19, CYP2C9 and CYP3A4 may increase the voriconazole plasma concentrations.[3] According to one study, the administration of ritonavir, a potent CYP3A4 inhibitor, resulted in a higher exposure with voriconazole, which might increase the risk of adverse reactions, particularly in CYP2C19 PMs.[15]

Possible Outcomes: Poor Metabolizer, Intermediate Metabolizer, Extensive Metabolizer, Ultrarapid Metabolizer

Markers Tested: CYP2C19 [CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17]

Ethnic Distribution of Tested Alleles:

CYP2C19	Allele	Caucasian	African	East Asian	Middle Eastern	Enzyme activity
Wild-type	*1	63%	68%	60%	87%	Normal
rs4244285	*2	15%	15%	29%	12%	None
rs4986893	*3	0.42%	0.52%	8.9%	1.1%	None
rs28399504	*4	0.25%	0.093%	0.049%	ND[a]	None
rs56337013	*5	0.0073%	ND	0.062%	ND	Reduced
rs72552267	*6	0.017%	0%	0%	ND	None
rs41291556	*8	0.35%	0%	0%	ND	Reduced
rs12248560	*17	21%	16%	2.7%	ND	Increased

[a]Not Determined

Predicted CYP2C19 Metabolizer Status[9]

CYP2C19 Diplotype	Predicted Metabolizer Status
*2-*8/*2-*8	Poor Metabolizer
*1/*2-*8, *17/*2-*8	Intermediate Metabolizer
*1/*1	Extensive Metabolizer
*1/*17, *17/*17	Ultrarapid Metabolizer

Limitations and Warnings: Many rare CYP2C19 variants have been identified, but are not part of this test. It is possible, but unlikely, that the patient may have a variant that is not included in this test.

CYP2C19 genotype and metabolizer status may also affect responses to other drugs.[26]

Known CYP2C19 Substrates[27]	Known CYP2C19 Inhibitors[27]
Proton-pump Inhibitors	Proton-pump Inhibitors
lansoprazole	lansoprazole
omeprazole	omeprazole
pantoprazole	pantoprazole
rabeprazole	rabeprazole
Anti-epileptics	Other
diazepam	chloramphenicol
phenytoin	cimetidine
S-mephenytoin	felbamate
phenobarbitone	fluoxetine
	fluvoxamine
Other	indomethacin
amitriptyline	ketoconazole
carisoprodol	modafinil
citalopram	oxcarbazepine
chloramphenicol	probenicid
clomipramine	ticlopidine
clopidogrel	topiramate
cyclophosphamide	
hexobarbital	
imipramine N-deME	
indomethacin	
R-mephobarbital	
moclobemide	
nelfinavir	
nilutamide	
primidone	
progesterone	
proguanil	
propranolol	
teniposide	
R-warfarin	

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
N/A	V58.83 Encounter for therapeutic drug monitoring

References

1. Lat A, Thompson GR 3rd. Update on the optimal use of voriconazole for invasive fungal infections. *Infection and drug resistance.* 2011;4:43-53.
2. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R. Voriconazole therapeutic drug monitoring: focus on safety. *Expert opinion on drug safety.* 2010;9:125-37.
3. VFEND [package insert]. Pfizer, New York, NY; June 2011. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ce3ef5cf-3087-4d92-9d94-9eb8287228db. Accessed November 6, 2012.
4. Thompson GR 3rd, Cadena J, Patterson TF. Overview of antifungal agents. *Clinics in chest medicine.* 2009;30:203-15, v.
5. Ikeda Y, Umemura K, Kondo K, et al. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clinical pharmacology and therapeutics.* 2004;75:587-8.
6. Ashbee HR, Gilleece MH. Has the era of individualised medicine arrived for antifungals? A review of antifungal pharmacogenomics. *Bone marrow transplantation.* 2012;47:881-94.
7. Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics.* 2011;12:861-72.
8. Johnson HJ, Han K, Capitano B, et al. Voriconazole pharmacokinetics in liver transplant recipients. *Antimicrobial agents and chemotherapy.* 2010;54:852-9.
9. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clinical pharmacology and therapeutics.* 2011;90:328-32.
10. Weiss J, Ten Hoevel MM, Burhenne J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. *Journal of clinical pharmacology.* 2009;49:196-204.
11. Lee S, Kim BH, Nam WS, et al. Effect of CYP2C19 polymorphism on the pharmacokinetics of voriconazole after single and multiple doses in healthy volunteers. *Journal of clinical pharmacology.* 2012;52:195-203.
12. Hassan A, Burhenne J, Riedel KD, et al. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. *Therapeutic drug monitoring.* 2011;33:86-93.
13. Wang G, Lei HP, Li Z, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *European journal of clinical pharmacology.* 2009;65:281-5.
14. Shi HY, Yan J, Zhu WH, et al. Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. *European journal of clinical pharmacology.* 2010;66:1131-6.
15. Mikus G, Schöwel V, Drzewinska M, et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clinical pharmacology and therapeutics.* 2006;80:126-35.
16. Kim SH, Yim DS, Choi SM, et al. Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases.* 2011;15:e753-8.

17. Levin MD, den Hollander JG, van der Holt B, et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. *The Journal of antimicrobial chemotherapy.* 2007;60:1104-7.
18. Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2010;16:927-33.
19. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2002;34:563-71.
20. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. *Antimicrobial agents and chemotherapy.* 2006;50:1570-2.
21. Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2008;46:201-11.
22. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *Journal of clinical pharmacology.* 2006;46:235-43.
23. Matsumoto K, Ikawa K, Abematsu K, et al. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. *International journal of antimicrobial agents.* 2009;34:91-4.
24. Racil Z, Winterova J, Kouba M, et al. Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience. *Mycoses.* 2012;55:483-92.
25. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clinical pharmacology and therapeutics.* 2011;89:662-73.
26. Desta Z, Zhao X, Shin JG, Flockhart DA. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. *Clinical pharmacokinetics.* 2002;41:913-58.
27. P450 Drug Interaction Table. Indiana University School of Medicine Division of Clinical Pharmacology web site. http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Updated January 2012. Accessed June 25, 2012.

Warfarin

(DC:TB-0230.002 31JUL2013)

Report Type: Pharmacogenetics

About: Warfarin is the most frequently used oral anticoagulant worldwide, prescribed for prophylaxis and treatment of thrombotic disorders and thromboembolic events. Such indications include venous thrombosis, pulmonary embolism, atrial fibrillation and cardiac valve replacement. Warfarin is highly efficacious, but its narrow therapeutic index and large interindividual dosing variability lead to a high incidence of adverse events. Improper warfarin dosing is the second leading cause of drug-related emergency room visitation[1] and the number one cited reason for drug-related mortality.[2]

Warfarin acts as an anticoagulant through its ability to inhibit reduction of vitamin K by the vitamin K epoxide reductase complex subunit 1 (VKORC1) enzyme complex. Reduced vitamin K is an essential cofactor of gamma-glutamyl carboxylase, the enzyme that activates coagulation factors II, VII, IX and X. By decreasing the amount of reduced vitamin K available, warfarin depresses the activation of factors II, VII, IX and X into functional, coagulant proteins, and, therefore, decreases the ability of blood to clot. The primary metabolizing enzyme of warfarin is cytochrome P450 2C9 (CYP2C9).[3]

In 2010, the United States Food and Drug Administration (FDA) released a table of dosing recommendations for initiation of warfarin therapy based on VKORC1 and CYP2C9 genotypes. This pharmacogenetics-based dosing table significantly improved accuracy of therapeutic dose prediction compared to the traditional strategy of empirically determined dose.[4]

Genetics: The A allele of the -1639G>A mutation in the VKORC1 gene has been shown to decrease hepatic expression of VKORC1 and, therefore, increase patient sensitivity to warfarin.[5,6,7] Research studies have shown that the therapeutic dose of warfarin in patients with two copies of the A allele was less than the dose of patients with two copies of the G allele, with a difference up to 2.0 to 4.5-fold.[7,8,9]

Individuals carrying *2 or *3 genetic variants of CYP2C9 clear warfarin at a 30% to 50% or 80% to 90% slower rate, respectively, and exhibit increased serum levels of warfarin compared to carriers of only the reference wild-type variant *1.[10,11] CYP2C9*2 and CYP2C9*3 variants may decrease the dose required for effective anticoagulation and may increase the time necessary to achieve stable, therapeutic effect.[9,12] The CYP2C9*6 variant may also reduce metabolic activity and the dose required for effective anticoagulation.[11,13]

Customizing initial warfarin dose to VKORC1 and CYP2C9 genotypes may decrease patient risk of bleeding complications and may reduce the time required to achieve a stable, therapeutic effect.[12,14,15]

Recommendations: The FDA-approved label for warfarin recommends initial dosing based on VKORC1 and CYP2C9 genotypes in addition to clinical factors.[16] The National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium guidelines recommend initial dosing based on VKORC1 and CYP2C9 genotypes.[11]

Standard doses of warfarin may cause bleeding complications in patients whose genotypes indicate increased or substantially increased sensitivity to warfarin. These patients may require lower initial doses of warfarin. Increased laboratory monitoring may be appropriate.

Classes of drugs that potentially interact with warfarin include the following:[16] inhibitors or inducers of CYP2C9, CYP1A2 and/or CYP3A4, anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory agents, serotonin reuptake inhibitors, antibiotics, antifungals, and botanical (herbal) products and foods. This list is not complete. Consult the warfarin drug label[16] and the labels of all concurrently used drugs for more specifics about warfarin drug interactions.

Possible Outcomes: Substantially Increased Sensitivity, Increased Sensitivity, Typical Sensitivity

Markers or Alleles Tested: VKORC1 -1639G>A [rs9923231]; CYP2C9 [CYP2C9*2/rs1799853, CYP2C9*3/rs1057910, CYP2C9*6/rs9332131]

Ethnic Distribution of Tested Alleles

Frequency of VKORC1 and CYP2C9 alleles differs significantly between racial and ethnic groups.[17]

Gene	Allele	Caucasian	African American	Asian	Hispanic
VKORC1	-1639: G	59.4%	89.2%	33.3%	56.4%
VKORC1	-1639: A	40.6%	10.8%	66.7%	43.6%
CYP2C9	*1	78.8%	86.7%	92.2%	82.2%
CYP2C9	*2	15.1%	2.8%	2.9%	6.9%
CYP2C9	*3	5.7%	2.0%	3.9%	6.4%
CYP2C9	*6	0.0%	1.0%	0.0%	0.5%

Predicted Warfarin Sensitivity Status

	VKORC1 -1639G>A genotype		
CYP2C9 genotype (below)	G/G	G/A	A/A
*1/*1	Typical sensitivity	Typical sensitivity	Increased sensitivity
*1/*2	Typical sensitivity	Increased sensitivity	Increased sensitivity
*1/*3	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*1/*6	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*2	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*3	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*2/*6	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*3	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*6/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity

Limitations and Warnings: Warfarin can cause major or fatal bleeding. Additional genetic variants within VKORC1, CYP2C9, and other genes not included in this test are known to affect warfarin sensitivity. Not all genetic factors influencing warfarin sensitivity have been identified. Regular monitoring of INR (international normalized ratio) should be performed on all treated patients.

Not all factors influencing warfarin response are known. Important non-genetic factors include age, sex, weight, height, race, ethnicity, comorbidities, warfarin indication, target INR, and use of tobacco and interacting medications.[11]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E934.2 Anticoagulants causing adverse effects in therapeutic use	N/A

References

1. Budnitz DS, Pollock DA, Weidenbach KN, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA.* 2006;296:1858-66.
2. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Archives of internal medicine.* 2007;167:1414-9.
3. Pereira NL, Weinshilboum RM. Cardiovascular pharmacogenomics and individualized drug therapy. *Nature reviews. Cardiology.* 2009;6:632-8.
4. Finkelman BS, Gage BF, Johnson JA, Brensinger CM, Kimmel SE. Genetic warfarin dosing: tables versus algorithms. *Journal of the American College of Cardiology.* 2011;57:612-8.
5. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clinical pharmacology and therapeutics.* 2008;84:326-31.
6. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *The New England journal of medicine.* 2005;352:2285-93.
7. Yuan HY, Chen JJ, Lee MT, et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. *Human molecular genetics.* 2005;14:1745-51.
8. Zhu Y, Shennan M, Reynolds KK, et al. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. *Clinical chemistry.* 2007;53:1199-205.
9. Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood.* 2005;106:2329-33.
10. Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics.* 2002;12:251-63.
11. Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clinical pharmacology and therapeutics.* 2011;90:625-9.
12. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. *Genetics in medicine : official journal of the American College of Medical Genetics.* 2005;7:97-104.
13. Cavallari LH, Langaee TY, Momary KM, et al. Genetic and clinical predictors of warfarin dose requirements in African Americans. *Clinical pharmacology and therapeutics.* 2010;87:459-64.
14. Gage BF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *Journal of thrombosis and thrombolysis.* 2008;25:45-51.
15. Limdi NA, McGwin G, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 1173C/T genotype on the risk of hemorrhagic complications in African-American and European-American patients on warfarin. *Clinical pharmacology and therapeutics.* 2008;83:312-21.
16. Warfarin [package insert]. American Health Packaging, Columbus, OH; July 2012. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ab047628-67d0-4a64-8d77-36b054969b44. Accessed November 6, 2012.

17. Scott SA, Khasawneh R, Peter I, Kornreich R, Desnick RJ. Combined CYP2C9, VKORC1 and CYP4F2 frequencies among racial and ethnic groups. *Pharmacogenomics.* 2010;11:781-91.