

Clinical Appropriateness Guidelines

Pharmacogenetic Testing and Genetic Testing for Thrombotic Disorders

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8600 West Bryn Mawr Avenue
South Tower - Suite 800 Chicago, IL 60631
www.aimspecialtyhealth.com

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Scope

This document addresses genetic testing for the purpose of informing medication selection, dosage, and risk of adverse side effects. It also addresses genetic testing to predict risk of thrombosis. All tests listed in these guidelines may not require prior authorization; please refer to the health plan.

Appropriate Use Criteria

Pharmacogenetic Testing

Pharmacogenetic testing of common variants associated with drug metabolism is medically necessary when either of the following criteria is met:

- All of the following:
 - The individual is a candidate for a targeted drug therapy associated with a specific genotype
 - The results of the pharmacogenetic test will directly impact clinical decision-making and clinical outcome for the individual
 - Published, peer-reviewed studies have proven that identifying the specific genetic variant improves clinical outcomes
- Identification of the genetic variant is required prior to initiating therapy with the target drug as noted by the U.S. Food and Drug Administration (FDA)-approved prescribing label

Multi-gene pharmacogenetic genotyping assays in which each included target does not meet the above criteria are not medically necessary.

Thrombophilia Testing

Testing for common variants in Factor V Leiden (F5) and prothrombin (F2) is medically necessary for any of the following indications:

- Pregnant woman who has a personal history of an unprovoked venous thromboembolism (VTE) (e.g. not associated with fracture, surgery, prolonged immobilization, cancer)
- In an individual with an unprovoked VTE when test results will impact long term medication management and at least one of the following:
 - There is concern for homozygous F2 or F5 or compound heterozygous F2/F5
 - The annual risk of recurrent VTE is estimated to be between 5% and 10%
- Individual who has a first-degree relative with F5 or F2 thrombophilia and one of the following:
 - Surgery is planned

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- The patient is pregnant
- Females considering estrogen contraception or hormone replacement therapy if results would influence decision to use estrogen

The following tests are not medically necessary:

- MTHFR

CPT Codes

The following codes are associated with the guidelines in the document. This list is not all inclusive.

Covered when medical necessity criteria are met:

- 81225 CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
- 81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- 81240 F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
- 81241 F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
- 81335 TPMT (thiopurine S-methyltransferase) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3)
- 0034U TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(eg, thiopurine metabolism), gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
- 0070U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)

Codes that do not meet medical necessity criteria:

- 81227 CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (e.g, *2, *3, *5, *6)
- 81230 CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)

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- 81231 CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
- 81291 MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
- 81328 SLC01B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction), gene analysis, common variant(s) (eg, *5)
- 81346 TYMS (thymidylate synthetase) (eg, 5-fluorouracil/5-FU drug metabolism), gene analysis, common variant(s) (eg, tandem repeat variant)
- 81350 UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
- 81355 VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
- 0029U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLC01B1, VKORC1 and rs12777823)
- 0030U Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823)
- 0031U CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7)
- 0032U COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
- 0033U HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (eg, citalopram metabolism) gene analysis, common variants (ie, HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.- 759C>T] and rs1414334 [c.551-3008C>G])
- 0071U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure) (Use 0071U in conjunction with 0070U)
- 0072U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure) (Use 0072U in conjunction with 0070U)
- 0073U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure) (Use 0073U in conjunction with 0070U)
- 0074U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when

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duplication/multiplication is trans) (List separately in addition to code for primary procedure) (Use 0074U in conjunction with 0070U)

- 0075U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure) (Use 0075U in conjunction with 0070U)
- 0076U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure) (Use 0076U in conjunction with 0070U)
- 0078U Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder

Background

Pharmacogenetic Testing

Pharmacogenomic testing describes the genotyping of specific genes to predict response to certain medications. Pharmacogenomic testing has most recently been utilized as a tool in the emerging field of personalized medicine. Personalized medicine can be described as a prospective and comprehensive approach to prevention, diagnosis, and treatment of disease to achieve optimal individual healthcare decisions (Lesko 2007). As this approach to clinical practice is growing, so is the availability of pharmacogenomic testing in the clinical realm.

The CYP450 gene superfamily is composed of many isoenzymes that are involved in the metabolism of about 75% of commonly prescribed drugs. Many of the clinically available pharmacogenomic tests include genes related to the CYP450 superfamily: CYP2C19, CYP2D6 and CYP2C9 enzymes metabolize approximately 15%, 20-25%, and 10% of all currently used drugs, respectively. These medications are most often prescribed as treatments for oncologic, psychiatric, neurologic, or cardiovascular conditions (Drozda et al. 2014). However, genetic variability accounts for only a portion of the individual differences in drug response, rendering the clinical utility of this testing uncertain in many scenarios.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenetic Working Group (PWG) have established guidelines to assist clinicians in guiding drug therapy and dosage based on existing pharmacogenetic results. However, neither of these groups have guidelines outlining when genetic testing for medication management should be implemented, but rather only guide clinicians when genetic results are available. With the exception of a limited number of FDA labels requiring genotyping prior to dosing, there is limited evidence to guide the use of pharmacogenetic testing in clinical practice.

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While targeted gene testing for polymorphisms in some genes have been proposed to predict patient-specific drug metabolism of specific drugs, the clinical utility of panel testing for multiple genes is unproven. Although the importance of choosing and dosing the appropriate medication is recognized, there are many variables in the pharmacokinetics and pharmacodynamics of medications. To date, there is a lack of large, controlled studies that address whether the use of pharmacogenomic panels in prescribing medications improves outcomes (Drozda et al. 2014).

Thrombophilia Testing

Thrombophilia describes a state of hypercoagulability that leads to an increased risk of thrombotic events. Venous thromboembolism (VTE) is a common, complex disease associated with both environmental and genetic risk factors. Risk factors for VTE include advancing age, travel, surgery, organ transplantation, central venous catheter use, injury, family history of VTE, and certain genetic polymorphisms leading to excessive clotting. In women, pregnancy, hormonal contraceptive use, selective estrogen receptor modulators (SERMs), and hormone replacement therapy (HRT) are additional risk factors for VTE.

It has been suggested that genetic testing for inherited thrombophilias may allow for prophylactic treatment of individuals at risk for VTE or enhance the prediction of recurrence risk for patients who have already had a VTE. However, the clinical utility of such genetic testing is controversial. An increased risk for VTE has been associated with mutations in several genes including; F5, F2, PROC, PROS1 and SERPINC1 as well as others.

While standard of care for work up of VTE or DVT is to perform protein activity and antigen studies, Factor V and Prothrombin studies are easiest to perform as molecular genotyping given that these conditions are almost always caused by a common variant. There have been conflicting recommendations as to how to approach genetic testing for thrombophilias. ACMG and ACOG have recommended testing for F2 and F5 in certain scenarios, while the Evaluation of Genomic Applications and Prevention Working Group (EGAPP) found insufficient evidence to perform this testing for any indication. The population for which F2/F5 genetic testing results have direct implications for treatment is pregnant women with a previous history of VTE associated with a transient risk factor (e.g., surgery, trauma). These women would typically not be treated with antepartum anticoagulant prophylaxis unless they were found to have a genotype associated with a high risk of VTE recurrence (FVL homozygosity, F2 G20210A homozygosity, or compound heterozygosity for FVL and F2 G20210A). Genetic testing for these patients is indicated. There may also be benefit to screening pregnant women with a family history of known thrombophilia, as those women found to have a high risk genotype would be offered antenatal prophylactic anticoagulant therapy even in the absence of a personal history of VTE.

Because standard of care for evaluation of thrombophilias includes protein assays for common anticoagulants and single-site mutation studies, large NGS panels are not considered medically necessary.

Factor V Leiden

The Factor V Leiden (FVL) variant (1691G>A; R506Q) in the F5 gene is the most common known inherited risk factor for thrombosis. This mutation leads to reduced inactivation of clotting factor V by activated protein C (ie. APC resistance), which causes increased thrombin generation. Heterozygous carriers of the FVL mutation have an approximately 3-fold to 8-fold increased risk of VTE compared to non-carriers. However, the absolute risk of VTE in heterozygotes remains low, with only ~5% of carriers

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developing a VTE by age 65 (Rodeghiero and Tosetto 1999; Heit et al. 2005). Homozygous carriers of the FVL mutation have a much higher increased risk of VTE, approximately 9-fold to 80-fold (Rosendaal 2009, EGAPP 2011). This increased risk corresponds to an absolute incidence of 15 VTE events/1,000 persons/year (Juul et al. 2004).

The prevalence of FVL mutations varies according to population. Approximately 3-8% of the general US and European population carry a heterozygous FVL mutation, while the mutation is rarely identified in individuals from Asian and African populations. Homozygosity of the FVL mutations is seen in approximately 1/5000 individuals in the general US and European population.

Prothrombin (F2)

The second most common inherited risk factor for VTE is the 20210G>A (G20210A) variant in the F2 gene. This activating mutation leads to higher circulating levels of prothrombin, which results in an increased risk for clot formation. Heterozygous carriers of the F2 mutation have a 2-fold to 4-fold increased risk of VTE compared to non-carriers (Rosendaal and Reitsma 2009). Again, however, the absolute risk of a VTE in heterozygotes remains quite low: 0.19%/year to 0.41%/year in asymptomatic carriers (Lijfering et al. 2009).

The prevalence of F2 heterozygosity varies by population. Approximately 2-3% of the general US and European population are carriers of the F2 variant, while individuals from African and Asian populations have a much lower prevalence. F2 homozygotes are very rare, approximately 1/10,000 in the general US and European population, and the increased risk associated with this genotype is not well-defined.

Professional Society Guidelines

American College of Obstetricians and Gynecologists. Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. *Obstet Gynecol.* 2018 Jul;132(1):e18-e34. PubMed PMID: 29939939.

Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012 Feb;141(2 Suppl):e691S-e736S. PubMed PMID: 22315276.

Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther.* 2017 Aug;102(2):213-18. Epub 2017 Apr 6. PubMed PMID: 28002639.

Caudle KE, Thorn CF, Klein TE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clinical Pharmacology and Therapeutics.* 2013;94(6):640-645. Epub 2013 Aug 29. PubMed PMID: 23988873.

Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014 Apr; 95(4):376-82. Epub 2014 Jan 23. PubMed PMID: 24458010.

Dean L. Warfarin therapy and the genotypes CYP2C9 and VKORC1. 2012 Mar 8 [Updated 2016 Jun 8]. In: Pratt V, McLeod H, Dean L, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK84174/>

Duhl AJ, Paidas MJ, Ural SH, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. *Am J Obstet Gynecol.* 2007;197:457. PubMed PMID: 17980177.

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. *Genet Med.* 2007 Dec;9(12):819-25. PubMed PMID: 18091431.

Flockhart DA, O'Kane D, Williams MS, et al. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med.* 2008 Feb;10(2):139-50. PubMed PMID: 18281922.

Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. *Clin Pharmacol Ther.* 2018 May;103(5):770-777. PubMed PMID: 29385237.

Grody WW, Griffin JH, Taylor AK, et al. American College of Medical Genetics consensus statement on Factor V Leiden mutation testing. *Genet Med.* 2001 Mar-Apr;3(2):139-48. PubMed PMID: 11280951.

Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015 Aug;98(2):127-34. Epub 2015 Jun 29. PubMed PMID: 25974703.

Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther.* 2017 Jul 102(1):37-44. Epub 2017 Feb 13. PubMed PMID: 27997040.

Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 Update. *Clin Pharmacol Ther.* 2017 Sep;102(3):397-404. Epub 2017 Apr 4. PubMed PMID: 28198005.

Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: chest guideline and expert panel report. *Chest.* 2016;149(2):315-52. Epub 2016 Jan 7. PubMed PMID: 26867832.

Kujovich JL. Factor V Leiden Thrombophilia. 1999 May 14 [Updated 2018 Jan 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1368/>

Kujovich JL. Prothrombin-Related Thrombophilia. 2006 Jul 25 [Updated 2014 Aug 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1148/>

National Comprehensive Cancer Network®. (NCCN®) Clinical Practice Guidelines in Oncology, Breast Cancer. (v.1.2018). Accessed at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

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Practice Committee of the American Society for Reproductive Medicine. Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. *Fertil Steril*. 2017 Jan;107(1):43-51. Epub 2016 Oct 25. PubMed PMID: 27793376.

Pratt VM, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Scott SA, Weck KE. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J Mol Diagn* 2018. May;20(3):269-276. Epub 2018 Feb 21. PubMed PMID: 29474986.

Relling M, Gardner E, Sandborn W, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clinical Pharmacology and Therapeutics*. 2011 Mar;89(3):387-391. Epub 2011 Jan 26. PubMed PMID: 21270794.

Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 Update. *Clin Pharmacol Ther*. 2013 Sep;94(3):317-23. Epub 2013 May 22. PubMed PMID: 23698643.

Vassy JL, Stone A, Callaghan JT, et al.; VHA Clinical Pharmacogenetics Subcommittee. Pharmacogenetic testing in the Veterans Health Administration (VHA): policy recommendations from the VHA Clinical Pharmacogenetics Subcommittee. *Genet Med*. 2018 Jun 1. [Epub ahead of print]. PubMed PMID: 29858578.

Selected References

Pharmacogenetics

- 1 Aka I, Bernal CJ, Carroll R, et al. Clinical Pharmacogenetics of Cytochrome P450-Associated Drugs in Children. *J Pers Med*. 2017 Nov 2;7(4). PubMed PMID: 29099060.
- 2 Beckett RD, Kisor DF, Smith T, Vonada B. Systematic evaluation of clinical practice guidelines for pharmacogenomics. *Pharmacogenomics*. 2018 Jun 1;19(8):693-700. Epub 2018 May 23. PubMed PMID: 29790417.
- 3 Bernstein E and Levy A. Recent developments and future directions for the use of pharmacogenomics in cardiovascular disease treatments. *Expert Opin Drug Metab Toxicol*. 2017 Sep;13(9):973-983. Epub 2017 Aug 20. PubMed PMID: 28792790.
- 4 Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J*. 2018 Sep;18(5):613-622. Epub 2018 May 25. PubMed PMID: 29795409.
- 5 Bousman CA, Reynolds CF, Ng C, et al. Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. *BMC psychiatry*. 2017 Dec;17(1):60. PubMed PMID: 28178974.
- 6 Brandl EJ, Tiwari AK, Zhou X, et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessive-compulsive disorder. *Pharmacogenomics J*. 2014 Apr;14(2):176-81. Epub 2013 Apr 2. PubMed PMID: 23545896.
- 7 Campbell JM, Bateman E, Peters MDj, et al. Fluoropyrimidine and platinum toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Pharmacogenomics*. 2016 Mar;17(4):435-51. Epub 2016 Feb 19. PubMed PMID: 26894782.
- 8 Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab*. 2014 Feb;15(2):209-17. PubMed PMID: 24479687.
- 9 Chin L, Devine B, Baradaran S, et al. Characterizing the strength of evidence in FDA labels for pharmacogenomic biomarker-guided medication use. *AMIA Jt Summits Transl Sci Proc*. 2017 Jul 26;2017:30-39. PubMed PMID: 28815101.
- 10 Dean L. Warfarin Therapy and VKORC1 and CYP Genotype. 2012 Mar 8 [Updated 2018 Jun 11]. In: Pratt V, McLeod H, Rubinstein W, et al., editors. *Medical Genetics Summaries* [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-. Available from: <https://www.ncbi.nlm.nih.gov.proxy.lib.mcu.edu/books/NBK84174/>
- 11 Dong AN, Tan BH, Pan Y, Ong CE. Cytochrome P450 genotype-guided drug therapies: An update on current states. *Clin Exp Pharmacol Physiol*. 2018 Oct;45(10):991-1001. Epub 2018 Jul 2. PubMed PMID: 29858511.
- 12 Drozda K, Müller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. *Pharmacotherapy*. 2014 Feb;34(2):166-84. PubMed PMID: 24523097.

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- 13 Gage BF, Bass AR, Lin H, et al. Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial. *JAMA*. 2017 Sep 26;318(12):1115-1124. PubMed PMID: 28973620.
- 14 Gong L, Thorn CF, Bertagnolli MM, et al. Celecoxib pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics*. 2012 Apr;22(4):310-8. PubMed PMID: 22336956.
- 15 Ji Y, Skierka JM, Blommel JH, et al. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. *J Mol Diagn*. 2016 May;18(3):438-45. Epub 2016 Mar 3. PubMed PMID: 26947514.
- 16 Jürgens G, Rasmussen HB, Werge T, et al. Does the medication pattern reflect the CYP2D6 genotype in patients with diagnoses within the schizophrenic spectrum? *J Clin Psychopharmacol*. 2012 Feb;32(1):100-5. PubMed PMID: 22198443.
- 17 Landau R, Smiley R. Pharmacogenetics in obstetric anesthesia. *Best Pract Res Clin Anaesthesiol*. 2017 Mar;31(1):23-34. Epub 2017 Feb 6. PubMed PMID: 28625302.
- 18 Lesko LJ. Personalized medicine: elusive dream or imminent reality? *Clin Pharmacol Ther*. 2007 Jun;81(6):807-16. PubMed PMID: 17505496.
- 19 Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005 Sep 22;353(12):1209-23. Epub 2005 Sep 19. PubMed PMID: 16172203.
- 20 Matchar DB, Thakur ME, Grossman I, et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). *Evid Rep Technol Assess (Full Rep)*. 2007 Jan;(146):1-77. PubMed PMID: 17764209.
- 21 Murphy GM Jr, Hollander SB, Rodrigues HE. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry*. 2004 Nov;61(11):1163-9. PubMed PMID: 15520364.
- 22 Murphy GM Jr, Kremer C, Rodrigues HE, et al. Pharmacogenetics of antidepressant medication intolerance. *Am J Psychiatry* 2003 Oct;160(10):1830-35. PubMed PMID: 14514498.
- 23 Niitsu T, Fabbri C, Bentini F, et al. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013 Aug 1;45:183-94. Epub 2013 Jun 1. PubMed PMID: 23733030.
- 24 Offer SM, Fossum CC, Wegner NJ, et al. Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. *Cancer Res*. 2014 May 1;74(9):2545-54. Epub 2014 Mar 19. PubMed PMID: 2468345.
- 25 Perez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC psychiatry*. 2017; 17(1), 250. PubMed PMID: 28705252.
- 26 Peterson K, Dieperink E, Anderson J, et al. Rapid evidence review of the comparative effectiveness, harms, and cost-effectiveness of pharmacogenomics-guided antidepressant treatment versus usual care for major depressive disorder. *Psychopharmacology*. 2017 Jun;234(11):1649-1661. Epub 2017 Apr 29. PubMed PMID: 28456840.
- 27 Poland RE, Lesser IM, Wan YJ, et al. Response to citalopram is not associated with SLC6A4 genotype in African-Americans and Caucasians with major depression. *Life Sci*. 2013 May 30;92(20-21):967-70. Epub 2013 Apr 3. PubMed PMID: 23562852.
- 28 Reynolds GP, Zhang ZJ, Zhang XB. Polymorphism of the promoter region of the serotonin 5-HT2C receptor gene and clozapine-induced weight gain. *Am J Psychiatry* 2003 Apr;160(4):677-9. PubMed PMID: 12668355.
- 29 Rosenblat JD, Lee Y, McIntyre RS. Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. *J Clin Psychiatry*. 2017 Jun;78(6):720-729. PubMed PMID: 28068459.
- 30 Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther*. 2013 Jun; 17(3):165-184. PubMed PMID: 23588782.
- 31 Samwald M, Xu H, Blagec K, et al. Incidence of exposure of patients in the United States to multiple drugs for which pharmacogenomic guidelines are available. *PLoS One*. 2016 Oct 20;11(10):e0164972. PubMed PMID: 27764192.
- 32 Serretti A, Calati R, Massat I, et al. Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes are not associated with response and remission in a sample of depressive patients. *Int Clin Psychopharmacol*. 2009;24(5):250-6. PubMed PMID: 19593158.
- 33 Smits KM, Smits LJ, Schouten JS, et al. Influence of SERTPR and STin2 in the serotonin transporter gene on the effect of selective serotonin reuptake inhibitors in depression: a systematic review. *Mol Psychiatry*. 2004 May;9(5):433-41. PubMed PMID: 15037864.
- 34 Somogyi AA, Coller JK, Barratt DT. Pharmacogenetics of opioid response. *Clin Pharmacol Ther*. 2015 Feb;97(2):125-7. Epub 2014 Dec 9. PubMed PMID: 25670515.
- 35 Syn NL, Wong AL-A, Lee S-C, et al. Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial. *BMC Medicine*. 2018;16:104. PubMed PMID: 29986700.
- 36 Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? *Pharmacogenomics J*. 2017 Oct;17(5):395-402. Epub 2017 Jun 13. PubMed PMID: 28607506.
- 37 Wang B, Canestaro WJ, Choudhry NK. Clinical evidence supporting pharmacogenomic biomarker testing provided in US Food and Drug Administration drug labels. *JAMA Intern Med*. 2014 Dec;174(12):1938-44. PubMed PMID: 25317785.
- 38 Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012 Oct;92(4):414-7. PubMed PMID: 22992668.
- 39 Yu YW, Tsai SJ, Chen TJ, et al. Association study of the serotonin transporter promoter polymorphism and symptomatology and antidepressant response in major depressive disorders. *Mol Psychiatry*. 2002;7(10):1115-9. PubMed PMID: 12476327.
- 40 Zhao XQ, Cao WJ, Yang HP, et al. DPYD gene polymorphisms are associated with risk and chemotherapy prognosis in pediatric patients with acute lymphoblastic leukemia. *Tumour Biol*. 2016 Aug;37(8):10393-402. Epub 2016 Feb 4. PubMed PMID: 26846104.

Thrombophilias

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- 1 Bushnell C, McCullough LD, Awad IA, et al. American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council for High Blood Pressure Research Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 May;45(5):1545-88. Epub 2014 Feb 6. PubMed PMID: 24503673.
- 2 Croles FN, Nasserinejad K, Duvekot JJ, et al. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ*. 2017 Oct 26; 359:j4452. Epub 2017 Oct 26. PubMed PMID: 29074563.
- 3 Gupta A, Sarode R, Nagalla S. Thrombophilia testing in provoked venous thromboembolism: a teachable moment. *JAMA Intern Med*. 2017 Aug;177(8):1195-6. PubMed PMID: 28586816.
- 4 Heit JA, Sobell JL, Li H, et al. The incidence of venous thromboembolism among Factor V Leiden carriers: a community-based cohort study. *J Thromb Haemost* 2005;3:305-11. PubMed PMID: 15670037.
- 5 Juul K, Tybjaerg-Hansen A, Schnohr P, Nordestgaard BG. Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. *Ann Intern Med*. 2004 Mar 2;140(5):330-7. PubMed PMID: 14996674.
- 6 Li X, Liu Y, Zhang R, et al. Meta-analysis of the association between plasminogen activator inhibitor-1 4G/5G polymorphism and recurrent pregnancy loss. *Med Sci Monit*. 2015 Apr 11;21:1051-6. PubMed PMID: 25862335.
- 7 Lijfering WM, Brouwer JL, Veeger NJ, et al. Selective testing for thrombophilia in patients with first venous thrombosis: results from a retrospective family cohort study on absolute thrombotic risk for currently known thrombophilic defects in 2479 relatives. *Blood*. 2009;113:5314-22. Epub 2009 Jan 12. PubMed PMID: 19139080.
- 8 MacCallum P, Bowles L, Keeling D. Diagnosis and management of heritable thrombophilias. *BMJ*. 2014 Jul 17;349. PubMed PMID: 25035247.
- 9 Montagnana M, Lippi G, Danese E. An overview of thrombophilia and associated laboratory testing. *Methods Mol Biol*. 2017; 1646:113-35. PubMed PMID: 28804823.
- 10 Pruthi RK. Optimal utilization of thrombophilia testing. *Int J Lab Hematol*. 2017 May;39 Suppl 1:104-110. PubMed PMID: 28447412.
- 11 Rodeghiero F, Tosi A. Activated protein C resistance and factor V Leiden mutation are independent risk factors for venous thromboembolism. *Ann Intern Med* 1999;130:643-50. PubMed PMID: 10215560.
- 12 Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. *J Thromb Haemost*. 2009 Jul;7 Suppl 1:301-4. PubMed PMID: 19630821.
- 13 Rühle F, Stoll M. Advances in predicting venous thromboembolism risk in children. *Br J Haematol*. 2018 Mar;180(5):654-665. Epub 2017 Dec 19. PubMed PMID: 29265336.
- 14 Said JM, Tsui R, Borg AJ, et al. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women. *J Thromb Haemost*. 2012 May;10(5):881-6. PubMed PMID: 2243640.
- 15 Stevens SM, Woller SC, Bauer KA, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis*. 2016 Jan;41(1):154-64. PubMed PMID: 26780744.
- 16 van Ommen CH, Nowak-Göttl U. Inherited Thrombophilia in Pediatric Venous Thromboembolic Disease: Why and Who to Test. *Front Pediatr*. 2017 Mar 14;5:50. PubMed PMID: 28352625.
- 17 Wu O, Robertson L, Twaddle S, et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health Technol Assess*. 2006 Apr;10(11):1-110. PubMed PMID: 16595080.

Revision History

Medical Advisory Board Review:

v1.2019 11/07/2018: Reviewed

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v1.2019 10/03/2018: Approved

v1.2018 02/28/2018: Approved

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Revisions:

Version	Date	Editor	Description
v1.2019	10/03/2018	Kate Charyk, MS, CGC	Semi-annual review. Professional society guidelines and references updated. Renumbered to 2019. Reformatted CPT code list. PMID added.
v1.2018	03/31/2018	Heather Dorsey, MS, CGC	Semi-annual review. Expanded F2/F5 criteria to allow additional management changes for unprovoked VTE and estrogen changes with significant family history. Disclaimer sentence added to scope. Professional society guidelines and references updated. Renumbered to 2018.
v1.2017	11/1/2017	Gwen Fraley, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	09/15/2017	Megan Czarniecki, MS, CGC	Formatted references to NLM style. Moved methodological considerations to appropriate use criteria and background. Updated associated CPT codes. Approved by Policy Lead.
v1.2017	07/03/2017	Heather Dorsey, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	04/18/2017	Megan Czarniecki, MS, CGC	Quarterly review. No criteria changes. Updated references.
v1.2017	01/23/2017	Cheryl Thomas, MS, CGC	Quarterly review. No criteria changes. Updated references. Renumbered for 2017.
v1.2016	10/05/2016	Gwen Fraley, MS, CGC	Combined Thrombophilias and Pharmacogenetic testing into same guidelines. Updated references.
v1.2015	10/08/2015	Marie Schuetzle, MS, CGC	Original version

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Primary Author: Marie Schuetzle, MS, CGC

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