

Clinical Appropriateness Guidelines

Pharmacogenetic Testing and Genetic Testing for Thrombotic Disorders

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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 this guideline 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 that do 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
 - The patient is pregnant

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

The following tests are experimental, investigational, or unproven:

- MTHFR

CPT Codes

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

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, common variants (e.g., *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant

Background

Pharmacogenetic Testing

Pharmacogenomics testing describes the genotyping of specific genes to predict response to certain medications. Pharmacogenomics 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 health care 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

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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 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.

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 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

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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 developing a VTE by age 65 (Rodeghiero 1999, Heit 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/1000 persons/year (Juul 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 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 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

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Revision History

Medical Advisory Board Review:

v1.2018 03/31/2018: Reviewed

Clinical Steering Committee Review:

v1.2018 02/28/2018: Approved

v1.2017 01/25/2017: Approved

Revisions:

Version	Date	Editor	Description
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.

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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 guideline. Updated references.
v1.2015	10/08/2015	Marie Schuetzle, MS, CGC	Original version

Original Effective Date: 10/08/2015

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