

Overview

Useful For

Ascertaining a pathogenic alteration in the *PROCR* gene in patients with recurrent unprovoked venous thromboembolism (VTE) before the age of 40, a strong family history of unexplained and unprovoked VTE, and prior genetic testing for more common genetic variants associated with thrombophilia that does not correlate with the severity of the patient's thrombophilia or clinical presentation

This test is **not intended for** prenatal diagnosis

Genetics Test Information

This test detects alterations in the *PROCR* gene associated with increased risk for venous thromboembolism.

The gene target for this test is:

Gene name (transcript): *PROCR* (GRCh37 [hg19] NM_006404)

Chromosomal location: 20q11.22

Testing Algorithm

No screening tests exist for defects in *PROCR*. A set of clinical guidelines from the British Society for Haematology on testing for heritable thrombophilia is freely available.(1) A genetic consultation is strongly recommended prior to ordering *PROCR* sequencing.

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)
- [Rare Coagulation Disorder Patient Information](#)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS) Followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing When Appropriate

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Indiscriminate testing for alterations in *PROCR* or other genes related to coagulation in unselected patients presenting with a first episode of venous thrombosis is NOT indicated.(1)

Routine testing of *PROCR* for genetic risk factors for thromboembolism is not recommended and may be of limited use in most cases.

Shipping Instructions

Ambient and refrigerated specimens **must** arrive within 7 days (168 hours of draw), and frozen specimens must arrive within 14 days (336 hours of draw).

Collect and package specimen as close to shipping time as possible.

Necessary Information

[Rare Coagulation Disorder Patient Information](#) is required, see Special Instructions. Testing may proceed without the patient information, however, the information aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to fill out the form and send with the specimen.

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Peripheral blood

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Yellow top (ACD) or green top (sodium citrate)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Specimen Stability: Ambient (preferred)/Refrigerated/Frozen

Specimen Type: Extracted DNA

Container/Tube: 1.5- to 2-mL tube

Specimen Volume: Entire specimen

Collection Instructions:

1. Label specimen as extracted DNA and source of specimen.
2. Provide indication of volume and concentration of the DNA.

Specimen Stability: Frozen (preferred)/Refrigerated/Ambient

Forms

1. [Rare Coagulation Disorder Patient Information \(T824\)](#) is required, see Special Instructions. Fax the completed form to 507-284-1759.

2. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

[-Informed Consent for Genetic Testing](#) (T576)

[-Informed Consent for Genetic Testing-Spanish](#) (T826)

3. If not ordering electronically, complete, print, and send a [Coagulation Test Request](#) (T753) with the specimen.

Specimen Minimum Volume

Blood: 1 mL

Extracted DNA: 100 mcL at 50 ng/mcL concentration

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)	7 days	
	Frozen	14 days	
	Refrigerated	7 days	

Clinical and Interpretive

Clinical Information

Venous thromboembolism (VTE) can describe: 1) a deep vein thrombosis (DVT), characterized by leg pain or tenderness typically in only one thigh or calf, leg swelling, skin that feels warm to the touch, and reddish discoloration or streaks, or 2) a pulmonary embolism (PE), characterized by unexplained shortness of breath, rapid breathing, chest pain under the rib cage, fast heart rate, and light headedness or passing out.

VTEs affect about an estimated 900,000 individuals in the US per year.(2) While most individuals who experience a VTE do so only once in their life, some individuals may experience recurrent thrombotic episodes or have close relatives who do. The tendency to thrombose, sometimes referred to as thrombophilia or hypercoagulability, is considered a multifactorial disorder with many different factors increasing the risk for abnormal clotting. Thrombophilia is more likely to happen in people who are older, obese or overweight, and have conditions that promote blood coagulation like cancer or lupus. Other causes of acquired (non-genetic) thrombophilia include recent surgery, trauma, fractures, hospital or nursing home confinement, varicose veins, neurological disease with leg paresis, chronic renal disease, oral contraceptive use and hormone therapy, pregnancy and the post-partum period.(2) Less commonly, certain alterations in genes involved in blood coagulation may also increase the risk for thrombosis. A genetic cause for increased VTE may be considered in situations where a VTE occurs before the age of 40, is recurrent, occurs in multiple closely-related family members, and occurs in unusual locations in the body such as the portal, hepatic, mesenteric, or cerebral veins. Å

The *PROCR* gene encodes for endothelial cell protein C receptor (EPCR), a transmembrane protein that plays a crucial role in the negative regulation of blood coagulation by increasing protein C activation five- to 20 fold via the thrombin-thrombomodulin complex.(3) Activated protein C (APC) then down regulates thrombin generation by

inactivating factor VIIIa and factor Va. Rare alterations in the *PROCR* gene may increase the risk of thrombosis, especially in carriers of other prothrombotic alterations, by an unknown amount. As a whole, the *PROCR* gene and alterations in it are not well characterized and thus genetic testing has limited clinical utility. As of January 2019, only 3 missense alterations and a single nucleotide polymorphism (SNP) in the 5'UTR in *PROCR* are reported to be associated with increased risk for venous thromboembolism in the Human Gene Mutation Database (HGMD Professional 2018.4). The prevalence of individuals with pathogenic alterations in the *PROCR* gene in the general population or among individuals with VTE is unknown.

Reference Values

An interpretative report will be provided

Interpretation

An interpretive report will be provided.

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Consultations with the Mayo Clinic Special Coagulation Clinic, Molecular Hematopathology Laboratory or Thrombophilia Center are available for DNA diagnosis cases. This may be especially helpful in complex cases or in situations where the diagnosis is atypical or uncertain.

Cautions

[Clinical:](#)

Some individuals may have a mutation that is not identified by the methods performed. The absence of a mutation, therefore, does not eliminate the possibility of an increased risk of venous thromboembolism. This assay does not distinguish between germline and somatic alterations, particularly with variant allele frequencies (VAF) significantly lower than 50%. Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Technical Limitations:

Next-generation sequencing (NGS) may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false negative or positive results. Therefore test results should be interpreted in the context of activity and antigen measurements, clinical findings, family history, and other laboratory data. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If multiple alterations are identified, NGS is not able to distinguish between alterations that are found in the same allele ("in cis") and alterations found on different alleles ("in trans"). This limitation may complicate diagnosis or classification and has implications for inheritance and genetic counseling. To resolve these cases, molecular results must be correlated with clinical history, activity and antigen measurements, and/or family studies.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants Policy: At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory

encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference

1. Baglin T, Gray E, Greaves M, et al: Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol.* 2010;149(2):209-220
2. Heit, JA: The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol.* 2008;28(3):370-372
3. Stearns-Kurosawa DJ, Kurosawa S, Mollica JS: The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. *Proc Natl Acad Sci USA.* 1996;93(19):10212-6
4. Bouwne EA, Stavenuiter F, Mosnier LO: Mechanisms of anticoagulant and cytoprotective actions of the protein C pathway. *J Thromb Haemost.* 2013;11 Suppl 1:242-253
5. Nayak RC, Sen P, Ghosh S, et al: Endothelial cell protein C receptor cellular localization and trafficking: potential functional implications. *Blood.* 2009;114(9):1974-1986
6. Medina R, Navarro S, Estelles A, et al: Polymorphisms in the endothelial protein C receptor gene and thrombophilia. *Thromb Haemost.* 2007;98(3):564-569
7. Mohan Rao LV, Esmon CT, Pendurthi UR: Endothelial cell protein C receptor: a multiliganded and multifunctional receptor. *Blood.* 2014;124(10):1553-1562
8. Wu C, Dwivedi D, Pepler L, et al: Targeted Gene Sequencing Identifies Variants in the Protein C and Endothelial Protein C Receptor Genes in Patients With Unprovoked Venous Thromboembolism. *Arterioscler Thromb Vasc Biol.* 2013;33(11):2674-2681
9. Gleeson E, O'Connell J, Preston R: The endothelial cell protein C receptor: cell surface conductor of cytoprotective coagulation factor signaling. *Cell Mol Life Sci.* 2012;69(5):717-726

Performance**Method Description**

Next-generation sequencing and/or Sanger sequencing are performed.

Regions of homology, high guanine-cytosine (GC)-rich content, and repetitive sequences may not provide accurate sequence. Therefore, all reported alterations detected by next generation-sequencing in these regions are confirmed by an independent reference method. However, this does not rule out the possibility of a false-negative result in these regions.

Sanger sequencing is used to confirm alterations detected by next-generation sequencing when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Varies

Report Available

21 to 28 days

Specimen Retention Time

Whole Blood: 2 weeks; DNA: Indefinitely

Performing Laboratory Location

Rochester

Fees and Codes
Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81479

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
PRCNG	PROCR Gene, Full Gene NGS	92993-5

Result ID	Test Result Name	Result LOINC Value
113092	PRCNG Result	50397-9
113086	Alterations Detected	82939-0
113085	Interpretation	69047-9
113087	Additional Information	48767-8
113088	Method	85069-3
113089	Disclaimer	62364-5
113090	Panel Gene List	48018-6
113091	Reviewed By	18771-6