MAYO CLINIC LABORATORIES

# Test Definition: PRCNG

PROCR Gene, Next-Generation Sequencing, Varies

## 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 of collection, and frozen specimens must arrive within 14 days.**

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

## Necessary Information

**Rare Coagulation Disorder Patient Information is required.** 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:** Whole blood
**Container/Tube:**
**Preferred:** Lavender top (EDTA)
**Acceptable:** Yellow top (ACD) or light-blue top (3.2% sodium citrate)
**Specimen Volume:** 3 mL
**Collection Instructions:**
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
**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.**
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:
-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 & Interpretive

### Clinical Information

Venous thromboembolism (VTE) can describe:

A deep vein thrombosis (DVT) characterized by leg pain or tenderness typically in only 1 thigh or calf, leg swelling, skin that feels warm to the touch, and reddish discoloration or streaks.

-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 (nongenetic) thrombophilia include recent surgery, trauma, fractures, hospital or nursing home confinement, varicose veins, neurological disease with leg paresis, chronic kidney disease, oral contraceptive use and hormone therapy, pregnancy and the postpartum 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.

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 5- 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 variant (SNV) in the 5' untranslated region (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 variant that is not identified by the methods performed. The absence of a variant, 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 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 variants (ie, polymorphisms) may be present that could lead to false-negative or false-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 alterations (ie, 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 Apr;149(2):209-220
2. Heit JA: The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008 Mar;28(3):370-372
3. Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, Ferrell GL, Esmon CT: The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. Proc Natl Acad Sci USA. 1996 Sep 17;93(19):10212-10216
4. Bouwnes EAM, Stavenuiter F, Mosnier LO: Mechanisms of anticoagulant and cytoprotective actions of the protein C pathway. J Thromb Haemost. 2013 Jun;11 Suppl 1(0 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 Aug 27;114(9):1974-1986
6. Medina P, Navarro S, Estelles A, Espana F: Polymorphisms in the endothelial protein C receptor gene and thrombophilia. Thromb Haemost. 2007 Sep;98(3):564-569
7. Mohan Rao LV, Esmon CT, Pendurthi UR: Endothelial cell protein C receptor: a multiliganded and multifunctional receptor. Blood. 2014 Sep 4;124(10):1553-1562
8. Wu C, Dwivedi DJ, 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 Nov;33(11):2674-2681
9. Gleeson EM, O'Donnell JS, Preston RJS: The endothelial cell protein C receptor: cell surface conductor of cytoprotective coagulation factor signaling. Cell Mol Life Sci. 2012 Mar;69(5):717-726

## Performance

### Method Description

Next-generation sequencing (NGS) 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 NGS 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 NGS 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 & 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 US 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 |