

## Overview

### Useful For

Evaluating protein C deficiency in patients with a personal or family history suggestive of this hereditary thrombophilia

Confirming a diagnosis of autosomal dominant protein C deficiency with the identification of a known or suspected disease-causing alteration in the *PROC* gene

Confirming a diagnosis of autosomal recessive severe protein C deficiency with the identification of homozygous or compound heterozygous disease-causing alteration(s) in the *PROC* gene

Determining the disease-causing alteration(s) within the *PROC* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of protein C deficiency

Prognosis and risk assessment based on the genotype-phenotype correlations

Ascertaining the variant status of family members related to an individual with a confirmed *PROC* variant for the purposes of informing clinical management and genetic counseling

Carrier testing for close family members of an individual with a diagnosis of autosomal recessive severe protein C deficiency

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

### Genetics Test Information

This test utilizes next-generation sequencing to detect single nucleotide and copy number variants in the *PROC* gene, associated with protein C deficiency, a rare blood clotting disorder. See Method Description for additional details.

Identification of a disease-causing variant may assist with diagnosis, prognosis, clinical management, recurrence risk assessment, familial screening, and genetic counseling for protein C deficiency.

### Testing Algorithm

The clinical workup for protein C deficiency should begin with special coagulation testing for protein C activity.

Genetic testing for protein C deficiency is indicated if:

- Protein C activity is less than 75% of normal (Note: reference range may vary depending on the locally established reference range)
- There is a clinical suspicion of hereditary thrombophilia and possible protein C deficiency due to family history or atypical clinical presentation
- Acquired causes of protein C deficiency have been excluded (eg, vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, and intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

**Method Name**

Sequence Capture and Targeted Next-Generation Sequencing (NGS) followed by Polymerase Chain Reaction (PCR) and Sanger Sequencing

**NY State Available**

Yes

**Specimen**

**Specimen Type**

Varies

**Ordering Guidance**

This test should only be considered if clinical and family history, initial coagulation screens, and initial protein C activity and antigen tests indicate a diagnosis of antithrombin deficiency (see Testing Algorithm). This test does not measure protein C activity or antigen levels.

For assessment of protein C activity, order CFX / Protein C Activity, Plasma. If protein C activity is low, protein C antigen testing could help distinguish between type I and type II deficiencies; order PCAG / Protein C Antigen, Plasma.

For assessment of protein C antigen, order PCAG / Protein C Antigen, Plasma.

If genetic testing for hereditary blood clotting disorders using a larger panel is desired, a 16-gene comprehensive thrombosis panel is available; order GNTHR / Thrombosis Disorders, Comprehensive Gene Panel, Next-Generation Sequencing, Varies.

Testing for the *PROC* gene as part of a customized panel is available. For more information see CGPH / Custom Gene Panel, Hereditary, Next-Generation Sequencing, Varies.

Targeted testing for familial variants (also called site-specific or known variants testing) is available for variants identified in the *PROC* gene. See FMTT / Familial Variant, Targeted Testing, Varies. To obtain more information about this testing option, call 800-533-1710.

**Shipping Instructions**

Specimen preferred to arrive within 96 hours of collection.

**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**

**Specimen Type:** Whole blood

**Patient Preparation:** A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

**Container/Tube:**

**Preferred:** Lavender top (EDTA)

**Acceptable:** Yellow top (ACD)

**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 Information:** Ambient (preferred) 4 days/Refrigerated

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 an [Coagulation Test Request \(T753\)](#) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---------------|-------------|------|-------------------|
| Varies        | Varies      |      |                   |

Clinical & Interpretive

Clinical Information

Hereditary protein C deficiency is a rare inherited blood clotting disorder (thrombophilia) associated with germline variants in the *PROC* gene. Protein C is an important component of the body’s natural anticoagulant system. A deficiency results in an unchecked clotting cascade and an increased risk of thromboembolism.(1)

Individuals who are heterozygous for a disease-causing variant in *PROC* have [mild protein C deficiency](#), which is inherited in an autosomal dominant manner. Mild protein C deficiency is characterized by an increased risk for venous thromboembolism and warfarin-induced skin necrosis. The coinheritance of additional thrombotic risk factors (eg, factor V Leiden) can compound the clotting risk. The estimated prevalence of mild protein C deficiency is between 1 in 200 to 1 in 500.(1-3)

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Homozygosity or compound heterozygosity for disease-causing variants in *PROC* is associated with severe protein C deficiency, which is extremely rare (estimated prevalence of 1 in 500,000 to 1 in 750,000) and is inherited in an autosomal recessive manner. This disorder typically presents with purpura fulminans and disseminated intravascular coagulation within 72 hours of birth but, occasionally, in later infancy. Infants with severe deficiency typically have protein C levels that are virtually undetectable.(1,2,4)

Several causes of acquired (nongenetic) protein C deficiency should be excluded prior to genetic testing, including [vitamin K deficiency, oral anticoagulation with coumarin compounds, liver disease, and intravascular coagulation and fibrinolysis/disseminated intravascular coagulation](#).(2,5)

The British Society for Haematology provides guidelines regarding diagnosis, management, and laboratory testing for individuals with hereditary thrombophilias, including protein C deficiency.(6)

### Reference Values

An interpretive report will be provided.

### Interpretation

All detected variants are evaluated according to American College of Medical Genetics and Genomics recommendations.(7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

### Cautions

Clinical Correlations:

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a clinically significant family history, it is often useful to first test an affected family member. Detection of a reportable variant in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of additional testing options or for assistance in the interpretation of these results, contact the Mayo Clinic Laboratories genetic counselors at 800-533-1710.

Technical Limitations:

Next-generation sequencing may not detect all types of genomic variants. In rare cases, false-negative or false-positive results may occur. The depth of coverage may be variable for some target regions; assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences. Confirmation of select reportable variants will be performed by alternate methodologies based on internal laboratory criteria.

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This test is validated to detect 95% of deletions up to 75 base pairs (bp) and insertions up to 47 bp. Deletions-insertions (delins) of 40 or more bp, including mobile element insertions, may be less reliably detected than smaller delins.

**Deletion/Duplication Analysis:**

This analysis targets single and multi-exon deletions/duplications; however, in some instances, single exon resolution cannot be achieved due to isolated reduction in sequence coverage or inherent genomic complexity. Balanced structural rearrangements (such as translocations and inversions) may not be detected.

This test is not designed to detect low levels of mosaicism or to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

For detailed information regarding gene specific performance and technical limitations, see Method Description or contact a laboratory genetic counselor.

If the patient has had an allogeneic hematopoietic stem cell transplant or a recent blood transfusion, results may be inaccurate due to the presence of donor DNA. Call Mayo Clinic Laboratories for instructions for testing patients who have received a bone marrow transplant.

**Reclassification of Variants:**

Currently, it is not standard practice for the laboratory to systematically review previously classified variants on a regular basis. The laboratory encourages healthcare providers to contact the laboratory at any time to learn how the classification of a particular variant may have changed over time. Due to broadening genetic knowledge, it is possible that the laboratory may discover new information of relevance to the patient. Should that occur, the laboratory may issue an amended report.

**Variant Evaluation:**

Evaluation and categorization of variants is performed using published American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommendations as a guideline.<sup>(7)</sup> Other gene-specific guidelines may also be considered. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Variants classified as benign or likely benign are not reported.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and periodic updates to these tools may cause predictions to change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Rarely, incidental or secondary findings may implicate another predisposition or presence of active disease. These findings will be carefully reviewed to determine whether they will be reported.

**Clinical Reference**

1. Cooper PC, Hill M, Maclean RM: The phenotypic and genetic assessment of protein C deficiency. Int J Lab Hematol. 2012 Aug;34(4):336-346

2. Dinarvand P, Moser KA: Protein C Deficiency. Arch Pathol Lab Med. 2019 Oct;143(10):1281-1285
3. Mustafa S, Mannhalter C, Rintelen C: Clinical features of thrombophilia in families with gene defects in protein C or protein S combined with factor V Leiden. Blood Coagul Fibrinolysis. 1998 Jan;9(1):85-89
4. Minford A, Brandao LR, Othman M: Diagnosis and management of severe congenital protein C deficiency (SCPCD): Communication from the SSC of the ISTH. J Thromb Haemost. 2022 Jul;20(7):1735-1743
5. Varga EA, Kujovich JL: Management of inherited thrombophilia: guide for genetics professionals. Clin Genet. 2012 Jan;81(1):7-17
6. Arachchillage DJ, Mackillop L, Chandratheva A: Thrombophilia testing: A British Society for Haematology guideline. Br J Haematol. 2022 Aug;198(3):443-458
7. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-424

## Performance

### Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing are performed to test for the presence of variants in coding regions and intron/exon boundaries of the *PROC* gene, as well as some other regions that have known disease-causing variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for deletions-insertions (delins) less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS and/or a polymerase chain reaction-based quantitative method is performed to test for the presence of deletions and duplications in the *PROC* gene.

There may be regions of the *PROC* gene that cannot be effectively evaluated by sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC) content, and repetitive sequences.(Unpublished Mayo method)

The reference transcript for *PROC* is NM\_000312.3. Reference transcript numbers may be updated due to transcript re-versioning. Always refer to the final patient report for gene transcript information referenced at the time of testing. Confirmation of select reportable variants may be performed by alternate methodologies based on internal laboratory criteria.

### PDF Report

Supplemental

### Day(s) Performed

Varies

### Report Available

28 to 42 days

### Specimen Retention Time

Whole blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

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 account representative. 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. It 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 |
|---------|--------------------------|--------------------|
| GNPRC   | PROC Gene, Full Gene NGS | 93815-9            |

| Result ID | Test Result Name       | Result LOINC® Value |
|-----------|------------------------|---------------------|
| 619174    | Test Description       | 62364-5             |
| 619175    | Specimen               | 31208-2             |
| 619176    | Source                 | 31208-2             |
| 619177    | Result Summary         | 50397-9             |
| 619178    | Result                 | 82939-0             |
| 619179    | Interpretation         | 69047-9             |
| 619180    | Additional Results     | 82939-0             |
| 619181    | Resources              | 99622-3             |
| 619182    | Additional Information | 48767-8             |
| 619183    | Method                 | 85069-3             |
| 619184    | Genes Analyzed         | 82939-0             |
| 619185    | Disclaimer             | 62364-5             |
| 619186    | Released By            | 18771-6             |