

## Overview

### Useful For

Genetic confirmation of a factor VII deficiency diagnosis with the identification of a known or suspected pathogenic alteration in the *F7* gene

Carrier testing for close family members of an individual with a factor VII deficiency diagnosis

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

### Genetics Test Information

This test detects pathogenic alterations in the *F7* gene to delineate the underlying molecular defect in a patient with a laboratory diagnosis of Factor VII deficiency (F7D), a rare bleeding disorder.

The gene target for this test is:

Gene name (transcript): *F7* (GRCh37 [hg19] NM\_000131)

Chromosomal location: 13q34

### Testing Algorithm

The clinical workup for factor VII deficiency (F7D) begins with coagulation testing consisting of coagulation factor VII assay (see F\_7 / Coagulation Factor VII Activity Assay, Plasma).

Genetic testing for F7D is indicated if:

- Factor VII activity is reduced (less than 65% of normal)
- Acquired causes of FVII deficiency have been excluded

### 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

### Advisory Information

Genetic testing for factor VII deficiency should only be considered after coagulation screening is performed and if

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factor VII activity is less than 65% of normal (Note: reference range may vary depending on the locally established reference range).

### Shipping Instructions

Ambient and refrigerate 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 specimens 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

Factor VII (FVII) deficiency (F7D) is a bleeding diathesis. Most patients with mild FVII deficiency do not experience spontaneous bleeding but may experience prolonged bleeding after trauma or surgical interventions. For patients with severe factor VII deficiency, symptoms include epistaxis, menorrhagia, easy bruising, gum bleeding, and post-surgical bleeding. Joint and muscle bleeds are less common. In severe deficiencies, bleeding starts within the first 6 months of life and can include life-threatening intracranial and gastrointestinal hemorrhages.(1) Additionally, FVII deficiency does not protect patients from venous thromboembolism. Between 3% and 4% of F7D patients experience thrombotic events, particularly deep vein thrombosis. These events are associated with surgery and factor replacement therapy, but spontaneous thrombosis may also occur.(2) The severity of these symptoms is highly variable, ranging from mild to lethal.(3)

Hereditary factor VII deficiency has an estimated prevalence of 1 in 500,000. If genetic, F7D is inherited in an autosomal recessive manner with variable expressivity. Both males and females may be affected.

Hereditary F7D results from defects in the concentration or function of coagulation factor VII, a critical activator of the coagulation cascade. When an injury to a blood vessel releases tissue factor into the blood stream, coagulation factor VII binds with tissue factor to initiate the blood coagulation cascade. However, disease severity correlates poorly with FVII activity levels in blood plasma. FVII levels of less than 2% typically result in severe hemorrhagic

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disease, but not always. Conversely, plasma factor VII levels greater than 20% do not typically cause symptoms, yet some patients with levels ranging from 20% to 50% have abnormal bleeding.(4)

The F7 gene encodes factor VII. Alterations in the *F7* gene that reduce the amount of FVII can lead to an impaired response to vascular injuries and abnormal bleeding. Genetic testing may be indicated if a coagulation screen shows increased prothrombin time (PT), and factor VII activity that is less than 65% (note: Reference range may vary depending on the locally established reference range). Of note, normal full-term newborn infants or healthy premature infants have factor VII levels equal to or greater than 20%, which increases within the first postnatal week but may not reach adult levels for 180 days or more.

Causes of acquired (non-genetic) factor VII deficiency that should be excluded prior to genetic testing include Vitamin K deficiency, use of vitamin K antagonists like warfarin, liver disease, sepsis, can cause acquired factor VII deficiency (6, 7). Warfarin or similar anticoagulants also decrease factor VII synthesis. These acquired causes of FVII deficiency should be considered prior to genetic testing.

### 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 factor VII deficiency (F7D). 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 family studies.

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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. Lapecorella M, Mariani G: International Registry on Congenital Factor VII Deficiency. Factor VII deficiency: defining the clinical picture and optimizing therapeutic option. *Haemophilia* 2008;14(6):1170-1175
2. Mariani G, Herrmann FH, Schulman S, et al: International Factor VII Deficiency Study Group. Thrombosis in inherited factor VII deficiency. *J Thromb Haemost* 2003;1(10):2153-2158
3. Palla R, Peyvandi F, Shapiro A: Rare bleeding disorders: diagnosis and treatment. *Blood* 2015;125(13):2052-2061
4. de Moerloose P, Schved JF, Nugent D: Rare coagulation disorders: fibrinogen, factor VII and factor XIII. *Haemophilia* 2016;22 suppl 5:61-65
5. Rath M, Najm J, Sirb H, et al: Large deletions play a minor but essential role in congenital coagulation factor VII and X deficiencies. *Hamostaseologie* 2015;35 Suppl:S36-42
6. da Silva VA, Silva SS, Martins FF: Acquired deficiency of coagulation factor VII. *Revista Brasileira de Hematologia e Hemoterapia* 2015;37(4):269-271
7. Mulliez SM, Devreese KM: Isolated acquired factor VII deficiency: a review of the literature. *Acta Clinica Belgica* 2016;71(2):63-70
8. Giansily-Blaizot M, Thorel D, Khau Van Kien P: Characterization of a large complex intragenic re-arrangement in the FVII gene (F7) avoiding misdiagnosis in inherited factor VII deficiency. *Br J Haematol* 2007;138(3):359-365

### 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) and Time(s) Test Performed

Performed weekly; Varies

### Analytic Time

21 days

### Maximum Laboratory Time

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 |
|---------|------------------------|-------------------|
| F7NGS   | F7 Gene, Full Gene NGS | 94235-9           |

| Result ID | Test Result Name       | Result LOINC Value |
|-----------|------------------------|--------------------|
| 113035    | F7NGS Result           | 50397-9            |
| 113029    | Alterations Detected   | 82939-0            |
| 113028    | Interpretation         | 69047-9            |
| 113030    | Additional Information | 48767-8            |
| 113031    | Method                 | 85069-3            |
| 113032    | Disclaimer             | 62364-5            |
| 113033    | Panel Gene List        | 21671-3            |
| 113034    | Reviewed By            | 18771-6            |