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, a rare bleeding disorder.

The gene target for this test is:

Gene name (transcript): *F7* (GRCh37 [hg19] NM_000131)

Chromosomal location: 13q34

Testing Algorithm

Genetic testing for factor VII deficiency (F7D) should only be considered after coagulation screening is performed and if factor VII activity is less than 65% of normal (Note: reference range may vary depending on the locally established reference range).

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

Ordering Guidance

The clinical workup for factor VII deficiency (F7D) begins with coagulation testing consisting of coagulation factor VII assay. Order F_7 / Coagulation Factor VII Activity Assay, Plasma.

Shipping Instructions

Ambient and refrigerate specimens must arrive within 7 days of collection, and frozen specimens must arrive within 14 days.

Collect and package specimens 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.

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK

Specimen Minimum Volume

Blood: 1 mL

Extracted DNA: 100 mcL at 50 ng/mcl concentration

Specimen Stability Information

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

Clinical & 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 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 variant that is not identified by the methods performed. The absence of a variant, therefore, does not eliminate the possibility of factor VII deficiency. 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 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. Lapecorella M, Mariani G: International Registry on Congenital Factor VII Deficiency. Factor VII deficiency: defining the clinical picture and optimizing therapeutic option. Haemophilia. 2008 Nov;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 Oct;1(10):2153-2158

3. Palla R, Peyvandi F, Shapiro A: Rare bleeding disorders: diagnosis and treatment. Blood 2015 Mar;125(13):2052-2061

4. de Moerloose P, Schved JF, Nugent D: Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia 2016 Jul;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. Rev BrasHematol Hemoter. 2015 Jul-Aug;37(4):269-271

7. Mulliez SM, Devreese KM: Isolated acquired factor VII deficiency: a review of the literature. Acta Clin Belg. 2016 Apr;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 Aug;138(3):359-365

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

Specimen Retention Time

Whole Blood: 2 weeks; DNA: Indefinitely

Performing Laboratory Location

Rochester

Fees & Codes

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
F7NGS	F7 Gene, Full Gene NGS	94235-9

Result ID	Reporting Name	LOINC®
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