Comprehensive Bleeding Disorder Panel

Versiti offers comprehensive genetic analysis to detect sequence variants and large deletions and duplications in 60 genes, plus one targeted variant, known to cause bleeding due to disorders of coagulation and/or platelet function. This panel can be ordered as:

- **Next Generation Sequencing (NGS) only*;**
- **NGS with reflex to Array Comparative Genomic Hybridization (aCGH) Deletion/Duplication if sequencing does not identify clinically significant variants that fully explain the patient's phenotype;**
- **NGS with concurrent aCGH Deletion/Duplication (both testing methodologies performed simultaneously); or**
- **Deletion/Duplication by aCGH only.**

*** Includes *PLAU* performed by aCGH**

Coagulation disorders and inherited platelet function disorders are a heterogeneous group of inherited bleeding disorders with overlapping clinical phenotypes. Bleeding symptoms can include epistaxis, easy bruising, gingival bleeding, prolonged bleeding following an injury, surgery or dental extractions, gastrointestinal or urinary bleeding, hematomas, hemoptysis, intracranial bleeding, and menorrhagia or postpartum bleeding in women. Symptoms can present at any age and range in severity: in mild cases, individuals remain asymptomatic until the event of a trauma or surgery, and in severe cases, patients may present with spontaneous life threatening hemorrhage or bleeding symptoms in the newborn period.

Although results of functional hemostasis testing often guide molecular testing for a specific inherited coagulation disorder, there are situations where functional tests are not definitive or cannot be obtained. For cases in which the laboratory phenotype is not fully consistent with clinical symptoms, or the specific bleeding disorder is unclear, the Comprehensive Bleeding Disorder Panel offers an efficient and cost-effective means of diagnostic genetic evaluation. Accurate diagnosis provides information about phenotype and prognosis, guides medical management decisions, assists with the identification of affected family members, and allows for accurate genetic recurrence risk assessment.

Variants in several different genes known to cause syndromic or non-syndromic bleeding disorders may be inherited in an autosomal recessive, autosomal dominant or X-linked manner. Heterozygous carriers of autosomal recessive clotting factor deficiencies and female carriers of X-linked disorders can present with moderate decreased factor activity and a milder or absent bleeding phenotype. More common and rare types of inherited coagulation and platelet function disorders will be identified with this panel. This panel does not specifically identify vascular bleeding disorders such as hereditary hemorrhagic telangiectasia (HHT) or collagen vascular disorders.

The NGS panel evaluates for single nucleotide variants and small deletions and duplications, which are most commonly responsible for genetic disease. However, large deletions and duplications, also referred to as copy number variations (CNVs), are a known cause of genetic disorders, but can escape detection by next generation sequence analysis. Additional testing with aCGH Deletion/Duplication analysis is available for all genes on this panel to evaluate for large deletions and duplications encompassing one or more exons, or affecting an entire gene. Note that the Quebec Platelet Disorder (QPD) is associated with a heterozygous 77.9-kb tandem duplication of the *PLAU* gene which will be detected by aCGH and not by NGS; analysis of *PLAU* by aCGH is included in the otherwise NGS-only version of this panel.

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Analysis of genes included in the Comprehensive Bleeding Disorder Panel may also be ordered as a stand-alone single gene test as dictated by the patient's laboratory phenotype. Alternatively, custom panels (2 to 10 genes) may be ordered if a patient's history suggests a specific bleeding disorder with multiple causative genes, or if functional testing results narrow the diagnosis to specific phenotypes that can be due to different underlying genetic conditions.

Targeted familial variant testing can also be performed on any gene in the panel when the specific genetic variant is known in a family.

Refer to the table for further information about each gene in the Comprehensive Bleeding Disorder Panel, including the clinical phenotype and inheritance pattern.

Comprehensive Bleeding Disorder Panel: gene, clinical phenotype and inheritance pattern.

Gene	Clinical Phenotype	Inheritance
ANO6	**Scott syndrome:** platelet dysfunction with mild to moderate bleeding phenotype with normal platelet aggregation and platelet counts, and decreased platelet procoagulant activity with characteristic flow cytometry findings	Autosomal Recessive
AP3B1	**Hermansky-Pudlak syndrome type 2** (HPS2): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and neutropenia	Autosomal Recessive
AP3D1	**Hermansky-Pudlak syndrome type 10** (HPS10): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as neutropenia, seizures and developmental delay	Autosomal Recessive
ARPC1B	***ARPC1B*-related thrombocytopenia:** microthrombocytopenia, decreased platelet dense granules, allergic and inflammatory disease	Autosomal Recessive
BLOC1S3	**Hermansky-Pudlak syndrome type 8** (HPS8): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
BLOC1S6	**Hermansky-Pudlak syndrome type 9** (HPS9): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
DTNBP1	**Hermansky-Pudlak syndrome type 7** (HPS7): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
F2	**Factor II deficiency** (prothrombin deficiency): severe bleeding including post procedure bleeding, umbilical stump bleeding, hemarthrosis, muscle hematomas and mucosal bleeding	Autosomal Recessive
F5	**Factor V deficiency:** moderate to severe bleeding, including mucocutaneous bleeding, postoperative bleeding, menorrhagia and gastrointestinal bleeding	Autosomal Recessive
F7	**Factor VII deficiency:** bleeding diathesis of variable severity	Autosomal Recessive
F8	**Factor VIII deficiency** (Hemophilia A): severe, moderate or mild bleeding disorder that primarily affects males. Female carriers may show varying degrees of factor VIII deficiency and related bleeding symptoms.	X-linked Recessive
F9	**Factor IX deficiency** (Hemophilia B): severe, moderate or mild bleeding disorder primarily affecting males. Female carriers may show varying degrees of factor IX deficiency and related bleeding symptoms.	X-linked Recessive
F10	**Factor X deficiency:** bleeding of variable severity and a weak association between coagulation factor activity and severity of bleeding phenotype	Autosomal Recessive
F11	**Factor XI deficiency:** typically presents with bleeding after trauma or surgery; homozygotes are more severely affected; there are variable bleeding problems in heterozygotes.	Autosomal Recessive
F13A1	**Factor XIII deficiency:** umbilical cord bleeding, spontaneous intracranial bleeding, delayed bleeding after surgery, menorrhagia, impaired wound healing and infertility.	Autosomal Recessive
F13B		Autosomal Recessive
FERMT3	**Leukocyte adhesion deficiency-III** (LAD-III): characterized by severe bleeding with a Glanzmann thrombasthenia-like phenotype on platelet aggregation studies and associated immunodeficiency	Autosomal Recessive
FGA	**Afibrinogenemia:** severe/delayed bleeding from markedly decreased or absent fibrinogen.	Autosomal Recessive
FGB *FGG*	**Hypofibrinogenemia:** mild to moderate delayed bleeding due to decreased fibrinogen levels	Autosomal Dominant (most common)/ Autosomal Recessive
	Hypodysfibrinogenemia: mild to moderate delayed bleeding with or without thrombosis due to deficient and dysfunctional fibrinogen	Autosomal Dominant (most common)/ Autosomal Recessive
	Dysfibrinogenemia: absent or mild/moderate delayed bleeding with or without thrombosis due to dysfunctional fibrinogen	Autosomal Dominant (most common)/ Autosomal Recessive

Comprehensive Bleeding Disorder Panel: gene, clinical phenotype and inheritance pattern.		
Gene	Clinical Phenotype	Inheritance
FLI1	***FLI1*-related thrombocytopenia** (platelet-type bleeding disorder-21): macrothrombocytopenia with moderate bleeding from platelet dysfunction due to alpha granule deficiency (large/fused platelet alpha granules on platelet electron microscopy), with or without delta granule deficiency	Autosomal Dominant
FLNA	***FLNA*-related thrombocytopenia:** macrothrombocytopenia and platelet dysfunction with or without associated periventricular heterotopia.	X-linked
FYB1	***FYB1*-related thrombocytopenia** (thrombocytopenia 3): non-syndromic microthrombocytopenia and platelet dysfunction leading to increased bleeding	Autosomal Recessive
GATA1	***GATA1*-related X-linked cytopenia:** characterized by macrothrombocytopenia and/or anemia with moderate bleeding due to platelet alpha granule deficiency	X-linked Recessive
GFI1B	***GFI1B*-related thrombocytopenia** (platelet-type bleeding disorder-17): macrothrombocytopenia with platelet alpha granule deficiency leading to variable bleeding tendency, red cell anisopoikilocytosis, increased numbers of dysplastic megakaryocytes and increased platelet CD34 expression	Autosomal Dominant
GGCX	**Combined deficiency of vitamin K-dependent clotting factors type 1** (VKCFD1): bleeding tendency of variable severity due to deficiency of factors II, VII, IX and X	Autosomal Recessive
GP1BA	**Bernard Soulier syndrome** (BSS): macrothrombocytopenia with normal platelet granularity and moderate to severe bleeding due to decreased/absent/dysfunctional platelet GPIb/IX expression with decreased/absent platelet aggregation with ristocetin	Autosomal Recessive
	Platelet-type von Willebrand disease: thrombocytopenia with mild bleeding due to loss of VWF high molecular weight multimers from increased binding of platelets and VWF	Autosomal Dominant
GP1BB	**Bernard Soulier syndrome (BSS):** macrothrombocytopenia with normal platelet granularity and moderate to severe bleeding due to decreased/absent/dysfunctional platelet GPIb/IX expression with decreased/absent platelet aggregation with ristocetin.	Autosomal Recessive
GP6	***GP6*-related platelet dysfunction** (platelet- type bleeding disorder 11): mild bleeding and decreased aggregation response to collagen on platelet aggregation studies due to deficiency of platelet glycoprotein VI	Autosomal Recessive
GP9	**Bernard Soulier syndrome (BSS):** macrothrombocytopenia with normal platelet granularity and moderate to severe bleeding due to decreased/absent/dysfunctional platelet GPIb/IX expression with decreased/absent platelet aggregation with ristocetin.	Autosomal Recessive
HPS1	**Hermansky-Pudlak syndrome type 1** (HPS1): oculocutaneous albinism of variable severity and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and granulomatous colitis	Autosomal Recessive
HPS3	**Hermansky-Pudlak syndrome type 3** (HPS3): mild ocular albinism and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
HPS4	**Hermansky-Pudlak syndrome type 4** (HPS4): oculocutaneous albinism and mild bleeding due to a platelet storage pool disorder, as well as pulmonary fibrosis and granulomatous colitis	Autosomal Recessive
HPS5	**Hermansky-Pudlak syndrome type 5** (HPS5): mild ocular albinism and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
HPS6	**Hermansky-Pudlak syndrome type 6** (HPS6): mild ocular albinism and mild bleeding due to a platelet storage pool disorder	Autosomal Recessive
ITGA2B	**Glanzmann thrombasthenia:** normal platelet count with severe bleeding and decreased/absent platelet aggregation with all agonists except ristocetin due to decreased/absent/dysfunctional expression of platelet glycoprotein (GP) IIb/IIIa	Autosomal Recessive
ITGB3	**Glanzmann thrombasthenia:** normal platelet count with severe bleeding and decreased/absent platelet aggregation with all agonists except ristocetin due to decreased/absent/dysfunctional expression of platelet glycoprotein (GP) IIb/IIIa	Autosomal Recessive
KDSR	**KDSR-related thrombocytopenia** (Erythrokeratodermia variabilis et progressiva 4): thrombocytopenia with normal platelet size and platelet dysfunction with or without skin hyperkeratosis and ichthyosis	Autosomal Recessive
LMAN1	**Combined factor V and VIII deficiency:** decreased factor levels (between 5% and 30%) leading to mild to moderate bleeding	Autosomal Recessive
LYST	**Chediak-Higashi syndrome:** partial oculocutaneous albinism, immunodeficiency, and a mild bleeding from platelet delta granule deficiency	Autosomal Recessive
MCFD2	**Combined factor V and VIII deficiency:** decreased factor levels (between 5% and 30%) leading to mild to moderate bleeding	Autosomal Recessive
NBEA	***NBEA*-related platelet dysfunction:** neurodevelopmental disorders, including autism and seizures, and moderate bleeding due to platelet delta storage pool disorder.	Autosomal Dominant
NBEAL2	**Gray platelet syndrome (GPS)**: macrothrombocytopenia with mild to moderate bleeding due to alpha granule deficiency, splenomegaly and bone marrow fibrosis	Autosomal Recessive

Comprehensive Bleeding Disorder Panel: gene, clinical phenotype and inheritance pattern.		
Gene	Clinical Phenotype	Inheritance
P2RY12	***P2RY12*-related platelet dysfunction** (platelet-type bleeding disorder 8): mild-moderate mucocutaneous bleeding and excessive bleeding in response to trauma or surgery due to impaired platelet aggregation responses to ADP	Autosomal Recessive
PLA2G4A	***PLA2G4A*-related platelet dysfunction** (cytosolic phospholipase-A2 alpha deficiency): platelet dysfunction from a metabolic defect and small bowel ulcers caused by decreased production of eicosanoids	Autosomal Recessive
*PLAU**	**Quebec Platelet Disorder** (QPD): delayed onset bleeding, large trauma induced hematomas, hemarthrosis, muscle bleeds and hematuria from hyperfibrinolysis due to increased platelet urokinase plasminogen activator from a tandem 77.9kb duplication encompassing the PLAU gene	Autosomal Dominant
PRKACG	***PRKACG*-related thrombocytopenia** (platelet-type bleeding disorder 19), characterized by severe macrothrombocytopenia with associated platelet dysfunction leading to moderate to severe bleeding	Autosomal Recessive
RASGRP2	***RASGRP2*-related platelet dysfunction** (platelet-type bleeding disorder 18): moderate to severe bleeding and decreased platelet aggregation with ADP and epinephrine and in some cases arachidonic acid, collagen and thrombin	Autosomal Recessive
RUNX1	**Familial platelet disorder with predisposition to myeloid leukemia** (FPD/AML): mild to moderate thrombocytopenia with normal platelet size, bleeding due to platelet delta storage pool disorder and a predisposition to development of myeloid malignancies	Autosomal Dominant
SERPINA1§	**Antithrombin Pittsburgh:** the pathogenic variant *SERPINA1* c.1145T>G (p.Met358Arg) is associated with variable bleeding due to enhanced inhibition of thrombin. Targeted analysis of the Pittsburgh variant ONLY; NGS and aCGH of *SERPINA1* otherwise not available.	Autosomal Dominant
SERPINE1	**Plasminogen activator Inhibitor 1 (PAI-1) deficiency:** variable bleeding due to increased fibrinolysis	Autosomal Recessive
SERPINF2	**Alpha 2-antiplasmin deficiency**: variable bleeding tendency due to increased fibrinolysis	Autosomal Recessive
SLFN14	***SLFN14*-related thrombocytopenia** (platelet-type bleeding disorder 20): mild to moderate macrothrombocytopenia with associated platelet dysfunction from dense granule deficiency leading to variable bleeding	Autosomal Dominant
SRC	***SRC*-related thrombocytopenia** (thrombocytopenia 6): thrombocytopenia and platelet dysfunction with associated myelofibrosis and bone pathology	Autosomal Dominant
STIM1	***STIM1*-related thrombocytopenia** (Tubular aggregate myopathy and Stormorken syndrome): variable muscle weakness, miosis, thrombocytopenia with normal platelet size, hyposplenism, ichthyosis, dyslexia and short stature. Electron dense platelet inclusions and target-like organelles are characteristic	Autosomal Dominant
TBXA2R	**Thromboxane receptor defect:** pathogenic variants in *TBXA2R* have been proposed as contributing to a bleeding phenotype in the presence of additional pathogenic variants in genes affecting platelet function; these variants cause impaired platelet response to arachidonic acid and U46619 in vitro, but have not been shown to consistently correlate with a clinical phenotype	Risk allele
TBXAS1	***TBXAS1*-related platelet dysfunction** (Ghosal syndrome; platelet-type bleeding disorder 14): increased bone density and platelet dysfunction due to impaired aggregation with arachidonic acid	Autosomal Recessive
VIPAS39	**Arthrogryposis, renal dysfunction, and cholestasis syndrome type 2 (ARCS2):** macrothrombocytopenia with platelet dysfunction from alpha granule deficiency with associated arthrogryposis, renal dysfunction, and cholestasis	Autosomal Recessive
VKORC1	**Combined deficiency of vitamin K-dependent clotting factors type 2 (VKCFD2):** bleeding tendency of variable severity due to deficiency of factors II, VII, IX and X	Autosomal Recessive
VPS33B	**Arthrogryposis, renal dysfunction, and cholestasis syndrome type 1 (ARCS1):** macrothrombocytopenia with platelet dysfunction from alpha granule deficiency with associated arthrogryposis, renal dysfunction, and cholestasis	Autosomal Recessive
VWF	**von Willebrand Disease (VWD):** mild to severe bleeding due to quantitative (types 1 and 3) or qualitative defects (type 2) in VWF	Autosomal Dominant (most common) / Autosomal Recessive (type 2N and 3)

*Available by aCGH only

§ Targeted variant of the Pittsburg allele in exon 5 only

Indications for testing:

Comprehensive Bleeding Disorder Panel (NGS and/or aCGH), order code 4825:

The Comprehensive Bleeding Disorder Panel should be considered:

- In patients with a suspected congenital bleeding disorder in which the laboratory phenotype is not fully consistent with clinical symptoms, or the specific bleeding disorder is unclear
- In patients with a suspected congenital bleeding disorder that have inconclusive functional hemostatic testing or in situations where functional hemostatic testing cannot be obtained
- In patients in whom a family history of a bleeding disorder is reported but unspecified, without an affected relative available for confirmation

Single Gene Analysis (order code 4855) or Custom Blood Disorder Panel (Order Code 4850), (NGS and/or aCGH):

- Analysis of genes included in this panel may also be ordered as a standalone Single Gene Analysis or as a Custom Blood Disorder Panel (2-10 genes), by NGS and/or by aCGH, as dictated by the patient's clinical and laboratory phenotype, as well as their ancestry, or to supplement previous genetic testing.

Targeted Familial Variant Analysis (order code 4970):

Targeted variant analysis for clinical diagnosis, carrier identification, or prenatal diagnosis can also be performed on any gene in the panel when the pathogenic variant(s) is known in the family. If the proband was not tested at Versiti, a control sample may be needed (please call the laboratory to discuss). If the familial variant is a large deletion or duplication, aCGH for the involved gene is required.

For clinical questions about laboratory tests and test utilization support, contact Versiti Client Services: (414) 937-6396 or 800-245-3117, Option 1, to be directed to our genetic counselors and clinical support team.

Informed Consent

It is recommended that healthcare providers obtain informed consent from the patient when genetic testing is ordered, consistent with any applicable state laws and regulations, documenting that the patient has been advised of and understands the indications for and implications of the genetic test. This panel is designed for clinical detection of germline genetic variants in genes with strong or definitive evidence for causality of platelet function disorders and coagulation disorders. Test results may nonetheless yield genetic findings that may be unrelated to the current clinical presentation, and/or may carry individual or familial implications such as risk for syndromic manifestation, predisposition to malignancy, and/or reproductive implications (such as carrier status). If needed, an informed consent form for Versiti Hematology Genetics testing can be found at http://www.versiti.org/hg under forms.

Test method:

NGS: This next-generation sequencing assay analyzes the complete coding region of 60 genes (excluding *PLAU*) plus a minimum 30bp of non-coding DNA, including intron-exon boundaries, as well as one targeted variant, and is compared to the build GRCh37.p13 reference sequence. In addition to the complete coding regions, *F7* analysis includes 59 bp upstream of exon 1 to cover HNF-4 and Sp1 binding sites in the promoter region, 67 bp upstream of *F9* exon 1 is analyzed to cover *F9* Leyden variants, and *VWF* includes the 5' UTR. These targeted regions are captured by hybridization, amplified, and sequenced by massively parallel sequencing. Regions will have a minimum coverage of 50x and those regions with less than 50 sequencing reads or low quality coverage are supplemented with Sanger sequencing. All regions are covered by bidirectional analysis. Variants are identified by a customized bioinformatics pipeline, analyzed and comprehensively interpreted by our team of practicing hematologists with expertise in non-malignant hematology and laboratory diagnostics, scientists, and genetic counselors. All reported variants, including pathogenic, likely pathogenic, and variants of uncertain significance, are confirmed by Sanger sequencing. For prenatal testing, analysis of variable number tandem repeats (VNTR) is used to confirm results are not affected by maternal cell contamination.

aCGH: The specific genes are analyzed for copy number variations due to deletion or duplication by high density gene-focused array Comparative Genomic Hybridization. Probes are approximately 60bp in length and density of coverage in exonic regions is a minimum of 4 probes per 500 bp. Genomic DNA for the samples and gender-matched references are denatured, labeled with fluorescent dye and hybridized, the array is washed and scanned, and analysis is performed for the specific genes requested.

Assay sensitivity and limitations:

NGS: The analytical sensitivity of the NGS test is >99% for single nucleotide changes and insertions and deletions of less than 20 bp. NGS analysis is not designed to detect large deletions or duplications (>20 bp), or variants that are outside the regions sequenced. Low level mosaicism will not be detected by this sequencing methodology.

aCGH: Balanced chromosomal rearrangements (i.e., translocations, inversions) or point mutations that may be the cause of the clinical phenotype cannot be detected via aCGH. Any exonic deletion or duplication smaller than 500bp may not be detected. Low level of mosaicism will not be detected by aCGH. Probe performance could be affected by multiple SNPs in a given region. Breakpoints occurring outside the targeted gene(s) will not be defined.

Clinical Sensitivity

The clinical sensitivity of comprehensive genetic testing (NGS and aCGH) of the 60 genes and one targeted variant in this panel is highest in patients with a history of lifelong clinically significant bleeding who have a family history of bleeding and present with persistent abnormalities on functional hemostatic testing.

Reporting of results:

Results are classified and reported in accordance with ACMG next-generation sequencing and copy number variation standards. Sequence variants and large deletions and duplications predicted to be pathogenic, likely pathogenic, and of uncertain significance will be reported; variants classified as likely benign or benign are typically not reported but such data are available upon request. Sequence variants are described using standard Human Genome Variation Society (HGVS) nomenclature (http://hgvs.org); copy number variants are described in accordance with the International System for Human Cytogenomic Nomenclature (ISCN).

Specimen requirements:

Parental/Patient/Pediatric: 3-5 mL Whole blood (EDTA tube, lavender top), 2-5 mL Bone marrow (EDTA tube, lavender top), 3-4 Buccal swabs, or ≥1ug of DNA at ≥50ng/uL of High Quality DNA.

Fetal: 7-15 mL amniotic fluid, 5-10 mg chorionic villi; back up culture of amniocytes or chorionic villi is highly recommended. Cultured: Two T25 flasks cultured amniocytes or chorionic villi ($2x10^6$ minimum). Maternal blood sample of 3-5 mL Whole blood (EDTA tube, lavender top) is requested for all prenatal samples for maternal cell contamination studies. For questions please contact the laboratory to discuss sample requirements.

SHIP

Shipping requirements:

Ship on an ice pack at room temperature. Protect from freezing. Place the specimen and the requisition into plastic bags and seal. Insert into a Styrofoam container, seal and place into a sturdy cardboard box, and tape securely. Ship the package in compliance with your overnight carrier guidelines. Label with the following address:

Client Services/Diagnostic Laboratory
Versiti
638 N. 18th St
Milwaukee, WI, 53233

ORDER

Required forms:

Please complete all pages of the requisition form. Clinical history (including patient's ethnicity, clinical diagnosis, family history, and relevant laboratory findings) is necessary for optimal interpretation of genetic test results and recommendations. Clinical and laboratory history can either be recorded on the requisition form or clinical and laboratory reports can be submitted with the sample.

CPT Codes/Billing/Turnaround time:

Test code: 4825

For suggested CPT codes, visit the Versiti.org/test menu

Turnaround time: 21 days

The CPT codes provided are subject to change as more information becomes available. CPT codes are provided only as guidance to assist clients with billing.

For additional information related to shipping, billing or pricing, please contact, Versiti Client Services: (414) 937-6396 or 800-245-3117, Option 1, or labinfo@versiti.org.

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Inherited Bleeding Disorder references

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Variant interpretation references

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