Comprehensive Bleeding Disorder Panel

Versiti offers comprehensive genetic analysis to detect sequence variants and large deletions and duplications in 66 genes, plus one targeted variant, known to cause bleeding due to disorders of coagulation, platelet function, and/or hereditary hemorrhagic telangiectasia (HHT). 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**

Additional Description

Clinically significant bleeding is a nonspecific clinical presentation with multiple and complex etiologies; inherited causes of bleeding include platelet function disorders, coagulation disorders and hereditary hemorrhagic telangiectasia (HHT).

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.

Hereditary hemorrhagic telangiectasia (HHT), previously known as Osler-Weber-Rendu disease, is a group of disorders affecting vascular formation. Spontaneous and recurrent epistaxis is the most common presenting clinical feature. As additional manifestations develop with age and may go unrecognized, reliance on established clinical diagnostic criteria for HHT, the Curaçao criteria, can result in delayed or missed diagnosis, particularly in younger people or those without an established family history. Given that epistaxis is the common presentation and most frequent manifestation of HHT, six genes which have been identified as causative of or having significant phenotypic overlap with HHT are included in the Comprehensive Bleeding Disorder Panel.

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. Moreover, studies analyzing platelet function may be difficult to perform, results may be nonspecific and a coagulation workup for epistaxis would not reveal a diagnosis of HHT. For cases in which the laboratory phenotype is not 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 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. Variants associated with common and rare types of inherited coagulation

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and platelet function disorders will be identified with this panel, as will variants associated with HHT and HHT-like conditions. This panel does not assess for 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.

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
ACVRL1	**Hereditary hemorrhagic telangiectasia type 2**: epistaxis, mucocutaneous telangiectasias and arteriovenous malformations. Variants in *ACVRL1* are also reported in patients with pulmonary arterial hypertension.	Autosomal Dominant
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
ENG	**Hereditary hemorrhagic telangiectasia type 1:** epistaxis, mucocutaneous telangiectasias and arteriovenous malformations	Autosomal Dominant
*EPHB4**	**Capillary malformation-arteriovenous malformation 2**: capillary malformations on the face or limbs, telangiectasias, epistaxis and AVMs or arteriovenous fistulas. Variants in *EPHB4* can also cause Parkes Weber syndrome, with cutaneous malformations and soft-tissue and skeletal overgrowth of an affected limb.	Autosomal Dominant
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
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
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 *F13B*	**Factor XIII deficiency:** umbilical cord bleeding, spontaneous intracranial bleeding, delayed bleeding after surgery, menorrhagia, impaired wound healing and infertility.	Autosomal Recessive
FERMT3	**Leukocyte adhesion deficiency-III** (LAD-III): severe bleeding with a Glanzmann thrombasthenia-like phenotype on platelet aggregation studies and associated immunodeficiency.	

Comprehensive Bleeding Disorder Panel: gene, clinical phenotype and inheritance pattern.		
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FGA *FGB* *FGG*	**Afibrinogenemia:** severe/delayed bleeding from markedly decreased or absent fibrinogen.	Autosomal Recessive
	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
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:** macrothrombocytopenia and/or anemia with moderate bleeding due to platelet alpha granule deficiency.	X-linked
GDF2	***GDF2*-related vascular anomaly syndrome:** pulmonary arterial hypertension, cerebral arteriovenous malformations, telangiectasias and epistaxis. **Hereditary hemorrhagic telangiectasia type 5**: epistaxis, mucocutaneous telangiectasias and arteriovenous malformations.	Autosomal Dominant
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 *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

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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
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): severe macrothrombocytopenia with associated platelet dysfunction leading to moderate to severe bleeding.	Autosomal Recessive
*RASA1**	**Capillary malformation-arteriovenous malformation 1:** capillary malformations on the face or limbs and AVMs or arteriovenous fistulas. Pathogenic biallelic variants in *RASA1* can also cause Parkes Weber syndrome, with cutaneous malformations and soft-tissue and skeletal overgrowth of an affected limb.	Autosomal Dominant
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§*	**α1-Antitrypsin (α1-AT) 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
SMAD4	**Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome**: predisposition to gastrointestinal hamartomatous polyps, often seen along with features of hereditary hemorrhagic telangiectasia, characterized by epistaxis, mucocutaneous telangiectasias and arteriovenous malformations. Pathogenic gain-of-function variants in *SMAD4* cause Myhre syndrome, characterized by growth deficiency, intellectual disability, facial dysmorphisms, skeletal anomalies, and cardiovascular defects.	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

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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)

§ Targeted variant of the Pittsburgh allele in exon 5 only

* Somatic pathogenic variants in *EPHB4* and *RASA1* have been described and associated with Parkes Weber syndrome. Please note that this assay is not designed for detection of somatic variants. See Assay Sensitivity and Limitations below.

**Available by aCGH 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 inherited bleeding disorder in which the laboratory phenotype is not consistent with clinical symptoms, or the specific bleeding disorder is unclear
- with a suspected inherited bleeding disorder that have inconclusive functional hemostatic testing or in situations where functional hemostatic testing cannot be obtained
- 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 neutropenia or neutrophil dysfunction, inherited bleeding disorders including platelet function disorders, coagulation disorders and HHT. 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 versiti.org/hg under *forms*.

Test method:

NGS: This next-generation sequencing assay analyzes the complete coding region of 66 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, *F2* analysis includes the 3' UTR, *F7* analysis includes 59

bp upstream of exon 1 to cover HNF-4 and Sp1 binding sites in the promoter region, *F9* analysis includes 67 bp upstream of exon 1 to cover *F9* Leyden variants, *VWF* and *F8* analysis includes the 5' UTR, analysis of *ACVRL1* and *ENG* includes the 3' UTR and targeted sequencing of *SERPINA1* (NM_000295.4) c.1145T is included. 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 (including *PLAU*) 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 sex-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 this panel is highest in patients with a history of lifelong clinically significant bleeding who also have features suggesting an inherited cause, such as family history of similar bleeding, persistent abnormalities on functional hemostatic testing and/or extra-hematologic symptoms consistent with syndromic presentation.

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-reported ancestry, 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: NGS only, aCGH only, or NGS and aCGH concurrently: 21 days

NGS reflex to aCGH: 21 days (if NGS only, aCGH not needed) or 42 days (with reflex to aCGH)

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.

References

Inherited Bleeding Disorder references

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Variant interpretation references

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