

von Willebrand Disease

Laboratory Support of Diagnosis

Clinical Background

von Willebrand disease (vWD), the most common inherited bleeding disorder, is due to either a quantitative or qualitative defect of von Willebrand Factor (vWF). vWF is synthesized by endothelial cells and megakaryocytes and circulates as a high molecular weight glycoprotein multimer non-covalently bonded to factor VIII and, as such, functions as a carrier protein that protects factor VIII from proteolysis. vWF multimers range in size from 500,000 to >20 million Daltons, and multimer size is correlated with hemostatic activity, ie, larger multimers are more hemostatically active. vWF is stored in platelet alpha granules and endothelial cell Weibel-Palade bodies.

In normal clotting, vWF mediates platelet-platelet and platelet-vessel wall adhesion via glycoprotein 1b (GP1b) on the platelet surface. When the level of vWF is decreased, hemostasis is impaired due to inadequate platelet binding and a reduction in factor VIII activity, which is caused by

decreased levels of factor VIII (ie, lack of protection from proteolysis).

The incidence of vWD is estimated to be 1% to 3%.^{1,2} Inherited vWD is divided into 3 types reflecting pathophysiology (Table 1).^{2,4} Additionally, acquired vWD, frequently called von Willebrand syndrome, and platelet-type vWD have been described.

Type 1 vWD accounts for approximately 70% of cases. It is characterized by a partial deficiency (10% to 45% of normal) of vWF secondary to decreased production or release. Additionally, a subset of type 1 vWD secondary to increased clearance of vWF has recently been identified.⁵ Individuals with type 1 vWD may be asymptomatic or have mild symptoms (eg, bleeding from gums or heavy menstrual cycles) until a severe injury or operation precipitates a significant bleeding episode.^{1,2}

Type 2 vWD accounts for approximately 30% of cases and is characterized by defective vWF function. Circulating vWF

Table 1. Characteristics and Differential Diagnosis of Inherited von Willebrand Disease

Type	Frequency (% of vWD)	Bleeding	Genetic Transmission ^a	Response to DDAVP	vWF Antigen	Ristocetin Cofactor (vWF Activity)	Factor VIII Clotting Activity	vWF Collagen Binding Assay	Molecular Weight Multimer
1	70	Asymptomatic to moderately severe	Autosomal dominant	Good	↓	↓	↓	Normal or ↓	Normal
2A	10-15	Moderate to moderately severe	Autosomal dominant or recessive	Mild to moderate	Normal or ↓	Normal or ↓	Normal or ↓	↓↓↓	High & intermediate missing
2B	<5	Moderate to moderately severe	Autosomal dominant	DDAVP not indicated ^b	Normal or ↓	Normal or ↓	Normal or ↓	↓↓↓	High missing
2M	10-15	Significant	Autosomal dominant	Mild to moderate	Normal or ↓	↓ or ↓↓	Normal or ↓	Normal	Normal
2N	Uncommon	Mild to moderate	Autosomal recessive	Suboptimal	Normal	Normal	↓ or ↓↓	Normal	Normal
3	Rare	Severe	Autosomal recessive	No response ^c	↓↓↓ ^e	↓↓↓ ^e	↓↓↓ ^e	↓↓↓	Absent
Platelet ^d	Uncommon	Moderate to moderately severe	Autosomal dominant	DDAVP not indicated	Normal or ↓	↑↑↑	Normal or ↓	Normal	High often missing

DDAVP, desamino-8-arginine vasopressin; vWD, von Willebrand disease; vWF, von Willebrand factor.

^a Incomplete penetrance is typically seen.

^b Some patients have a mild to moderate response without untoward events, while others have worsening thrombocytopenia and increased risk of stroke or heart attack.

^c Mild to moderate response in double heterozygotes (ie, type 1 and 3 heterozygote).

^d Also referred to as pseudo-von Willebrand disease.

^e Levels must be <10% to be classified as type 3 vWD.

levels are normal or marginally decreased. Individuals have bleeding symptoms similar to those with type 1 vWD.^{1,2} Type 2 vWD subtypes, reflecting distinct defects of vWF processing and multimeric composition, have been identified (Table 1). von Willebrand type 2N (Normandy) is an unusual variant associated with a defect in factor VIII binding to vWF, which causes a low factor VIII activity, mimicking hemophilia.²

Type 3 vWD affects approximately 1 in 500,000 individuals and is characterized by an almost complete deficiency of vWF and very low levels of factor VIII. Affected individuals have severe bleeding that can be life-threatening if not recognized and treated.^{1,2}

Acquired vWD is associated with malignancies, immunologic diseases, circulatory dysfunction such as aortic stenosis, and other medical conditions (eg, hypothyroidism); it is also frequently associated with myeloproliferative disorders.^{6,7} In acquired vWD, vWF is produced normally but is rapidly removed from circulation by tumor cell adhesion, vWF antibody mediated disruption of large multimers, or proteolytic digestion. Some experts believe that up to 20% of individuals diagnosed with vWD have an acquired form of the disorder.^{6,7}

Platelet-type vWD is uncommon and characterized by a gain of function of the von Willebrand binding protein located on the surface of platelets, the loss of large multimers, and thrombocytopenia.⁸

Classification of vWD is crucial, as risk of bleeding and treatment vary with type. Treatment for type 1 vWD is desmopressin (DDAVP), which induces the release of stored vWF from endothelial cells. DDAVP may also be effective in treating some individuals with type 2A and 2M vWD, but it is ineffective in type 2N and 3 disease. DDAVP is not indicated for type 2B and platelet vWD. Exogenous factor VIII and vWF are used to treat types 2N and 3 vWD and individuals with type 2A or 2M when they don't respond to DDAVP (Table 1). Some individuals with acquired vWD respond to DDAVP; those that do not are typically treated with exogenous factor VIII and vWF.^{6,7}

Individuals Suitable for Testing

- Individuals with a history of unexplained menorrhagia, lifelong bruising, unexplained epistaxis, or significant bleeding from minor surgical procedures
- Individuals with a family history of vWD
- Some individuals with autoimmune disorders and/or lymphoma/myeloma and new-onset bleeding

Test Availability

Tests available to assist in diagnosis of von Willebrand disease are listed in the Appendix. Refer to the Quest Diagnostics Directory of Services for ordering information.

Test Selection and Interpretation

A laboratory work-up for individuals suspected of having a bleeding disorder such as vWD begins with a personal and family history. Individuals with vWD will frequently have a history of epistaxis, which may be prolonged or unusually severe; easy bruisability; gingival bleeding; prolonged bleeding from minor wounds; or prolonged and heavy menstrual

Table 2. Bleeding Characteristics of von Willebrand Disease

Bleeding from skin and mucous membranes (gingivae, nares, GI and genitourinary tract)
Petechiae
Small, superficial ecchymoses
Hemarthroses, muscle hematomas (rare)
Significant bleeding after minor cuts
Immediate, mild bleeding after surgery

bleeding (Table 2). The severity of bleeding, however, does not always correlate with the degree of vWF deficiency, and symptoms can vary between patients with the same type of vWD as well as between family members.^{1,3,9} Though vWD is inherited in an autosomal dominant or recessive manner, many affected individuals will have a negative family history due to incomplete penetrance. Additionally, it is important to rule out the use of drugs that alter platelet function in individuals suspected of having vWD, eg, non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics.¹⁰

Testing typically begins with a complete blood count (to assess hemoglobin, hematocrit, platelet count, and morphology), bleeding time, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Measurement of the bleeding time has been largely replaced by determination of closure time measured with the platelet function analyzer, PFA-100® (Dade Behring, Newark, DE).¹¹ In this document "bleeding time" refers to a traditionally measured bleeding time and closure time. Individuals with vWD will usually have a normal PT and platelet count and an increased bleeding time and aPTT. While an increased bleeding time and/or aPTT is consistent with vWD, the aPTT may be normal in untreated mild or moderate disease and alone cannot exclude vWD.^{1,12} It will be prolonged in severe disease due to very low vWF and factor VIII and may be decreased in platelet-type vWD. Likewise, bleeding time may be normal in mild or moderate vWD.

Consequently, individuals with an increased bleeding time and/or aPTT, or individuals with a strong family or personal history suggestive of vWD, should be tested for vWF antigen, ristocetin cofactor (vWF activity), factor VIII activity, and ABO blood group (Figure).

A decreased level of vWF antigen, ristocetin cofactor, and/or factor VIII clotting activity is consistent with vWD. Additional testing is then warranted to identify the type of vWD and includes vWF collagen binding assay, vWF:factor VIII binding activity ratio (von Willebrand Disease Type 2N Panel), and multimeric analysis.¹² vWF collagen binding assay results are reported as a collagen binding:vWF antigen ratio; a ratio <0.5 is consistent with types 2A and 2B vWD. A normal ratio (≥0.5) is associated with type 2M and 2N vWD.¹³ The vWF:factor VIII binding activity ratio is typically <0.73 in individuals with type 2N. Table 1 summarizes the expected results of tests used in the diagnosis and typing of inherited vWD. Though no definitive pattern of test results are found in individuals with acquired vWD, typically, vWF antigen levels are decreased and factor VIII activity levels may be decreased or normal. von Willebrand mutation analysis may be useful in select

cases to differentiate hemophilia A from type 2N vWD, distinguish the various type 2 subtypes, and counsel individuals with type 3 vWD.³

Additional information useful in the interpretation of tests used in the diagnosis of vWD follows. Test results should be interpreted in conjunction with other laboratory and clinical findings. A full clinical consultation is available upon request.

Additional Information for Tests Useful in von Willebrand Disease

Activated Partial Thromboplastin Time (aPTT)

The aPTT will be prolonged if there is deficiency or inhibition of factors in the intrinsic pathway including high molecular weight kininogen (HMWK); prekallikrein; factors V, VIII, IX, X, XI, and XII; prothrombin; and fibrinogen. Levels of factor V or X typically have to be <15% of normal before a prolongation of aPTT is seen. Prolongation is also seen in individuals with lupus anticoagulant. Most individuals with severe vWD or type 2N will have an increased aPTT, whereas approximately 25% to 50% of individuals with type 1 vWD will have an aPTT outside the reference range.

Bleeding Time

Bleeding time is a measure of the interaction of platelets with blood vessel walls and is increased in individuals with thrombocytopenia, vWD, vascular purpura, severe fibrinogen deficiency, qualitative platelet abnormalities (eg, uremia), and the use of certain drugs (eg, NSAIDs). A normal value does not rule out the presence of vWD; conversely, an abnormal result in the absence of other causes justifies specific testing for vWD. Measurement of platelet function by determining closure time with the PFA-100 has largely replaced bleeding time measurements. The PFA-100 is an in vitro system that simulates the in vivo function of platelets in primary hemostasis. Testing is performed using a small whole blood sample anti-coagulated with citrate.

Complete Blood Count (CBC)

Hemoglobin and hematocrit may range from normal to markedly decreased depending on the type and severity of vWD. See also Platelet Count.

DDAVP Response

DDAVP (desamino-8-arginine vasopressin) is a synthetic analogue of antidiuretic hormone. It is considered the

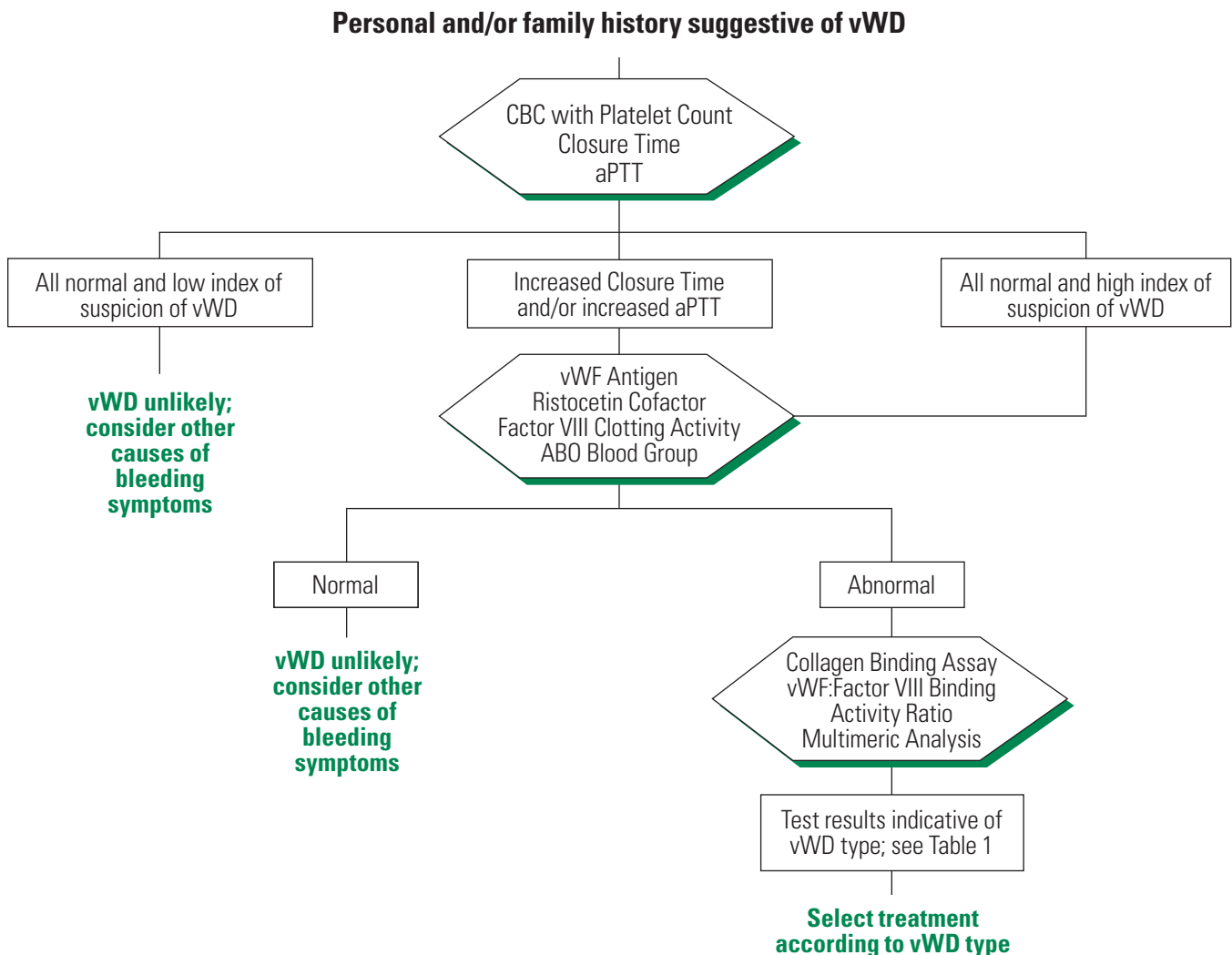


Figure. Diagnostic testing for von Willebrand disease (vWD). See Test Selection and Interpretation for details.

primary treatment for bleeding in individuals with mild vWD (type 1, sometimes types 2A and 2M) and works by causing the release of vWF from endothelial storage sites. An individual's therapeutic response to DDAVP is usually tested before prescribing the medication. A positive response is an increase of vWF antigen, factor VIII, and/or ristocetin cofactor of 2- to 5-fold over baseline 30 to 90 minutes after the administration of DDAVP. DDAVP is contraindicated in individuals with type 2B vWD due to the possibility of platelet clumping and subsequent increased risk of thrombosis. It is ineffective in individuals with type 2N, 3, and platelet vWD.

Factor VIII

Factor VIII is an acute phase reactant and increased levels are found during periods of stress, postoperatively, and in inflammatory conditions. Elevated levels are also found at birth and during pregnancy. Increased levels are associated with increased risk for venous thrombosis. vWF binding normally protects factor VIII from proteolysis; thus, decreased levels of vWF lead to decreased levels of factor VIII. Levels are typically in the low normal range in mild vWD. Low levels (6% to 45% of normal) are found in type 2N, and very low levels (<10%) in type 3 vWD. Decreased levels are also associated with hemophilia A, disseminated intravascular coagulation (DIC), and with specific factor VIII inhibitors (antibodies).

Mixing/Correction Study

Test results are consistent with an intrinsic factor deficiency when a prolonged aPTT is normalized after mixing patient plasma with normal plasma and the normalized result does not reverse after incubation of the mixed sample. A specific factor inhibitor, lupus inhibitor, fibrinolysis, or fibrinogenolysis is suggested when 1) the PT is normal, and the aPTT is prolonged initially, normalizes after mixing, and reverses to prolonged after incubation of the mixed sample; 2) the PT is normal, and the aPTT remains prolonged after mixing; 3) a prolonged PT is corrected in the mixing study, and a prolonged aPTT remains prolonged; and 4) a prolonged PT remains prolonged, and a prolonged aPTT normalizes after mixing and reverses to prolonged after incubation. A prolonged PT that is corrected in the mixing study, along with a normal aPTT, suggests a factor VII deficiency. Test results are consistent with a single or multiple deficiency of factors II, V, or X (common pathway) when a prolonged PT is normalized after mixing studies and when a prolonged aPTT normalizes after mixing studies and remains normalized after incubation.

Platelet Count

The platelet count is normal in most individuals with vWD; it is decreased, however, in those with type 2B and platelet type vWD. A normal platelet count, in the presence of an increased bleeding time, is consistent with vWD, vasculopathies, connective tissue diseases, and qualitative platelet abnormalities and warrants further testing for vWD. A normal platelet count and normal bleeding time is consistent with fibrinolytic disorders and may be seen in individuals with vWD; thus, further vWD testing is warranted when clinical suspicion is high.

Prothrombin Time (PT)

The PT measures the time for clot formation after the

addition of tissue factor (thromboplastin) and calcium to citrated blood and, as such, is prolonged with deficiencies of factors II, V, VII, X, and fibrinogen; liver disease; coumadin use; and vitamin K deficiency. PT is within the reference range in individuals with vWD.

Ristocetin Cofactor (von Willebrand Factor Activity)

Ristocetin is an antibiotic that causes vWF to bind and subsequently activate platelets. In plasma of normal individuals, platelets rapidly agglutinate in response to ristocetin due to the presence of vWF (ie, ristocetin cofactor). In individuals with vWD, the degree of platelet agglutination is proportional to the amount of vWF (and ristocetin) present; thus, the level of ristocetin cofactor (von Willebrand factor activity) is variably decreased in individuals with vWD. In type 2B and platelet vWD, a supranormal (exaggerated) response to ristocetin is seen.

von Willebrand Antigen, Multimeric Analysis

The size distribution of vWF multimers is determined by gel electrophoresis and used in determining the type of vWD present. High molecular weight multimers are missing in type 2B and platelet vWD, whereas high and intermediate weight multimers are absent in type 2A. All multimers are missing in type 3 vWD. In types 2M and 2N vWD, the multimeric analysis is typically normal.

von Willebrand Disease Mutation Analysis

This assay identifies mutations in the vWF gene associated with types 2A, 2B, 2M, 2N, and some forms of type 1 and 3 vWD. While this assay has limited clinical utility in the diagnosis of vWD (ie, diagnosis is typically made based on vWF antigen/activity levels and multimeric structure), it is useful for differentiating mild hemophilia A from type 2N vWD, distinguishing type 2A from type 2B vWD (useful due to the relative contraindication of DDAVP in individuals with type 2B vWD), and determining the causative mutation in families with type 3 vWD for the management of future pregnancies.³ Additional information regarding the use and interpretation of this test may be obtained by calling Quest Diagnostics' genetic counselors at 1-866-GENEINFO.

von Willebrand Disease Type 2N Panel

This test is used to identify type 2N vWD. A vWF:factor VIII binding activity ratio of 0.73 to 1.42 is considered normal. A normal ratio may be seen in vWD other than type 2N because factor VIII activity and vWF antigen may be reduced proportionally. In type 2N vWD, factor VIII activity is reduced, but vWF antigen levels are normal; thus, the ratio is decreased. A ratio <0.73 is consistent with type 2N vWD.

von Willebrand Factor Activity (Gp1b-specific EIA; functional vWF)

This assay directly measures the functional activity of vWF, and is used to confirm low (<20%) ristocetin cofactor levels. Levels <35% are consistent with vWD, while levels above the reference range (35% to 134%) have no known clinical significance.

von Willebrand Factor Antigen

This test measures total amount of the vWF protein. Levels are decreased in types 1 and 3 vWD. Levels may be normal

or decreased in types 2A, 2B, and 2M due to abnormal multimeric structure. This test is normal in type 2N vWD.

Levels of vWF vary by blood type and ethnicity. The mean level of vWF in individuals with blood type O is approximately 30% lower than in individuals with blood types A, B, or AB.¹⁴ Higher mean levels of vWF are found in African Americans than in other ethnic groups.¹⁵ Debate exists whether reference ranges should be specific for blood group type or ethnicity; however, bleeding tendency is primarily related to vWF antigen level and multimeric composition.^{1,12}

Increased levels of vWF may be seen secondary to stress, inflammation, acute infection, physical exercise, following

surgery, during the second and third trimesters of pregnancy, and in individuals receiving estrogen therapies; thus, serial testing may be necessary to confirm or rule out vWD.

von Willebrand Factor Collagen Binding Assay

The activity of vWF is determined by measuring the ability of vWF to bind collagen. The ability of vWF to bind collagen is a function of large multimers; thus, collagen binding activity is abnormal in types 2A and 2B vWD, but may be normal in types 2M and 2N. Collagen binding is compared to the vWF antigen value by calculating a collagen binding ratio (vWF collagen binding:vWF antigen). Typically, a ratio ≥ 0.5 is considered normal, whereas, a ratio < 0.5 is consistent with vWD.

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Appendix. Tests Used in the Diagnosis of von Willebrand Disease

The Appendix Table contains a comprehensive list of tests used in the diagnosis of von Willebrand disease.

Appendix Table. Tests Used in The Diagnosis of von Willebrand Disease

Test Code	Test Name	Method	Description
763X	Activated Partial Thromboplastin Time (aPTT)	Photo-optical clot detection	A phospholipid reagent is mixed with patient plasma, and calcium chloride is then added to initiate clot formation. The time elapsed for formation of a fibrin clot is measured.
8504X	Bleeding Time	Template (in vivo clotting)	A standard incision is made by an automated device in the forearm and blood is blotted away every 30 seconds. The time until bleeding has ceased is measured. (Measurement of the bleeding time has been largely replaced by determination of closure time measured with the platelet function analyzer, PFA-100®.)
6399X	CBC with Differential and Platelet Count	Electronic cell sizing, sorting/cytometry/microscopy	Flow cytometry with specific gating is used to quantify individual components. Significant abnormalities are reviewed microscopically.
See individual tests	DDAVP Response	Perturbation test	Baseline vWF antigen, factor VIII clotting activity, and/or ristocetin cofactor are measured followed by administration of DDAVP. Levels are then measured again 30 to 90 minutes after DDAVP administration.
347X	Factor VIII Activity, Clotting	Photo-optical clot detection	Patient plasma is mixed with factor VIII-deficient normal plasma. The APTT clotting time of the mixed plasma is compared to that of reference plasma. Results are reported as percent of normal factor VIII activity.
8922X	Mixing/Correction Study	Photo-optical clot detection	A PT and/or aPTT is measured after mixing patient plasma and normal plasma to determine the cause (eg, factor deficiency, factor inhibitor, and/or nonspecific inhibitor) of a prolonged PT and/or aPTT test result.
8847X	Prothrombin Time	Photo-optical clot detection	Thromboplastin and calcium chloride is mixed with patient plasma and the time to clot formation is measured photometrically.
4459X	Ristocetin Cofactor (ie, vWF antigen activity)	Platelet Agglutination	Ristocetin cofactor (vWF) in the sample causes agglutination of stabilized platelets in the presence of ristocetin. Activity is measured by a change in turbidity.
16028X	vWF Activity (ie, Gp1b-specific EIA, functional vWF)	ELISA	A monoclonal antibody specific to the portion of vWF that binds platelets is used to capture vWF. This bound vWF antigen is quantified using horseradish peroxidase conjugated anti-human vWF antibody.
4919X	vWF Antigen	Immunoturbidimetric	Patient plasma is mixed with vWF antibody-coated latex particles. vWF from the sample causes aggregation of the latex particles, which is measured photo-optically.
5168X	von Willebrand Antigen, Multimeric Analysis	Electrophoresis	vWF multimers are separated on agarose gel, the gel is electro-blotted onto a PVDF membrane and the multimeric pattern is visualized via chemiluminescence.
10924X	vWF Collagen Binding Assay	ELISA	vWF in patient plasma binds collagen immobilized on microtiter plates. Bound vWF is detected using peroxidase conjugated anti-vWF antibody.
15540X	vWF Comprehensive Panel	See individual tests	Panel includes: aPTT; factor VIII activity, clotting; vWF antigen; ristocetin cofactor; vWF factor collagen binding assay; vWF antigen, multimeric analysis; interpretation.
19837X	von Willebrand Disease Mutation Analysis	PCR	Exons 11, 12, 14, 15, 16, 18, 19, 20, 24, 27, 28, and 52 of the vWF gene are amplified in a single-plex PCR reaction. Known and novel mutations in the exons sequenced are identified.
19735X	von Willebrand Disease Type 2N Panel	ELISA, Photo-optical clot detection, Immunoturbidimetric	Two assays performed simultaneously are used to determine exogenous recombinant factor VIII binding to patient vWF and to quantify patient vWF. The vWF:Factor VIII binding activity ratio is calculated.

DDAVP, desamino-8-arginine vasopressin; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; PVDF, polyvinylidene difluoride; vWF, von Willebrand factor.

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Nichols Institute

von Willebrand Comprehensive Panel

Test code: 15540X

Clinical Use

- Diagnose and type von Willebrand disease

Clinical Background

von Willebrand disease (vWD) is an inherited bleeding disorder due to either a quantitative or qualitative defect of von Willebrand Factor (vWF). vWF is synthesized by endothelial cells, circulates as a high molecular weight glycoprotein multimer, and is a carrier protein for factor VIII. In normal clotting, vWF mediates platelet-platelet and platelet-vessel wall adhesion. In the complete absence of vWF, initiation of the coagulation cascade is prolonged and clot formation is impaired due to marked reduction in factor VIII activity. vWD is divided into 3 categories reflecting pathophysiology.^{1,2} Additionally, a number of extremely rare forms of vWD have been described.

Type 1 vWD accounts for approximately 70% of the cases of vWD. It is characterized by a partial deficiency (10% to 45% of normal) of vWF secondary to decreased production or release. Affected individuals may be asymptomatic or have mild symptoms (eg, bleeding from gums or heavy menstrual cycles) until a severe injury or operation precipitates a significant bleeding episode.^{1,2} Type 2 vWD accounts for approximately 25% of the cases of vWD and is characterized by defective vWF functioning. Circulating levels of vWF may be normal or marginally decreased. Individuals have bleeding symptoms similar to those with type 1 vWD.^{1,2} Subtypes of type 2 vWD reflecting distinct defects of vWF processing and multimeric composition have been identified. Type 3 vWD affects approximately 1 in 500,000 individuals and is characterized by an almost complete deficiency of vWF and very low levels of factor VIII. Affected individuals have severe bleeding that can be life-threatening if not recognized and treated.^{1,2}

Rare forms of vWD include platelet-type vWD and acquired vWD. Platelet-type vWD is characterized by a gain of function of the von Willebrand binding protein located on the surface of platelets, the loss of large multimers, and thrombocytopenia.³ Acquired vWD is associated with

malignancies, immunologic diseases, and myeloproliferative disorders.⁴ In acquired vWD, vWF is produced but may be rapidly removed from circulation by tumor cell adhesion or disruption of large multimers.

This panel includes assays that measure the quantity and functional activity of vWF, as well as assays that ascertain the multimeric structure of vWF in order to determine the type of vWD present. Treatment for type 1 vWD includes desmopressin (DDAVP), which induces the release of stored vWF from endothelial cells. Exogenous factor VIII and vWF are used to treat types 2 and 3 vWD.

Individuals Suitable for Testing

- Individuals with a history of unexplained menorrhagia, lifelong bruising, unexplained epistaxis, or significant bleeding from minor surgical procedures
- Individuals with a family history of vWD
- Some individuals with autoimmune disorders and/or lymphoma-myeloma and new-onset bleeding

Specimen Requirements

Three 1-mL aliquots of frozen 3.2% sodium citrate plasma (light blue-top tube); one 1-mL aliquot minimum.

Method

- This panel includes tests for activated partial thromboplastin time (aPTT), factor VIII clotting activity, vWF antigen, ristocetin cofactor, vWF collagen binding assay (CBA), and von Willebrand multimeric analysis. The ratio of CBA to vWF antigen is calculated.
- Methods used include: photometric clot detection, immunoassay, platelet agglutination, electrophoresis, immunoturbidimetric assay
- CPT codes:* 85730; 85240; 85246; 85245; 83520; 85247

Reference Range

See Table 1.

Table 1. Reference Ranges for von Willebrand Comprehensive Panel Assays

	aPTT (seconds)	Factor VIII Clotting Activity (%)*	vWF Antigen (%)*	Ristocetin Cofactor (%)*	vWF Collagen Binding Assay (%)*	CBA:vWF Ratio
Reference Range	22-34	60- 180	≥50	42-200	45-198	0.75 to 1.32

*Normal is defined as the mean of pooled plasma obtained from apparently healthy individuals. Reference ranges are based on a percentage of this mean and are reported as % of normal.

Table 2. Typing Inherited von Willebrand Disease

Type	Factor VIII Clotting Activity	vWF Antigen	Ristocetin Cofactor	vWF Collagen Binding Assay	Molecular Weight Multimer	DDAVP Response
1	↓	↓	↓	Normal or ↓	Normal	Good
2A	Normal or ↓	Normal or ↓	Normal or ↓	↓↓↓	High & intermediate missing	Mild to moderate
2B	Normal or ↓	Normal or ↓	Normal or ↓	↓↓↓	High missing	DDAVP not indicated*
2M	Normal or ↓	Normal or ↓	↓ or ↓↓	Normal	Normal	Mild to moderate
2N	↓ or ↓↓	Normal	Normal	Normal	Normal	Ineffective
3	↓↓↓	↓↓↓	↓↓↓	↓↓↓	Absent	None†
Platelet	Normal or ↓	Normal or ↓	↑↑↑	Normal	High often missing	DDAVP not indicated

*Some patients have a mild to moderate response without untoward events while others have worsening thrombocytopenia and increased risk of stroke or heart attack.
 †Mild to moderate response in double heterozygotes (ie, type 1 and 3 heterozygote).

Interpretive Information

The aPTT may be normal in untreated mild or moderate disease and alone cannot exclude vWD. It will be prolonged in severe disease due to very low vWF and factor VIII and may be decreased in platelet-type vWD. A CBA to vWF antigen ratio <0.75 is consistent with vWD; however, a ratio within the normal range does not rule out vWD. A low ratio confirms vWD when other tests are equivocal. See Table 2 for characteristics of inherited von Willebrand disease.

Levels of vWF vary by blood type and ethnicity. The mean level of vWF in individuals with blood type O is approximately

30% lower than in individuals with blood types A, B, or AB.⁵ Higher mean levels of vWF are found in African Americans than in other ethnic groups.⁶ Increased levels of vWF may be seen secondary to stress, inflammation, acute infection, physical exercise, following surgery, during the second and third trimesters of pregnancy, and in individuals receiving estrogen therapies.

Test results should be interpreted in conjunction with other laboratory and clinical findings. A full clinical consultation is available upon request.

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* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payor being billed.



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