Setting a new standard in von Willebrand Factor Activity Determination

INNOVANCE VWF Ac assay

↗ **siemens-healthineers.us/hemostasis**

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Von Willebrand disease: physiological causes and effects

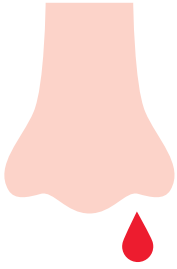
Disturbances in the primary hemostasis system are the major cause of bleeding events. Patients with these disturbances are at increased risk for severe bleeding, especially during surgical interventions. Careful evaluation of primary hemostasis, which is principally determined by platelet function and von Willebrand factor activity, is important to minimize adverse outcomes in these patients.

Von Willebrand factor (VWF) is a multimeric, high-molecular glycoprotein involved in primary hemostasis, supporting platelet adhesion and aggregation under high-shear stress at the site of injury. Furthermore, VWF is the specific carrier protein of coagulation factor VIII, protecting factor VIII against inactivation and rapid clearance.

Von Willebrand disease (VWD), a dysfunction of primary hemostasis caused by quantitative or qualitative deficiency of von Willebrand factor, is the most common hereditary bleeding disorder. Leading symptoms of VWD include nosebleeds, menorrhagia, and bleeding after tooth extraction. In contrast, strong elevated VWF levels due to endothelial activation or dysfunction are frequently associated with cardiovascular disease and the risk for future ischemic heart disease or stroke.

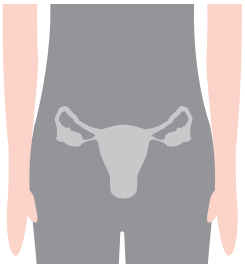
Von Willebrand disease is present in roughly 1% of the general population. In patients undergoing surgery, a correct diagnosis allows targeted prophylactic treatment of the identified bleeding risk with the potential to significantly reduce the need for blood transfusions.[1]

Leading symptoms of VWD



Nosebleeds

Bleeding after tooth extraction



Menorrhagia

Distribution of VWF levels

A wide range of VWF levels is seen in the general population. There are several genes that affect VWF levels, with the major genetic influence coming from the ABO blood-group gene. Individuals with blood group O have 15–25% lower VWF levels than individuals with non-O blood group. However, a substantial fraction of the variation in VWF is not heritable and is related to inflammatory activity. VWF shows a fast and strong increase with acute phase reaction, which complicates the detection of mild VWD in the presence of stress or inflammation.[2]

NHLBI interpretation guide for VWF levels[2]

50–200% VWF	Normal VWF
30–50% VWF	Low VWF; probably modestly increased bleeding risk
<30% VWF	Decreased VWF; increased bleeding tendency; presence of VWF mutations likely

Subtypes of von Willebrand disease[2]

The most common type is VWF with quantitative defects, but a normal distribution of multimers.

VWD Type 1	Reduction of VWF defined; antigen and activity are in the same range due to decreased synthesis or increased degradation
VWD Type 3	Complete absence of VWF multimers (<5%)

Qualitative defects of VWF are less common.

VWD Type 2A	Selective reduction in or deficiency of large VWF multimers and reduction of platelet-dependent function
VWD Type 2B	Characterized by a strong affinity of VWF to GPIb, usually in conjunction with a low platelet count and reduced VWF activity
VWD Type 2M	Low platelet-dependent function of the VWF with large multimers present
VWD Type 2N	The FVIII binding site of VWF is defective; FVIII cannot bind and thus FVIII cannot be protected from premature degradation; clinical symptoms such as with hemophilia A

Management of VWD

To prevent or control bleeding in VWD patients, two major strategies are available. The first option is to increase plasma VWF concentration by stimulation and release of endogenous VWF stores in platelet and endothelial cells through application of desmopressin. This approach works well in most VWD type 1 patients and certain type 2 patients.

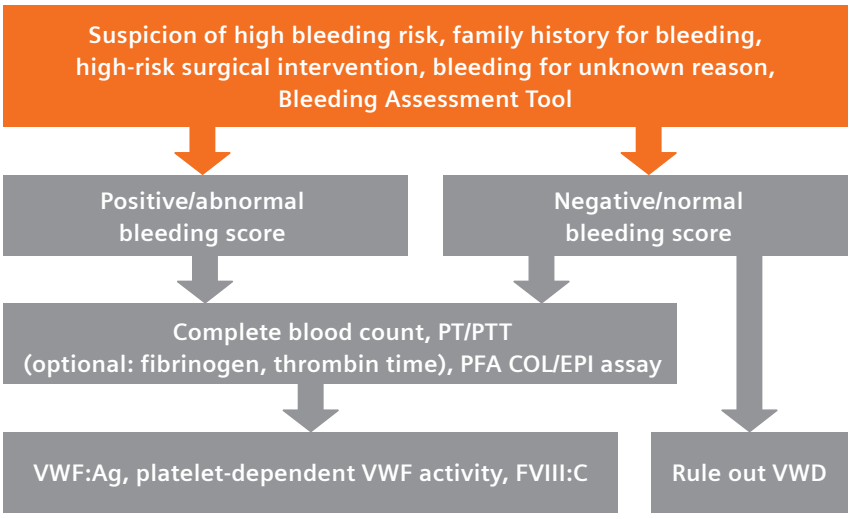
Replacement of VWF is the second alternative. Several human, plasma-derived VWF concentrates are available for therapy of those patients with insufficient response to desmopressin. However, before therapy can be started, a thorough anamnesis including appropriate lab testing is required.

Caveat: for VWD type 2B there is a clear contraindication.

Diagnosis and monitoring of von Willebrand disease

To correctly diagnose cases involving a bleeding anamnesis or a family history of von Willebrand disease and subsequently monitor patient response to therapy, physicians require a specific test for von Willebrand factor. A functional assay is the preferred screening method for detecting quantitative as well as qualitative defects of von Willebrand factor.[3]

Patients suspected of VWD[3]



Subtyping of VWD by additional specialty assays

VWD subtype characteristics (modified from Reference 2)

Assay	Normal	Type 1	Type 2				Type 3
			2A	2B	2M	2N	
Screening tests							
PFA COL/EPI assay	N	N or↑↑	↑↑	↑↑	↑↑	N	↑↑↑↑↑↑
Platelet count	N	N	N	N or↓↓↓	N	N	N
VWF activity: • Platelet-dependent VWF activity	N	Borderline to ↓↓	↓↓ or ↓↓↓↓	↓↓↓↓	↓ ↓or ↓↓↓↓	N or borderline	↓↓↓↓↓↓
Further VWF-related routine tests							
VWF Ag	N	Borderline to ↓↓ ↓↓	Borderline or ↓↓	Borderline or ↓↓	Borderline or ↓↓	N or borderline	↓↓↓↓↓↓
FVIII:C	N	N or ↓↓	N or ↓↓	N or ↓↓	N	↓↓↓↓	↓↓↓↓↓↓
VWF structure analysis							
VWF multimer analysis	Normal multimer distribution	Normal multimer distribution	Lack of HMWM	Lack of HMWM	Normal distribution	Normal multimer distribution	Absent
RIPA • High dose • Low dose	N NR	N or ↓↓ NR	↓↓ NR	N ↑↑	↓↓ NR	N NR	NR NR

N = Normal
NR = No reaction

A real functional assay for the automated determination of von Willebrand factor activity in human citrated plasma

INNOVANCE VWF Ac assay

The INNOVANCE® VWF Ac assay is a turbidimetric latex-based assay that requires no stirring and allows testing on all Siemens Healthineers and Sysmex® automated coagulation instruments.†

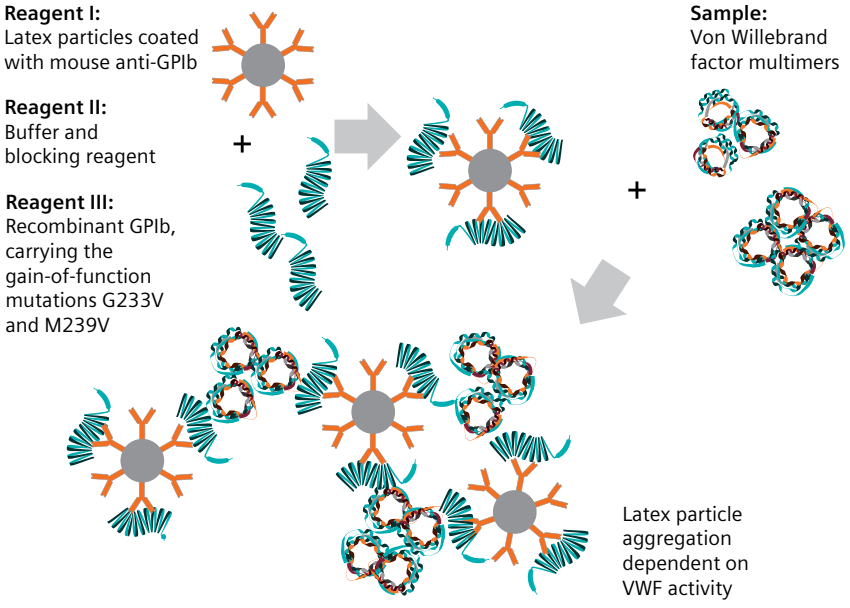
- Excellent precision and lot-to-lot consistency.
- Provides the ability to measure samples from 4–300% of norm based on three different settings in single-determination.
- Reagents are liquid and ready to use.

Assay performance

	BCS® XP System	Sysmex CS-2500 System	Sysmex CS-5100 System
Required sample volume (µl)	45	16	16
Measuring range (% of norm)	4 - 300	4 - 300	4 - 300
Onboard stability (hours)†	36	24 / 72*	24 / 72*
Repeatibility (CV %) of Control Plasma N	1.3	3	2.4
Within-Device/ Lab (CV %) of Control Plasma N	1.7	3.3	3

**Reagent I+II 24 hours, Reagent III 72 hours*

INNOVANCE VWF Ac assay principle



INNOVANCE VWF Ac assay employs an advanced new technology, allowing the assay to mimic the way in which VWF binds to glycoprotein Ib (GPIb), the major VWF receptor protein on platelets. Latex particles are coated with an antibody against GPIb, to which recombinant GPIb is added. The addition of patient plasma induces a VWF-dependent agglutination, which is detected turbidimetrically. Because the recombinant receptor protein includes two gain-of-function mutations, the assay does not require ristocetin.

†Except for Sysmex CA-620/600 Systems.

Reliable, precise and sensitive

Bleeding disorders are a clinically severe complication requiring a reliable assay result to allow further therapeutic decisions within the shortest time.

High precision

The INNOVANCE VWF Ac assay provides excellent reproducibility over the full range of measurements.

	VWF Mean (% of norm)	Reproducibility (CV %)
Control Plasma N	87.75	2.95
Control Plasma P	28.97	5.30
Plasma pool (low)	9.14	3.48
Plasma pool (decision range)	49.26	2.83
Plasma pool (normal)	128.29	6.29
Plasma pool (high)	251.63	5.04

**1 of 90 measurements (1.1%) was measured outside the measuring interval*

Multicentric reproducibility evaluation (5 days x 2 runs x 3 replicates design, one reagent/calibrator lot combination at three external sites with 89/90* samples).

Control and pool plasmas containing a range of 8–270% VWF were tested in two separate runs in two single determinations over 20 consecutive days without recalibration on all automated coagulation systems.

	Control N	Control P	Plasma pool (low)	Plasma pool (decision range)	Plasma pool (normal)	Plasma pool (high)
BCS XP System						
VWF Mean (% of norm)	84.83	28.62	10.06	52.23	129.74	271.47
Repeatibility (CV %)	1.33	4.26	1.44	1.64	5.00	5.00
Within-Device/ Lab (CV %)	1.69	4.82	2.04	2.65	6.43	6.40
CS-2500 System						
VWF Mean (% of norm)	82.56	28.80	8.08	45.02	134.95	272.12
Repeatibility (CV %)	3.03	2.38	2.20	2.14	3.44	2.60
Within-Device/ Lab (CV %)	3.33	2.63	2.41	3.52	4.25	3.06
CS-5100 System						
VWF Mean (% of norm)	81.46	30.16	8.82	46.44	133.98	253.08
Repeatibility (CV %)	2.37	2.15	1.61	1.24	1.44	1.19
Within-Device/ Lab (CV %)	3.01	2.19	2.13	2.79	3.56	1.75

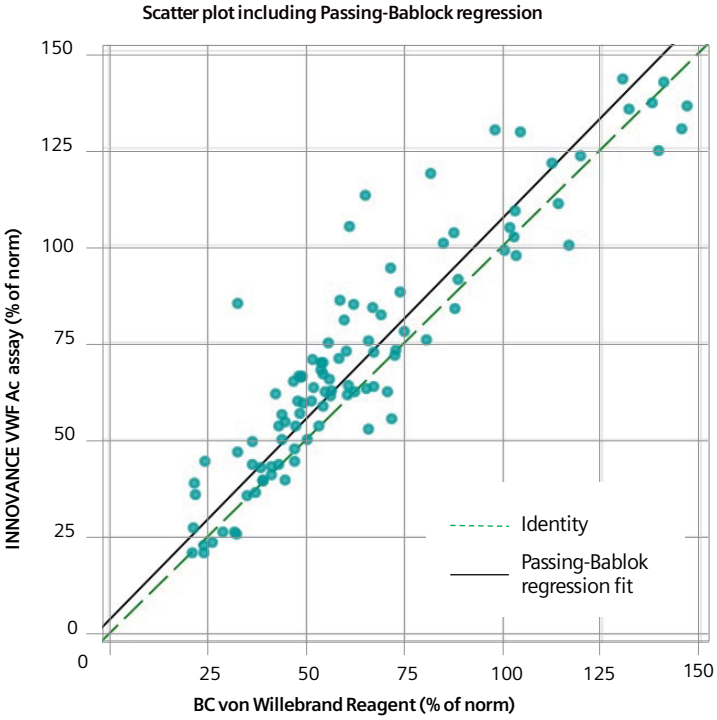
Diagnostic accuracy

Excellent correlation to VWF:RCo method

In the past, VWF:RCo assays such as BC von Willebrand Reagent were the recommended screening method for VWD. Ristocetin can also induce decapping of the A1 binding domain, the mechanism employed in VWF:RCo assays. However, ristocetin is an artificial substance, and in the presence of certain polymorphisms, false-low VWF levels may be measured that are not connected to bleeding risk.[4] In contrast to VWF:RCo assays, assays such as the INNOVANCE VWF Ac assay directly determine real activity of VWF. Both assays show excellent correlation.

"The automated VWF:GPIbM has demonstrated excellent clinical performance and has been favored by experts as interchangeable with VWF:RCo."

Higgins, et al. Am J Hematol. 2019;94:496-503.5



Method comparison measured on BCS® XP System

Number of samples (n)	102
Pearson Correlation Coefficient (r)	0.916
Slope	1.04
Intercept (% of norm)	3.50
Predicted Bias at 30% of norm	4.60% of norm
Predicted Bias at 50% of norm	10.14%

Siemens Healthineers offers a comprehensive portfolio of systems and assays for the diagnosis of bleeding disorders and therapy monitoring:

Platelet diseases
- PFA-100 System

Von Willebrand disease
- PFA-100 System
- BC von Willebrand Reagent
- INNOVANCE VWF Ac assay
- vWF Ag assay

FVIII, IX deficiency, hemophilia A+B
- Coagulation Factor VIII Deficient Plasma
- Coagulation Factor IX Deficient Plasma
- Factor VIII Chromogenic Assay

Contact your Siemens Healthineers representative today for more information on our bleeding portfolio or explore more on:

↗ siemens-healthineers.us/hemostasis

Diagnostic accuracy

Diagnostic accuracy of the INNOVANCE VWF Ac assay was evaluated in a method comparison study and a concordance study with patients representing the intended use population. Four clinical sites evaluated a total number of 144 patients with confirmed or suspected VWD. The patient cohort included 60 patients previously diagnosed with VWD [29 patients with VWD Type 1, 19 patients with VWD Type 2 (7 patients with Type 2A, 5 patients with Type 2B, 4 patients with Type 2M, 3 patients with Type 2N), 8 patients with Type 3, 4 patients with acquired VWD].

Additionally, 5 patients with haemophilia A, 1 patient with platelet dysfunction and 78 patients without final VWD related diagnosis at the time of enrollment where included.

After the exclusion of 6 patients due to therapy with increasing agents and diluted samples, an independent physician interpreted the laboratory values and classified the remaining patients (n=138) patients into one of the following categories: VWD, Low VWF, VWD Excluded, or Inconclusive Diagnosis.

Concordance Evaluation		Laboratory classification using the Standard of Care (SOC) VWF activity device in the initial VWD test panel				
		VWD (either type)	"low" VWF acc. to NIH guideline	VWD excluded	Inconclusive diagnosis	Total
Laboratory classification using the INNOVANCE VWF Ac assay in the initial VWD test panel	VWD (either type)	**26**	1	0	0	27
	"low" VWF acc. to NIH guideline	3	**10**	2	0	15
	VWD excluded	2	7	**68**	2	79
	Inconclusive diagnosis	4	1	1	**11**	17
	Total	35	19	71	13	**138**

Patients for whom the classifications of the initial VWD test panel results were discordant were further assessed: The discordances were evaluated in a Second Line Assessment. This assessment included an evaluation of potential benefits or risks of using either the SOC VWF activity device or the INNOVANCE VWF Ac assay in the initial VWD test panel.

VWF activity assay used in the initial test panel	No Impact	Potential Benefit	Potential Risk	Potential Benefit and Potential Risk
INNOVANCE VWF Ac	12	9	3	1*
SOC	14	2	8	1*

**The diagnostic classification/interpretation of one was evaluated as potentially beneficial and potentially risky for both VWF activity methods.*

Positive benefit-risk-analysis

Results

The results demonstrate that the benefit of using INNOVANCE VWF Ac assay is higher compared to using the SOC VWF activity assay whereas the risk of using INNOVANCE VWF Ac assay is lower compared to the SOC VWF activity assay.

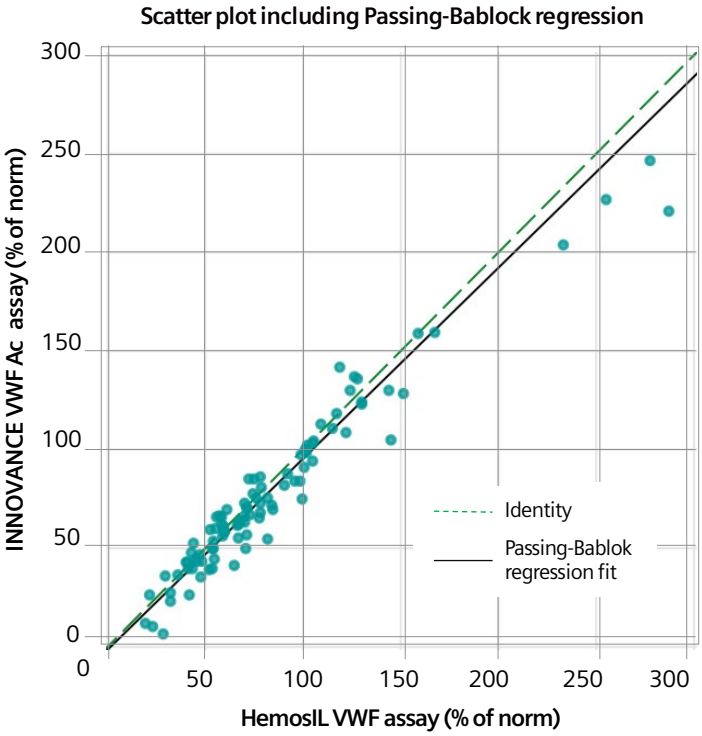
Conclusion

3-fold higher number of benefits associated with the use of INNOVANCE VWF Ac assay!

Be state of the art

The ASH/ISTH/NHF/WFH 2021 guideline on the diagnosis of von Willebrand disease suggests the use of VWF:GPIbM and VWF:GPIbR assay over the VWF:RCo assay

'The panel suggests newer assays that measure the platelet binding activity of VWF (eg, VWF:GPIbM, VWF:GPIbR) over the VWF:RCo assay (automated or non-automated) for the diagnosis of VWD [...].'



Good comparison to automated competitive assays

In the U.S., there are only a few automated von Willebrand activity assays available.

The HemosIL von Willebrand Factor Activity assay is a latex particle enhanced immunoturbidimetric assay based on the binding of a specific anti-VWF antibody against the platelet binding site of VWF.

Number of samples: 97

Pearson correlation coefficient: 0.972
y=0.969x – 1.495

"After the positive experience we had using this assay in a study, we as caregivers in the U.S. are urgently waiting to use the INNOVANCE VWF Ac assay to diagnose our patients as we believe it supports improved von Willebrand disease (VWD) diagnosis and patient management, particularly now given the new recommendations from the ASH ISTH NHF WFH 2021 guidelines on the diagnosis of VWD."

Steven Pipe, MD,
Professor of Pediatrics and Pathology
Laurence A. Boxer Research Professor of Pediatrics and Communicable Diseases
Pediatric Medical Director, Hemophilia and Coagulation Disorders Program
Director, Special Coagulation Laboratory
University of Michigan, MI US

Convenient and economical

Bleeding patients are always emergency cases who frequently come in at night or during the weekend.

Fast test results are required to support timely therapeutic decisions. The INNOVANCE VWF Ac assay is an automated, easy-to-use method available 24 hours a day/7 days a week to help physicians make the correct diagnosis quickly.

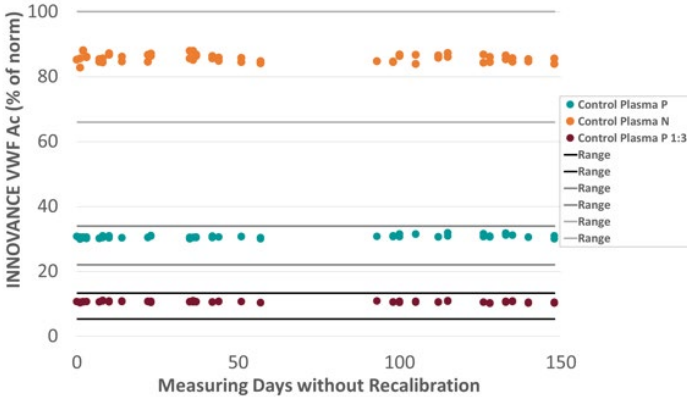
Convenient and easy to use

The test features liquid, ready-to-use reagents, with no processing preparation steps required for fully automated testing.

Stable calibration and control recovery

Controls Plasma N and P as well as Control Plasma P 1:3 diluted were tested over approx. 150 days without recalibration; all control results were well within the target range. Data from internal study.

Stable calibration of 8 month or longer with excellent control recovery minimizes recalibration requirements and increases availability of VWD testing.



Stable reagents

Excellent reagent stability minimizes waste and maximizes the number of tests obtainable from a given volume of reagent:

Stability at 2–8°C once opened (BCS XP System)	
Reagent I and II	37 days
Reagent III	113 days

Onboard stability	BCS XP	CS-Systems
Reagent I and II	36 hours	24 hours
Reagent III	36 hours	72 hours

If the reagents are removed and stored closed at 2 to 8 °C in between the measurement periods, the maximum accumulated on board stability time on rack line 1 to 4 on the BCS XP System is 24 hours for INNOVANCE VWF Ac REAGENT I and INNOVANCE VWF Ac REAGENT II and 36 hours for INNOVANCE VWF Ac REAGENT III.
(see Instruction for Use or Application sheet for further information)

Stable, robust method with low influence from interfering substances

With the INNOVANCE VWF Ac assay, no interference is observed up to:

- 656% VWF with regard to high-dose hook effect
- 1000 mg/dL hemoglobin
- 60 mg/dL bilirubin (unconjugated)
- 40 mg/dL bilirubin (conjugated)
- 726 mg/dL Lipids evaluated with lipemic samples
- 438 IU/mL rheumatoid factor

Available for labs of all sizes

The INNOVANCE VWF Ac assay makes it easy to perform comprehensive, highly accurate VWF testing.

Availability of the test across different platforms makes around-the-clock VWF Ac testing possible for labs of all sizes, eliminating the need to outsource testing.

The assay is available for:

- BCS XP Systems
- Sysmex CS-2500 System
- Sysmex CS-5100 System

Economical to use

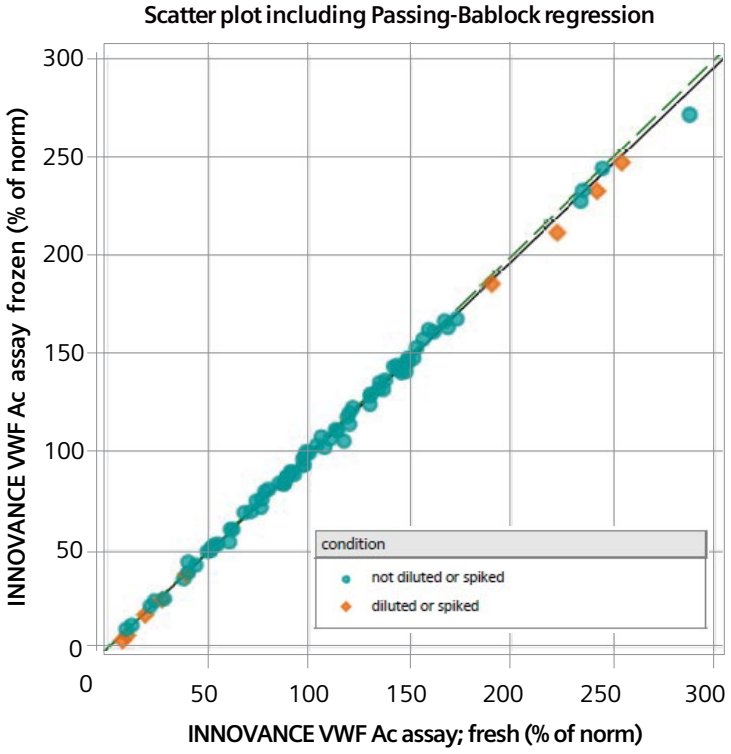
The INNOVANCE VWF Ac assay is economical to use because of its:

- Single-run determination with excellent precision
- Low recalibration frequency (up to 8 month calibration stability)
- Long reagent stability
- Long shelf-life (24 months)

Optimize your lab's VWF testing capability

"The INNOVANCE VWF Ac assay is reliable and precise with high sensitivity. The absence of ristocetin ensures result accuracy and minimizes the risk of misdiagnosis, especially in patients with a particular variant."

Professor Dr. Reinhard Schneppenheim, MD, PhD, Professor of Pediatrics, Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf



Good stability of specimen

The INNOVANCE VWF Ac assay can be used with fresh or frozen samples without further sample preparation.

15-25°C	Plasma stored on cells	4 hours
15-25°C	Plasma siphoned from cells	4 hours
≤-20°C	Plasma siphoned from cells	3 months
≤-74°C	Plasma siphoned from cells	12 months

Ordering information		
SMN #10487040	INNOVANCE VWF Ac assay	BCS XP System 120 tests per kit CS-Systems 110 test per kit
Siemens Material Number (SMN) #10487040 contains:		
3 x 2.0 mL Reagent I (latex reagent) 3 x 3.5 mL Reagent II (buffer + blocking reagent) 1 x 2.5 mL Reagent III (GPIb reagent)		
Also required:		
ORKL 19ORKE 45	Standard Human Plasma	for calibration
SMN# 10446235	Control Plasma N	for quality control
SMN# 10446472	Control Plasma P	
SMN# 10445724	Owren's Veronal Buffer	for sample dilution

The INNOVANCE VWF Ac assay sets a new standard for automated determination of VWF activity. Now you can quickly and economically provide physicians with reliable, precise, and sensitive VWF test results, regardless of the size of your lab.

Contact your Siemens Healthineers representative for more information.

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Further information is available at www.siemens-healthineers.com.

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References:

1. *Koscielny J, von Tempelhoff GF, Ziemer S, et al. A practical concept for preoperative management of patients with impaired primaryhemostasis. Clin Appl Thrombosis/Haemostasis. 2004;10:155–66.*
2. *Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guideline, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia. 2008;14:171–232.*
3. *James PD, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. 2021 Jan 12 [published online]. DOI 10.1182/*
4. *Flood VH, Gill JC, Morateck PA, et al. Common VWF exon 28 polymorphisms in African Americans affecting the VWF activity assay by ristocetin cofactor. Blood. 2010;116:280–6. bloodadvances.2020003265*
5. *Higgins, et al. Automated assays for von Willebrand factor activity. Am J Hematol. 2019;94:496–503.*

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