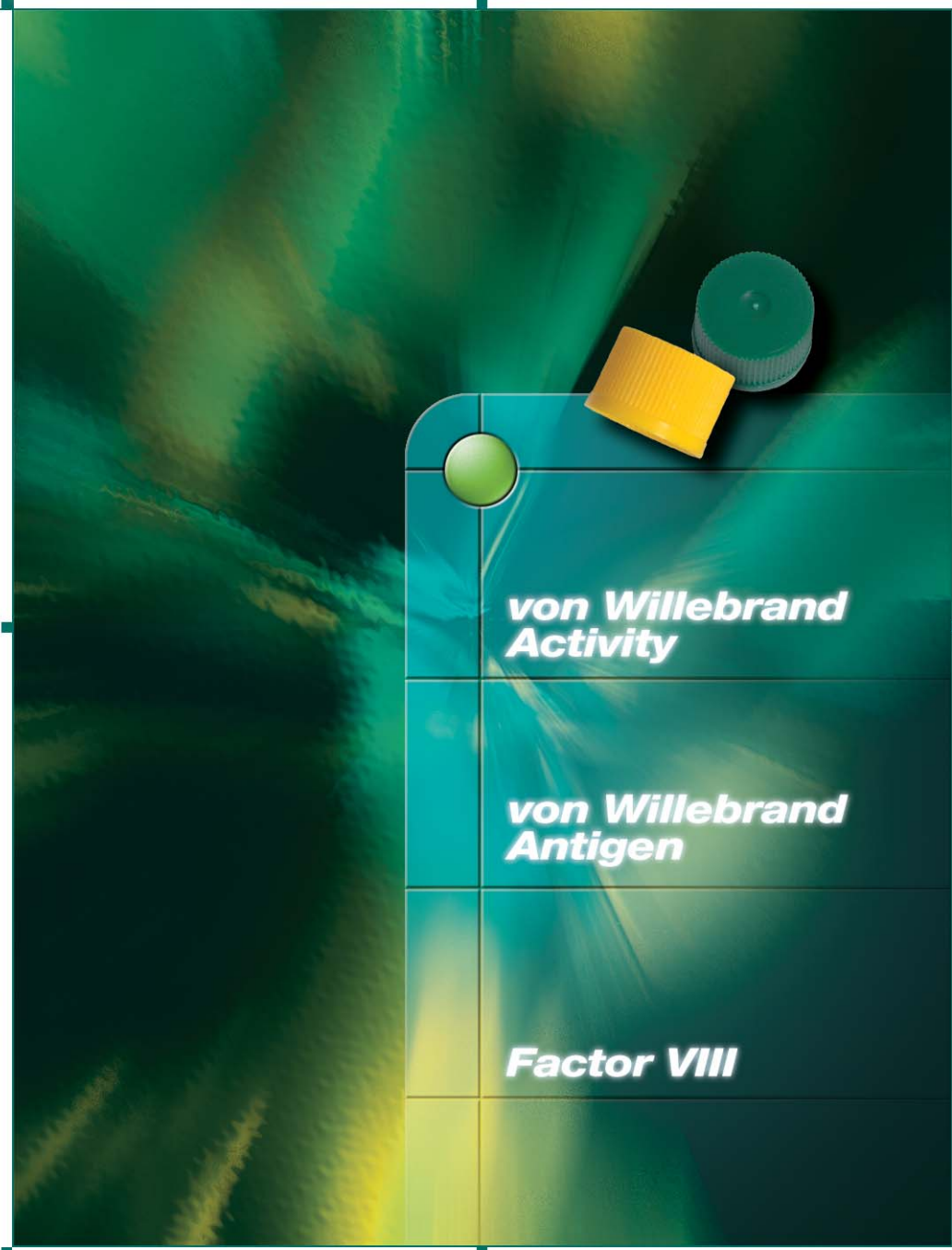


HemosIL[®]

Screening Assay for von Willebrand Disease

Hemostasis



Automated, Fast and Accurate
Simplifying VWD Diagnosis
*Detecting Qualitative
and Quantitative Defects*

Screening Assay for von Willebrand Disease

von Willebrand Disease

von Willebrand Factor (VWF) is a large protein that takes part in primary hemostasis, where it is essential for the interaction between platelets and damaged vessel walls, and indirectly in the coagulation process as it protects the labile coagulation Factor VIII (FVIII) from inactivation.

von Willebrand Disease (VWD) is a congenital bleeding disorder which, in contrast to hemophilia, affects both sexes and is caused by a quantitative or qualitative defect of the VWF.

The prevalence of VWD is estimated to be one percent worldwide.¹ There are three main subtypes of von Willebrand disease. Type 1 constitutes approximately 85% of confirmed cases. Most of the remaining 15% are Type 2 variants (Type 2A, 2B, 2M, 2N). Type 3, which has a prevalence of one in a million, is the most severe type.²

VWD can be either inherited or acquired. Acquired VWD can occur when an individual has a serious autoimmune problem, such as rheumatoid arthritis,

systemic lupus erythematosus, certain types of kidney failure or certain cancers. It may also develop without any other underlying conditions.

Individuals with mild-to-moderate Type 1 VWD may remain undiagnosed until they undergo surgery or have a serious injury. The diagnosis is usually confirmed by laboratory tests. An abnormal bleeding time may detect it, but diagnosis depends on more specific assays such as FVIII, VWF Antigen and a functional VWF assay.

The ABO blood group has a significant influence on VWF and FVIII:C values. More specifically, Type O shows a significantly lower normal range than the other blood groups. It is important to establish ABO-specific normal ranges, at least distinguishing Type O from the rest.¹⁰

Some individuals of blood group AB with a genetic defect of VWF may have the diagnosis overlooked because VWF levels are elevated with this blood type.

von Willebrand Disease Classification

The correct diagnosis and classification of VWD patients is directly related to the respective treatment. The table below summarizes the main characteristics of VWD types.

Type	Phenotype	Molecular origin	Treatment
Quantitative deficiency of VWF			
Type 1	Partial quantitative deficiency of VWF.	Often dominant. Its molecular origin is not fully understood.	Desmopressin usually effective.
Type 3	Virtually complete deficiency of VWF.	Autosomal recessive. Homozygous/ compound heterozygous for a defective VWF allele. Large deletions or nonsense, missense and frameshift mutations.	Desmopressin ineffective. VWF concentrates recommended.
Qualitative deficiency of VWF			
Type 2A	Decreased platelet-dependent function that is associated with absence of HMW VWF multimers.	Usually autosomal dominant. Missense mutations mainly located in the A2 domain.	Desmopressin effect variable. VWF concentrates recommended.
Type 2B	Increased affinity for platelet Glycoprotein Ib.	Usually autosomal dominant. Molecular defects located in the A1 domain.	Utility of desmopressin controversial. VWF concentrates might be recommended.
Type 2M	Decreased platelet-dependent function that is not associated with absence of HMW VWF multimers.	Usually autosomal dominant. Molecular defects located in the A1 loop.	Desmopressin effect variable. VWF concentrates recommended.
Type 2N	Markedly decreased affinity for FVIII.	Recessive homozygous or compound heterozygous. Mutations on the D' and D3 domains responsible for FVIII binding.	Desmopressin effective but brief. Patients may be misdiagnosed with mild to moderate hemophilia A.





von Willebrand Factor Activity

- Fully automated on IL coagulation systems for significant labor-savings
- Uses a specific monoclonal antibody, directed against the platelet-binding site of VWF (Gplb receptor), which is covalently coupled to latex particles
- Active VWF causes agglutination of latex particles, directly proportional to the active VWF in sample
- Excellent precision
- Correlates with Ristocetin Cofactor Activity Assays
- Fast turnaround time, less than twelve minutes

von Willebrand Antigen Assay

- Fully automated latex particle immunoturbidimetric assay on IL coagulation systems
- Quantifies VWF:Ag in human citrated plasma which, when mixed with coated latex particles, agglutinates directly proportional to the concentration of VWF:Ag, causing a decrease in transmitted light
- Liquid reagents, ready to use
- Excellent on-board stability
- Fast turnaround time, less than seven minutes

Factor VIII

Clotting

- Immunodepleted plasma
- One-stage clotting assay
- Used in combination with HemosIL APTT reagents
- Automated on IL coagulation systems

Chromogenic

- High sensitivity and precision
- Reference method for the European Pharmacopoeia
- Automated on IL coagulation systems

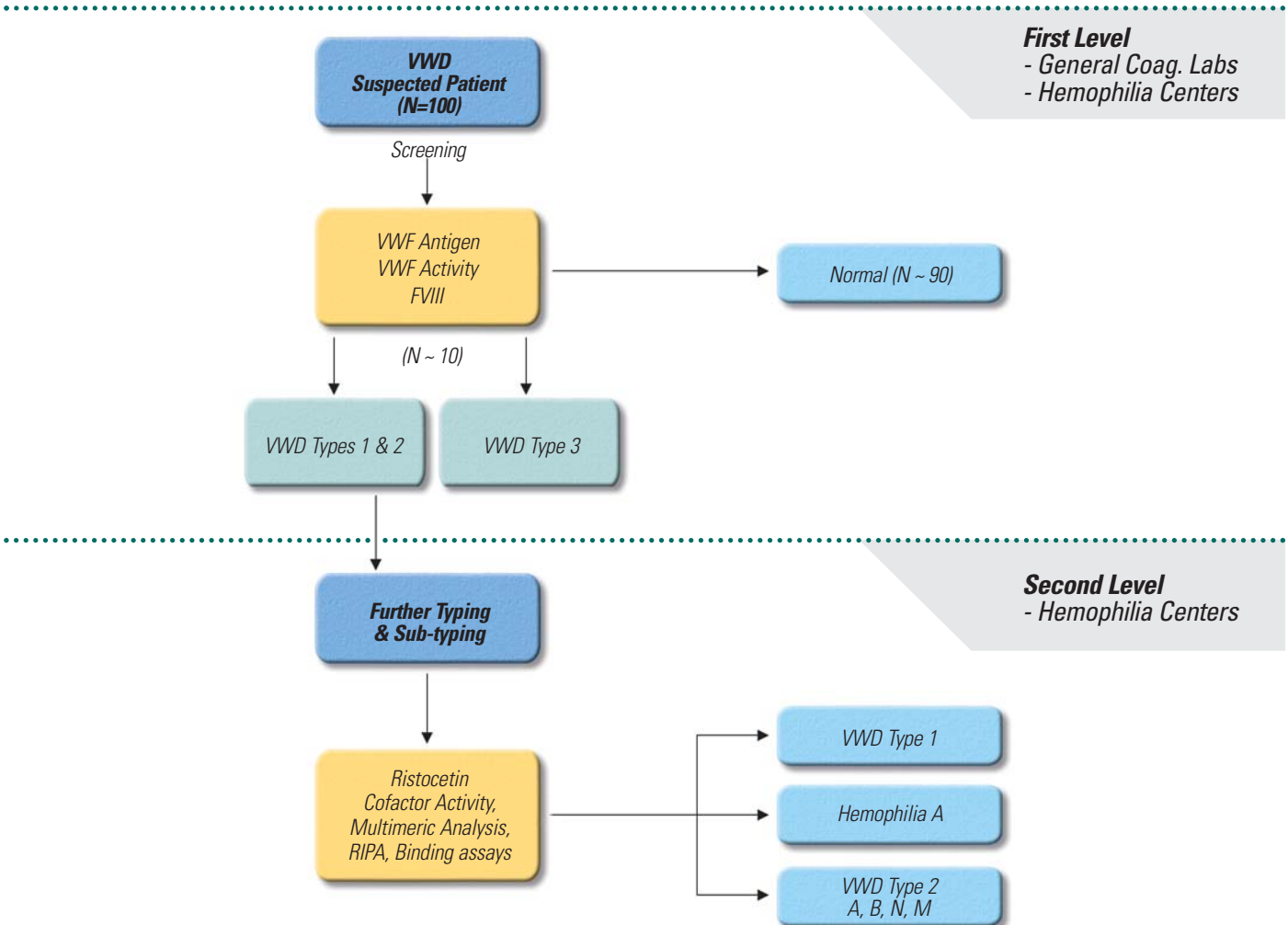
Screening Algorithm for VWD with HemosIL Kits

To identify the VWD type, laboratories should use HemosIL VWF Activity (PN 0020004700) with HemosIL VWF Antigen (PN 0020002300) and the FVIII assays, chromogenic (PN 49730503) or clotting (PN 0008466450).

Tests results should be compared to the scheme reported in the table below. Diagnosis cannot be based solely on the test results, but must consider the clinical history of the patient, as well as the results of other specialized laboratory techniques for confirmation and sub-typing.

VWD-Suspected Patient

	VWD Type 1	VWD Type 2		VWD Type 3	Normal
		2A, 2B, 2M	2N		
VWF Antigen levels	Below the normal range	Normal to low	Normal	Very low or undetectable	Normal
VWF Activity levels	Normal to low	Borderline to very low	Normal	Very low or undetectable	Normal
VWF Act/Ag Ratio	> 0.7	< 0.7	> 0.7	N/A	N/A
FVIII Activity levels	Normal to low	Normal to low	Low & Ratio FVIII/Ag < 0.7	Very low	Normal





HemosIL VWF Antigen and Activity Performance Data

	HemosIL VWF Antigen			HemosIL VWF Activity		
<i>P/N</i>	0020002300			0020004700		
<i>Package</i>	2 x 3 mL Latex Reagent			2 x 4.5 mL Latex Reagent		
	2 x 4 mL Reaction Buffer			2 x 4.5 mL Buffer		
<i>Tests/kit</i>	Approx 50			Approx 50		
<i>Time to result</i>	7 minutes			12 minutes		
<i>Open Vial Stability 2-8 °C</i>	3 months			1 month		
<i>Precision</i>		<i>Range %</i>	<i>CV% (Total)</i>		<i>Range %</i>	<i>CV% (Total)</i>
	Normal Control	80 - 120	< 3.5	Normal Control	80 - 120	< 6.0
	Special Test Control Level 2	30 - 40	< 6.0	Special Test Control Level 2	30 - 40	< 9.0
<i>Linearity</i>	Up to 600 % VWF:Ag			Up to 200 % VWF Activity		
<i>Normal range *</i>		% VWF:Ag			% VWF Activity	
	Blood Type 0	41 - 126			38 - 125	
	Blood Type A+B+AB	61 - 158			49 - 170	
<i>Prozone effect</i>	None up to 1600% VWF:Ag			None up to 350% VWF Activity **		
<i>RF Interference</i>	May produce an overestimation			May produce an overestimation		

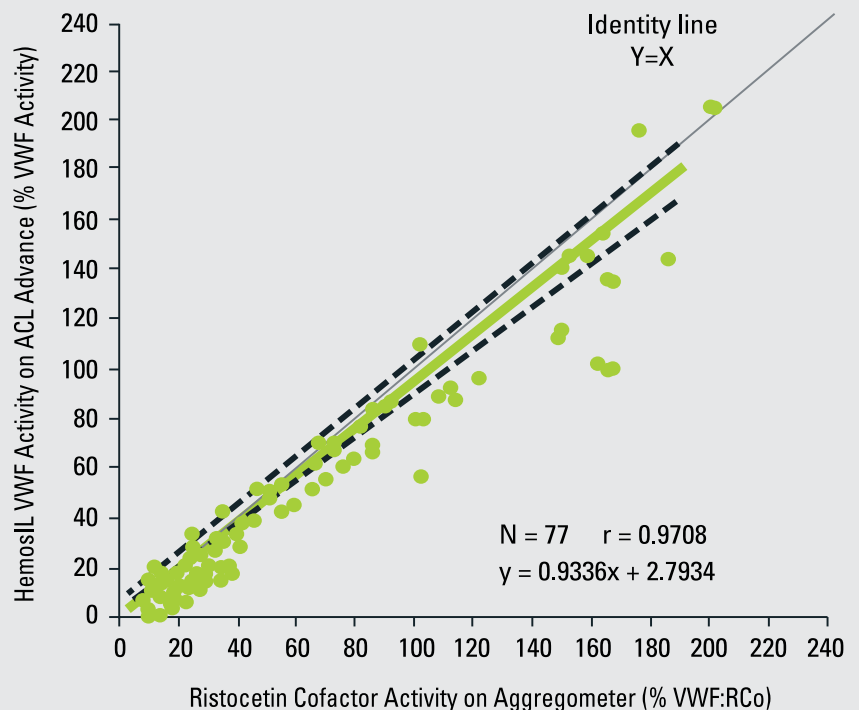
* These results were obtained using specific lots of reagent. Due to many variables, which may affect results, each laboratory should establish its own normal range.

** On the ACL Advance

Method Comparison

A comparison study was conducted using 77 patient plasma samples, analyzed in duplicate, with HemosIL VWF Activity on an ACL Advance versus Ristocetin Cofactor Activity on ag-gregometer. The comparison shows good correlation between the two methods.

HemosIL VWF Activity vs Ristocetin Cofactor Activity





HemosIL

Screening Assay for von Willebrand Disease

IL Tests for Diagnosing and Monitoring von Willebrand Disease

Reagent	Part Number	Packaging Configuration	Type of Assay
HemosIL von Willebrand Factor Activity	0020004700	Latex 2 x 4.5 mL Buffer 2 x 4.5 mL	Latex
HemosIL von Willebrand Factor Antigen	0020002300	Latex 2 x 3 mL Buffer 2 x 4 mL	Latex
HemosIL Factor VIII Deficient Plasma	0008466450	5 x 1 mL	Clotting
HemosIL ELECTRACHROME Factor VIII	49730503	Factor Reagent 2 x 3 mL Substrate 1 x 6 mL Buffer 2 x 24 mL	Chromogenic

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