AN OVERVIEW OF VON WILLEBRAND DISEASE

Leebeek FG, et al. von Willebrand's Disease. *N Engl J of Med.* 2016;375:2067-2080.

Updated with Recommendations from 2021 ASH ISTH NHF WFH Guidelines on Diagnosis

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Overview

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Overview

- von Willebrand's disease (VWD) is an inherited bleeding disorder characterized by defective platelet adhesion and aggregation[1]
- VWD arises from reduced levels of functional von Willebrand factor (VWF)[1]
- VWD is the most common inherited bleeding disorder, affecting 0.6 to 1.3% of people[1]

There are 3 major subtypes of VWD, differing by prevalence, molecular characteristics, and bleeding propensity[2]

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080; 2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024

2021 Guidelines: ASH, ISTH, NHF, WFH
Interpretation of Statements

Strong recommendations

- **For patients:** Most individuals in this situation would want the recommended course of action, and only a small proportion would not
- **For clinicians:** Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences

Conditional recommendations

- **For patients:** The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences
- **For clinicians:** Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences

Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation

1. James PD, et al. *Blood Advances* 2021;5:280-300.

Clinical Presentation

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CLINICAL PRESENTATION[1,2]

- Symptoms of VWD vary among patients, depending on VWF activity, disease subtype, age, sex
- The most common clinical presentation is mucocutaneous bleeding and bruising
- Life threatening bleeds can occur in severe patients

Common Symptoms of VWD

Bleeding from minor wounds	Postoperative bleeding
Cutaneous bleeding	Postpartum hemorrhage
Menorrhagia	Joint bleeding
Bleeding from tooth extraction	Muscle hematoma
Oral cavity bleeding	Gastrointestinal bleeding
Epistaxis	

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080; 2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024

Key Elements of Diagnostic Workup

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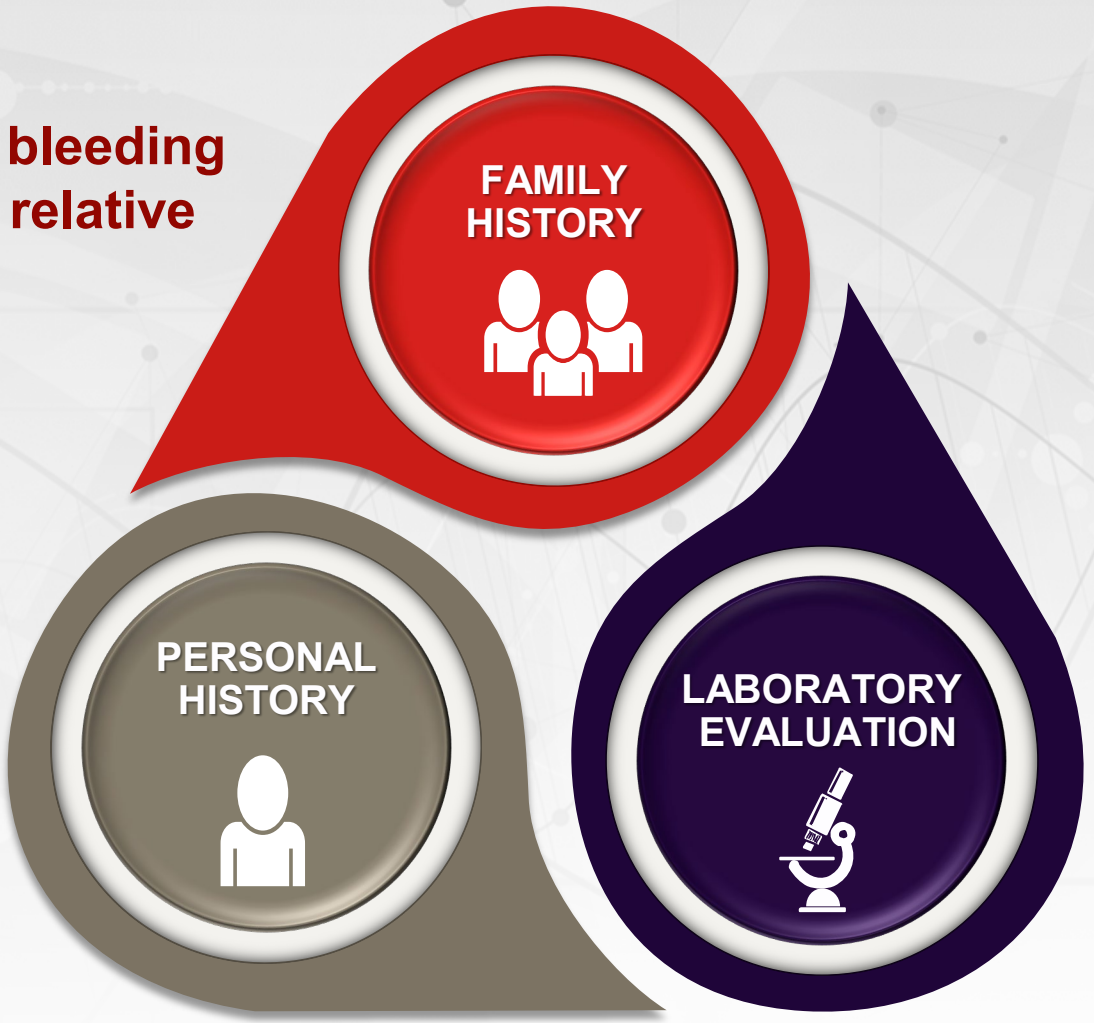
Key Elements of Diagnostic Workup

History of bleeding in a blood relative



History of bleeding and Bleeding Assessment Tool (BAT) score

Laboratory Evaluations

1. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024

Personal and Family History

- Assessment of bleeding phenotype starts with a detailed history of all bleeding symptoms in the patient and blood relatives[1,2]
  - Personal or family history of need for medical attention for a bleeding problem
- Personal history of liver or kidney disease, blood or bone marrow disorder, high or low platelet count
- Use of anticoagulant or antiplatelet drugs

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080; 2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024

2021 Guidelines: Bleeding Assessment Tools

Pre-test Probability of VWD	Recommendation	Remarks
Low (eg, seen in primary care setting)	Use validated BAT to determine who needs specific blood testing[a] (Strong)	Applies predominantly to adult women, as the data supporting the use of a BAT as a screening tool is strongest in this patient group
Intermediate (eg, referred to a hematologist)	Suggest against relying on BAT to decide whether to order specific blood testing* (Conditional)	Addresses patients with an intermediate VWD pretest probability (~20%) corresponding to those typically referred for hematology evaluation because of an abnormal personal bleeding history or abnormal initial laboratory tests
High (eg, affected first-degree relative)	Recommends against relying on a BAT to decide whether to order specific blood testing (Strong)	Addresses patients with a high VWD pretest probability (~50%) corresponding to those typically referred for hematology evaluation because of an affected first-degree relative regardless of their bleeding symptoms or initial laboratory tests (including men and children

The primary benefit of a BAT is to identify patients who have VWD but would be missed without the use of a BAT

*Specific blood testing refers to VWF antigen (VWF: Ag), platelet-dependent vWF activity (eg, VWF glycoprotein IbM [VWF:GPIbM]), and factor VIII (FVIII) coagulant activity (FVIII:C).

1. James PD, et al. *Blood Advances* 2021;5:280-300.

ISTH/SSC Bleeding Assessment Tool (BAT)[1]

BACK

Assesses the following symptom classes:

- Epistaxis
- Cutaneous bleeding
- Bleeding from minor wounds
- Hematuria
- Gastrointestinal bleeding
- Oral cavity bleeding
- Bleeding after tooth extraction
- Bleeding after surgery or major trauma
- Menorrhagia
- Post-partum hemorrhage
- Muscle hematoma
- Hemarthrosis
- Spontaneous CNS bleeding
- Other bleeding

Sample Detail: Bleeding from minor wounds

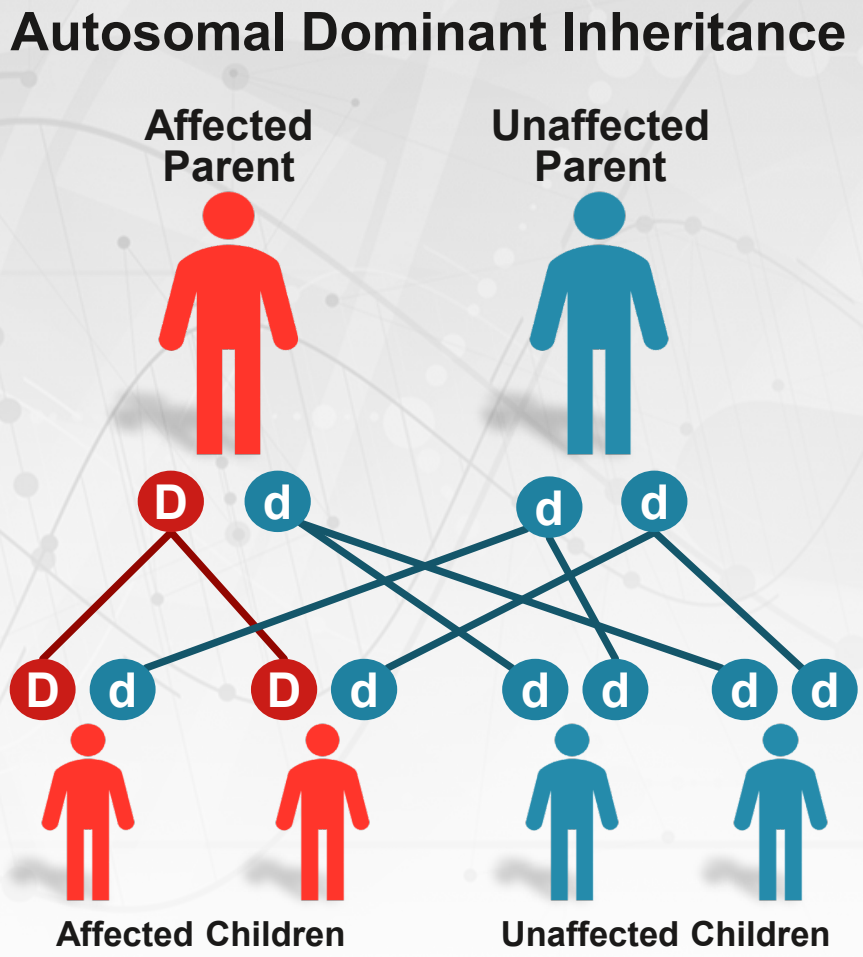
Paraphrased Question	Type
Ever had prolonged bleeding from a minor wound?	Y/N
Ever required medical attention for this symptom?	Y/N
Type of medical attention required	7 levels
How many times in your life?	4 levels
Age of first episode	5 levels
Number of episodes NOT requiring medical attention	5 levels
Duration of average episode	≤10 min >10 min

ISTH=international Society on Thrombosis and Haemostasis; SSC=Scientific and Standardization Committee

1. Rodeghiero F, et al. *J Thromb Haemost.* 2010;8(9):2063-2065.

Family History[1,2]

- Nearly all cases of VWD are inherited
  - Rare acquired cases may occur
- Most common inheritance pattern is autosomal dominant
- Exceptions:
  - Type 2N usually recessive
  - Type 3 VWD may be autosomal recessive or codominant



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Laboratory Evaluation of Suspected von Willebrand Disease

Initial Tests

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Laboratory Evaluation of Suspected von Willebrand Disease – Initial Tests[1,2]

VWF:Ag (VWF antigen) – immunoassay that measures the concentration of VWF protein in plasma

VWF:GPIbM or VWF:GPIbR – measures platelet-binding activity of VWF

Preferred over the older vWF:RCo[a] assay (Conditional)[2]

FVIII:C (Factor VIII coagulant activity) – assay that measures the function of FVIII as a cofactor in coagulation

VWF:CB (VWF Collagen Binding) – assay of VWF binding to collagen

RIPA[b] – assay that measures abnormal VWF binding and aggregation of platelets

Multimers – a qualitative assay that indicates abnormalities in the concentrations of VWF multimers

a. Ristocetin cofactor activity assay, a functional assay that measures the ability of VWF to bind platelets; b. Ristocvetin-Induced Platelet Aggregation

1. Laffan MA, Lester W, O'Donnell JS, et al. *Br J Hematol.* 2014;167:453-465; 2. James PD et al. *Blood Advances* 2021;5:280-300

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All Levels

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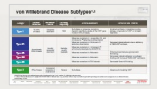
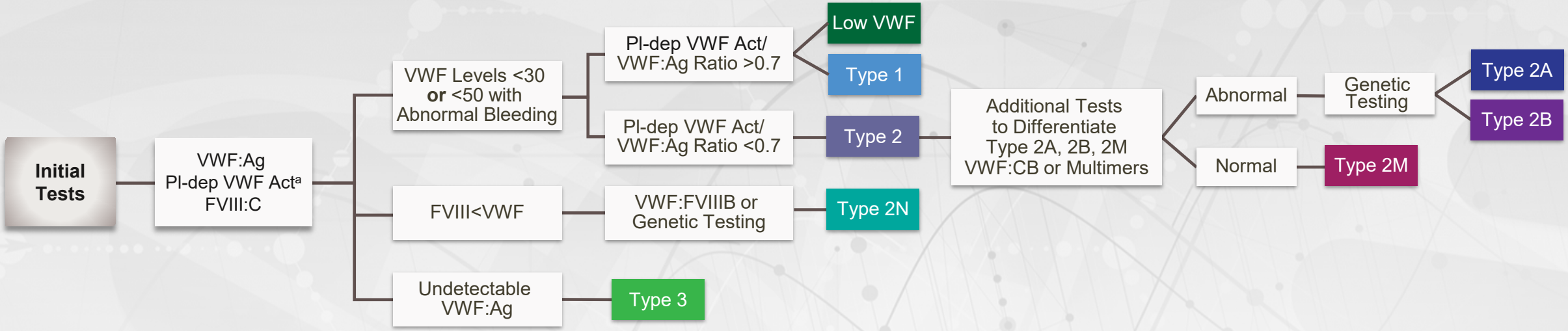
Laboratory Evaluation of Suspected von Willebrand Disease[1,2,3]





Good practice statement: VWF activity assays should be performed in a laboratory with appropriate expertise[5]

VWF=Von Willebrand Factor; VWF:Ag=VWF antigen; VWF:CB=VWF collagen binding; FVIII=factor VIII; FVIII:C=factor VIII coagulant activity; HMW=high molecular weight; RIPA=ristocetin-induced platelet agglutination

a. Platelet-dependent VWF Activity, VWF:GPIbM, or VWF:GPIbR preferred over VWF:Rco (Conditional recommendation)

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080; 2. Laffan MA, Lester W, O'Donnell JS, et al. *Br J Hematol.* 2014;167:453-465; 3. James PD, et al. *Blood Advances* 2021;5:280-300.

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Type 1 / Low VWF

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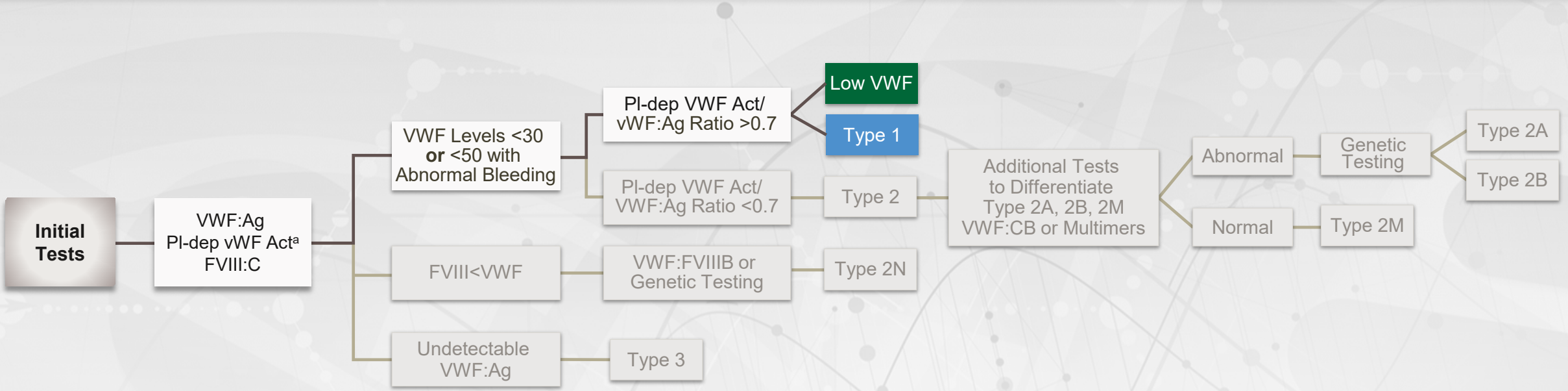

Condition	Diagnostic Features				Treatment Options		
	Pl-dep VWF Act/vWF:AG Ratio	VWF:Ag	Factor VIII:C	Description	Desmopressin	VWF Replacement Products*	Tranexamic Acid
Low vWF		30-50	Normal	VWF activity 0.3-0.5 IU/mL	✓		Alternative or Additional
Type 1	>0.7	<30 **or** <50 with abnormal bleeding	Low or Normal	Partial quantitative VWF deficiency	✓		Additional

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a. Platelet-dependent VWF Activity, VWF:GPIbM, or VWF:GPIbR preferred over VWF:Rco (Conditional recommendation)
*VWF:RCo concentrate, VWF-Factor VIII concentrate, or VWF concentrate
1. Leebeck FWG and Eikenboom JCJ. *NEJM*. 2016;375:2067-2080; 2. Laffan MA, Lester W, O'Donnell JS, et al. *Br J Hematol*. 2014;167:453-465; 3. James PD, et al. *Blood Advances* 2021;5:280-300.

Laboratory Evaluation of Suspected von Willebrand Disease

Type 2

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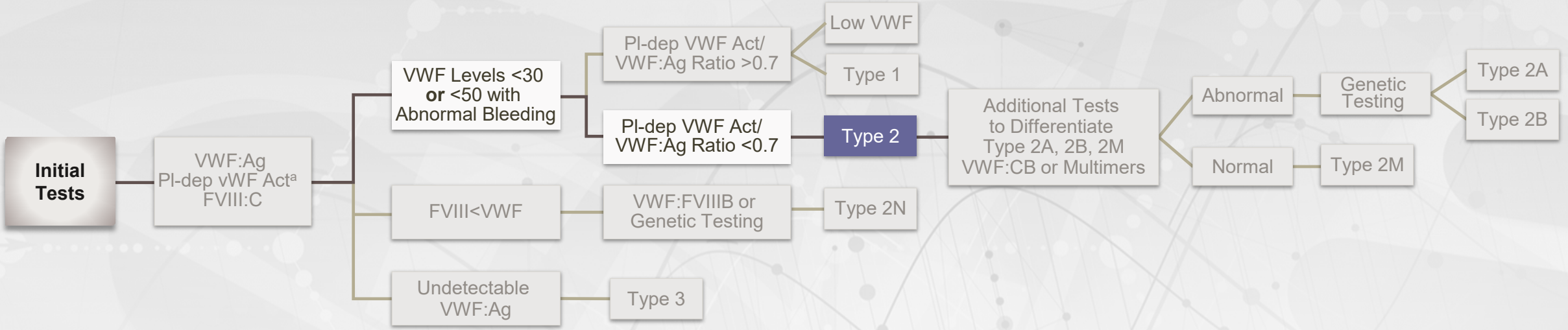

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a. Platelet-dependent VWF Activity, VWF:GPIbM, or VWF:GPIbR preferred over VWF:Rco (Conditional recommendation)

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080; 2. Laffan MA, Lester W, O'Donnell JS, et al. *Br J Hematol*. 2014;167:453-465; 3. James PD, et al. *Blood Advances* 2021;5:280-300.

Laboratory Evaluation of Suspected von Willebrand Disease

TYPES 2A, 2B, 2M, 2N

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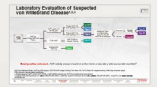
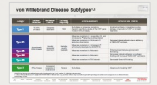
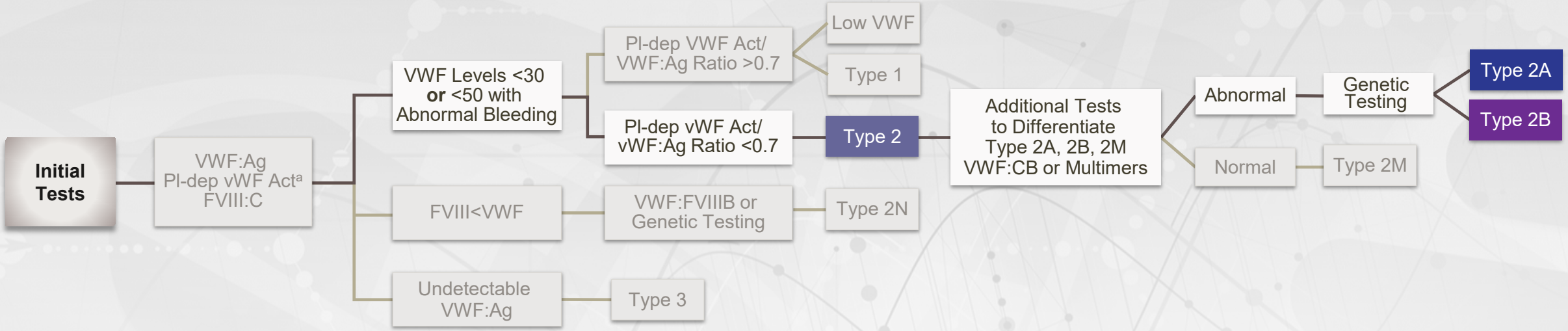
Laboratory Evaluation of Suspected von Willebrand Disease[1,2,3]







Condition	Diagnostic Features				Treatment Options		
	Pl-dep VWF Act/vWF:AG Ratio	VWF:Ag	Factor VIII:C	Description	Desmopressin	VWF Replacement Products*	Tranexamic Acid
Type 2A	<0.7	<30-200	Low or Normal	Decreased VWF-dependent platelet adhesion with selective deficiency of HMW multimers	✓	✓	Additional
Type 2B	<0.7	<30-200	Low or Normal	Increased affinity for platelet glycoprotein 1b	Contraindicated	✓	Additional

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*VWF:RCo concentrate, VWF-Factor VIII concentrate, or VWF concentrate

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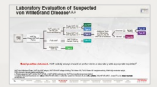
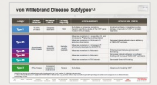
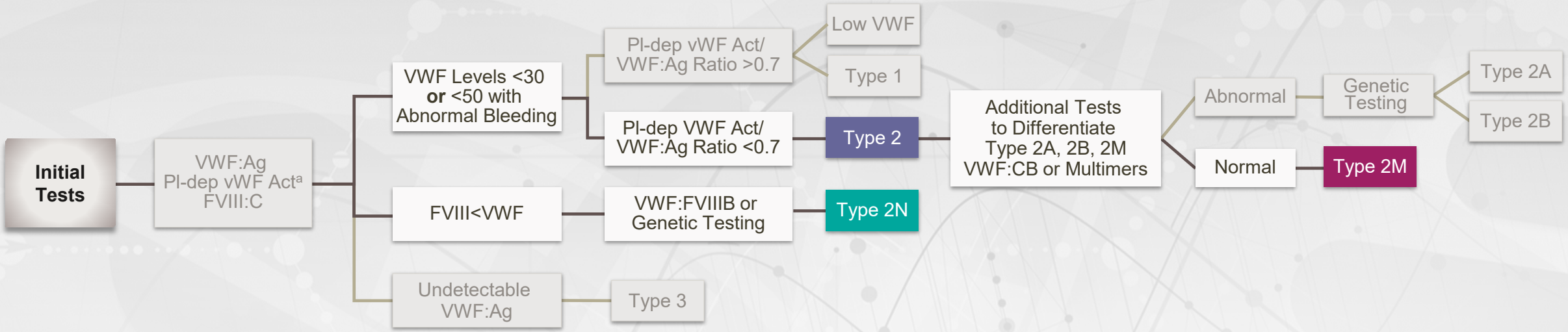
Laboratory Evaluation of Suspected von Willebrand Disease[1,2,3]







Condition	Diagnostic Features				Treatment Options		
	Pl-dep VWF Act/vWF:AG Ratio	VWF:Ag	Factor VIII:C	Description	Desmopressin	VWF Replacement Products*	Tranexamic Acid
Type 2M	<0.7	<30-200	Low or Normal	Decreased VWF-dependent platelet adhesion without selective deficiency of HMW multimers	✓	✓	Additional
Type 2N	<0.7	30-200	Very Low	Markedly decreased binding affinity for FVIII	✓	✓	Additional

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Laboratory Evaluation of Suspected von Willebrand Disease

TYPE 3

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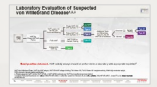
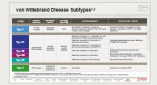
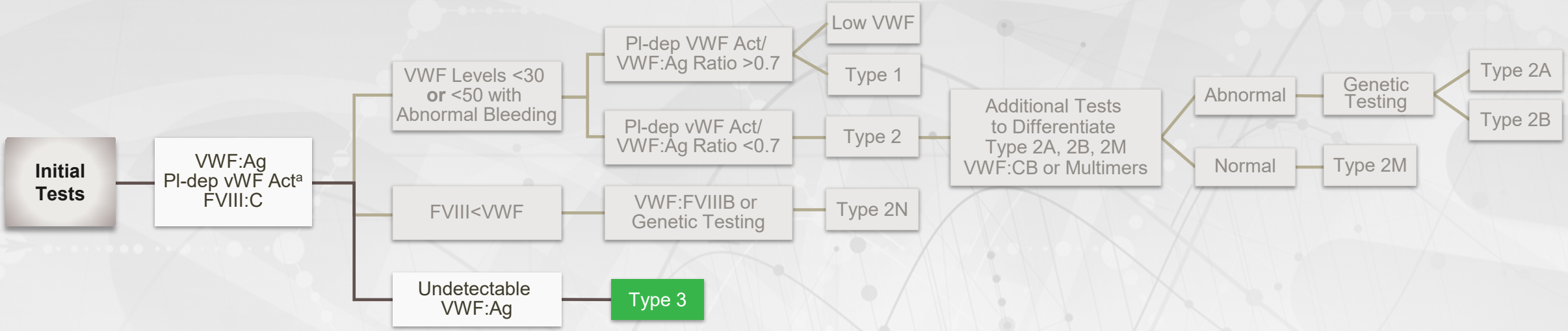
Laboratory Evaluation of Suspected von Willebrand Disease[1,2,3]







Condition	Diagnostic Features				Treatment Options		
	PI-dep VWF Act	VWF:Ag	Factor VIII:C	Description	Desmopressin	VWF Replacement Products*	Tranexamic Acid
Type 3	<3	<3	Extremely Low (<10 IU/dL)	Virtually complete deficiency of VWF		✓	Additional

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von Willebrand Disease Subtypes

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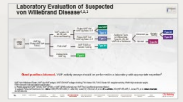
von Willebrand Disease Subtypes[1,2]



Subtype	Relative Prevalence	Inheritance Pattern	Bleeding Propensity	Genetic Mutations	Defect in VWF Protein
Type 1	70-80% of cases	Autosomal dominant	Mild	Null alleles or missense mutations (Genetic modifiers outside of the VWF gene in about 30% of cases)	Impaired synthesis, intracellular routing, storage, or secretion of VWF or to faster clearance
Type 2A	Approximately 20% of cases	Usually autosomal dominant	Variable; usually moderate	Missense mutations in propeptide, D3, and A2 domains → defective multimerization	Decreased platelet adhesion due to deficiency of HMW-VWF multimers
				Missense mutations in CK domain → defective dimerization	
				Missense mutations in A2 domain → enhanced proteolysis by ADAMTS13	
Type 2B				Missense mutations in A1 domain	Enhanced spontaneous glycoprotein 1b binding
Type 2M				Missense mutations in A1 domain	Decreased platelet adhesion or collagen binding with no loss of HMW-VWF multimers
Type 2N				Missense mutations in D'D3 domain	Decreased factor VIII binding
Type 3	<5% of cases	Autosomal recessive or codominant	Severe	Null alleles	Absence of circulating VWF

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HMW=high molecular weight

1. Leebeck FWG and Eikenboom JCJ. *NEJM*. 2016;375:2067-2080; 2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024

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REFERENCES

1. Leebeck FWG and Eikenboom JCJ. *NEJM.* 2016;375:2067-2080.
2. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health-topics/diagnosis-evaluation-and-management-of-von-willebrand-disease. Accessed May 15, 2024
3. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders (supplementary materials). *J Thromb Haemost.* 2010;8(9):2063-2065.
4. Laffan MA, Lester W, O'Donnell JS, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *Br J Hematol.* 2014;167:453-465.
5. James PD, Connell NT, Ameer N. et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease *Blood Advances* 2021;5:280-300

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