ASH ISTH NHF WFH 2021 guidelines on diagnosis of von Willebrand disease

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Background Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans. Accurate and timely diagnosis presents numerous challenges.

Objective These evidence-based guidelines of the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) are intended to support patients, clinicians, and other health care professionals in their decisions about VWD diagnosis.

Methods ASH, ISTH, NHF, and WFH established a multidisciplinary guideline panel that included 4 patient representatives and was balanced to minimize potential bias from conflicts of interest. The Outcomes and Implementation Research Unit at the University of Kansas Medical Center (KUMC) supported the guideline-development process, including performing or updating systematic evidence reviews up to 8 January 2020. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subsequently subject to public comment.

Results The panel agreed on 11 recommendations.

Conclusions Key recommendations of these guidelines include the role of bleeding-assessment tools in the assessment of patients suspected of VWD, diagnostic assays and laboratory cutoffs for type 1 and type 2 VWD, how to approach a type 1 VWD patient with normalized levels over time, and the role of genetic testing vs phenotypic assays for types 2B and 2N. Future critical research priorities are also identified.

Subjects Clinical Guidelines, Thrombosis and Hemostasis

Topics Eustachian tube disorders, guidelines, hemorrhage, international society of thrombosis and haemostasis, von willebrand disease, genetic screening, blood platelets, bleeding diathesis, blood coagulation disorders

Reference: James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv. 2021;5(1):280-300. doi: https://doi.org/10.1182/bloodadvances.2020003265

Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the Outcomes and Implementation Research Unit at the University of Kansas Medical Center (KUMC). The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network (G-I-N).[1-3] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[4-10] to assess the certainty in the evidence and formulate recommendations.

Von Willebrand disease (VWD) is a common, inherited bleeding disorder. The current classification includes types 1 and 3, which are characterized by quantitative deficiencies of von Willebrand factor (VWF), as well as types 2A, 2B, 2M, and 2N, which are qualitative variants. Clinically, VWD patients experience excessive mucocutaneous bleeding, including heavy menstrual bleeding, epistaxis, easy bruising, prolonged bleeding from minor wounds and the oral cavity, and gastrointestinal bleeding, as well as bleeding after dental work, childbirth, and surgery, with musculoskeletal bleeding also seen in the most severe cases. Treatment includes adjunctive therapies, such as tranexamic acid, and therapies that directly increase the levels of VWF, such as desmopressin and VWF concentrates. The accurate and timely diagnosis of VWD remains a challenge for clinicians and patients.

Please see Figure 1 for an overall algorithm addressing the diagnosis of VWD.

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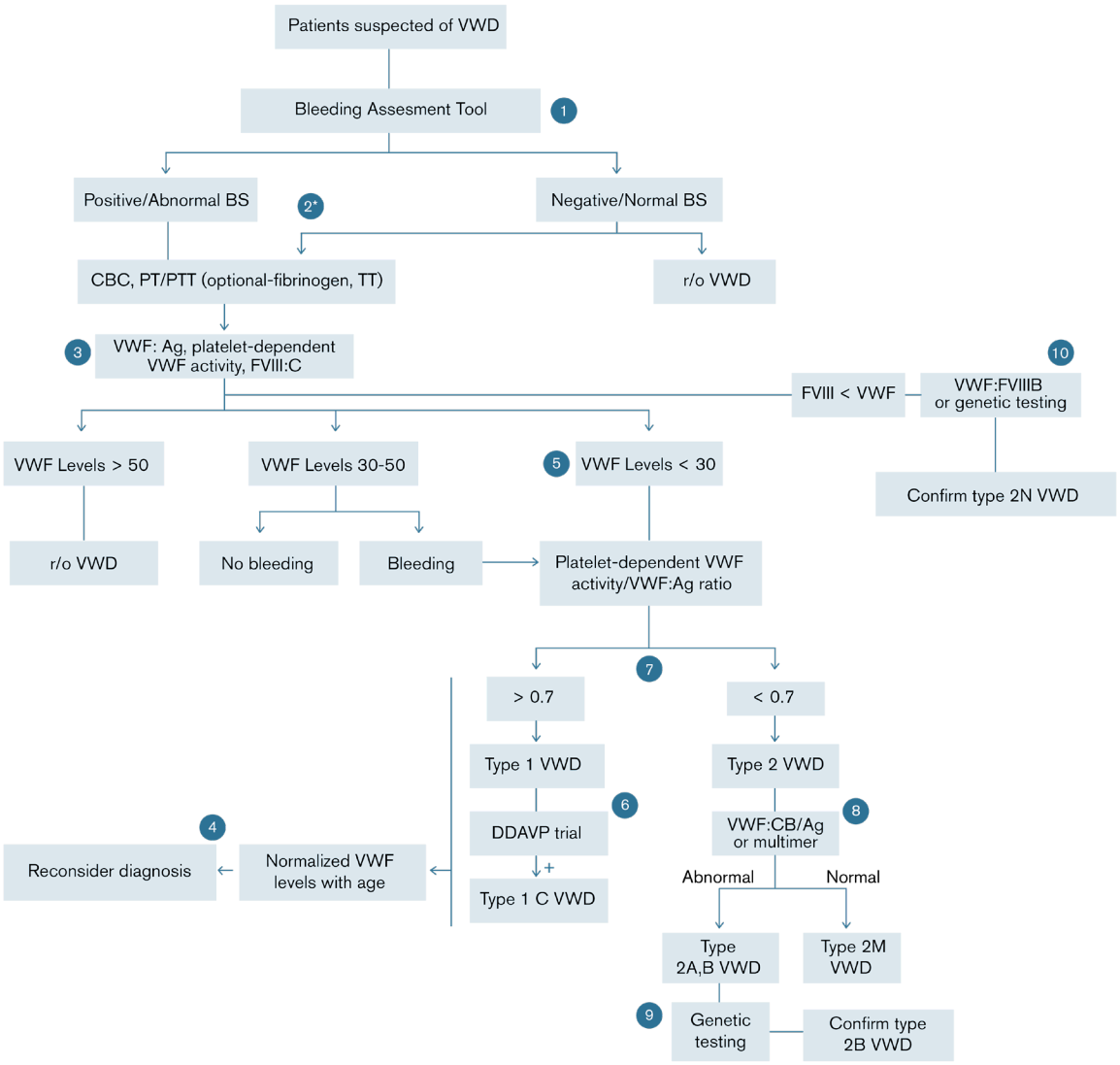

Figure 1.

An overall algorithm addressing the diagnosis of VWD. The numbers in the yellow circles correspond to guideline questions. VWF levels refer to VWF antigen (VWF:Ag) and/or platelet-dependent VWF activity. The algorithm says VWF level 30 to 50 for simplicity; this refers to VWF levels of 0.30 to 0.50 IU/mL, with the caveat that the lower limit of the normal range as determined by the local laboratory should be used if it is <0.50 IU/mL.

*Men and children, referred to a hematologist and/or first-degree relative affected with VWD. BS, bleeding score; CBC, complete blood count; DDAVP, desmopressin; FVIII, factor FVIII; FVIII:C, FVIII coagulant activity; PT, prothrombin time; PTT, partial thromboplastin time; r/o, rule out; TT, thrombin time; VWF:CB/Ag, ratio of VWF collagen binding to antigen; VWF:FVIIIB, VWF FVIII binding.

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Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel *recommends*..."), or conditional ("the guideline panel *suggests*…") and has the following interpretation:

Strong recommendation

- 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.
- For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- 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.
- For policy makers: Policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.[11] Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

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Recommendations

Bleeding-assessment tools.

RECOMMENDATION 1.

For patients with a low probability of VWD (e.g., seen in the primary care setting), the panel *recommends* using a validated bleeding-assessment tool (BAT) as an initial screening test to determine who needs specific blood testing over nonstandardized clinical assessment (strong recommendation based on moderate certainty in the evidence from diagnostic accuracy studies ⊕⊕⊕◯).

Remarks:

- This recommendation applies predominantly to adult women, as the data supporting the use of a BAT as a screening tool is strongest in this patient group.
- The quality of nonstandardized clinical assessment will vary among the users of these guidelines.
- Specific blood testing for VWD refers to VWF antigen (VWF:Ag), platelet-dependent VWF activity (e.g., VWF glycoprotein IbM [VWF:GPIbM]), and factor VIII (FVIII) coagulant activity (FVIII:C).

RECOMMENDATION 2.

For patients with an intermediate probability of VWD (e.g., referred to a hematologist), the panel *suggests against* relying on a BAT to decide whether to order specific blood testing (conditional recommendation based on moderate certainty in the evidence from diagnostic accuracy studies ⊕⊕⊕◯).

Remarks:

- This recommendation 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 (e.g., prolonged activated partial thromboplastin time [aPTT]) (including men and children).
- Beyond their utility as a screening test in the primary care setting, BATs can be used in the referral setting to assess and document the severity of bleeding and can be used in conjunction with specific blood testing as part of the initial diagnostic approach.
- Specific blood testing for VWD refers to VWF:Ag, platelet-dependent VWF activity (e.g., VWF:GPIbM), and FVIII:C.

RECOMMENDATION 3.

For patients with a high probability of VWD (e.g., affected first-degree relative), the panel *recommends against* relying on a BAT to decide whether to order specific blood testing (strong recommendation based on moderate certainty in the evidence from diagnostic accuracy studies ⊕⊕⊕◯).

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Remarks:

- This recommendation 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).
- Beyond their utility as a screening test in the primary care setting, BATs can be used in the referral setting to assess and document the severity of bleeding and can be used in conjunction with specific blood testing as part of the initial diagnostic approach.
- Specific blood tests for VWD refer to VWF:Ag, platelet-dependent VWF activity (e.g., VWF:GPIbM), and FVIII:C.

Assays of platelet-binding activity of VWF.

RECOMMENDATION 4.

The panel *suggests* newer assays that measure the platelet-binding activity of VWF (e.g., VWF:GPIbM, VWF:GPIbR) over the VWF ristocetin cofactor assay (VWF:RCo) (automated or nonautomated assay) for the diagnosis of VWD (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies ⊕⊕◯◯).

Good practice statement:

VWF activity assays should be performed in a laboratory with appropriate expertise.

VWF levels that normalize with age.

RECOMMENDATION 5.

The panel *suggests* reconsidering the diagnosis as opposed to removing the diagnosis for patients with previously confirmed type 1 VWD who now have VWF levels that have normalized with age (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Remarks:

- With this recommendation, the panel worked under the assumption that the original diagnosis of type 1 VWD was accurate.
- Aging and comorbidities are known to increase VWF levels. However, the association between the increased VWF levels and bleeding symptoms is not established.
- Decisions about reconsidering or removing the diagnosis should consider the patient's values and preferences and be informed by a shared decision-making process.

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Type 1 VWD.

RECOMMENDATION 6.

The panel *recommends* a VWF level of <0.30 IU/mL regardless of bleeding, and for patients with abnormal bleeding, a VWF level of <0.50 IU/mL to confirm the diagnosis of type 1 VWD (strong recommendation based on low certainty in the evidence of effects ⊕⊕◯◯).

Remarks:

- VWF level(s) refers to VWF:Ag and/or platelet-dependent VWF activity (e.g., VWF:GPIbM).
- The lower limit of the normal range as determined by the local laboratory should be used if it is <0.50 IU/mL. ABO-specific reference ranges are not required.
- VWF is an acute-phase reactant that increases in response to a variety of stimuli (e.g., bleed, trauma, pregnancy). VWD diagnostic testing should be performed when patients are at a baseline state of health.

Type 1C VWD.

RECOMMENDATION 7.

The panel *suggests against* using VWF propeptide (VWFpp)/VWF:Ag (the ratio of VWF propeptide to antigen) and rather using a desmopressin trial with 1- and 4-hour postinfusion blood work to confirm increased VWF clearance for patients with VWD suspected of type 1C (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies ⊕⊕◯◯).

Type 2 VWD.

RECOMMENDATION 8.

The panel *suggests against* a platelet-dependent VWF activity/VWF:Ag ratio <0.5 cutoff, and rather using a higher cutoff of <0.7 to confirm type 2 VWD (2A, 2B, or 2M) for patients with an abnormal initial VWD screen (conditional recommendation based on very low certainty in the evidence from diagnostic studies ⊕◯◯◯).

Remark:

- Some patients with type 2 VWD have normal VWF:Ag and platelet-dependent VWF activity but a low ratio of platelet-dependent VWF activity/VWF:Ag.

RECOMMENDATION 9.

The panel *suggests* either VWF multimer analysis or VWF collagen binding (VWF:CB)/VWF:Ag (the ratio of VWF collagen binding to antigen) to diagnose type 2 VWD for patients suspected of type 2A, 2B, or 2M in need of additional testing (conditional recommendation based on very low certainty in the evidence from diagnostic accuracy studies ⊕◯◯◯).

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Remark:

- Most laboratories that do the VWF:CB assay use type I and/or III collagen, which is known to be a surrogate for the presence of high-molecular-weight VWF.

RECOMMENDATION 10.

The panel *suggests* targeted genetic testing over low-dose ristocetin-induced platelet agglutination (RIPA) to diagnose type 2B VWD for patients suspected of type 2A or 2B in need of additional testing (Figure 2) (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies ⨁⨁◯◯).

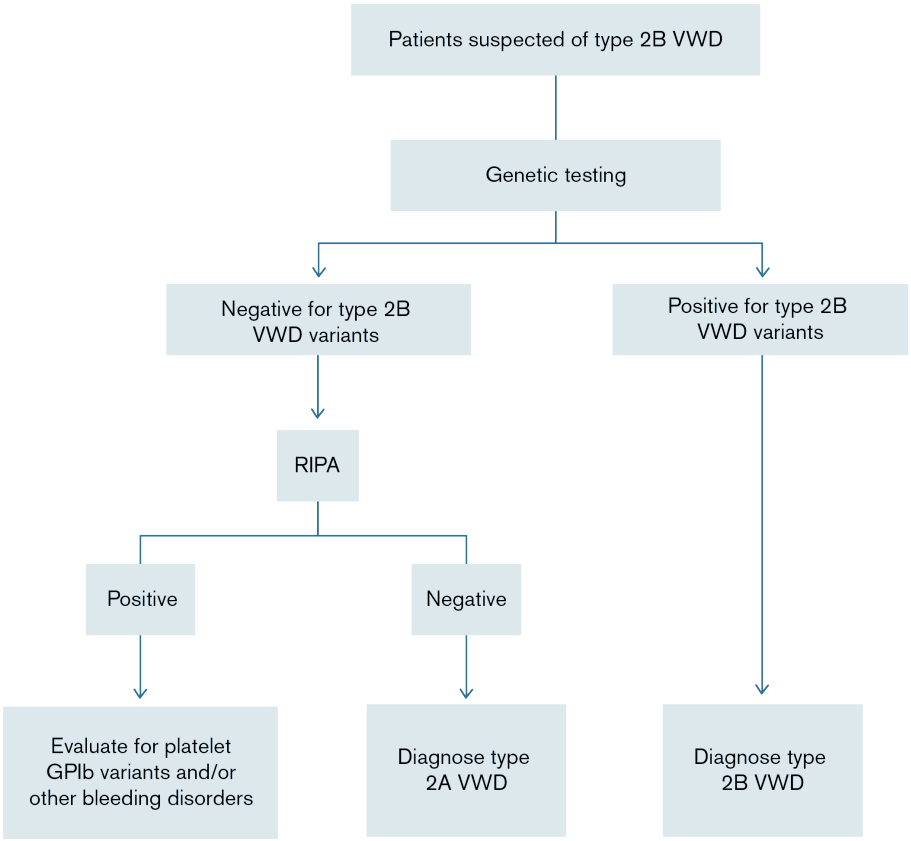

Figure 2.
An algorithm for the diagnosis of type 2B VWD. GPIb, glycoprotein Ib; RIPA, ristocetin-induced platelet agglutination.

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RECOMMENDATION 11.

The panel *suggests* using either VWF FVIII binding (VWF:FVIIIB) or targeted genetic testing (when available) for patients with suspected type 2N VWD in need of additional testing (Figure 3) (conditional recommendation based on low certainty in the evidence from diagnostic accuracy studies ⨁⨁◯◯).

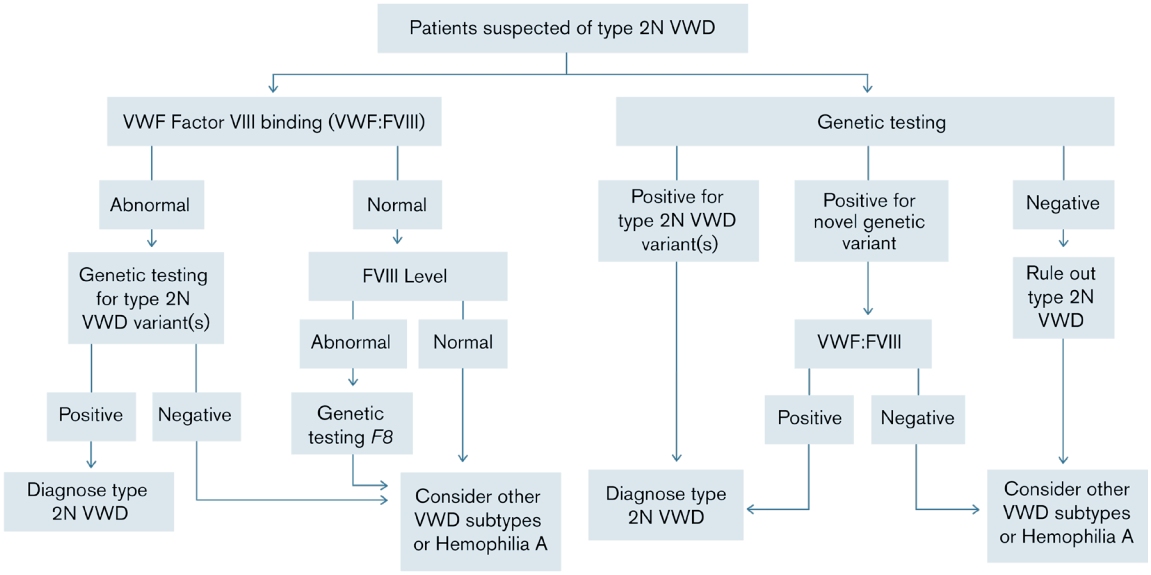

Figure 3.
An algorithm for the diagnosis of type 2N VWD.

Values and preferences

These recommendations place the highest value on not missing the diagnosis in affected patients in order to ensure access to care. The panel considered the following outcomes as critical for clinical decision-making across questions: major bleeding, transfusion and treatment, gastrointestinal bleeding, blood loss, symptom severity, minor bleeding, mortality, and unnecessary testing. These outcomes will be affected by the accurate diagnosis of different subtypes of VWD and avoiding inaccurate mislabeling of patients.

Explanations and other considerations

These recommendations take into consideration cost and cost-effectiveness, resource requirements, impact on health equity, acceptability, and feasibility. Many included studies suffered from a high risk of bias due to the lack of clear reference standards and issues with patient selection.

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