Laboratory Diagnosis of von Willebrand Disease (VWD) – the 2008 NHLBI Guidelines

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VWD NHLBI Guidelines
Objectives & Disclosures (Nichols)

- Objectives
  - Summarize initial clinical assessment
  - Review initial & supplementary VWD testing
  - Describe testing variables and limitations
    - Pre-analytical, Analytical, Post-analytical
  - Identify mildly low VWF vs. VWD diagnosis
  - Address impact of ABO type on VWD/VWF
- Disclosures
  - Relevant Financial Relationships: NONE
  - Off-Label Product Usage: NONE
  - Mayo was central lab for Humate-P® study

VWD NHLBI Guidelines
Background

- NHLBI (National Heart, Lung, & Blood Institute, USA) convened an expert panel to develop evidence-based guidelines for VWD diagnosis & management (April 2004ff)
- **VWD Expert Panel**
  - Dr. Mae Hultin: SUNY Stony Brook (Hematology & Pathology)
  - Dr. Andra James: Duke University (Gynecology/Obstetrics)
  - Dr. Marilyn Manco-Johnson: Colorado U. (Pediatric Hematology)
  - Dr. Robert Montgomery: BC Wisconsin (Ped Hem & Basic Science)
  - Dr. Tom Ortel: Duke University (Hematology & Lab Medicine)
  - Dr. Margaret Rick: NIH (Hematology & Laboratory Medicine)
  - Dr. Evan Sadler: Washington University (Hematology & Basic Sci)
  - Dr. Mark Weinstein: FDA (Basic Science)
  - Dr. Barbara Yawn: Olmsted / U. Minn. (Fam Med & Public Hlth)
  - Dr. William Nichols (chair): Mayo Clinic (Hematology & Lab Med)

NHLBI VWD Expert Panel
2004-2008 (portrait - August 2006)

VWD NHLBI Guidelines
Methodology

Level of Evidence (Published Studies / Expert Opinion)
Ia = meta-analyses of RCTs*
Ib = ≥1 randomized control trial (RCT*)
IIa = ≥1 controlled trial
IIb = ≥1 other type of well designed trial
III = ≥1 correlative or case-controlled study
IV = evidence from expert committees / opinion

Recommendations: Grade A = levels Ia, Ib; Grade B = levels IIa - III; Grade C = level IV

*RCTs, randomized controlled trials

VWD NHLBI Guidelines
Overall Outcome / Results

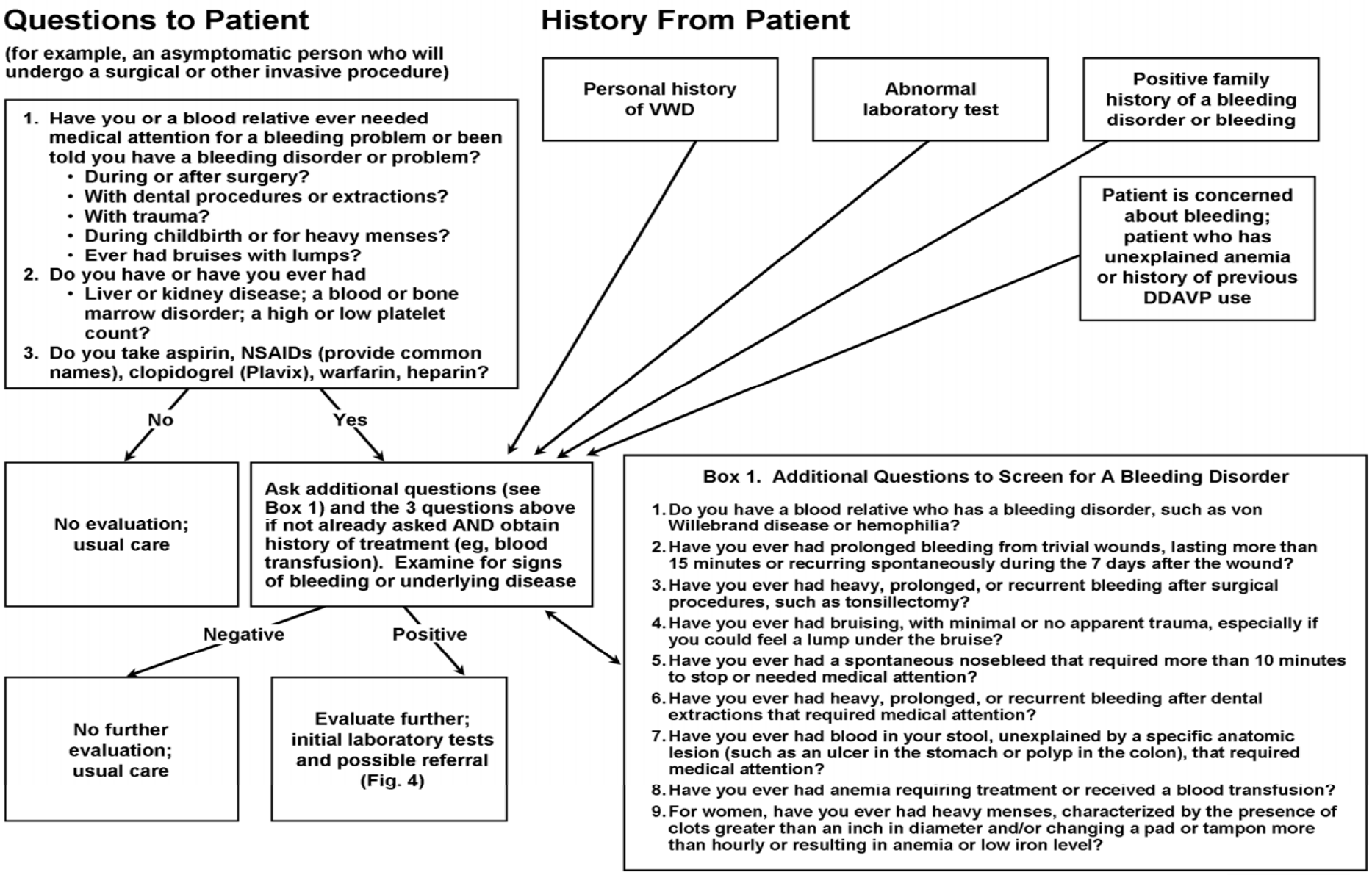
- ~ 400 cited references
- Background & Scientific Overview; Diagnosis (clinical & lab); Management; Opportunities & Needs
- 17 Tables & 6 Figures (+ 13 Evidence Tables)
- ≥54 Recommendations (Dx or Rx/Management)
  - Grade A = NONE
  - Grade B = 21 with 13 Evidence Tables (≥2 refs)
  - Grade C = Remainder (reflects paucity of studies)
- Many additional "soft" recommendations (within the text)
- Caveat: Users of these guidelines (developed for practitioners and laboratorians) should be aware that individual professional judgment is not abrogated by these recommendations

VWD Classification (Sadler et al. JTH 2006)

Type	Description
1	Partial quantitative deficiency of VWF (75% of VWD)
2	Qualitative VWF defect (~20-25% of VWD)
2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight (HMWM) multimers
2B	Increased affinity for platelet GPIb (↓ HMWM VWF)
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers
2N	Markedly decreased binding affinity for FVIII
3	Virtually complete deficiency of VWF (<1% of VWD)

Initial Evaluation for VWD or Other Bleeding Disorders

Figure 3 – NHLBI VWD Guidelines (2008)



VWD NHLBI Guidelines

Initial Patient Evaluation - History*

Item	Univariate OR (95% CI)	Multivariate OR (95% CI)
Family history (dx)	97.5 (38.3-248)	50.5 (12.5-203)
Wound bleeding	67.2 (28.4-159)	30 (8.1-111.1)
Dental extractions	39.4 (20.6-75.5)	3.2 (0.9-11.3)
Tonsillectomy	27.7 (8-96.1)	11.5 (1.2-111.9)
Postoperative	23 (10.6-50.1)	5.8 (1.3-26.4)
Easy bruising	12.7 (8-20.2)	9.9 (3-32.3)
Menorrhagia	5.4 (3.0-9.8)	2.5 (0.6-9.9)

*Sramek A et al. Arch Intern Med 1995;155:1409-15. Usefulness of patient interview in bleeding disorders. 222 pts with known bleeding disorder (43% mild VWD) vs. 341 healthy volunteers.

From Table 8, NHLBI VWD Guidelines (2008)

NHLBI VWD Guidelines (2008)

Table 8. Prevalences of Characteristics in Patients Who Have Diagnosed Bleeding Disorders Versus Healthy Controls

Symptom	Univariate analysis*		Multivariate analysis*		Women who have VWD†		Type 1 VWD families‡	
	Odds ratio	95% CI	Odds ratio	95% CI	Sensitivity	95% CI	Odds ratio	95% CI
Family members have an established bleeding disorder	97.5	38.3–248	**50.5**	12.5–202.9	–	–	–	–
Profuse bleeding from small wounds	67.2	28.4–159	**30.0**	8.1–111.1	–	–	**16.7**	2.0–137.7
Profuse bleeding at site of tonsillectomy/adenoidectomy	27.7	8.0–96.1	**11.5**	1.2–111.9	–	–	–	–
Easy bruising	12.7	8.0–20.2	**9.9**	3.0–32.3	9.8	4.8–17.3	**8.1**	2.1–30.5
Profuse bleeding after surgery	23.0	10.6–50.1	**5.8**	1.3–26.4	52.9	42.8–62.9	**8.9**	3.6–21.8
Muscle bleeding (ever)	13.3	6.4–27.7	4.8	0.7–31.4	9.8	4.8–17.3	–	–
Frequent nosebleeds	3.5	2.0–6.2	**3.8**	0.9–15.7	61.8	51.6–71.2	**4.9**	2.4–10.0
Profuse bleeding at site of dental extraction	39.4	20.6–75.5	**3.2**	0.9–11.3	54.9	44.7–64.8	**4.6**	2.5–8.4
Blood in stool (ever)	2.8	1.7–4.6	2.8	0.7–11.7	13.7	7.7–22.0	1.6	0.6–4.3
Family members with bleeding symptoms	28.6	15.0–54.6	2.5	0.7–9.4	–	–	–	–
Joint bleeding (ever)	8.6	4.8–15.2	2.5	0.6–10.2	20.6	13.2–29.7	–	–
Menorrhagia	5.4	3.0–9.8	**2.5**	0.6–9.9	–	–	**5.1**	2.6–10.1
Hemorrhage at time of delivery	5.3	2.3–12.0	2.1	0.3–13.5	50.0	39.9–60.1	0.9	0.3–3.2
Frequent gingival bleeding	2.8	1.9–4.2	0.7	0.3–2.0	76.5	67.0–84.3	1.3	0.3–6.7
Hematuria (ever)	3.2	1.8–5.6	0.5	0.1–2.3	–	–	–	–

Sources: Sramek A et al. *Arch Intern Med* 1995;155(13):1409–1415; Drews CD et al. *J Am Med Womens Assoc* 2002;57(4):217–218; and Tosetto A et al. *J Thromb Haemost* 2006;4:766–773.

*Univariate and multivariate analyses from Sramek et al. comparing 222 patients who had a known bleeding disorder (43 percent mild VWD) to 341 healthy volunteers.

†Compiled from responses to a questionnaire sent to 102 women, who had type 1 VWD, in a hemophilia treatment center (Drrews et al.)

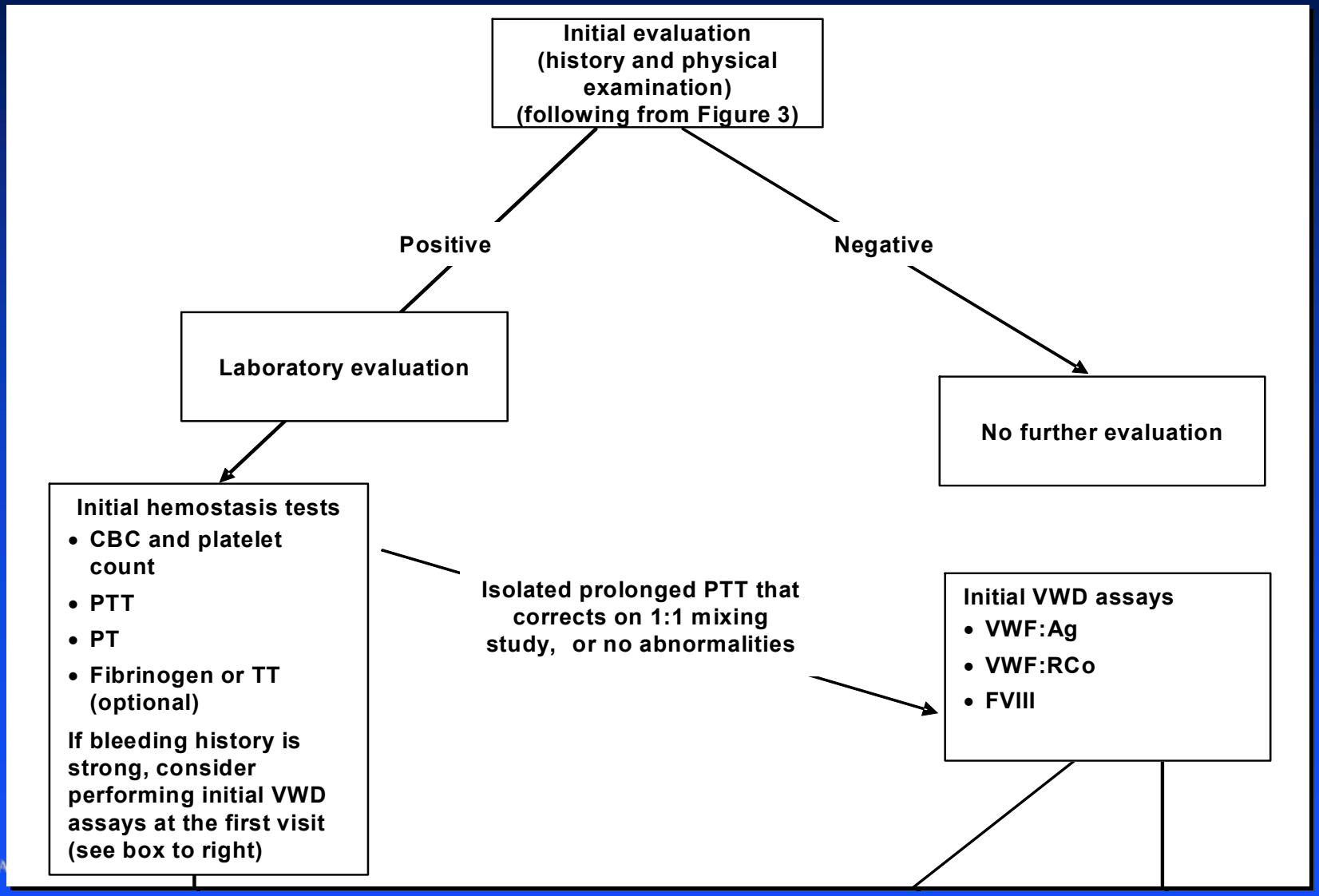
‡Compiled from interviews comparing affected vs. unaffected family members of patients who have type 1 VWD. The index cases (patients who have VWD) were not included in the analysis (Tosetto et al. and personal communication from Dr. Francesco Rodeghiero on behalf of coauthors).[154]

VWD NHLBI Guidelines
Initial Patient Evaluation - History

- Scoring systems for clinical bleeding history and probability of a bleeding disorder - examples:
  - Drews et al. J Am Med Womens Assoc 2002;57:217
  - Rodeghiero et al. J Thromb Haemost 2005;3:2619
  - Tosetto et al. J Thromb Haemost 2006;4:766
  - Castaman et al. J Thromb Haemost 2006;4:2164
- The above are studies of defined populations
- "Until further validation of scoring systems and criteria for assessing bleeding history and the probability of VWD, especially type 1 VWD, the Expert Panel suggests that an increasing number of positive responses to the questions about bleeding (Fig 3 & Box 1) and abnormal findings on physical examination increase the likelihood that an individual has a bleeding disorder, including possible VWD." Recommendation III.A. VWD Guidelines

VWD NHLBI Guidelines

Initial Patient Evaluation - Laboratory



VWD NHLBI Guidelines
Initial Patient Evaluation - Laboratory

- Initial Testing for VWD (grade B, level III)
  - VWF:Ag (antigen)
  - VWF:RCo (ristocetin cofactor activity)
  - FVIII (Factor VIII activity)
- The reference standard is critical and should be referenced to the WHO standard
- Test results should be reported in IU (international units) -- eg, IU/dL (= %)

(The two above are "Soft Recommendations")

VWD NHLBI Guidelines

Initial Laboratory Evaluation

How Well Do the Main VWD Tests Perform?

- VWF:RCo (ristocetin cofactor activity) – poor performance
  - Multiple assay types (≥5); many differing methods
  - Sensitivity typically 6-12 IU/dL (least detectable dose: LDD)
  - CV* ≥30% (inter-lab studies) & ≥15-20% within lab

- VWF:Ag (antigen) – fairly good performance (usually!)
  - Automated LIA (latex immunoassay) or ELISA most common
  - Sensitivity (LDD) typically 1-2 IU/dL
  - CV* ≥10-20% (inter-lab studies) & ≥10% within lab

- Ratio VWF:RCo/VWF:Ag (normal ≥0.5-0.7) – fair to poor
  - Poor VWF:RCo and fair VWF:Ag test performances limit the utility of this ratio for detecting or excluding type 2 VWD or loss of high molecular weight VWF multimers

- FVIII (factor VIII coagulant activity) – fairly good performance
  - Sensitivity ≤1 IU/dL; CV* ≥10-20%; FVIII is labile (false low)

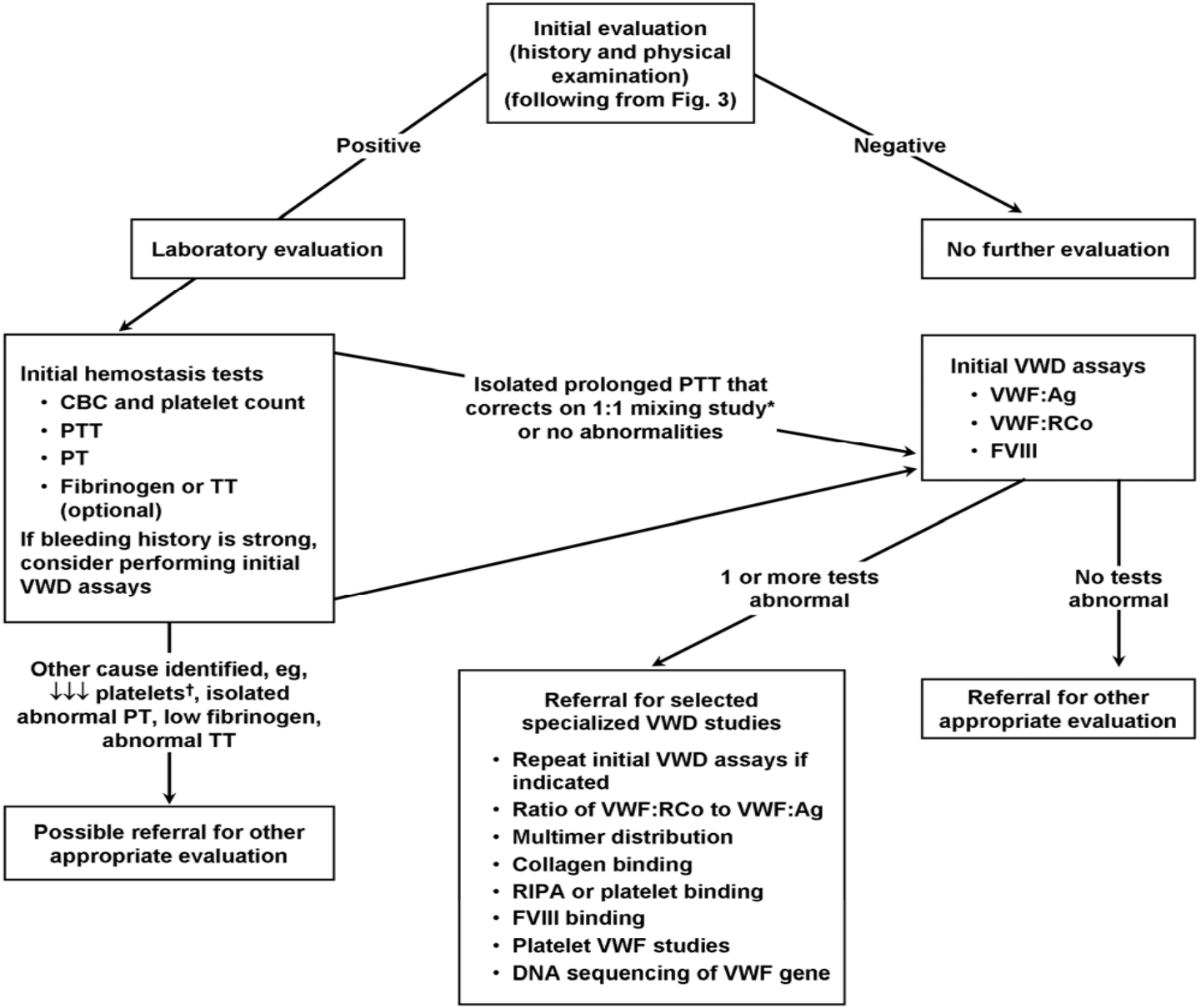
CV*, coefficient of variation (good = ≤10%; excellent = ≤5%)

VWD NHLBI Guidelines
Diagnostic Recommendations - Laboratory

- Tests such as the bleeding time, PFA-100®. or other automated functional platelet assays have been used but there are conflicting data with regard to sensitivity and specificity for VWD. Therefore, the panel believes current evidence does not support their routine use as screening tests for VWD.
- Additionally, the panel believes that platelet-based assays should be used for the ristocetin cofactor method.
- Last, the panel emphasizes the importance of the timing of the phlebotomy for assays, with the patient at his/her optimal baseline as far as possible. (For example, VWF levels may be elevated above baseline during the second and third trimesters of pregnancy or during estrogen replacement, during acute inflammation such as the perioperative period, during infections, and during acute stress.) The careful handling and processing of the sample is also critical, particularly if the sample will be sent out for testing at a distant location.

Laboratory Assessment for VWD or Other Bleeding Disorders

Figure 4 – NHLBI VWD Guidelines (2008)



VWD NHLBI Guidelines

Additional VWD Testing - Laboratory

Selected Patients (eg, abnormal initial test results)

- Repeat VWD "Panel" (VWF:Ag, VWF:RCo, FVIII)
  (if indicated)
- VWF:RCo/VWF:Ag ratio (NL = >0.5-0.7)
  (if the laboratory has defined ratio reference ranges)
- VWF multimer analysis
- Ristocetin-induced platelet aggregation (RIPA)
- VWF:CB (collagen binding activity) assay

(the above are Grade B recommendations)

VWD NHLBI Guidelines

Supplemental VWD Testing - Selected Cases

- VWF:FVIIIB (factor VIII binding assay)

(if FVIII is discordantly low vs. VWF: Grade B)

- Additional Studies (in selected persons)
  - Platelet binding studies (query Type 2B VWD)
  - Assays for antibodies to VWF
  - Gene sequencing

(the above are Grade C or B recommendations)

VWD NHLBI Guidelines
"Low VWF" versus "VWD Type 1"

- Low VWF is common
- Bleeding is more common
- Low VWF and bleeding often associate coincidentally
- Low VWF confers a modest risk of bleeding

VWD Type 1 = Often a false-positive Dx

Sadler JE. Blood 2003;101:2089-93

VWD NHLBI Guidelines

Prototypical Laboratory Data for VWD Diagnosis

Condition	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	Ratio of VWF:RCo/ VWF:Ag
Type 1	<30*	<30*	↓ or Normal	>0.5–0.7
Type 2A	<30*	<30–200*†	↓ or Normal	<0.5–0.7
Type 2B	<30*	<30–200*†	↓ or Normal	Usually <0.5–0.7
Type 2M	<30*	<30–200*†	↓ or Normal	<0.5–0.7
Type 2N	30–200	30–200	↓↓	>0.5–0.7
Type 3	<3	<3	↓↓↓ (<10 IU/dL)	Not applicable
'Low VWF'	30–50	30–50	Normal	>0.5–0.7
Normal	50–200	50–200	Normal	>0.5–0.7

*<30 IU/dL = level for definitive VWD Dx; some Type 1 or 2 may have 30-50 IU/dL

†VWF:Ag in most Types 2A, 2B, 2M VWD is <50 IU/dL. Prototypical cases listed.

VWD NHLBI Guidelines (2008)
Type 2 VWD: Prototypical Laboratory Data

Assay	Type 2A	Type 2B*	Type 2M	Type 2N†
Multimers	↓ HMW	↓ HMW	Normal	Normal
RIPA	↓ or Nl	↑	or Nl	Normal
VWF: RCo/Ag	↓	↓	↓	Normal*

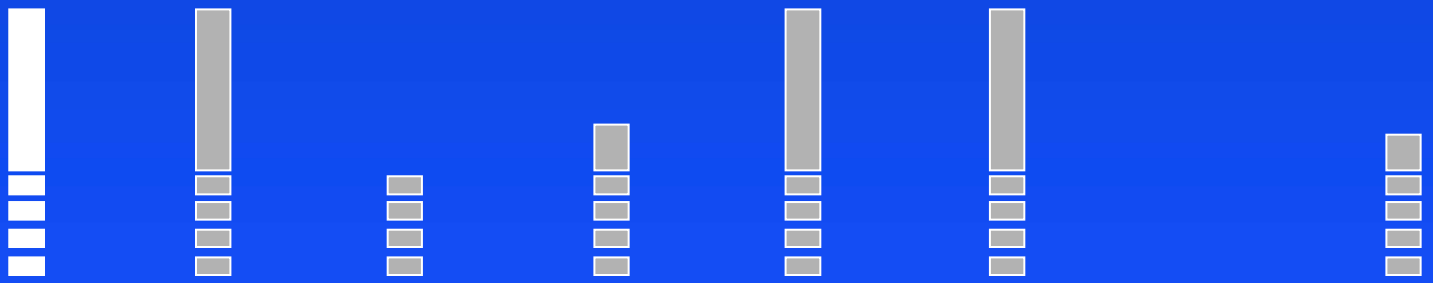
*Type 2B VWD results similar to those for platelet-type VWD (PLT-VWD; reflects platelet GP Ib mutations)

†Type 2N VWD has low Factor VIII, and therefore the ratio of FVIII/VWF is decreased, but the VWF level is usually normal (exception: compound 2N/1 VWD)

Expected Laboratory Values in VWD

Figure 5 - NHLBI VWD Guidelines (2008)

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	PLT-VWD*
VWF:Ag	N	L, ↓ or ↓↓	↓ or L	↓ or L	↓ or L	N or L	Absent	↓ or L
VWF:RCo	N	L, ↓ or ↓↓	↓↓ or ↓↓↓	↓↓	↓↓	N or L	Absent	↓↓
FVIII	N	N or ↓	N or ↓	N or ↓	N or ↓	↓↓	1-9 IU/dL	N or L
RIPA	N	Often N	↓	Often N	↓	N	Absent	Often N
LD-RIPA	Absent	Absent	Absent	↑↑↑	Absent	Absent	Absent	↑↑↑
PFA-100 CT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
BT	N	N or ↑	↑	↑	↑	N	↑↑↑	↑
Platelet count	N	N	N	↓ or N	N	N	N	↓
VWF multimer pattern	N	N	Abnormal	Abnormal	N	N	Absent	Abnormal



Prototypical cases; exceptions exist. *PLT-VWD, platelet-type VWD. Fig - RR Montgomery

VWD NHLBI Guidelines

ABO Blood Group & VWF/VWD*

ABO Type	Frequency Normals (n = 1117)	Frequency VWD Pts (114 Type 1)	VWF:Ag Mean (Normals)	VWF:Ag Range (Nl) (Normals)
O	45%	77%	74.8%	36-157% (41-179 IU/dL)**
A	45%	18%	105.9%	48-234%
B	7%	4%	116.9%	57-241%
AB	3%	0%	123.3%	64-238%

*Gill JC et al. Blood 1987;69:1691-5. (% or U/dL)

**IU/dL per Montgomery RR et al. (2008 VWD Guidelines NHLBI)

VWD NHLBI Guidelines

ABO Blood Group & VWF/VWD

Clinical Scenario

- Patients 1 & 2 are 35 y/o females with similar bleeding symptoms:
  - Menorrhagia; ease of bruising
- ABO blood groupings are different:
  - Pt 1 = Group O; Pt 2 = Group B

Test	VWF:Ag	VWF:RCo	FVIII
Pt 1 (O)	45 IU/dL	45 IU/dL	60 IU/dL
Ref Range	(40-180)	(40-180)	(55-205)
Pt 2 (B)	45 IU/dL	45 IU/dL	60 IU/dL
Ref Range	(65-215)	(65-215)	(55-205)

VWD NHLBI Guidelines

ABO Blood Group & VWF/VWD

Clinical Scenario

- Lab Report / Interpretation:
  - Pt 1 has normal VWF; Pt 2 has low VWF
- Does one pt have VWD, and the other does not?

Test	VWF:Ag	VWF:RCo	FVIII
Pt 1 (O)	45 IU/dL	45 IU/dL	60 IU/dL
Ref Range	(40-80)	(40-180)	(55-205)
Pt 2 (B)	45 IU/dL	45 IU/dL	60 IU/dL
Ref Range	(65-215)	(65-215)	(55-205)

VWD NHLBI Guidelines

ABO Blood Group & VWF/VWD

"Soft Recommendation"

- Although it has been recommended to stratify reference ranges for VWF:Ag and VWF:RCo with respect to blood group O and non-group O, evolving limited information supports the concept that, despite the ABO blood grouping and associated reference ranges, the major determinant of bleeding risk is low VWF.
- Therefore, referencing VWF testing results to the population reference range, rather than to ABO-stratified reference ranges, may be more useful clinically.

VWD NHLBI Guidelines

Collection & Handling of Samples for Laboratory Testing*

Phlebotomy conditions — Avoid lipemia and hemolysis. An atraumatic blood draw limits the exposure of tissue factor from the site and the activation of clotting factors, minimizing falsely high or low values.

Patient stress level — Undue stress, such as struggling or crying in children or anxiety in adults, may falsely elevate VWF and FVIII levels. Very recent exercise can also elevate VWF levels.

Additional conditions in the person — The presence of an acute or chronic inflammatory illness may elevate VWF and FVIII levels, as may pregnancy or administration of estrogen/oral contraceptives.

Sample processing — To prevent cryoprecipitation of VWF and other proteins, blood samples for VWF assays should be transported to the laboratory at **room temperature**. Plasma should be separated from blood cells promptly at room temperature, and the plasma should be centrifuged thoroughly to **remove platelets**. If plasma samples will be assayed within 2 hours, they should be kept at room temperature. Frozen plasma samples should be carefully thawed at 37°C and kept at room temperature for <2 hours before assay.

Sample storage — Plasma samples that will be stored or transported to a reference laboratory must be frozen promptly at or below –40°C and remain frozen until assayed. A control sample that is drawn, processed, stored, and transported under the same conditions as the tested person's sample may be helpful in indicating problems in the handling of important test samples.

*Table 10 (modified) VWD Guidelines

VWD NHLBI Guidelines

Summary of Laboratory Recommendations

- Pre-analytical conditions of the patient and the blood/plasma sample are important for optimum laboratory testing.
- Recommended testing for VWD includes assays of VWF:Ag, VWF:RCo & FVIII -- with reflexive or supplemental additional assays (eg, VWF multimer analysis, RIPA, etc.) – such as for further evaluation of abnormal results of the initial 3 tests.
- VWF:Ag, VWF:RCo & FVIII assays should be referenced to the WHO standard and reported in IU (eg, IU/dL).
- <30 IU/dL VWF is recommended as the "cut-off" for definite VWD Dx (especially Type 1 VWD). This does not preclude VWD Dx @ 30-50 IU/dL VWF if supporting clinical history present, nor Rx to elevate VWF if there is clinical bleeding risk.
- Referencing VWF testing results to the population reference range, rather than to ABO-stratified reference ranges, may be clinically useful.
- The high CV of VWD assays (VWF:RCo, VWF:Ag, FVIII), coupled with variability of VWF and FVIII contributed by conditions of the patient and the plasma sample, contribute substantially to difficulties in diagnosing VWD or classifying the subtype (eg, Types 1 vs. 2A, 2B, 2M using VWF:RCo/VWF:Ag ratio).

Acquired von Willebrand Syndrome (AVWS)

- Late onset; No personal or family history
- Uncommon; Typical VWD bleeding (muco-cutaneous, surgical)
- Lab features similar to congenital VWD
  - Low VWF:Ag, VWF:RCo, FVIII (usually; not always)
  - Often "type II" VWF multimers (loss of HMWM)
  - VWF inhibitor antibodies often not detectable
  - Shortened VWF survival (often)
- Disease associations (assess for them!)
  - Monoclonal gammopathies (MGUS, Myeloma, etc)
  - Lymphoproliferative dz (CLL, Lymphoma, Waldenström)
  - Myeloproliferative dz (ET, PV, AMM, Thrombocytosis)
  - Aortic Stenosis, Hypertrophic Obstructive Cardiomyopathy
  - Other: Tumors, Autoimmune, Hypothyroid, etc.
- Pathophysiology: Antibodies, Proteolysis, Cell absorpt, Other

Disorders Pathophysiologically Associated with Acquired von Willebrand Syndrome (AVWS)

Pathophysiologic Category	Disease or Association
• Antibodies to VWF	Monoclonal Gammopathies; Lympho-prolif. Dz; Autoimmune Dz (SLE etc)
• Shear-induced VWF proteolysis (ADAMTS13)	Aortic Stenosis; VSD; LVAD; HOCM; Primary Pulmonary Hyptertension
• Thrombocytosis (marked) & proteolysis (ADAMTS13)	Essential Thrombocythemia; P. vera; AMM + Myelofibrosis; other MPD
• Aberrant VWF binding to tumor cells	Wilm's tumor; certain plasma cell or lymphoproliferative disorders
• Decreased VWF synthesis	Hypothyroidism
• Drug-related AVWS	Ciprofloxacin, valproic acid, hydryoxyethyl starch, griseofulvin

AMM = agnogenic myeloid metaplasia; HOCM = hypertrophic obstructive cardiomyopathy; LVAD = left ventricular assist device; MPD = myeloproliferative disorder; VSD = ventricular septal defect

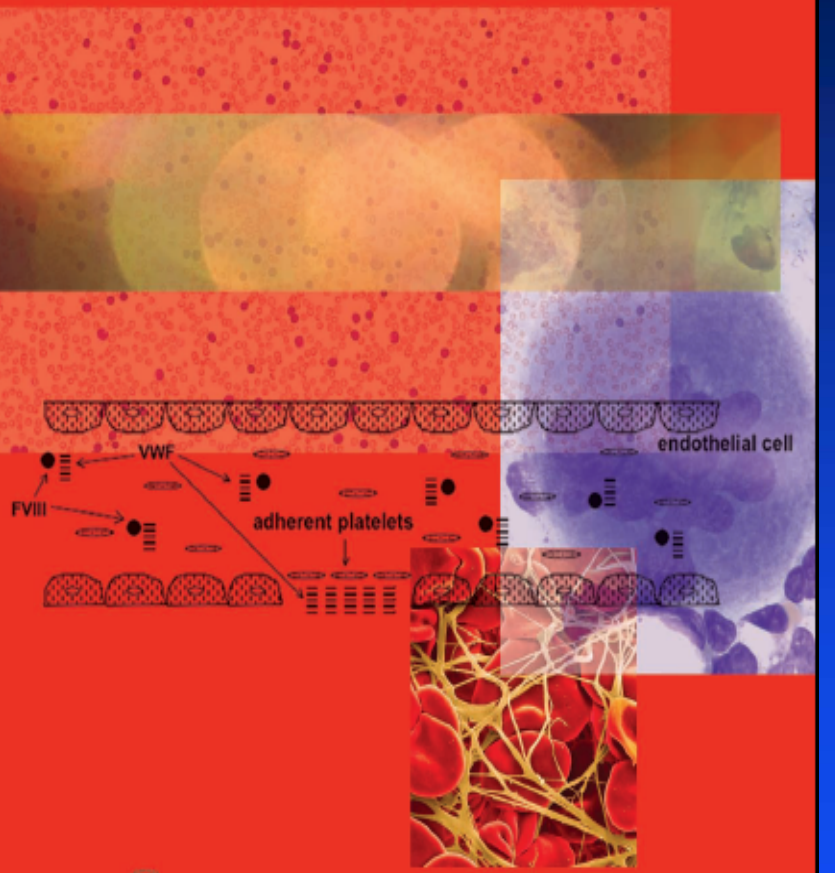
VWD NHLBI Guidelines
Acknowledgements & Publications

- Acknowledgements:
  - NHLBI VWD Expert Panel: Drs. Mae Hultin, Andra James, Marilyn Manco-Johnson, Bob Montgomery, Tom Ortel, Margaret Rick, Evan Sadler, Mark Weinstein, Barbara Yawn & Bill Nichols (chair)
  - NHLBI Support Staff: Sue Rogus, RN; Rebecca Link, PhD; Others at American Institutes for Research
- Publications (March 2008):
  - Full document: www.nhlbi.nih.gov/guidelines/vwd
  - Summaries, for professionals and for patients and the public, also available on-line and printed
  - *Haemophilia* 2008 (Mar);14(2):171-232
  - The first NHLBI guidelines for a blood disorder
    - Others exist for asthma, hyperlipidemia, hypertension, obesity

FULL REPORT

The Diagnosis, Evaluation, and Management of

von Willebrand Disease



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GUIDELINES

von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA)[1]

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Summary. von Willebrand disease (VWD) is a commonly encountered inherited bleeding disorder affecting both males and females, causing mucous membrane and skin bleeding symptoms, and bleeding with surgical or other haemostatic challenges. VWD may be disproportionately symptomatic in women of child-bearing age. It may also occur less frequently as an acquired disorder (acquired von Willebrand syndrome). VWD is caused by deficiency or dysfunction of von Willebrand factor (VWF), a plasma protein that mediates platelet haemostatic function and stabilizes blood coagulation factor VIII. The pathophysiology, classification, diagnosis and management of VWD are relatively complex, but understanding them is important for proper diagnosis and management of patients with VWD. These evidence-based guidelines for diagnosis and management of VWD from the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel (USA) review relevant publications, summarize current understanding of VWD pathophysiology and classification, and present consensus diagnostic and management recommendations based on analysis of the literature and expert opinion. They also suggest an approach for clinical and laboratory evaluation of individuals with bleeding symptoms, history of bleeding or conditions associated with increased bleeding risk. This document summarizes needs for further research in VWF, VWD and bleeding disorders, including clinical research to obtain more objective information about bleeding symptoms, advancements in diagnostic and therapeutic tools, and enhancement in the education and training of clinicians and scientists in bleeding and thrombotic disorders. The NHLBI Web site (http://www.nhlbi.nih.gov/guidelines/vwd) has a more detailed document, a synopsis of these recommendations, and patient education information.

[1]From The Diagnosis, Evaluation and Management of von Willebrand Disease, National Heart, Lung, and Blood Institute, National Institutes of Health (GPO #08-5832), which is available at http://www.nhlbi.nih.gov/guidelines/vwd and from the NHLBI Health Information Center, Bethesda, MD (telephone no. 301-592-8573).

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Which ONE of the following best describes recommended initial lab testing for VWD?

1. PFA-100 &/or Bleeding Time
2. APTT
3. VWF:RCo
4. VWF:RCo & VWF:Ag
5. ✓ VWF:RCo, VWF:Ag & FVIII
6. VWF:RCo, VWF:Ag, FVIII & VWF Multimer Analysis