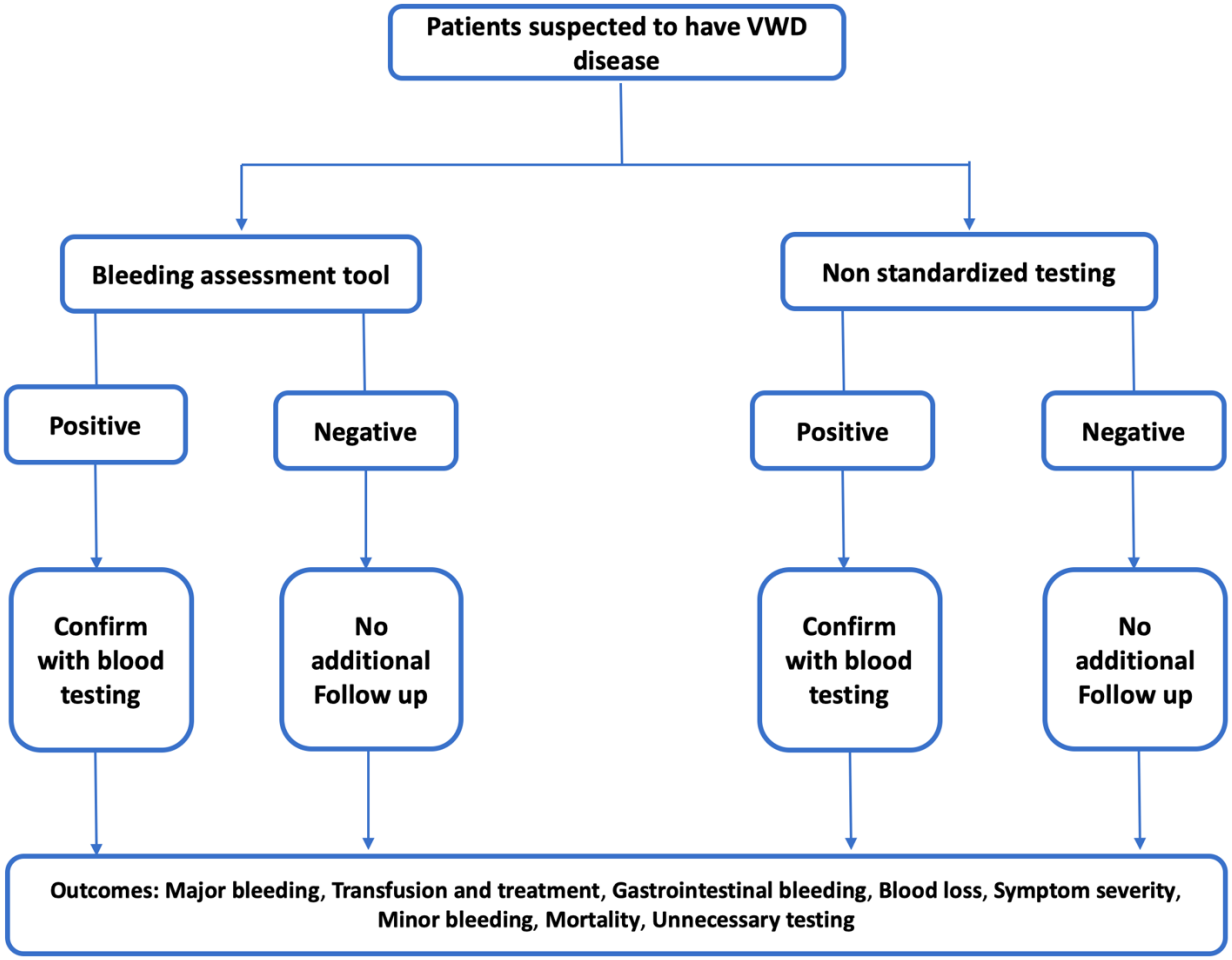
Supplement 5 EtDs for the ASH ISTH NHF WFH Guidelines on the Diagnosis of von Willebrand Disease

Question 1 and 2 (3%)

Should a bleeding assessment tool be used to diagnose patients suspected of having von Willebrand Disease?	
POPULATION:	Patients suspected of von Willebrand Disease
INTERVENTION:	Bleeding Assessment Tool
PURPOSE OF THE TEST:	Identify patients with VWD
ROLE OF THE TEST:	Identify patients with VWD
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	BATs – False positive, BATs – False negative, BATs – True positive, BATs – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent way. The importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)
SUBGROUPS:	This recommendation addresses patients with a VWD pretest probability of 3%, corresponding to the population of patients typically evaluated for suspected VWD because of a personal history of abnormal prolonged aPTT.
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent	This question was judged to be a priority among many candidate questions to address in these guidelines.

<table>
<tr><td>○ Don't know</td><td>way. The importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)</td><td></td></tr>
<tr><td colspan="3">Test accuracy
How accurate is the test?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr><td>○ Very inaccurate
○ Inaccurate
● Accurate
○ Very accurate
○ Varies
○ Don't know</td><td>Pooled sensitivity across 7 cohort studies with 112 patients was 0.75 (95% CI: 0.66 to 0.83)
Pooled specificity across 7 cohort studies with 863 patients was 0.54 (95% CI: 0.29 to 0.77)
<table>
<tr><th>Outcome</th><th>Study design</th><th>Test accuracy CoE</th><th>Effect per 1000 patients/year for pre-test probability of 3%</th></tr>
<tr><td>True positives</td><td rowspan="2">cross-sectional (cohort type accuracy study)</td><td rowspan="2">⨁⨁⨁⨁
HIGH</td><td>23 (20 to 25)</td></tr>
<tr><td>False negatives</td><td>7 (5 to 10)</td></tr>
<tr><td>True negatives</td><td rowspan="2">cross-sectional (cohort type accuracy study)</td><td rowspan="2">⨁⨁⨁◯
MODERATE[a]</td><td>523 (284 to 744)</td></tr>
<tr><td>False positives</td><td>447 (226 to 686)</td></tr>
</table></td><td>The studies assess Bleeding Assessment Tools (BATs) versus non-BATs and do not compare BATs with non-standardized testing.
The panel judged the test accuracy to be accurate for patients with a pretest probability of 3% corresponding to the population of patients typically evaluated for suspected VWD because of a personal history of abnormal laboratory blood testing.</td></tr>
</table>

	a. The heterogeneity measurement I2 is 98% and the point estimates of specificity are not homogenous which cannot be explained by the setting or risk of bias a priori Refer to the Appendix at the end of the document	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if they have other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	The benefit of a BAT is to identify patients who have VWD, who will be missed without this tool in the clinic. Using a BAT will allow for the quantification of bleeding symptoms in patients. The panel considered not missing a patient with VWD as the most important desirable effect, in addition to identify patients in a timely manner, in the appropriate center and to decrease unnecessary blood testing. BATs are educationally beneficial for patients and clinical experts and provides validation for patients about having the disease.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if they have other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	

Certainty of the evidence of test accuracy
What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The risk of bias assessed using the QUADAS tool is not serious. Additionally, the articles addressed the PICO question directly and the results were precise. However, the point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori. This gives an overall high certainty of evidence for sensitivity and moderate certainty of evidence for specificity. Refer to the Appendix at the end of the document.	The data presented in the studies consider mostly women. It is important also to consider BATs in the pediatric population, as children might have a negative bleeding score due to lack of adequate bleeding challenges. The bleeding score may become positive with age. Men are more likely to have a negative bleeding score.

Certainty of the evidence of test's effects
What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no relevant test effects since the intervention is a questionnaire and not an invasive test.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		Despite the lack of included studies, there is **variability and inconsistency** in what happens to patients during their diagnostic journey. Early detection of mild disease may help in management, especially in women who face additional bleeding challenges during reproductive years. Patients in the primary care setting (pre-test probability 3%) who are not recognized as having VWD will not be treated.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The diagnosis of VWD is challenging and requires the performance of multiple laboratory tests, that will also determine the type of the disease. There are some limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and VWD patients. Conducting a Bleeding Assessment Tool will guide the healthcare provider to perform laboratory tests for VWD.
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low	Refer to the Appendix at the end of the document.	

○ Moderate ○ High ○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Patients place high value on being heard, not having their diagnosis missed, and having guidance on appropriate management. Patients value the clarity and precise questions provided by the BATs. They benefit from the standardized and objective way of obtaining bleeding data and would expect the use of non-standardized testing to be poorly received due to the perception of being less reliable. Moreover, patients appreciate their direct input into the collection of personal medical history for making or confirming a diagnosis. Patients think of BATs as similar to surveys given to patients for other diagnoses in internal medicine or family medicine. On the other hand, although BATs are useful adjunct, patients may feel that their story is devalued if reduced entirely to a questionnaire. Since the answers in a structured questionnaire are less subtle than in open questions, patients may prefer an open discussion with the healthcare provider, rather than only a structured questionnaire that may not account for all their bleeding symptoms. Patients might want to know that blood tests are negative even if they have a negative bleeding score, especially if they were told they have VWD, bringing a concern of underdiagnosis or overtreatment; so patients may value a blood test more than BATs for confirmation of diagnosis, regardless of the bleeding score. Finally, privacy and security of sensitive health data are concerns to some patients with online BATs, however there is no universal online BAT that is currently administered.
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document.	There is an increasing need to use validated, standardized and sensitive bleeding questionnaires to assist in the determination of both the presence and severity of VWD.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know		No additional financial resources are required to administer BATs, except time (including training/educating the provider to administer BATs), which is important in the clinical setting. Doing BATs in this population would lead to net moderate savings.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		BATs are generally available for all patients, which might help patients receive equitable care. More work has been done with BATs in English language than other languages, although the ISTH-BAT has been translated and is available in German, Italian, Norwegian and Spanish.

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		BATs are generally accepted by all patients. The panel thinks that BATs are usually less acceptable in the primary care setting due to the type of relationship between the primary care physician and their patient, which makes the questionnaire less likely to be completed.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		BATs might be less feasible in the primary care setting because of the need for additional resources (ie: time) when administering the questionnaire although this varies depending on the setting. With minimal training, the BATs may be administered by any healthcare professional (usually nursing staff or clinicians); self-administered versions are also available for patients to complete unassisted. The healthcare professional should be very familiar with bleeding disorders to tease out information from the patient who may not realize that they have more symptoms than they appreciate. If administered by clinicians, the tool needs to have minimal risk of interpretation errors such as subjective judgment differences between clinicians. The Self-BAT minimizes the errors using lay terms without complex definitions and criteria. The data are collected through paper or electronic record after face to face or phone interview. Currently, paper-based is the most used way of collecting the data, computer-assisted BATs to rapidly pass through negative domains would be useful while taking into consideration the resource implications. It usually takes 10-20 minutes to complete the BAT, but may take up to 30 minutes depending on the version.

		Time use may have a feasibility implication, but the panel felt BATs are often quicker than unstructured history for bleeding symptoms. BATs become time-consuming specifically when administered by the nursing staff seeing a large volume of patients. The question tackles using BATs in secondary care. The primary screening would have been already performed by the primary care provider. This means that the incidence of bleeding problems is increased and the ability of the BATs alone to exclude a bleeding problem is limited (like d-dimer for thrombosis). The current BATs (e.g. ISTH, Self BAT, PBQ, etc) were not developed to serve primarily as a diagnostic tool, but to stratify patients in large cohort studies. Although a normal bleeding score and negative screening tests mean that no additional testing is needed, a normal bleeding score is not enough to rule out the diagnosis.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**

○	○	○	○	●

CONCLUSIONS

Recommendation

In patients with a low probability of VWD (e.g. evaluation triggered by a prolonged aPTT), the panel recommends using a bleeding assessment tool (BAT) as an initial screening test to determine who needs specific blood testing over non-standardized clinical assessment.
(Strong recommendation based on moderate certainty in the evidence)

Remarks:

- This recommendation addresses patients with a low VWD pretest probability (~3%), corresponding to those typically seen in the primary care setting.
- The quality of non-standardized clinical assessment will vary among the users of these guidelines.
- Specific blood testing for VWD refers to VWF:Ag, VWF activity and FVIII:C.

Justification

The guideline panel determined that there is moderate certainty in the evidence for a net health benefit from using BATs over no BATs in patients suspected of VWD with a history of abnormal blood laboratory results. Other EtD criteria were generally in favor of using BATs so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Studies regarding pediatric use of BATs.
- Studies regarding BATs use in adolescent males and females.

APPENDIX

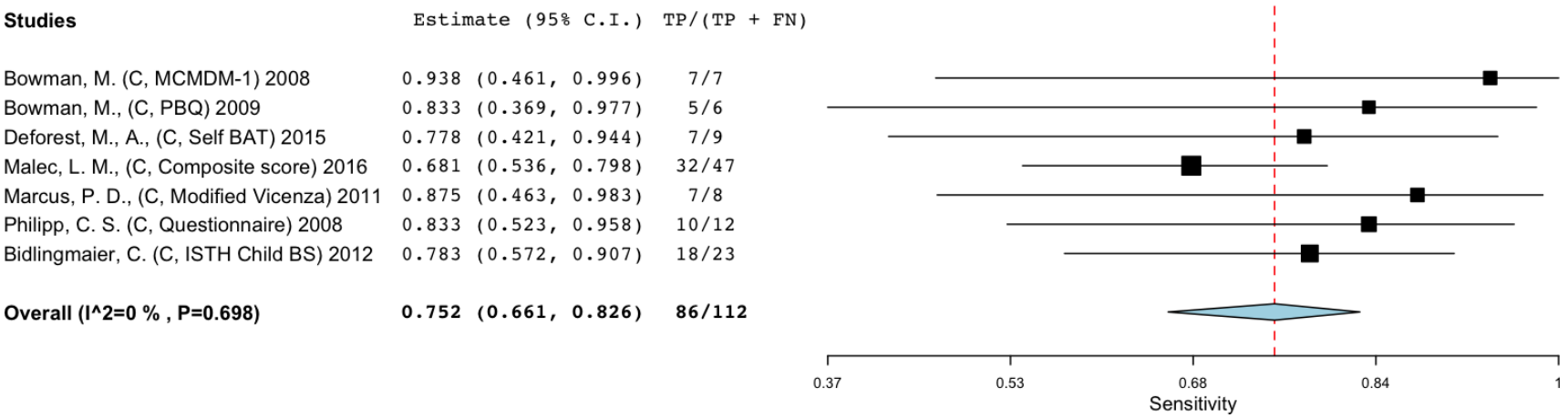
1. **Risk of Bias:**

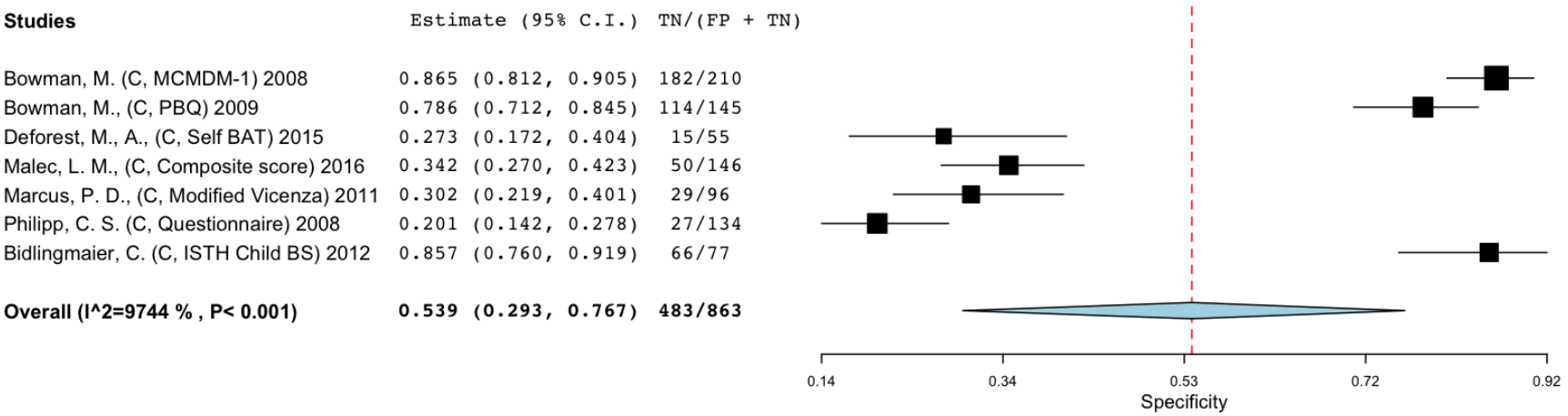
Author	Year	Patient Selection Risk of bias	Index test Risk of bias	Reference test Risk of bias	Flow and timing Risk of bias
Bowman, M.	2008	Low	Low	Low	Low
Bowman, M.	2009	Low	Low	Low	Low
Deforest, M.	2015	Low	Low	Low	Low
Malec, L. M.	2016	Low	Low	Low	Low
Marcus, P. D	2011	Low	Low	Low	Low
Bidlingmaier, C.	2012	Low	Low	Low	Low
Philipp, C. S.	2008	Moderate	Moderate	Low	Low
Faiz, A.	2017	High	Low	Moderate	Low
Belen, B.	2015	High	Low	Low	Low
Mittal, N.	2015	High	Moderate	High	Low
Pathare, A.	2018	High	Moderate	Low	Low
Bujnicki, H. C.	2011	High	Moderate	High	Low
Rodeghiero, F.	2005	High	Moderate	Moderate	Low

2. **Test Accuracy Results**

ID	Author	Year	Study Design	Number of patients	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI	Prevalence
629	Bidlingmaier, C.	2012	Cohort with DTA results	100	18	5	11	66	0.783	0.572	0.907	0.857	0.76	0.919	23%

795	Bowman, M.	2008	Cohort with DTA results	217	7	0	28	182	0.937	0.461	0.996	0.865	0.812	0.905	3%
620	Bowman, M.	2009	Cohort with DTA results	151	5	1	31	114	0.833	0.369	0.977	0.786	0.712	0.845	3%
488	Deforest, M.	2015	Cohort with DTA results	64	7	2	40	15	0.778	0.421	0.944	0.273	0.172	0.404	14%
446	Malec, L. M.	2016	Cohort with DTA results	193	32	15	96	50	0.681	0.536	0.798	0.342	0.27	0.423	22%
681	Marcus, P. D	2011	Cohort with DTA results	104	7	1	67	29	0.875	0.463	0.983	0.302	0.219	0.401	8%
135	Philipp, C. S.	2008	Cohort with DTA results	146	10	2	107	27	0.833	0.523	0.958	0.201	0.142	0.278	8%
146	Faiz, A.	2017	Case Control	53	21	5	19	8	0.808	0.613	0.918	0.296	0.156	0.49	27%
407	Belen, B.	2015	Case Control	84	46	0	15	17	0.989	0.851	0.999	0.53	0.363	0.691	25%
710	Mittal, N.	2015	Case Control	1316	34	1	36	1245	0.971	0.823	0.996	0.972	0.961	0.98	3%
673	Pathare, A.	2018	Case Control	96	33	13	8	42	0.717	0.572	0.828	0.84	0.711	0.918	48%
585	Bujnicki, H. C.	2011	Case control	160	75	5	4	76	0.937	0.858	0.974	0.95	0.874	0.981	50%
260	Rodeghiero, F.	2005	Case Control	341	81	2	45	213	0.976	0.909	0.994	0.826	0.774	0.867	25%





3. <u>Outcomes:</u>

- *For overall population*
  - ➢ Evidence profile:

Sensitivity	0.75 (95% CI: 0.66 to 0.83)
Specificity	0.54 (95% CI: 0.29 to 0.77)

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[b]	pre-test probability of 20%[c]	pre-test probability of 50%[d]	
True positives (patients with suspected patients)	7 studies 112 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	23 (20 to 25)	150 (132 to 165)	376 (331 to 413)	⊕⊕⊕⊕ HIGH
False negatives (patients incorrectly classified as not having								7 (5 to 10)	50 (35 to 68)	124 (87 to 169)	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[b]	pre-test probability of 20%[c]	pre-test probability of 50%[d]	
suspected patients)											
True negatives (patients without suspected patients)	7 studies 863 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	none	523 (284 to 744)	431 (234 to 614)	270 (147 to 384)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having suspected patients)								447 (226 to 686)	369 (186 to 566)	230 (116 to 353)	

Explanations

a. The point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori .

b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

c. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

d. Typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD.

- For a pre-test probability of 3%, which is typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT):

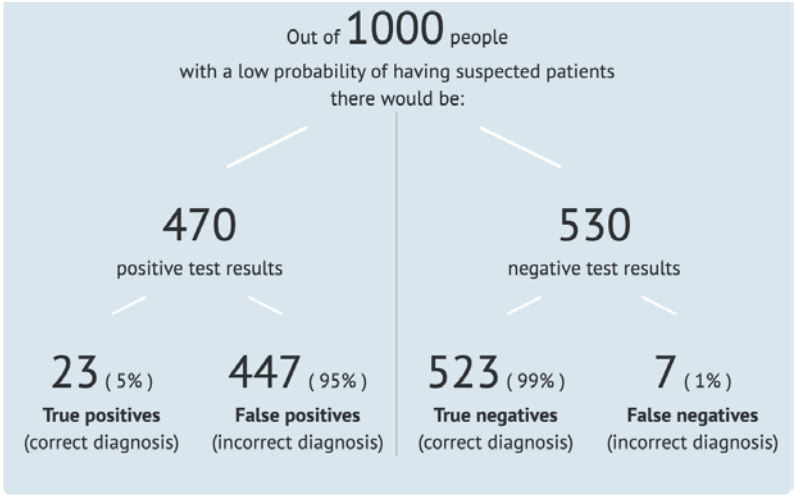
People's risk for suspected patients	Pre-test Probability of having suspected patients	Post-test Probability of a person having suspected patients with test results: With POSITIVE test result	Post-test With NEGATIVE test result	Certainty of the evidence (GRADE)
◉ Low probability Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT) ○ Medium probability Typically seen in patients investigat... ○ High probability Typically seen in in patients investig...	3% of the people in this risk group have suspected patients	5% of people with a positive test result have suspected patients (95% CI: 3% to 10%)	1% of people with a negative test result have suspected patients (95% CI: 3% to 1%)	⨁⨁◯◯ Low

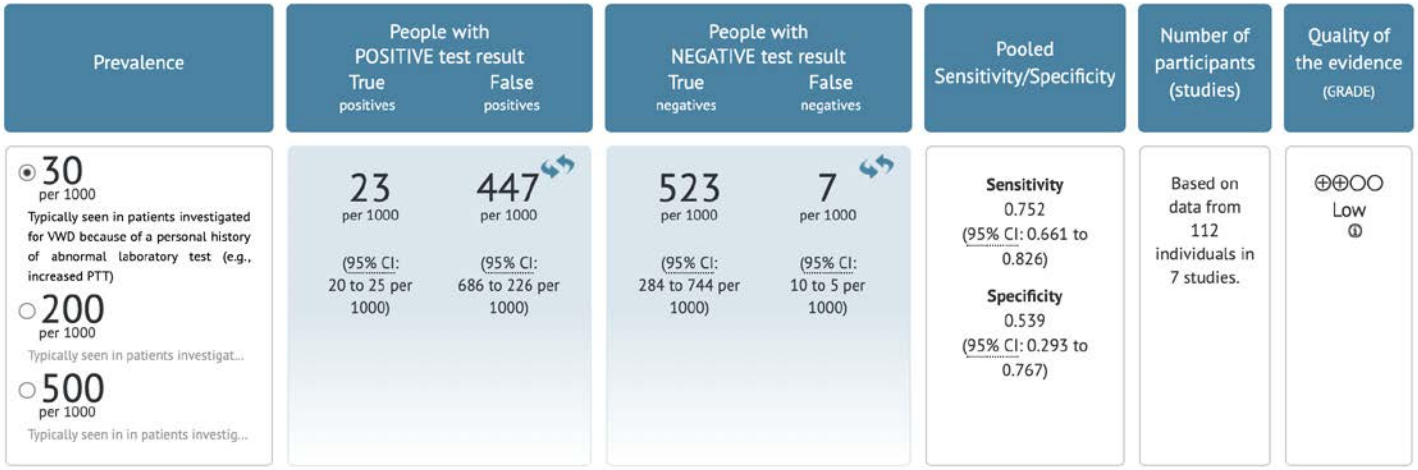
Hide confidence intervals

Show diagram

. Out of 100 people with a positive BAT, **5** would actually have VWD and **95** would not have VWD

. Out of 100 people with a negative BAT, **1** would actually have VWD and **99** would not have VWD





. 470 out of 1000 people tested with BAT will have a "positive" test result: 23 of these will have VWD (true positive), However, 447 of these people will not have VWD, even though their test result was positive (false positive).
. 530 out of 1000 people tested with BAT will have a "negative" test result. 523 of these will not have VWD (true negative). However, 7 of these people will actually have VWD, even though their test result was negative (false negative).

. 30 people (out of 1000 people in the Low probability group) have (as yet undetected) VWD. Of the 1000 people who take Bleeding Assessment tool test: 23 people will be correctly identified as having VWD (true positives). However, 7 people with VWD will remain undetected; their “negative” BAT results will be incorrect (false negatives).
. 970 people (out of 1000 people in the Low probability group) do not have VWD. Of the 1000 people who take the Bleeding Assessment tool test: 523 of these people will be correctly identified as not having VWD (true negatives). However, 447 people will be incorrectly identified; their “positive” test results will suggest they have VWD (false positives).

- For the pre-test probability of 20%, which is typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding), and the pre-test probability of 50%, which is typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD, the interactive summary of findings can be accessed using the following link:

https://gdt.gradepro.org/presentations/#/isof/isof_c5b33e22-a646-4654-9f09-b820aff36c5c-1569520689536?_k=eump67

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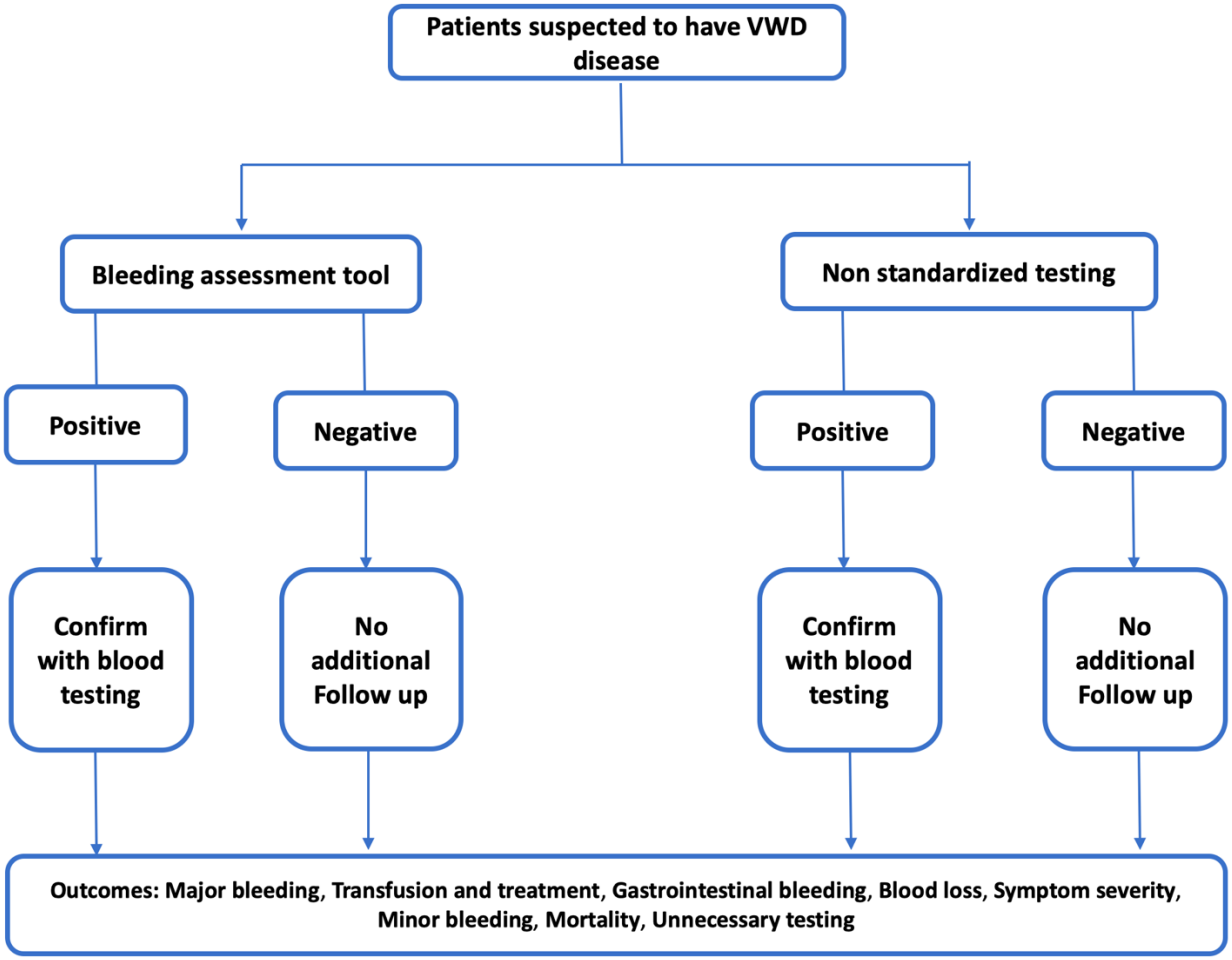
Question 1 and 2 (20%)

Should a bleeding assessment tool be used to diagnose patients suspected of having von Willebrand Disease?	
POPULATION:	Patients suspected of von Willebrand Disease
INTERVENTION:	Bleeding Assessment Tool
PURPOSE OF THE TEST:	Identify patients with VWD
ROLE OF THE TEST:	Identify patients with VWD
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	BATs – False positive, BATs – False negative, BATs – True positive, BATs – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent way. The importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)
SUBGROUPS:	This recommendation addresses patients with a VWD pretest probability of 20%, the typical incidence of VWD in patients referred because of a history of abnormal bleeding symptoms, with or without abnormal laboratory blood tests (including the pediatric population).
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent way. The	This question was judged to be a priority among many candidate questions to address in these guidelines.

○ Don't know	importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)	

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ● Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Pooled sensitivity across 7 cohort studies with 112 patients was 0.75 (95% CI: 0.66 to 0.83) Pooled specificity across 7 cohort studies with 863 patients was 0.54 (95% CI: 0.29 to 0.77)	The studies assess Bleeding Assessment Tools (BATs) versus non-BATs and do not compare BATs with non-standardized testing. The panel judged the test accuracy to be inaccurate for patients with a pretest probability of 20%, the typical incidence of VWD in patients referred because of a personal history of abnormal bleeding symptoms, with or without abnormal laboratory blood tests (including the pediatric population).

Outcome	Study design	Test accuracy CoE	Effect per 1000 patients/year for pre-test probability of 20%
True positives	cross-sectional (cohort type accuracy study)	⊕⊕⊕⊕ HIGH	150 (132 to 165)
False negatives			50 (35 to 68)
True negatives	cross-sectional (cohort type accuracy study)	⊕⊕⊕◯ MODERATE[a]	431 (234 to 614)
False positives			369 (186 to 566)

a. The heterogeneity measurement I2 is 98%, and the point estimates of specificity are not homogenous which cannot be explained by the setting or risk of bias a priori

Refer to the Appendix at the end of the document

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if they have other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	The benefit of a BAT is to identify patients who have VWD, who will be missed without this tool in the clinic. Using a BAT will allow for the quantification of bleeding symptoms in patients. The panel considered not missing a patient with VWD as the most important desirable effect, in addition to identify patients in a timely manner, in the appropriate center and to decrease unnecessary blood testing. BATs are educationally beneficial for patients and clinical experts and provides validation for patients about having the disease.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if	

	they have other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The risk of bias assessed using the QUADAS tool is not serious. Additionally, the articles addressed the PICO question directly and the results were precise. However, the point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori. This gives an overall high certainty of evidence for sensitivity and moderate certainty of evidence for specificity. Refer to the Appendix at the end of the document.	The data presented in the studies consider mostly women. It is important also to consider BATs in the pediatric population, as children might have a negative bleeding score due to lack of adequate bleeding challenges. The bleeding score may become positive with age. Men are more likely to have a negative bleeding score.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no relevant test effects since the intervention is a questionnaire and not an invasive test.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies		Despite the lack of included studies, there is **variability and inconsistency** in what happens to patients during their diagnostic journey. Early detection of mild disease may help in management, especially in women who face additional bleeding challenges during reproductive years. Patients in the primary care setting (pre-test probability 3%) who are not recognized as having VWD will not be treated.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The diagnosis of VWD is challenging and requires the performance of multiple laboratory tests, that will also determine the type of the disease. There are some limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and VWD patients. Conducting a Bleeding Assessment Tool will guide the healthcare provider to perform laboratory tests for VWD.
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		Patients place high value on being heard, not having their diagnosis missed, and having guidance on appropriate management. Patients value the clarity and precise questions provided by the BATs. They benefit from the standardized and objective way of obtaining bleeding data and would expect the use of non-standardized testing to be poorly received due to the perception of being less reliable. Moreover, patients appreciate their direct input into the collection of personal medical history for making or confirming a diagnosis. Patients think of BATs as similar to surveys given to patients for other diagnoses in internal medicine or family medicine. On the other hand, although BATs are useful adjunct, patients may feel that their story is devalued if reduced entirely to a questionnaire. Since the answers in a structured questionnaire are less subtle than in open questions, patients may prefer an open discussion with the healthcare provider, rather than only a structured questionnaire that may not account for all their bleeding symptoms. Patients might want to know that blood tests are negative even if they have a negative bleeding score, especially if they were told they have VWD, bringing a concern of underdiagnosis or overtreatment; so patients may value a blood test more than BATs for confirmation of diagnosis, regardless of the bleeding score. Finally, privacy and security of sensitive health data are concerns to some patients with online BATs, however there is no universal online BAT that is currently administered.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document.	There is an increasing need to use validated, standardized and sensitive bleeding questionnaires to assist in the determination of both the presence and severity of VWD.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		No additional financial resources are required to administer BATs, except time (including training/educating the provider to administer BATs), which is important in the clinical setting. However, not blood testing patients with a 20-50% pretest probability will lead to additional costs if a diagnosis is missed.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		No additional financial resources are required to administer BATs, except time (including training/educating the provider to administer BATs), which is important in the clinical setting. However, not blood testing patients with a 20-50% pretest probability will lead to additional costs if a diagnosis is missed.

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	In a Markov decision analytic model taking a societal perspective and costs expressed in 2007 US dollars, the cost of testing adolescents with menorrhagia for VWD was $1790, versus $1251 for not testing for VWD. The effectiveness of not testing in quality-adjusted life-years (QALYs) gained (14.237 QALYs) was similar to the VWD testing strategy (14.246 QALYs). Compared with not testing for VWD, screening for VWD had an incremental cost-effectiveness ratio of $62 791 per QALY, a value typically considered economically reasonable (Sidonio, 2010).	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		BATs are generally available for all patients, which might help patients receive equitable care. More work has been done with BATs in English language than other languages, although the ISTH-BAT has been translated and is available in German, Italian, Norwegian and Spanish.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		BATs are generally accepted by all patients referred to the hematology clinic.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		BATs might be less feasible in the primary care setting because of the need for additional resources (ie: time) when administering the questionnaire although this varies depending on the setting. With minimal training, the BATs may be administered by any healthcare professional (usually nursing staff or clinicians); self-administered versions are also available for patients to complete unassisted. The healthcare professional should be very familiar with bleeding disorders to tease out information from the patient who may not realize that they have more symptoms than they appreciate. If administered by clinicians, the tool needs to have minimal risk of interpretation errors such as subjective judgment differences between clinicians. The Self-BAT minimizes the errors using lay terms without complex definitions and criteria. The data are collected through paper or electronic record after face to face or phone interview. Currently, paper-based is the most used way of collecting the data, computer-assisted BATs to rapidly pass through negative domains would be useful while taking into consideration the resource implications. It usually takes 10-20 minutes to complete the BATs, but may take up to 30 minutes depending on the version. Time use may have a feasibility implication, but the panel felt BATs are often quicker than unstructured history for bleeding symptoms. BATs become time-consuming specifically when administered by the nursing staff seeing a large volume of patients.

		The question tackles using the BATs in secondary care. The primary screening would have been already performed by the primary care provider. This means that the incidence of bleeding problems is increased and the ability of the BATs alone to exclude a bleeding problem is limited (like d-dimer for thrombosis). The current BATs (e.g. ISTH, Self-BAT, PBQ, etc.) were not developed to serve primarily as a diagnostic tool, but to stratify patients in large cohort studies. Although a normal bleeding score and negative screening tests mean that no additional testing is needed, a normal bleeding score is not enough to rule out the diagnosis.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	**Inaccurate**	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	●	○	○	○

CONCLUSIONS

Recommendation

In patients with an intermediate probability of VWD (e.g. referred to a hematologist), the panel suggests against using a bleeding assessment tool (BAT) as an initial screening test to decide if specific blood testing is warranted, and rather performing specific blood testing in conjunction with the administration of a BAT for the diagnosis of VWD.
(Conditional recommendation based on moderate certainty in the evidence)

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 aPTT) (including the pediatric population).
- 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.
- Specific blood testing for VWD refers to VWF:Ag, VWF activity and FVIII:C.

Justification

The guideline panel determined that there is moderate certainty in the evidence for a net health benefit from using BATs and blood testing over BATs in patients suspected of VWD with a history of abnormal bleeding. Other EtD criteria were generally in favor of using blood testing so that the desirable consequences were greater than the undesirable consequences. This recommendation would also benefit patients with bleeding disorders other than VWD.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Studies regarding pediatric use of BATs.
- Studies regarding BATs use in adolescent males and females.

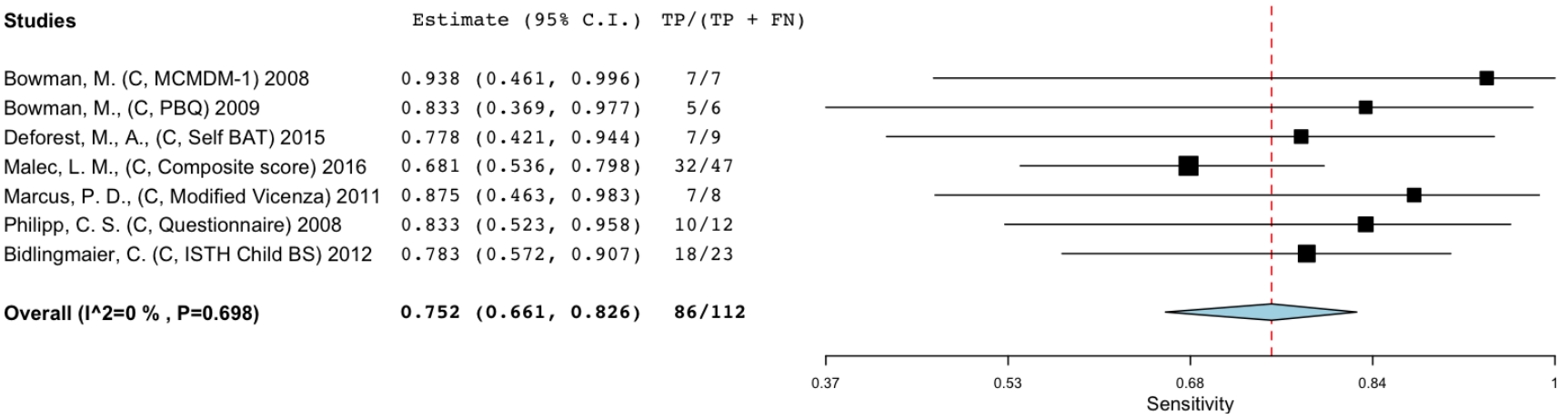
APPENDIX

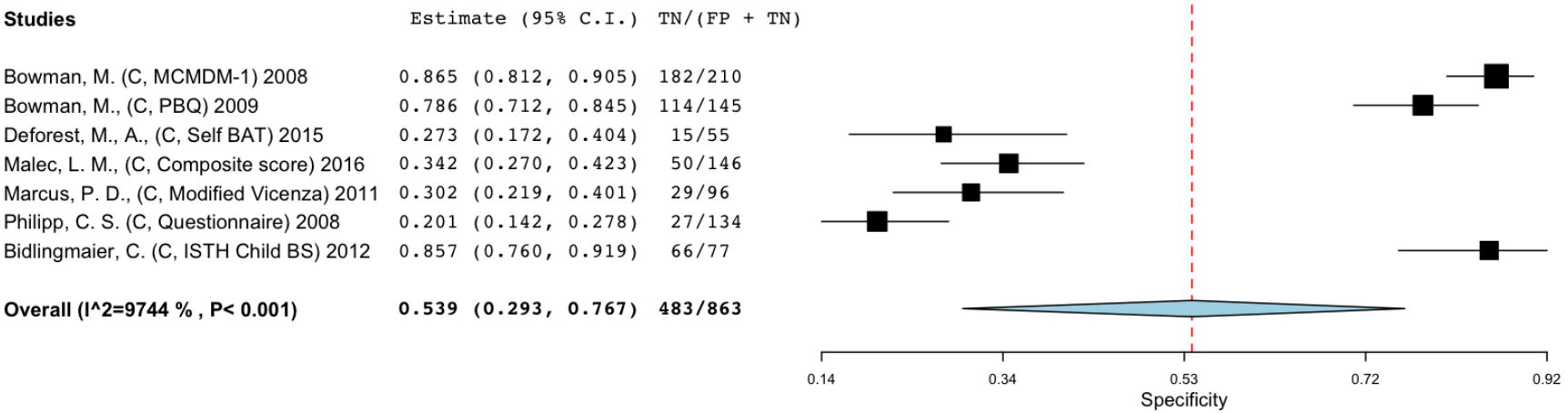
1. **Risk of Bias:**

Author	Year	Patient Selection Risk of bias	Index test Risk of bias	Reference test Risk of bias	Flow and timing Risk of bias
Bowman, M.	2008	Low	Low	Low	Low
Bowman, M.	2009	Low	Low	Low	Low
Deforest, M.	2015	Low	Low	Low	Low
Malec, L. M.	2016	Low	Low	Low	Low
Marcus, P. D	2011	Low	Low	Low	Low
Bidlingmaier, C.	2012	Low	Low	Low	Low
Philipp, C. S.	2008	Moderate	Moderate	Low	Low
Faiz, A.	2017	High	Low	Moderate	Low
Belen, B.	2015	High	Low	Low	Low
Mittal, N.	2015	High	Moderate	High	Low
Pathare, A.	2018	High	Moderate	Low	Low
Bujnicki, H. C.	2011	High	Moderate	High	Low
Rodeghiero, F.	2005	High	Moderate	Moderate	Low

2. Test Accuracy Results

ID	Author	Year	Study Design	Number of patients	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI	Prevalence
629	Bidlingmaier, C.	2012	Cohort with DTA results	100	18	5	11	66	0.783	0.572	0.907	0.857	0.76	0.919	23%
795	Bowman, M.	2008	Cohort with DTA results	217	7	0	28	182	0.937	0.461	0.996	0.865	0.812	0.905	3%
620	Bowman, M.	2009	Cohort with DTA results	151	5	1	31	114	0.833	0.369	0.977	0.786	0.712	0.845	3%
488	Deforest, M.	2015	Cohort with DTA results	64	7	2	40	15	0.778	0.421	0.944	0.273	0.172	0.404	14%
446	Malec, L. M.	2016	Cohort with DTA results	193	32	15	96	50	0.681	0.536	0.798	0.342	0.27	0.423	22%
681	Marcus, P. D	2011	Cohort with DTA results	104	7	1	67	29	0.875	0.463	0.983	0.302	0.219	0.401	8%
135	Philipp, C. S.	2008	Cohort with DTA results	146	10	2	107	27	0.833	0.523	0.958	0.201	0.142	0.278	8%
146	Faiz, A.	2017	Case Control	53	21	5	19	8	0.808	0.613	0.918	0.296	0.156	0.49	27%
407	Belen, B.	2015	Case Control	84	46	0	15	17	0.989	0.851	0.999	0.53	0.363	0.691	25%
710	Mittal, N.	2015	Case Control	1316	34	1	36	1245	0.971	0.823	0.996	0.972	0.961	0.98	3%
673	Pathare, A.	2018	Case Control	96	33	13	8	42	0.717	0.572	0.828	0.84	0.711	0.918	48%
585	Bujnicki, H. C.	2011	Case control	160	75	5	4	76	0.937	0.858	0.974	0.95	0.874	0.981	50%
260	Rodeghiero, F.	2005	Case Control	341	81	2	45	213	0.976	0.909	0.994	0.826	0.774	0.867	25%





3. Outcomes:

- *For overall population*
  - ➢ Evidence profile:

Sensitivity	0.75 (95% CI: 0.66 to 0.83)
Specificity	0.54 (95% CI: 0.29 to 0.77)

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[b]	pre-test probability of 20%[c]	pre-test probability of 50%[d]	
True positives (patients with suspected patients)	7 studies 112 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	23 (20 to 25)	150 (132 to 165)	376 (331 to 413)	⨁⨁⨁⨁ HIGH
False negatives (patients incorrectly classified as not having suspected patients)								7 (5 to 10)	50 (35 to 68)	124 (87 to 169)	
True negatives (patients without suspected patients)	7 studies 863 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	none	523 (284 to 744)	431 (234 to 614)	270 (147 to 384)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having suspected patients)								447 (226 to 686)	369 (186 to 566)	230 (116 to 353)	

Explanations

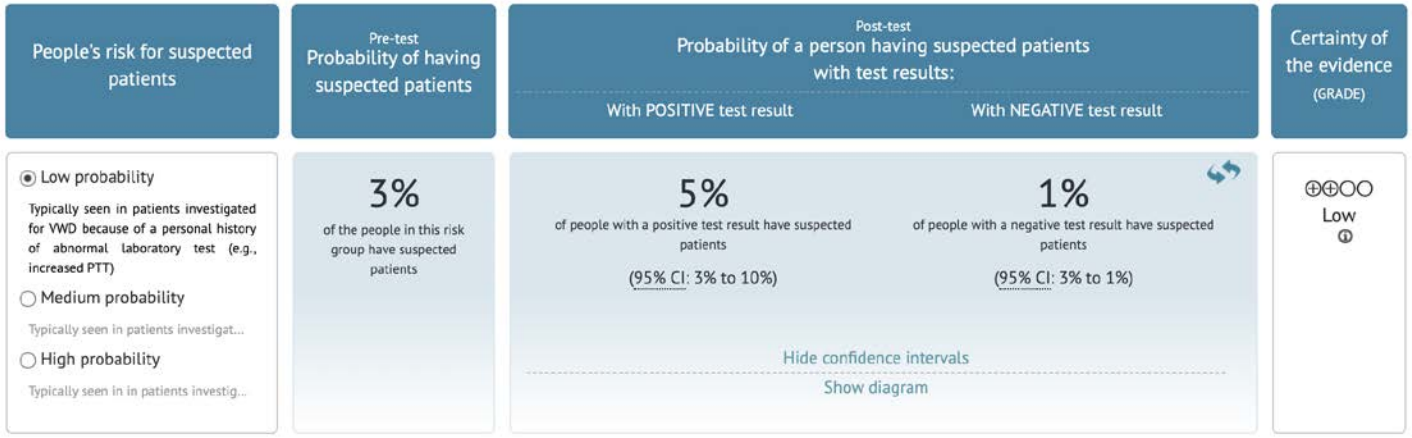
a. The point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori .

b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

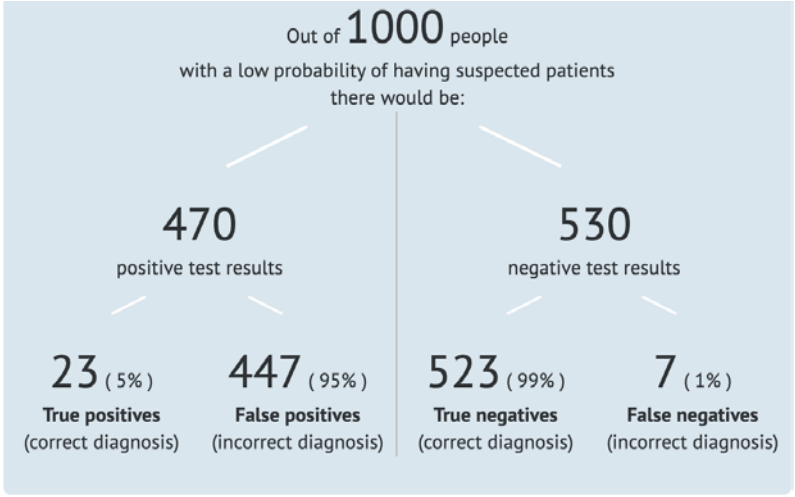
c. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

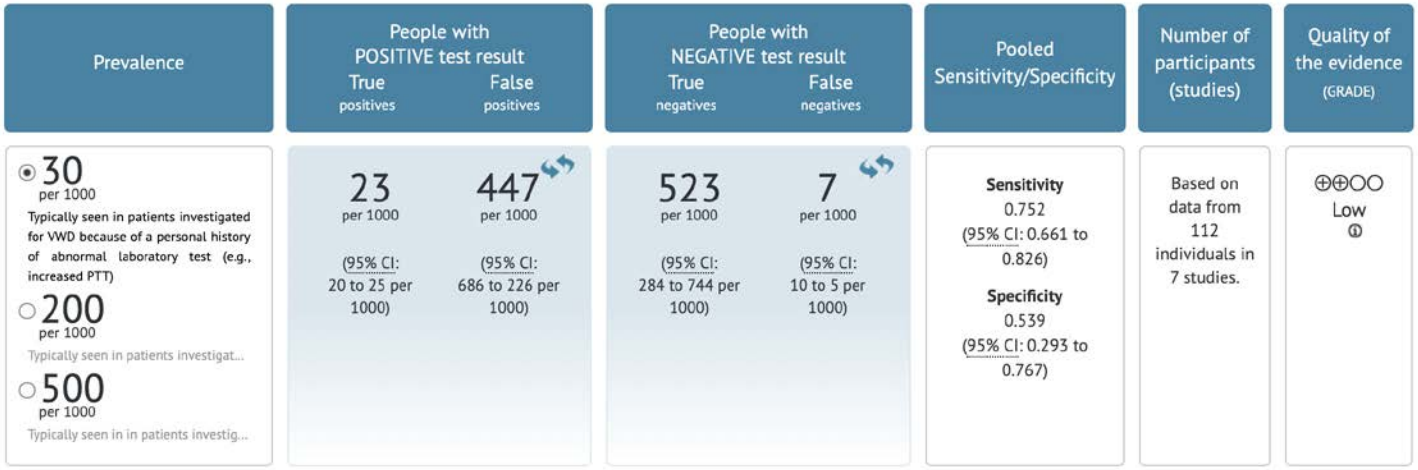
d. Typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD.

- For a pre-test probability of 3%, which is typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT):



. Out of 100 people with a positive BAT, **5** would actually have VWD and **95** would not have VWD
. Out of 100 people with a negative BAT, **1** would actually have VWD and **99** would not have VWD





. 470 out of 1000 people tested with BAT will have a "positive" test result: 23 of these will have VWD (true positive), However, 447 of these people will not have VWD, even though their test result was positive (false positive).
. 530 out of 1000 people tested with BAT will have a "negative" test result. 523 of these will not have VWD (true negative). However, 7 of these people will actually have VWD, even though their test result was negative (false negative).

. 30 people (out of 1000 people in the Low probability group) have (as yet undetected) VWD. Of the 1000 people who take Bleeding Assessment tool test: 23 people will be correctly identified as having VWD (true positives). However, 7 people with VWD will remain undetected; their “negative” BAT results will be incorrect (false negatives).
. 970 people (out of 1000 people in the Low probability group) do not have VWD. Of the 1000 people who take the Bleeding Assessment tool test: 523 of these people will be correctly identified as not having VWD (true negatives). However, 447 people will be incorrectly identified; their “positive” test results will suggest they have VWD (false positives).

- For the pre-test probability of 20%, which is typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding), and the pre-test probability of 50%, which is typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD, the interactive summary of findings can be accessed using the following link:

https://gdt.gradepro.org/presentations/#/isof/isof_c5b33e22-a646-4654-9f09-b820aff36c5c-1569520689536?_k=eump67

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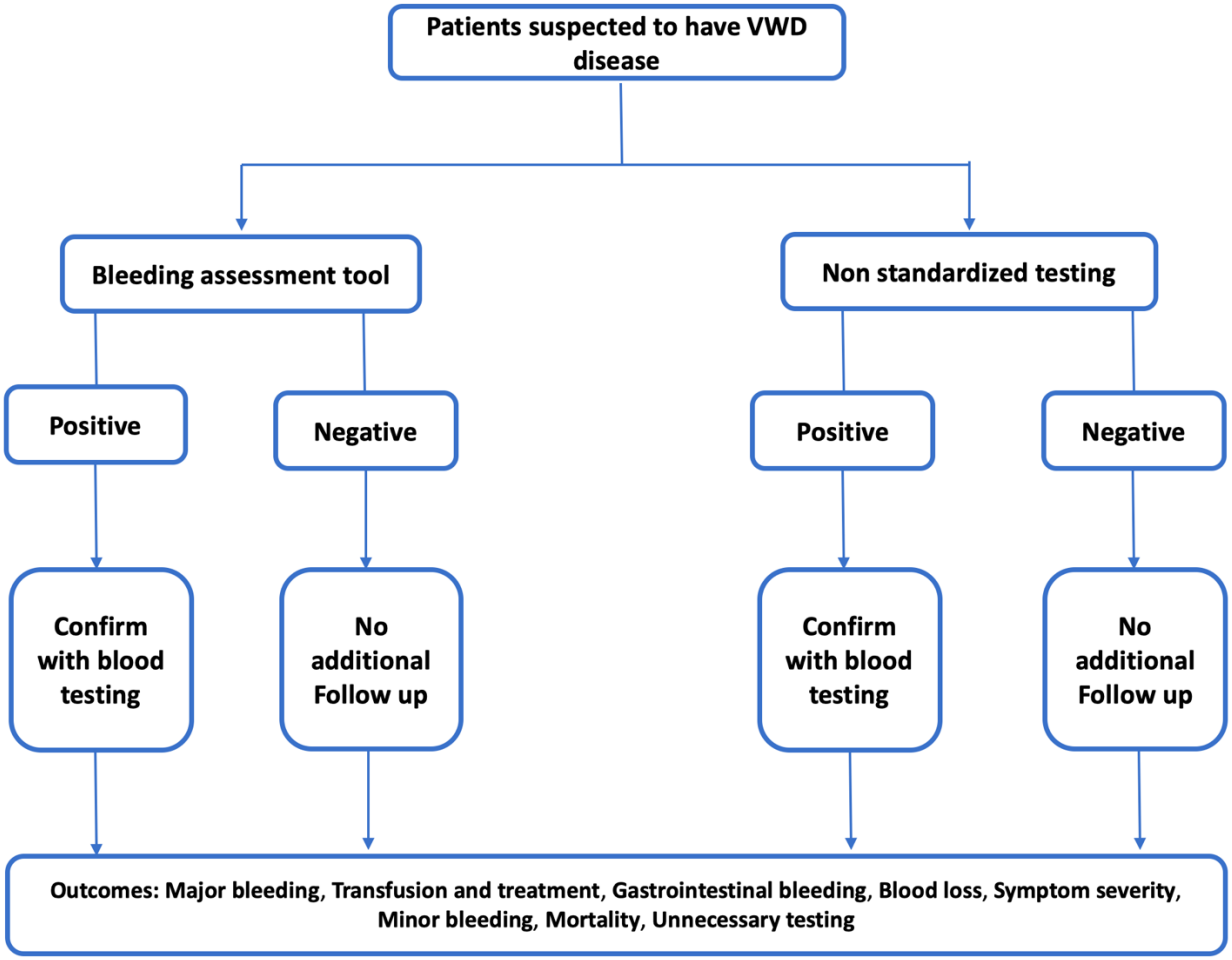
Question 1 and 2 (50%)

Should a bleeding assessment tool be used to diagnose patients suspected of having von Willebrand Disease?	
POPULATION:	Patients suspected of von Willebrand Disease
INTERVENTION:	Bleeding Assessment Tool
PURPOSE OF THE TEST:	Identify patients with VWD
ROLE OF THE TEST:	Identify patients with VWD
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	BATs – False positive, BATs – False negative, BATs – True positive, BATs – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent way. The importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)
SUBGROUPS:	This recommendation addresses patients with a VWD pretest probability of 50%, the typical incidence of VWD in patients referred because of a first degree relative with VWD regardless of their bleeding symptoms (including the pediatric population).
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. Assessment of the severity of bleeding symptoms is challenging because of the difficulties in reporting subjective bleeding symptoms in a consistent way. The	This question was judged to be a priority among many candidate questions to address in these guidelines.

○ Don't know	importance of the problem arises from the necessity of assessing the bleeding history to limit the need for unnecessary laboratory testing and also to avoid false-positive cases that are possible when diagnosing VWD. (Pathare, 2018)	

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Pooled sensitivity across 7 cohort studies with 112 patients was 0.75 (95% CI: 0.66 to 0.83) Pooled specificity across 7 cohort studies with 863 patients was 0.54 (95% CI: 0.29 to 0.77)	The studies assess Bleeding Assessment Tools (BATs) versus non-BATs and do not compare BATs with non-standardized testing. The panel judged the test accuracy to be very inaccurate for patients with a pretest probability of 50%, the typical incidence of VWD in patients referred because of a first degree relative with VWD regardless of their bleeding symptoms (including the pediatric population).

Outcome	Study design	Test accuracy CoE	Effect per 1000 patients/year for pre-test probability of 50%
True positives	cross-sectional (cohort type accuracy study)	⊕⊕⊕⊕ HIGH	376 (331 to 413)
False negatives			124 (87 to 169)
True negatives	cross-sectional (cohort type accuracy study)	⊕⊕⊕◯ MODERATE[a]	270 (147 to 384)
False positives			230 (116 to 353)

a. The heterogeneity measurement I2 is 98%, and the point estimates of specificity are not homogenous which cannot be explained by the setting or risk of bias a priori

Refer to the Appendix at the end of the document

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if they have other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	The benefit of a BAT is to identify patients who have VWD, who will be missed without this tool in the clinic. Using a BATs will allow for the quantification of bleeding symptoms in patients. The panel considered not missing a patient with VWD as the most important desirable effect, in addition to identify patients in a timely manner, in the appropriate center and to decrease unnecessary blood testing. BATs are educationally beneficial for patients and clinical experts and provides validation for patients about having the disease.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are individuals who do not have VWD but they will be labeled as potentially having a bleeding disorder by the BATs. Most of these patients will be reassured of not having VWD when they get additional blood testing. These patients may benefit from the treatment if they have	

	other bleeding disorders, but they will also suffer the side effects of treatment. Refer to the Appendix at the end of the document	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The risk of bias assessed using the QUADAS tool is not serious. Additionally, the articles addressed the PICO question directly and the results were precise. However, the point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori. This gives an overall high certainty of evidence for sensitivity and moderate certainty of evidence for specificity. Refer to the Appendix at the end of the document.	The data presented in the studies consider mostly women. It is important also to consider BATs in the pediatric population, as children might have a negative bleeding score due to lack of adequate bleeding challenges. The bleeding score may become positive with age. Men are more likely to have a negative bleeding score.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no relevant test effects since the intervention is a questionnaire and not an invasive test.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low		Despite the lack of included studies, there is **variability and inconsistency** in what happens

○ Moderate ○ High ● No included studies		to patients during their diagnostic journey. Early detection of mild disease may help in management, especially in women who face additional bleeding challenges during reproductive years. Patients in the primary care setting (pre-test probability 3%) who are not recognized as having VWD will not be treated.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The diagnosis of VWD is challenging and requires the performance of multiple laboratory tests, that will also determine the type of the disease. There are some limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and VWD patients. Conducting a Bleeding Assessment Tool will guide the healthcare provider to perform laboratory tests for VWD.
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability		Patients place high value on being heard, not having their diagnosis missed, and having

○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		guidance on appropriate management. Patients value the clarity and precise questions provided by the BATs. They benefit from the standardized and objective way of obtaining bleeding data and would expect the use of non-standardized testing to be poorly received due to the perception of being less reliable. Moreover, patients appreciate their direct input into the collection of personal medical history for making or confirming a diagnosis. Patients think of BATs as similar to surveys given to patients for other diagnoses in internal medicine or family medicine. On the other hand, although BATs are useful adjunct, patients may feel that their story is devalued if reduced entirely to a questionnaire. Since the answers in a structured questionnaire are less subtle than in open questions, patients may prefer an open discussion with the healthcare provider, rather than only a structured questionnaire that may not account for all their bleeding symptoms. Patients might want to know that blood tests are negative even if they have a negative bleeding score, especially if they were told they have VWD, bringing a concern of underdiagnosis or overtreatment; so patients may value a blood test more than BATs for confirmation of diagnosis, regardless of the bleeding score. Finally, privacy and security of sensitive health data are concerns to some patients with online BATs, however there is no universal online BAT that is currently administered.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document.	There is an increasing need to use validated, standardized and sensitive bleeding questionnaires to assist in the determination of both the presence and severity of VWD.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		No resources are required to conduct BATs, except time (including training/educating the provider to administer BATs), which is important in the clinical setting. However, not blood testing patients with a 20-50% pretest probability will lead to additional costs if a diagnosis is missed.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		No additional financial resources are required to administer BATs, except time (including training/educating the provider to administer BATs), which is important in the clinical setting. Doing BATs in this population would lead to net moderate savings.

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	In a Markov decision analytic model taking a societal perspective and costs expressed in 2007 US dollars, the cost of testing adolescents with menorrhagia for VWD was $1790, versus $1251 for not testing for VWD. The effectiveness of not testing in quality-adjusted life-years (QALYs) gained (14.237 QALYs) was similar to the VWD testing strategy (14.246 QALYs). Compared with not testing for VWD, screening for VWD had an incremental cost-effectiveness ratio of $62 791 per QALY, a value typically considered economically reasonable (Sidonio, 2010).	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		BATs are generally available for all patients, which might help patients receive equitable care. More work has been done with BATs in English language than other languages, although the ISTH-BAT has been translated and is available in German, Italian, Norwegian and Spanish. Not doing blood testing in a patient with a first degree relative with VWD would reduce health equity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		BATs are generally accepted by all patients with a family history of VWD.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		BATs might be less feasible in the primary care setting because of the need for additional resources (ie: time) when administering the questionnaire although this varies depending on the setting. With minimal training, the BATs may be administered by any healthcare professional (usually nursing staff or clinicians); self-administered versions are also available for patients to complete unassisted. The healthcare professional should be very familiar with bleeding disorders to tease out information from the patient who may not realize that they have more symptoms than they appreciate. If administered by clinicians, the tool needs to have minimal risk of interpretation errors such as subjective judgment differences between clinicians. The Self-BAT minimizes the errors using lay terms without complex definitions and criteria. The data are collected through paper or electronic record after face to face or phone interview. Currently, paper-based is the most used way of collecting the data, computer-assisted BATs to rapidly pass through negative domains would be useful while taking into consideration the resource implications. It usually takes 10-20 minutes to complete the BATs, but may take up to 30 minutes depending on the version. Time use may have a feasibility implication, but the panel felt BATs are often quicker than unstructured history for bleeding symptoms. BATs become time-consuming specifically when administered by the nursing staff seeing a large volume of

		patients. The question tackles using the BATs in secondary care. The primary screening would have been already performed by the primary care provider. This means that the incidence of bleeding problems is increased and the ability of the BATs alone to exclude a bleeding problem is limited (like d-dimer for thrombosis). The current BATs (e.g. ISTH, Self BAT, PBQ, etc) were not developed to serve primarily as a diagnostic tool, but to stratify patients in large cohort studies. Although a normal bleeding score and negative screening tests mean that no additional testing is needed, a normal bleeding score is not enough to rule out the diagnosis.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	**Very inaccurate**	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE	Very low	Low	Moderate	High			**No included**

	JUDGEMENT						
EVIDENCE OF TEST RESULT/MANAGEMENT							**studies**
CERTAINTY OF EFFECTS	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

In patients with a high probability of VWD (e.g. affected first degree relative), the panel recommends against using a bleeding assessment tool (BAT) as an initial screening test to decide if specific blood testing is warranted, and rather performing specific blood testing in conjunction with the administration of a BAT for the diagnosis of VWD.
(Strong recommendation based on moderate certainty in the evidence)

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 the pediatric population).
- 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
- Specific blood testing for VWD refers to VWF:Ag, VWF activity and FVIII:C.

Justification

The guideline panel determined that there is moderate certainty in the evidence for a net health harm from using BAT as the sole triage to determine who undergoes diagnostic testing versus blood testing in patients suspected of VWD because of a first relative with VWD. Other EtD criteria were generally against using BATs so that the undesirable consequences were greater than the desirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Studies regarding pediatric use of BATs.
- Studies regarding BATs use in adolescent males and females.

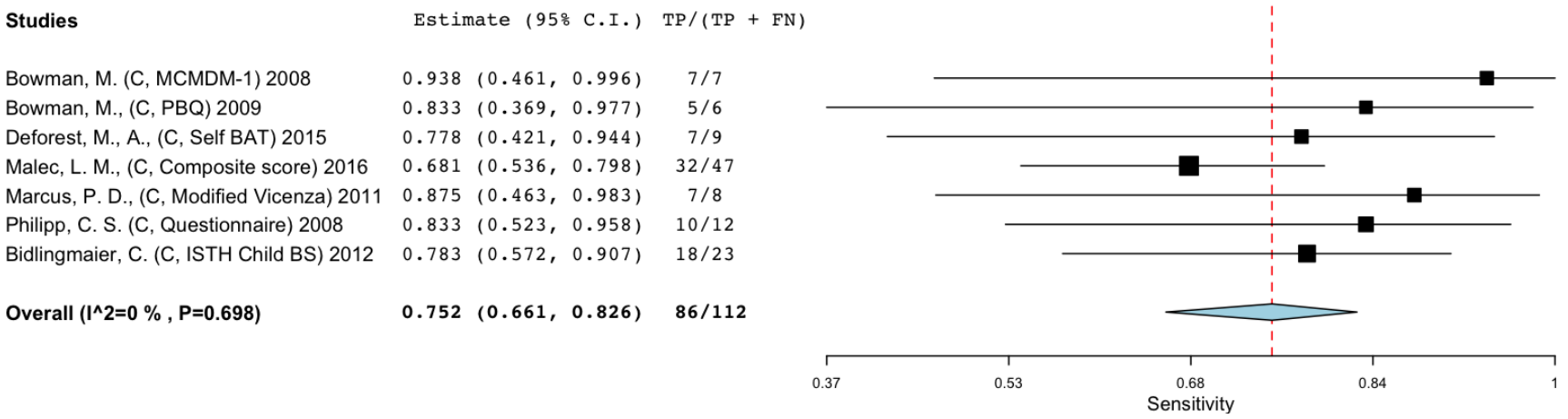
APPENDIX

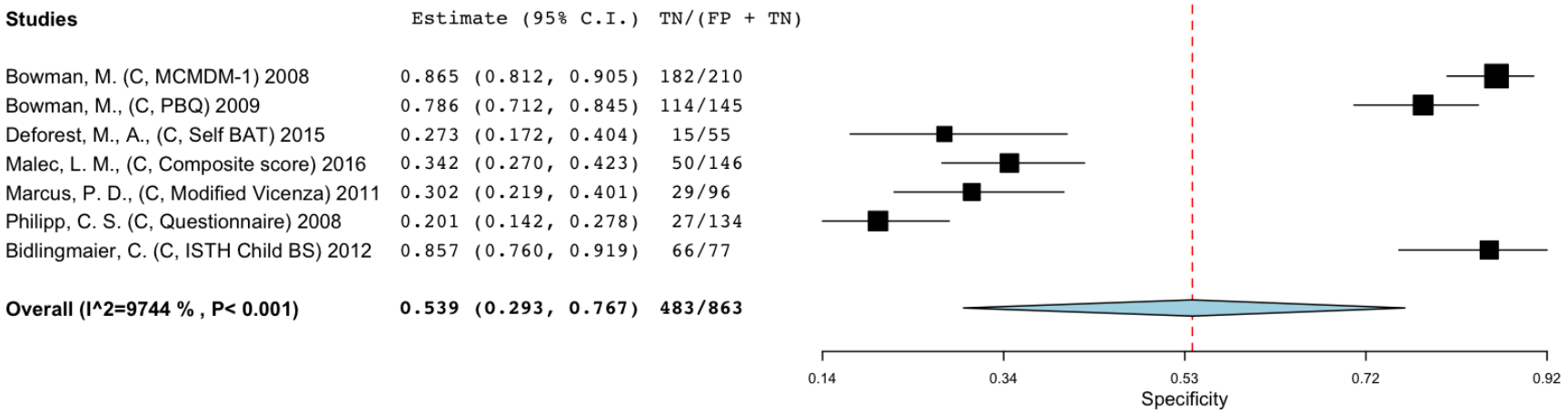
1. **Risk of Bias:**

Author	Year	Patient Selection Risk of bias	Index test Risk of bias	Reference test Risk of bias	Flow and timing Risk of bias
Bowman, M.	2008	Low	Low	Low	Low
Bowman, M.	2009	Low	Low	Low	Low
Deforest, M.	2015	Low	Low	Low	Low
Malec, L. M.	2016	Low	Low	Low	Low
Marcus, P. D	2011	Low	Low	Low	Low
Bidlingmaier, C.	2012	Low	Low	Low	Low
Philipp, C. S.	2008	Moderate	Moderate	Low	Low
Faiz, A.	2017	High	Low	Moderate	Low
Belen, B.	2015	High	Low	Low	Low
Mittal, N.	2015	High	Moderate	High	Low
Pathare, A.	2018	High	Moderate	Low	Low
Bujnicki, H. C.	2011	High	Moderate	High	Low
Rodeghiero, F.	2005	High	Moderate	Moderate	Low

2. **Test Accuracy Results**

ID	Author	Year	Study Design	Number of patients	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI	Prevalence
629	Bidlingmaier, C.	2012	Cohort with DTA results	100	18	5	11	66	0.783	0.572	0.907	0.857	0.76	0.919	23%
795	Bowman, M.	2008	Cohort with DTA results	217	7	0	28	182	0.937	0.461	0.996	0.865	0.812	0.905	3%
620	Bowman, M.	2009	Cohort with DTA results	151	5	1	31	114	0.833	0.369	0.977	0.786	0.712	0.845	3%
488	Deforest, M.	2015	Cohort with DTA results	64	7	2	40	15	0.778	0.421	0.944	0.273	0.172	0.404	14%
446	Malec, L. M.	2016	Cohort with DTA results	193	32	15	96	50	0.681	0.536	0.798	0.342	0.27	0.423	22%
681	Marcus, P. D	2011	Cohort with DTA results	104	7	1	67	29	0.875	0.463	0.983	0.302	0.219	0.401	8%
135	Philipp, C. S.	2008	Cohort with DTA results	146	10	2	107	27	0.833	0.523	0.958	0.201	0.142	0.278	8%
146	Faiz, A.	2017	Case Control	53	21	5	19	8	0.808	0.613	0.918	0.296	0.156	0.49	27%
407	Belen, B.	2015	Case Control	84	46	0	15	17	0.989	0.851	0.999	0.53	0.363	0.691	25%
710	Mittal, N.	2015	Case Control	1316	34	1	36	1245	0.971	0.823	0.996	0.972	0.961	0.98	3%
673	Pathare, A.	2018	Case Control	96	33	13	8	42	0.717	0.572	0.828	0.84	0.711	0.918	48%
585	Bujnicki, H. C.	2011	Case control	160	75	5	4	76	0.937	0.858	0.974	0.95	0.874	0.981	50%
260	Rodeghiero, F.	2005	Case Control	341	81	2	45	213	0.976	0.909	0.994	0.826	0.774	0.867	25%





3. Outcomes:

- *For overall population*
  - ➢ Evidence profile:

Sensitivity	0.75 (95% CI: 0.66 to 0.83)
Specificity	0.54 (95% CI: 0.29 to 0.77)

Prevalences	3%	20%	50%

Outcome	№ of	Study	Factors that may decrease certainty of evidence	Effect per 1,000 patients tested	Test

	studies (№ of patients)	design	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[b]	pre-test probability of 20%[c]	pre-test probability of 50%[d]	accuracy CoE
True positives (patients with suspected patients)	7 studies 112 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	23 (20 to 25)	150 (132 to 165)	376 (331 to 413)	⊕⊕⊕⊕ HIGH
False negatives (patients incorrectly classified as not having suspected patients)								7 (5 to 10)	50 (35 to 68)	124 (87 to 169)	
True negatives (patients without suspected patients)	7 studies 863 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	not serious	none	523 (284 to 744)	431 (234 to 614)	270 (147 to 384)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having suspected patients)								447 (226 to 686)	369 (186 to 566)	230 (116 to 353)	

Explanations

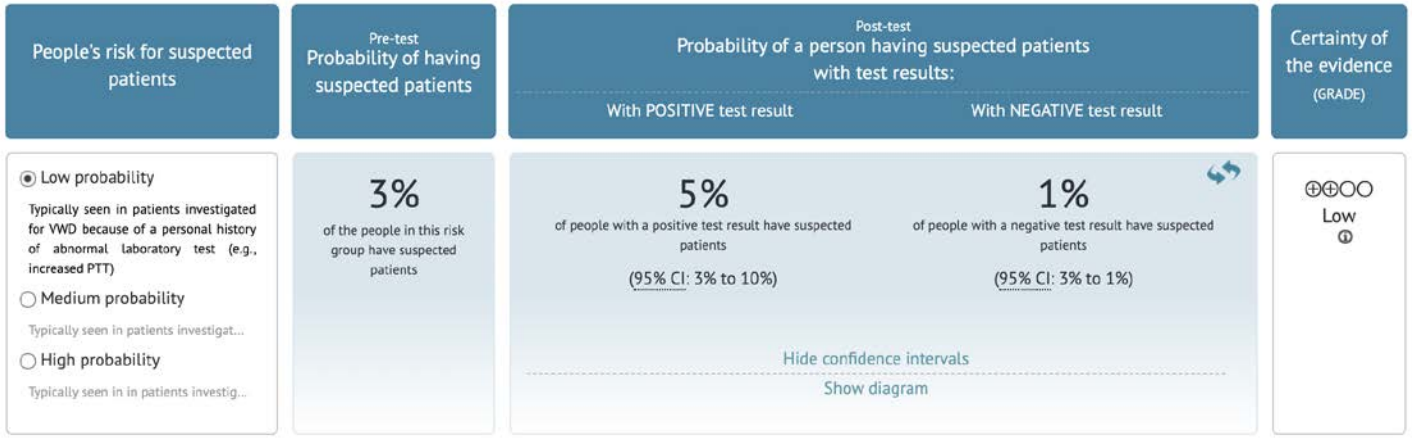
a. The point estimates of specificity are not homogenous which was not explained by the setting or risk of bias a priori .

b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

c. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

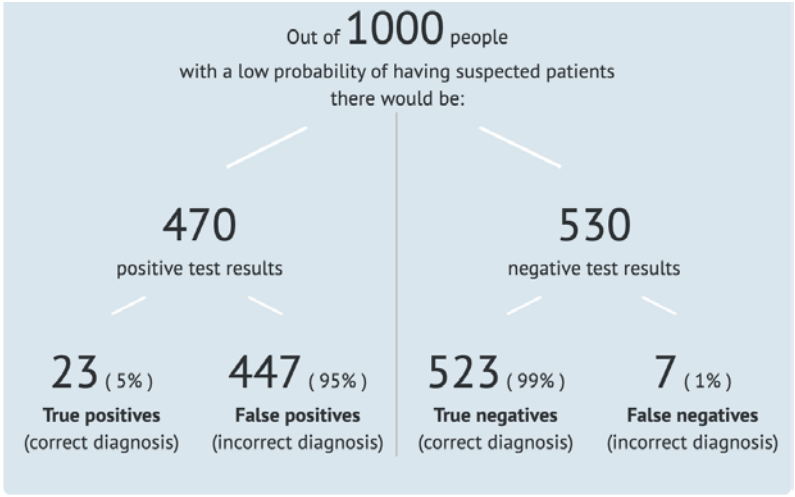
d. Typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD.

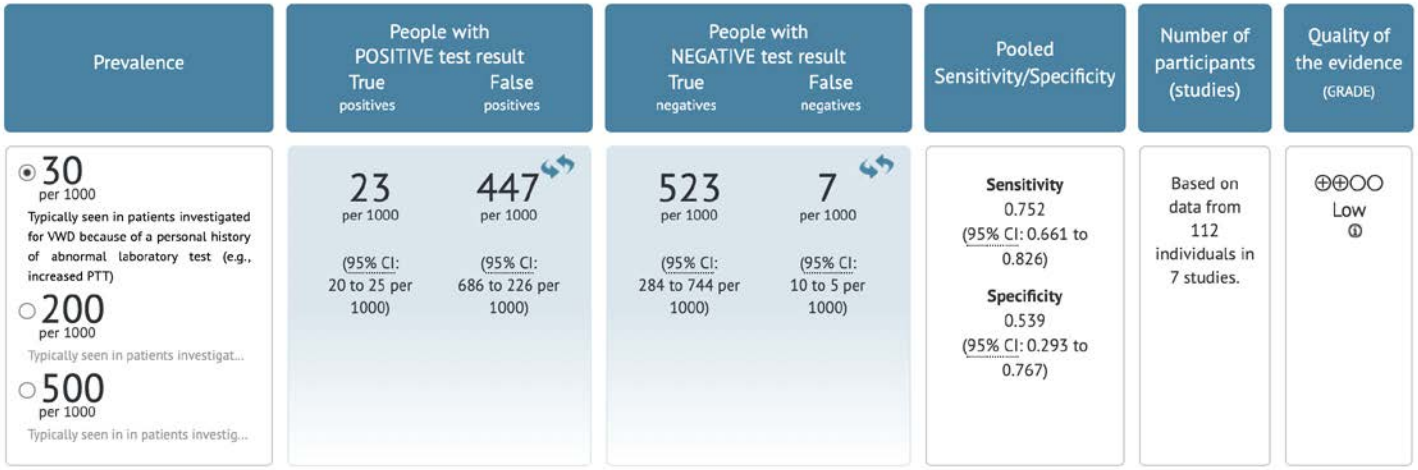
- For a pre-test probability of 3%, which is typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT):



. Out of 100 people with a positive BAT, **5** would actually have VWD and **95** would not have VWD

. Out of 100 people with a negative BAT, **1** would actually have VWD and **99** would not have VWD





. 470 out of 1000 people tested with BAT will have a "positive" test result: 23 of these will have VWD (true positive), However, 447 of these people will not have VWD, even though their test result was positive (false positive).
. 530 out of 1000 people tested with BAT will have a "negative" test result. 523 of these will not have VWD (true negative). However, 7 of these people will actually have VWD, even though their test result was negative (false negative).

. 30 people (out of 1000 people in the Low probability group) have (as yet undetected) VWD. Of the 1000 people who take Bleeding Assessment tool test: 23 people will be correctly identified as having VWD (true positives). However, 7 people with VWD will remain undetected; their “negative” BAT results will be incorrect (false negatives).
. 970 people (out of 1000 people in the Low probability group) do not have VWD. Of the 1000 people who take the Bleeding Assessment tool test: 523 of these people will be correctly identified as not having VWD (true negatives). However, 447 people will be incorrectly identified; their “positive” test results will suggest they have VWD (false positives).

- For the pre-test probability of 20%, which is typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding), and the pre-test probability of 50%, which is typically seen in in patients investigated for VWD as a first degree relative for a patient with VWD, the interactive summary of findings can be accessed using the following link:

https://gdt.gradepro.org/presentations/#/isof/isof_c5b33e22-a646-4654-9f09-b820aff36c5c-1569520689536?_k=eump67

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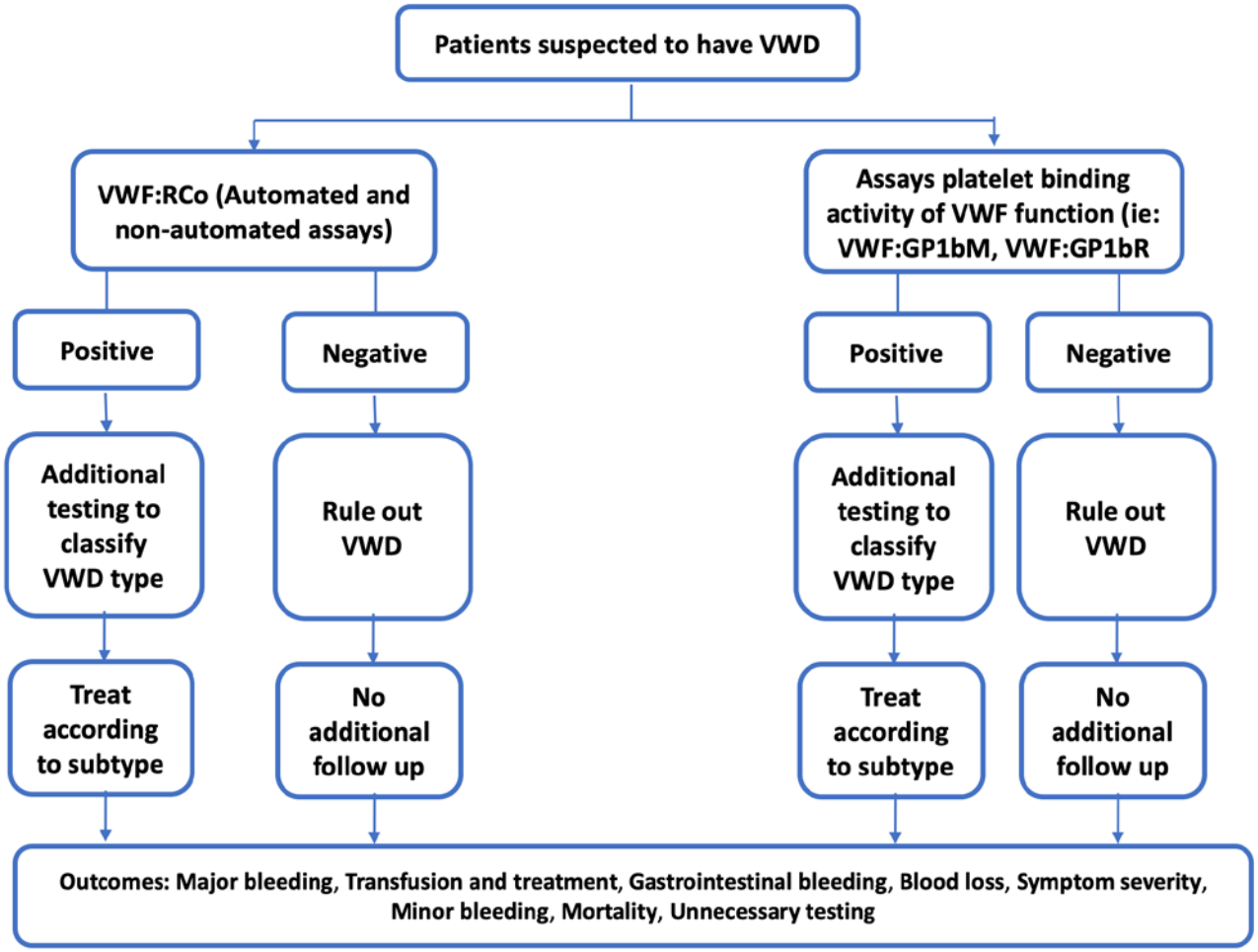
Question 3

Should newer tests of platelet binding activity of VWF function (VWF:GpIbR , VWF:GpIbM) vs. VWF:RCo be used to diagnose von Willebrand Disease in patients suspected of VWD?	
POPULATION:	Patients suspected of von Willebrand Disease (VWD)
INTERVENTION:	Newer tests (VWF:GpIbR , VWF:GpIbM)
COMPARISON:	VWF:RCo
PURPOSE OF THE TEST:	Identify patients with VWD
ROLE OF THE TEST:	Identify patients with VWD
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	VWF:RCo – False positive, VWF:RCo – False negative, VWF:RCo – True positive, VWF:RCo – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests (Pathare, 2018). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011, Favalaro, 2016). Automated methods of measuring VWF activity are becoming widely used, and have advantages and limitations (Kessler, 2017, Higgins, 2018,).
SUBGROUPS:	
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. Robert Montgomery was recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests (Pathare, 2018). Diagnosis and classification of VWD require a correlation between clinical findings and laboratory results. Recommended initial laboratory tests include	This question was judged to be a priority among many candidate questions to address in these guidelines.

yes ● Yes ○ Varies ○ Don't know	measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011).	

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	VWF:RCO: - the range of sensitivities across 4 studies* with 337 patients: 0.83 to 1.00 - the range of specificities across 4 studies* with 587 patients: 0.87 to 0.95 VWF:GpIbR: - the range of sensitivities across 4 studies* with 404 patients: 0.80 to 1.00 - the range of specificities across 4 studies* with 575 patients: 0.81 to 0.97 VWF:GpIbM: - the range of sensitivities across 2 studies with 249 patients: 0.62 to 0.82 - the range of specificities across 2 studies with 513 patients: 0.90 to 0.97 * Three of the four studies (Boender (2018), Vangenechten (2018) and Sagheer (2016)) investigated test accuracy for classifying Type 2 VWD patients (using a ratio of 0.6), not for diagnosing VWD.	Based on available diagnostic test accuracy, there appear to be comparable results between the different assays, however, there is concern about using assays in specific populations, which might affect the accuracy of this assay, such as the use of VWF:RCo in patients with D1472H variant (present in 67% of African American patients with low VWF, and 17% of Caucasians). The included studies do not include a large African population. the question becomes important when the patient has borderline levels, however, the studies included patients from the entire range of VWF making the borderline factor levels not an issue in the evidence. Additionally, the

Test result	Number of results per 1000 patients tested (95% CI)						№ of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 3%		Prevalence 20%		Prevalence 50%			
	Newer tests (VWF:GpIbR , VWF:GpIbM)	VWF:RCo	Newer tests (VWF:GpIbR , VWF:GpIbM)	VWF:RCo	Newer tests (VWF:GpIbR , VWF:GpIbM)	VWF:RCo		
True positives patients with Von Willebrand Disease	24 to 30	25 to 30	160 to 200	166 to 200	400 to 500	415 to 500	404 (4)	⨁⨁◯◯ LOW[a,b]
	1 fewer to 0 fewer TP in Newer tests (VWF:GpIbR , VWF:GpIbM)		6 fewer to 0 fewer TP in Newer tests (VWF:GpIR , VWF:GpIbM)		15 fewer to 0 fewer TP in Newer tests (VWF:GpIbR , VWF:GpIbM)			
False negatives patients incorrectly classified as not having Von Willebrand Disease	0 to 6	0 to 5	0 to 40	0 to 34	0 to 100	0 to 85		
	1 more to 0 fewer FN in Newer tests (VWF:GpIbR , VWF:GpIbM)		6 more to 0 fewer FN in Newer tests (VWF:GpIbR , VWF:GpIbM)		15 more to 0 fewer FN in Newer tests (VWF:GpIbR , VWF:GpIbM)			

True negatives patients without Von Willebrand Disease	786 to 941	844 to 922	648 to 776	696 to 760	405 to 485	435 to 475	584 (4)	⊕◯◯◯ VERY LOW[a,b,c]
	58 fewer to 19 more TN in Newer tests (VWF:GpIbR , VWF:GpIbM)		48 fewer to 16 more TN in Newer tests (VWF:GpIbR , VWF:GpIbM)		30 fewer to 10 more TN in Newer tests (VWF:GpIbR , VWF:GpIbM)			
False positives patients incorrectly classified as having Von Willebrand Disease	29 to 184	48 to 126	24 to 152	40 to 104	15 to 95	25 to 65		
	58 more to 19 fewer FP in Newer tests (VWF:GpIbR , VWF:GpIbM)		48 more to 16 fewer FP in Newer tests (VWF:GpIbR , VWF:GpIbM)		30 more to 10 fewer FP in Newer tests (VWF:GpIbR , VWF:GpIbM)			

a. Serious patient selection risk of bias due to case-control design
b. Studies do not include a considerable number of African American patients, and therefore do not consider the D1472H variant.
c. Considering the extremes of the confidence interval may lead to a different decision about which test to use

Author	Year	Pts	Test 1	Test 2	Test 3	Cor 1-2	Cor 2-3	Cor 1-3
Boender, J	2018	618	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.957	0.984	0.959
Szederjesi A	2018	95	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.963		0.989
Sagheer, S	2016	60	VWF:RCo[Agg]	VWF:GPIbR	VWF:Ab	0.954		0.938
Favaloro E	2016	535	VWF:RCo[Agg]	VWF:GPIbR	VWF:GPIbM	0.928		0.942
Timm A	2015	170	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.927	0.921	0.912
Stitt C	2014	37	BC-VWF:Rco	VWF:GPIbM		0.989		
Patzke, J	2014	580	BC-VWF:Rco	VWF:GPIbM		0.99		
Geisen, U	2014	432	BC-VWF:Rco	VWF:GPIbM		0.96		
Favaloro, E	2014	600	BC-VWF:Rco	VWF:GPIbM		0.958		
De Maistre	2014	122	VWF:RCo[Agg]	VWF:RCo[Acu]	VWF:GPIbM	0.977		0.965
Costa Pinto	2014	176	VWF:RCo[Agg]	VWF:RCo[Acu]		0.92		
Verfaillie, C	2013	50	VWF:GPIbR	VWF:Ab	VWF:RCo[Agg]	0.94		0.77
Lawrie, A	2013	180	BC-VWF:RCo	VWF:GPIbM		0.97		
Cabrera, N	2013	91	VWF:RCo[Agg]	VWF:GPIbR		0.92		
Trossaert, M	2011	268	VWF:Ab	BC-VWF:Rco		0.89		
Chen, D	2011	468	BC-VWF:Rco	VWF:Ab		0.93		

newer assays overcome the inaccuracy of the levels tested with VWF:RCo when the levels are low.

Bowyer, A	2011	53	VWF:RCo[Agg]	BC-VWF:Rco		0.91		
Chen, D	2008	35	VWF:Rco [Agg]	VWF:Rco (Flow Cyt)		0.86		
Pinol, M	2007	127	VWF:Rco [Agg]	VWF:Ab		0.956		
Vleeschauwer, A	2006	148	VWF:Rco [Agg]	VWF:Ab		0.84		
Sucker, C	2006	300	VWF:Ab	BC-VWF:Rco		0.88		
Strandberg, K	2006	478	VWF:Rco [Agg]	BC-VWF:Rco		0.96		
Vanhoorelbeke, K	2005	92	VWF:Rco [Agg]	VWF:RCo ELISA		0.963		
Lattuada, A	2004	95	VWF:Rco [Agg]	BC-VWF:Rco		0.61		
Federici, A	2004	122	VWF:Rco [Agg]	VWF:RCo ELISA		0.93		

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are patients who did not have VWD but they will be labeled as having VWD but will be identified as not having VWD on blood testing. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are patients who did not have VWD but they will be labeled as having VWD but will be identified as not having VWD on blood testing. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	Consequences and problems of overdiagnosis and underdiagnosis.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The risk of bias assessed using the QUADAS tool is serious, which is due to a serious patient selection risk of bias due to the case-control design used in some of the studies. Additionally, the articles addressed the PICO question indirectly since the diagnostic test accuracy results were used to classify VWD patients in the studies and not for diagnosing VWD. However, the results were precise and consistent between the different studies. This gives an overall low certainty of evidence for sensitivity and specificity in all tests. Refer to the Appendix at the end of the document	
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Because the VWF:RCo assay depends on ristocetin binding to VWF, variants in the *VWF* gene may affect the measurement of “VWF activity” by this assay and may not reflect a functional defect or true hemorrhagic risk (Flood, 2010). Reliance on VWF:RCo alone for diagnostic purposes may be an error in those with p.D1472H (Christopherson, 2019). Type 1 VWD subjects with D1472H had a significant decrease in the VWF:RCo/VWF:Ag ratio compared with those without D1472H, similar to the findings in the healthy control population (Flood, 2013).	There is variability in the VWF:RCo assay, which could be due to age-related change in factor levels, and quality assurance measures in the performing lab (sample handling, pre-analytical phase measures). Standardization among labs would help to get more accurate results.

Certainty of the evidence of management's effects
What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Because the VWF:RCo assay depends on ristocetin binding to VWF variants in the *VWF* gene may affect the measurement of "VWF activity" by this assay and may not reflect a functional defect or true hemorrhagic risk (Flood, 2010). Reliance on VWF:RCo alone for diagnostic purposes may be an error in those with p.D1472H (Christopherson, 2019). Type 1 VWD subjects with D1472H had a significant decrease in the VWF:RCo/VWF:Ag ratio compared with those without D1472H, similar to the findings in the healthy control population (Flood, 2013).	Treatment doses are based on ristocetin cofactor units. The diagnosis of VWD is challenging and requires the performance of multiple laboratory tests that will also determine the type of the disease. There are some limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and VWD patients. Results may confirm or exclude a prior diagnosis which may impact the patient's understanding of their bleeding and could help in the management to avoid excessive bleeding.

Certainty of the evidence of test result/management
How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Patients are very familiar with having blood drawn for lab testing for any reason. Well-trained phlebotomists at blood disorder treatment centers are efficient and have a good technique which means little or no bruising from blood draws for specialized hematology laboratory tests (Aschman, 2014). Patients desire assays that can be trusted and do not have to be repeated on multiple occasions. Patient concerns or preferences that are specific to these specialized labs are not different than other blood testing techniques, but concerns arise regarding the cut-off value used. (Baker, 2019).	While patients are interested in the results of the antigen and activity assays but frequently have little understanding of the tests and diagnostic thresholds, they desire an accurate diagnosis that will lead to proper treatment. Patients value clear and consistent guidelines on the reasons for different test choices and the diagnostic thresholds used, as patients are frustrated when they are not able to determine if they definitively do or do not have VWD. In speaking with others who have VWD, patients may desire the same testing regardless of

		need so they may compared results to each other. The VWF antigen and activity are continuous variables with a continuous increase in bleeding risk with lower levels. The clinical phenotype is determined by more than the levels only. Results may confirm or exclude a prior diagnosis which may impact the patient's understanding of their bleeding and its treatment and could provoke fear of bleeding (or thrombosis) if treatment is changed. It may also impact the patient's career choice and their surgical and procedural needs. Patients place value on the timing of getting the results of the test and sometimes they do not get the results back.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	<table><tr><th></th><th></th><th>VWF:Ag</th><th>VWF:RCo</th><th>VWF:Gp1bR</th><th>VWF:Gp1bM</th></tr><tr><td>USA</td><td>$</td><td>25-30</td><td>25-30</td><td>80</td><td></td></tr><tr><td>Canada</td><td>$</td><td>25-30</td><td>25-30</td><td></td><td>25-30</td></tr><tr><td>Australia</td><td>$</td><td>80-120</td><td>250</td><td>160-220</td><td></td></tr><tr><td>New Zealand</td><td>$</td><td>12</td><td>20</td><td>15</td><td></td></tr><tr><td>Europe</td><td>€</td><td>25-30</td><td>25</td><td></td><td>25</td></tr><tr><td>UK</td><td>£</td><td>8-20</td><td>30</td><td></td><td></td></tr></table> There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates. The data for	Usually, the price is comparable between the assays, however, the cost borne by the patient and the cost to the lab will be different depending on multiple factors, and there is variability to what the health insurance reimburses. For the USA, the price is the average insurance reimbursement price not

	required resources for some of the assays are not available because of lack of availability of the assay in different countries.	laboratory charge.
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The cost and difficulty of good quality control of these tests make these exams less accessible. There is difficulty in running multiple assays due to cost considerations, and reimbursement being only available for a limited number of tests in an individual patient. Physicians should choose the assays that have basic requirements and then identify those that could be of use in settings where the resource is not so much of an issue.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	In a Markov decision analytic model taking a societal perspective and costs expressed in 2007 US dollars, the cost of testing adolescents with menorrhagia for VWD was $1790, versus $1251 for not testing for VWD. The effectiveness of not testing in quality-adjusted life-years (QALYs) gained (14.237 QALYs) was similar to the VWD testing strategy (14.246 QALYs). Compared with not testing for VWD, screening for VWD had an incremental cost-effectiveness ratio of $62 791 per QALY, a value typically considered economically reasonable (Sidonio, 2010).	Considerations should be made for the overall cost of not testing for VWD.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		There is a subtle difference in comparisons between the tests in terms of equity. Not all tests are accessible to all patients. Therefore, a thorough and proper investigation may be limited due to the high cost and lack of exams with appropriate quality control. Insurance coverage for these tests is variable based on location and funding

		model. In the United States of America, most private insurance will cover VWF antigen and activity assays, but some patients may have a large deductible. Sometimes the reimbursed value does not cover the overall cost of the test, especially in public services. In New Zealand specifically, all residents get blood tests for free. This is also applicable in the United Kingdom, since there is no practical restriction on requesting these tests. In Italy, they are partly covered by insurance. In Australia, a limited number of antigen and activity assays are covered by insurance - above 3 assays the cost is not covered. In the Netherlands, all assays are covered by insurance. The VWF:RCo is potentially less useful in the African American population given the higher frequency of the D1472H variant in this population. Because of the higher rate of the benign variants that affect the VWF:RCo giving false positively low results, the VWF:GPIbM testing can be used in followup testing in Hispanic and African

		American populations more than Caucasian. The aforementioned populations may be less likely to have easy access to larger centers.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Generally, all patients accept the blood tests in question.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Antigen and activity assays have limited availability – available in most larger population centers will have centralized testing in specialist centers. It is usually not found in resource-poor countries and tertiary care centers even in high-income setting countries, specifically the activity assays. VWF:GPIbm

		or GPIbR is not available in most centers in the United States of America, but VWF:Ag and VWF:RCo are more readily available. VWF:Ag is only available in hospitals with special coagulation labs, and special coagulation labs usually only run either the VWF:RCo or one of the newer assays. Countries differ in the challenges to access the testing (referrals within the system and logistic issues like traveling hundreds of kilometers), so testing is often sent out reference laboratories (with all the issues of pre-analytical variables, including sample collection and transport that can affect the reliability of results) outside of medium to large academic centers in the United States. Even when the tests are available in smaller non-academic centers, results may differ when compared to those from large referral centers. Depending on where patients are allowed to undergo testing, there could be variation in results (e.g., in California, insurers may not reimburse repeat

		testing of VWF:Ag and VWF:RCo or VWF:GPIbm to be done at the respective academic center if performed already at private commercial laboratories). Often repeat testing is needed particularly if obtained at a time of stress (following a procedure) or in times of significant anemia. This issue is illustrated with teenage girls undergoing evaluation during an episode of heavy menstrual bleeding. Levels may be elevated over baseline and obscure the diagnosis of VWD or its subtype. It may be possible to say that one or two activity measures are not accurate and reduce their use, but many labs are bound by managed service contracts and performing all labs as a single 'best' assay is often not feasible. Another feasibility issue assay availability and turnaround time in the perioperative setting. Some of the tests, such as the VWF:RCo, have a considerable coefficient of variation, which may influence laboratory research. In addition, the

		physiological or induced variations of VWF plasma levels also may affect the diagnosis of borderline cases, especially of type 1 VWD and low levels of VWF.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	**High**			No included studies
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	**High**			No included studies
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests newer assays that measure the platelet binding activity of VWF (e.g. VWF:GPIbM, VWF:GPIbR) over the VWF:RCo (automated or non-automated assay) for the diagnosis of VWD.
(Conditional recommendation based on low certainty in the evidence)

Remark:

- A critical consideration is the poor performance of the VWF:RCo in specific patient groups such as African Americans

Good practice statement:

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

Justification

The guideline panel determined that there is low certainty in the evidence for a net health benefit from using VWF:GpIbR and VWF:GpIbM over VWF:RCo in patients suspected of VWD. Other EtD criteria were generally in favor of using VWF:GpIbR and VWF:GpIbM so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Variability of the different assays in different ethnic groups.

APPENDIX

1. **Risk of bias:**

Author	Year	Patient Selection	Index test	Reference test	Flow and timing
Vangenechten, K	2018	High	Low	Low	Low
Boender, J	2018	Moderate	Low	Moderate	Low
Sagheer, S	2016	High	Low	Low	Low
Costa Pento	2014	High	Low	Low	Low
Verfaillie, C	2013	High	Low	Low	Low
Cabrera, N	2013	High	Low	Moderate	Low
Lasne, D	2012	High	Low	Low	Low
Trossaert, M	2011	Low	Low	Low	Low
Chen, D	2011	High	Low	Low	Low
Salem, R	2007	Low	Low	Low	Low
Pinol, M	2007	High	Low	Low	Low
Vleeschauwer, A	2006	High	Low	Low	Low
Strandberg, K	2006	High	Low	Low	Low

2. **Outcomes:**

Author	Year	PICO arm	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI
Vangenechten, K	2018	VWF:RCo was measured by using the BC-VWF:Rco	43	7	11	76	0.86	0.734	0.932	0.874	0.786	0.929
		HemosIL VWF:RCo, ISTH nomenclature VWF: GPIbR	40	10	6	81	0.8	0.667	0.889	0.931	0.855	0.969
		The INNOVANCE VWF:Ac, VWF:GPIbM	41	9	9	79	0.82	0.689	0.904	0.898	0.815	0.946
Boender, J	2018	VWF:RCo was measured by using the BC-VWF:Rco	102	21	20	405	0.829	0.752	0.886	0.953	0.928	0.969
		HemosIL AcuStar VWF:RCo'	154	36	14	402	0.811	0.748	0.86	0.966	0.944	0.98
		VWF:GPIbM	123	76	12	413	0.618	0.549	0.683	0.972	0.951	0.984
Sagheer, S	2016	VWF:RCo[Agg]	17	1	5	37	0.944	0.693	0.992	0.881	0.744	0.95
		VWF:RCo[Acu]	18	0	8	34	0.974	0.69	0.998	0.802	0.657	0.896
Costa Pento	2014	VWF:RCo[Agg]	146	0	2	28	0.997	0.948	1	0.919	0.758	0.976
		VWF:RCo[Acu]	146	0	1	29	0.997	0.948	1	0.952	0.792	0.99
Verfaillie, C	2013	HemosIL VWF:Rco	11	0	7	32	0.958	0.575	0.997	0.812	0.662	0.906
Cabrera, N	2013	HemosIL AcuStar VWF:Rco	70	3	0	18	0.953	0.873	0.983	0.974	0.69	0.998
Trossaert, M	2011	VWF:RCo was measured by using the BC-VWF:Rco	86	28	9	146	0.754	0.667	0.825	0.942	0.892	0.97
Pinol, M	2007	VWF:RCo[Agg]	69	1	4	53	0.986	0.906	0.998	0.93	0.827	0.973
Strandberg, K	2006	VWF:RCo was measured by using the BC-VWF:Rco	70	33	5	246	0.68	0.584	0.762	0.98	0.953	0.992

- *VWF:RCo vs VWF:GpIbR:*

VWF:RCo		VWF:GpIbR	
Sensitivity	0.83 to 1.00	Sensitivity	0.80 to 1.00
Specificity	0.87 to 0.95	Specificity	0.81 to 0.97

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 3%[c]		pre-test probability of 20%[d]		pre-test probability of 50%[e]		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWF:RCo	VWF:GpIbR	VWF:RCo	VWF:GpIbR	VWF:RCo	VWF:GpIbR	
True positives (patients with VWD)	4 studies 404 patients	cohort & case-control type studies	serious [a]	serious [f]	not serious	not serious	none	25 to 30	24 to 30	166 to 200	160 to 200	415 to 500	400 to 500	⨁⨁⨁◯ MODERATE
								1 more to 0 fewer TP in VWF:RCo		**6 more to 0 fewer TP in VWF:RCo**		**15 more to 0 fewer TP in VWF:RCo**		
False negatives (patients incorrectly classified as not having VWD)								0 to 5	0 to 6	0 to 34	0 to 40	0 to 85	0 to 100	
								1 fewer to 0 fewer FN in VWF:RCo		**6 fewer to 0 fewer FN in VWF:RCo**		**15 fewer to 0 fewer FN in VWF:RCo**		
True negatives (patients without VWD)	4 studies 584 patients	cohort & case-control type studies	serious [a]	serious [f]	not serious	serious [b]	none	844 to 922	786 to 941	696 to 760	648 to 776	435 to 475	405 to 485	⨁⨁◯◯ LOW
								58 more to 19 fewer TN in VWF:RCo		**48 more to 16 fewer TN in VWF:RCo**		**30 more to 10 fewer TN in VWF:RCo**		
False positives (patients incorrectly classified as								48 to 126	29 to 184	40 to 104	24 to 152	25 to 65	15 to 95	
								58 fewer to 19 more FP in VWF:RCo		**48 fewer to 16 more FP in VWF:RCo**		**30 fewer to 10 more FP in VWF:RCo**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 3%[c]		pre-test probability of 20%[d]		pre-test probability of 50%[e]		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWF:RCo	VWF:GpIbR	VWF:RCo	VWF:GpIbR	VWF:RCo	VWF:GpIbR	
having VWD)														

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, three of the four studies (Boender (2018), Vangenechten (2018) and Sagheer (2016)) investigated test accuracy for classifying Type 2 VWD patients (using a ratio of 0.6), not for diagnosing VWD

b. Considering the extremes of the confidence interval may lead to a different decision about which test to use

c. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

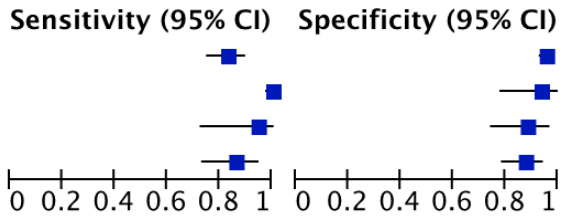
d. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

e. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD.

f. Studies do not include a considerable number of African American patients, and therefore do not consider the D1472H variant.

- *VWF:RCo:*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Boender, 2018	102	20	21	405	0.83 [0.75, 0.89]	0.95 [0.93, 0.97]
Costa Pento, 2014	146	2	0	28	1.00 [0.98, 1.00]	0.93 [0.78, 0.99]
Sagheer, 2016	17	5	1	37	0.94 [0.73, 1.00]	0.88 [0.74, 0.96]
Vangenechten, 2018	43	11	7	76	0.86 [0.73, 0.94]	0.87 [0.79, 0.94]



Sensitivity	0.83 to 1.00
Specificity	0.87 to 0.95

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[c]	pre-test probability of 20%[d]	pre-test probability of 50%[e]	
True positives (patients with VWD)	4 studies 337 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	25 to 30	166 to 200	415 to 500	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having VWD)								0 to 5	0 to 34	0 to 85	
True negatives (patients without VWD)	4 studies 584 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	844 to 922	696 to 760	435 to 475	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having VWD)								48 to 126	40 to 104	25 to 65	

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, three of the four studies (Boender (2018), Vangenechten (2018) and Sagheer (2016)) investigated test accuracy for classifying Type 2 VWD patients (using a ratio of 0.6), not for diagnosing VWD

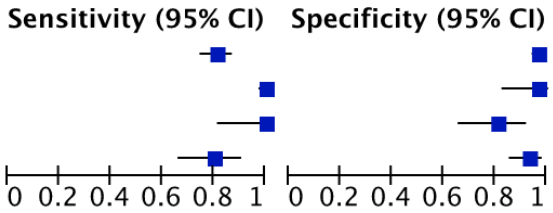
b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

c. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

d. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD.

- *VWF:GPIbR:*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Boender, 2018	154	14	36	402	0.81 [0.75, 0.86]	0.97 [0.94, 0.98]
Costa Pento, 2014	146	1	0	29	1.00 [0.98, 1.00]	0.97 [0.83, 1.00]
Sagheer, 2016	18	8	0	34	1.00 [0.81, 1.00]	0.81 [0.66, 0.91]
Vangenechten, 2018	40	6	10	81	0.80 [0.66, 0.90]	0.93 [0.86, 0.97]



Sensitivity	0.80 to 1.00
Specificity	0.81 to 0.97

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[c]	pre-test probability of 20%[d]	pre-test probability of 50%[e]	
True positives (patients with VWD)	4 studies 404 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	24 to 30	160 to 200	400 to 500	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having VWD)								0 to 6	0 to 40	0 to 100	
True negatives (patients without VWD)	4 studies 575 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	786 to 941	648 to 776	405 to 485	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having VWD)								29 to 184	24 to 152	15 to 95	

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, three of the four studies (Boender (2018), Vangenechten (2018) and Sagheer (2016)) investigated test accuracy for classifying Type 2 VWD patients (using a ratio of 0.6), not for diagnosing VWD

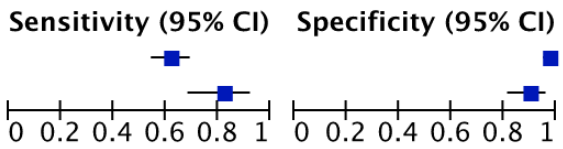
b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

c. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

d. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD.

- *VWF:GPIbM:*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Boender, 2018	123	12	76	413	0.62 [0.55, 0.69]	0.97 [0.95, 0.99]
Vangenechten, 2018	41	9	9	79	0.82 [0.69, 0.91]	0.90 [0.81, 0.95]



Sensitivity	0.62 to 0.82
Specificity	0.90 to 0.97

Prevalences	3%	20%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[c]	pre-test probability of 20%[d]	pre-test probability of 50%[e]	
True positives (patients with VWD)	2 studies 249 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	19 to 25	124 to 164	310 to 410	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having VWD)								5 to 11	36 to 76	90 to 190	
True negatives (patients without VWD)	2 studies 513 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	873 to 941	720 to 776	450 to 485	⨁⨁◯◯ LOW
False positives (patients								29 to 97	24 to 80	15 to 50	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 3%[c]	pre-test probability of 20%[d]	pre-test probability of 50%[e]	
incorrectly classified as having VWD)											

Explanations

a. Serious patient selection risk of bias due to case-control design. Diagnostic test accuracy results for classifying type 2 VWD patients (using a 0.6 ratio), not for diagnosing VWD.

c. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

d. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.

e. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD.

3. **Included assays:**

Assay nomenclature	Corresponds to:
VWF:RCo was measured by using the BC-VWF:Rco	VWF:RCo
VWF:RCo[Agg]	
VWF:RCo aggregometry using the BC von Willebrand Reagent (Siemens Healthcare Diagnostics).	
HemosIL VWF:RCo, ISTH nomenclature VWF: GPIbR	VWF:GPIbR
VWF:RCo[Acu]	
HemosIL VWF:Rco	
HemosIL AcuStar VWF:Rco	
The INNOVANCE VWF:Ac, ISTH nomenclature VWF:GPIbM	VWF:GPIbM
VWF:act HemosIL LIA	VWF:Ab
The HemosIL VWF activity assay (VWF:AC)	
VWF:Act HemosIL VWF Activity assay on a STA-R automated coagulometer (Stago)	
VWF:Lx activity using HemosIL von Willebrand Factor Activity latex immunoassay kits	

4. **Correlation between assays:**

Author	Year	Pts	Test 1	Test 2	Test 3	Cor 1-2	Cor 2-3	Cor 1-3
Boender, J	2018	618	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.957	0.984	0.959
Szederjesi A	2018	95	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.963		0.989
Sagheer, S	2016	60	VWF:RCo[Agg]	VWF:GPIbR	VWF:Ab	0.954		0.938
Favaloro E	2016	535	VWF:RCo[Agg]	VWF:GPIbR	VWF:GPIbM	0.928		0.942
Timm A	2015	170	BC-VWF:Rco	VWF:GPIbR	VWF:GPIbM	0.927	0.921	0.912
Stitt C	2014	37	BC-VWF:Rco	VWF:GPIbM		0.989		
Patzke, J	2014	580	BC-VWF:Rco	VWF:GPIbM		0.99		
Geisen, U	2014	432	BC-VWF:Rco	VWF:GPIbM		0.96		
Favaloro, E	2014	600	BC-VWF:Rco	VWF:GPIbM		0.958		
De Maistre	2014	122	VWF:RCo[Agg]	VWF:RCo[Acu]	VWF:GPIbM	0.977		0.965
Costa Pinto	2014	176	VWF:RCo[Agg]	VWF:RCo[Acu]		0.92		
Verfaillie, C	2013	50	VWF:GPIbR	VWF:Ab	VWF:RCo[Agg]	0.94		0.77
Lawrie, A	2013	180	BC-VWF:RCo	VWF:GPIbM		0.97		

Cabrera, N	2013	91	VWF:RCo[Agg]	VWF:GPIbR		0.92		
Trossaert, M	2011	268	VWF:Ab	BC-VWF:Rco		0.89		
Chen, D	2011	468	BC-VWF:Rco	VWF:Ab		0.93		
Bowyer, A	2011	53	VWF:RCo[Agg]	BC-VWF:Rco		0.91		
Chen, D	2008	35	VWF:Rco [Agg]	VWF:Rco (Flow Cyt)		0.86		
Pinol, M	2007	127	VWF:Rco [Agg]	VWF:Ab		0.956		
Vleeschauwer, A	2006	148	VWF:Rco [Agg]	VWF:Ab		0.84		
Sucker, C	2006	300	VWF:Ab	BC-VWF:Rco		0.88		
Strandberg, K	2006	478	VWF:Rco [Agg]	BC-VWF:Rco		0.96		
Vanhoorelbeke, K	2005	92	VWF:Rco [Agg]	VWF:RCo ELISA		0.963		
Lattuada, A	2004	95	VWF:Rco [Agg]	BC-VWF:Rco		0.61		
Federici, A	2004	122	VWF:Rco [Agg]	VWF:RCo ELISA		0.93		

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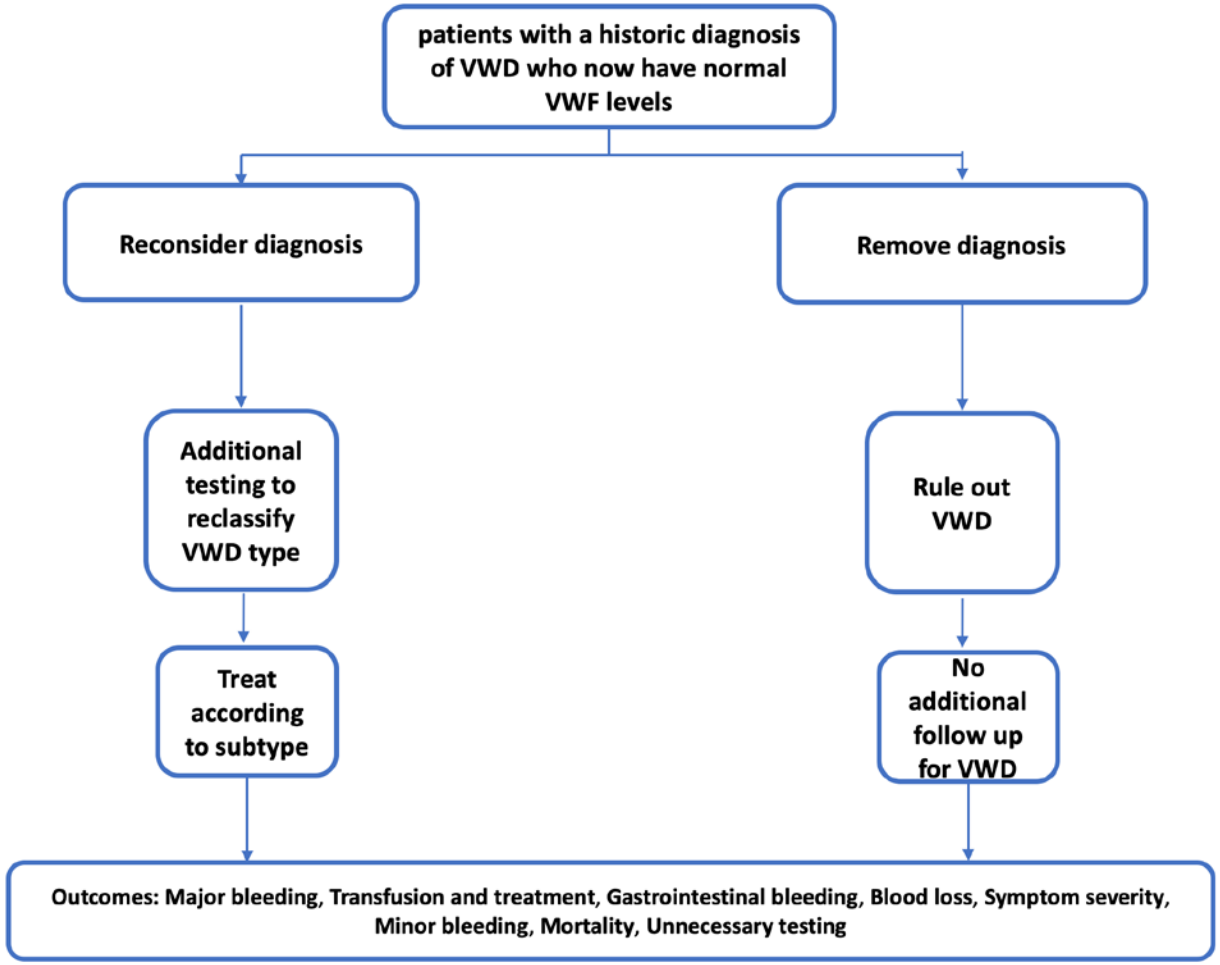
Question 4

Should reconsidering the diagnosis vs. removing the diagnosis be used for patients with previously confirmed VWD diagnosis and normalized VWF levels with age?	
POPULATION:	Patients with previously confirmed VWD diagnosis and normalized VWF levels with age
INTERVENTION:	reconsidering the diagnosis
COMPARISON:	removing the diagnosis
MAIN OUTCOMES:	Age change of VWF:Ag; Frequency of normalization of VWF levels.; Bleeding with normalization of levels; Bleeding score in patients with normalized levels;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Multiple variables that affect VWF levels can make a firm diagnosis of VWD difficult. In aggregate, mildly reduced VWF:Ag and VWF:RCo levels do not always establish a diagnosis of VWD; conversely, low normal VWF:Ag and VWF:RCo activity does not always exclude the diagnosis. In addition, although VWF:Ag assays have good precision and reproducibility, the VWF:RCo assay has greater variability, resulting in potential for misdiagnosis and/or misclassification (Bucciarelli, 2013). Data is not available to say that the age increase in VWF is accompanied by a change in symptoms while adjusting for comorbidities and until it can be proved that an increase in VWF levels prevents bleeding, healthcare providers have to be very careful in saying someone does not have VWD or a bleeding disorder. However, data shows that around 43% of previously diagnosed patients have normalized levels with age (Borghi, 2017; Nummi, 2017; Rydz, 2015; Abu Ismail, 2017).
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Multiple variables that affect VWF levels can make a firm diagnosis of VWD difficult. In aggregate, mildly reduced VWF:Ag and VWF:RCo levels do not always establish a diagnosis of VWD; conversely, low normal VWF:Ag and VWF:RCo activity does not always exclude the diagnosis. In addition, although VWF:Ag assays have good precision and	This question was judged to be a priority among many candidate questions to address in these guidelines.

	reproducibility, the VWF:RCo assay has greater variability, resulting in potential for misdiagnosis and/or misclassification (Bucciarelli, 2013). Data is not available to say that the age increase in VWF is accompanied by a change in symptoms while adjusting for comorbidities and until it can be proved that an increase in VWF levels prevents bleeding, healthcare providers have to be very careful in saying someone does not have VWD or a bleeding disorder. However, data shows that around 43% of previously diagnosed patients have normalized levels with age (Borghi, 2017; Nummi, 2017; Rydz, 2015; Abu Ismail, 2017).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Normalization would trigger repeat evaluation for bleeding phenotype and other bleeding disorders, particularly if not previously tested. Degree of normalization may influence the decision as to whether to manage expectantly or prophylactically with minor procedures. When levels normalize, and patients are still bleeding, physicians tend to screen for other bleeding disorders, especially platelet disorders, that usually come out to be negative, so the patients are treated as having VWD, but tranexamic acid is used alone as a common treatment for bleeding disorders and desmopressin is avoided because of cardiovascular comorbidities in the elderly. If the diagnosis is removed, there is a fear of undertreatment - particularly if prior issues with major bleeding. Refer to the Appendix at the end of the document	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Normalization would trigger repeat evaluation for bleeding phenotype and other bleeding disorders, particularly if not previously tested. Degree of normalization may influence the decision as to whether to manage expectantly or prophylactically with minor procedures. When levels normalize, and patients are still bleeding, physicians tend to screen for other bleeding disorders, especially platelet disorders, that usually come out to be negative, so the patients are treated as having VWD, but tranexamic acid is used alone as a common treatment for bleeding disorders and desmopressin is avoided because of cardiovascular comorbidities in the elderly. If the diagnosis is removed, there is a fear of undertreatment - particularly if prior issues with major bleeding. Refer to the Appendix at the end of the document	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	One important factor that should be considered is the ability to perform VWF:RCo better. VWF:Ag is much more consistent from center to center and is more consistent over time although age seems to affect levels over time. Gill et al 1988 published a cross-sectional study with blood donors and showed 1U/dL/per year increase in levels between age 20 to age 60 as a cross-sectional study suggesting the change in level with age, and another Zimmerman study in children showed the same results as a cross-sectional study, which shows that the increase in level is not likely due to the assay itself.	Potential unintended consequences of keeping the diagnosis include patients who may be denied necessary procedures due to concern over bleeding risk: physicians are willing to consider the use of antiplatelet therapy, cardiologists are willing to consider interventions based on the patients' VWD diagnosis.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability		Patients with a bleeding history will value a clear diagnosis, but they also want it to be accurate, so patients will differ in reaction to developing normal levels – liberation versus loss. Patients have a concern in having their diagnosis removed due to fear of

○ No important uncertainty or variability		undertreatment - particularly if prior issues with major bleeding. Diagnosis can bring a sense of meaning and belonging as well as 'illness'. Removing the diagnosis may limit access to timely care and create confusion for patients and medical staff regarding the appropriate treatment. So, it can be very distressing to a patient/family to have their diagnosis removed, especially if they are involved in patient advocacy groups. Female patients may be confused about how a genetic disorder can be cured at a time that it was considered to be incurable, especially when levels are normal, but they are still experiencing gynecological bleeding symptoms. On the other hand, for patients who are athletes or want to go into the military are often very relieved to have a diagnosis removed. For some individuals, it takes years to get a diagnosis. For those patients, a diagnosis gives their symptoms and experiences validity in the world. Prior to a diagnosis, a patient may experience skepticism and even discrimination in the workplace, for example, if they were not believed that they had a legitimate medical basis for time out of work or needing more time to complete a project. The changing insurance environment makes patients continually re-evaluate the upside and downside of their diagnosis. Some patients feel very strongly about their diagnosis as they've often had to go through a lengthy process. Taking away a diagnosis sometimes puts the availability of treatment options (for any bleeding disorder) at risk. Patients are usually told to call their healthcare provider if they develop future bleeding

		symptoms and they rarely come back and get retested with newer testing. This happens often when those with low VWF:RCo due to benign variants like (hetero or homozygotes) D1472H SNPs were identified and were found to have low VWF:RCo (regent artifact) but normlaVWF:CB or VWF:GPIbM.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document	Patients are often reassured when a specific name is given to their disease (i.e., they prefer "I have VWD" rather than "I have bleeding from an undetermined cause"). Patients may prefer the 'safety' of treatment over no treatment when the diagnosis is removed. Removal may increase anxiety about bleeding with the next intervention or procedure. The former diagnosis may have been embedded in the personality of the patient, so the patient may lose this identity.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No resource required to reconsidering or removing the diagnosis, except the time to have a complicated discussion about removing a diagnosis. Although reconsidering the diagnosis will require time for the patient to be reassessed and resources for additional lab tests, removing the diagnosis would require significant time for a complicated discussion.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No resource required to reconsidering or removing the diagnosis, except the time to have a complicated discussion about removing a diagnosis.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No resource required to reconsidering or removing the diagnosis, except the time to have a complicated discussion about removing a diagnosis.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		Removing the diagnosis may affect insurance coverage, however, this is a geographic-specific issue. For instance, insurance coverage would not be affected in Australia, the United Kingdom, the Netherlands, or Canada. In fact, as long as the consequence of removing the diagnosis is that no longer treatment is provided by expensive factor concentrates, the

		insurance coverage would not change, however for coverage of those concentrates a diagnosis is required. In the USA on the other hand, removing the diagnosis might help reduce insurance premiums - but if the patient has a bleeding phenotype with a VWF level of 40, then removing the diagnosis means the patient might not get funding for treatment. Specifically, if the patient uses intranasal desmopressin, removing the diagnosis could affect coverage of this medication, and the same applies for patients with "low VWF" who may only need small amounts of antifibrinolytics; getting coverage for that is tough outside of a 340B center.. Otherwise, the diagnosis of VWD is usually changed to Bleeding of Unknown Cause if the patient still has a bleeding phenotype (i.e. increased BAT score), which will not lead to any change in insurance coverage but can sometimes prevent patients from getting DDAVP. Patients with borderline levels who rely on funding for treatment costs to be covered could be more disadvantaged. On the other hand, removing the diagnosis is likely to disproportionately affect those patients without good primary insurance.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Patients often do not accept having their diagnosis removed, but their reaction is highly variable. For example, a patient who has a bleeding history may be reluctant, while a patient who carries the diagnosis, but has never had bleeding may not care.

		A change in terminology i.e. from VWD to alternative terms such as normalized VWD may be accepted more than just a simple removal of the diagnosis. Additionally, the patient would need to know that levels are now increased to the normal range but the impact on bleeding is uncertain. Having said that, the provided information should be based on patient values and can be a key determiner in driving acceptability: a thoughtful and non-rushed discussion, usually in person, and an expert needs to have reviewed all the labs on different timeframes (was a lab normal because of post-Stimate, OCP, pregnancy, etc), followed by several visits to help the patient accept the diagnosis removal knowing they can always reach out if anything changes
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		It is feasible to have a longitudinal study that provides data about patients' VWF levels given the expertise in the bleeding disorders community, with a need for multicenter collaboration and the right setting (e.g. the Zimmerman project), which requires significant resources. The study would have to be a very long one because although the changes are real, they are small on a year to year basis, and there are other factors that can affect variability in VWF levels. In fact, without the data, there may be incorrect assumptions about the causes/effects of late in life VWF level changes. This study could help uncover why the change is not in all patients. Patients would actually want to be tracked long term,

		to be confident that the disease is no longer active. They might need to be convinced that a disease they had their entire life, no longer exists. Understanding the changes in the lab platforms and methodology is important and some studies showing higher VWF levels may be due to poorer testing quality years ago compared to now. Also, in places like Ireland testing is in the same national lab, compared to the US where they may have testing in multiple different locations which can lead to less easy results to interpret. Removing the diagnosis means that hemophilia treatment centers may no longer have the ability to study those patients, and elderly patients might have delays in getting surgical procedures if they aren't diagnosed. Pragmatically, it is feasible to remove the diagnosis if the VWF levels are normal and there is no reason for false positive. So, the question remains whether normalization of levels results in lesser bleeding complications. Studies addressing this question are urgently needed while being careful to remove the diagnosis, as VWF levels may fluctuate and have a high biological variation. Furthermore, patients at higher age do have a higher risk of bleeding in general.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests reconsidering the diagnosis as opposed to removing the diagnosis in patients with previously confirmed VWD who now have VWF levels that have normalized with age.
(Conditional recommendation based on very low certainty in the evidence)

Remarks:

- 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.

Justification

The guideline panel determined that there is low certainty in the evidence for a net health benefit from reconsidering the diagnosis of VWD versus simply removing the disease in patients with normalized VWF with age. Other EtD criteria were generally in favor of reconsidering the diagnosis so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Longitudinal studies correlating normal levels with bleeding, while adjusting for co-morbidities

APPENDIX

1. **Risk of Bias:**

Author, year	Study Participation	Study Attrition	Prognostic Factor Measurement [a]	Outcome Measurement [a]	Study Confounding [b]	Statistical Analysis and Reporting
Sanders, 2014	Low	Low	High	Low	Low	Low
Borghi, 2017	Low	Low	High	Low	High	Low
Nummi, 2017	Low	Low	High	Low	High	Low
Lavin, 2017	Low	Low	High	Low	High	Low
Rydz, 2015	Moderate	Low	High	Low	High	Low
Abou-Ismail, 2017	Low	Low	High	Low	High	Low

a. Bleeding symptoms not measured in patients with normalized levels

b. Study confounding high in studies that did not adjust for comorbidities while measuring the outcome of interest

2. **Outcomes:**

Certainty assessment							Impact	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Age change of VWF:Ag								

Certainty assessment							Impact	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
5	observational studies	serious [a]	serious [b]	serious [c]	not serious	none	5 studies with 1142 patients report the change in VWF levels longitudinally (follow-up between 1 and 10 years). The mean change in VWF is 7.9 IU/dL/decade, ranging between 3.0 and 24.0 IU/dL/decade.	⊕◯◯◯ VERY LOW

Frequency of normalization of VWF levels.

4	observational studies	serious [a]	serious [d]	serious [c]	not serious	none	4 studies with 435 patients report the normalization of VWF levels over a period of 1-10 years. The number of patients with normalized levels ranged between 25% and 60%, with a weighted average of 43%.	⊕◯◯◯ VERY LOW

Bleeding with normalization of levels

1	observational studies	not serious	not serious	not serious	not serious	none	Binary logistic regression analysis with bleeding in the year prior to inclusion in the WiN study as dependent variable. After adjusting for age, sex, BMI and presence of any relevant comorbidities (hypertension, cancer, diabetes and thyroid dysfunction), normalization of VWF levels above 0.50 was still not associated with the incidence of bleeding requiring treatment in the year prior to inclusion in the study: Odds ratio=1.26 (95%CI 0.72-2.21), p=0.414. We can conclude that even after taking other important factors that influence VWF levels and bleeding into account, normalization of VWF levels is not associated with less incidence of bleeding episodes requiring hemostatic treatment. 27% of patients with normalized levels had bleeding symptoms at the time of the study, 21% of patients with abnormal levels had bleeding symptoms.	⊕⊕◯◯ LOW

Bleeding score in patients with normalized levels

Certainty assessment							Impact	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
2	observational studies	serious [a]	not serious	serious [e]	not serious	none	Nummi, 2017 showed that the mean BS in patients with diagnosis confirmed ranged between 10 and 24. Mean BS in patients with Low VWF diagnosis and those that have normal VWF levels was 6. Including all patients with historical VWD, BS showed weak and negative correlation with VWF:RCo (r = 0.43), VWF:Ag (r = 0.51), VWF:CB (r = 0.54), FVIII (r = 0.44), RIPA 0.6 mg/mL (r = 0.34), and RIPA 0.8 mg/ mL (r = 0.54) and positive correlation with PFA C/EPI (r = 0.45) and C/ ADP (r = 0.46) (in all P ≤ 0.001). Sanders, 2014 showed that bleeding score did not differ between elderly and younger patients.	⨁◯◯◯ VERY LOW

CI: Confidence interval

Explanations

a. Serious study confounding, as the studies have not adjusted for co-morbidities, except for Sanders, 2014 where more elderly patients reported one or more co-morbidities than younger ones, including Diabetes, cancer, cardiovascular disease and depression. Atiq , 2018 showed that comorbidities are associated with higher VWF and FVIII levels in type 1 VWD and may explain the age-related increase of VWF and FVIII levels.

b. The change of VWF levels varies between 3.0 IU/dL per decade and 24 IU/dL per decade, leading to serious inconsistency.

c. Although the change in VWF levels is presented, the bleeding symptoms of patients with normalized levels is not reported in the studies,

d. The normalization of VWF levels varies between 25% and 60%, leading to serious inconsistency.

e. The bleeding score does not predict the bleeding symptoms in patients in normal VWF but inform on the bleeding history in those patients

References:

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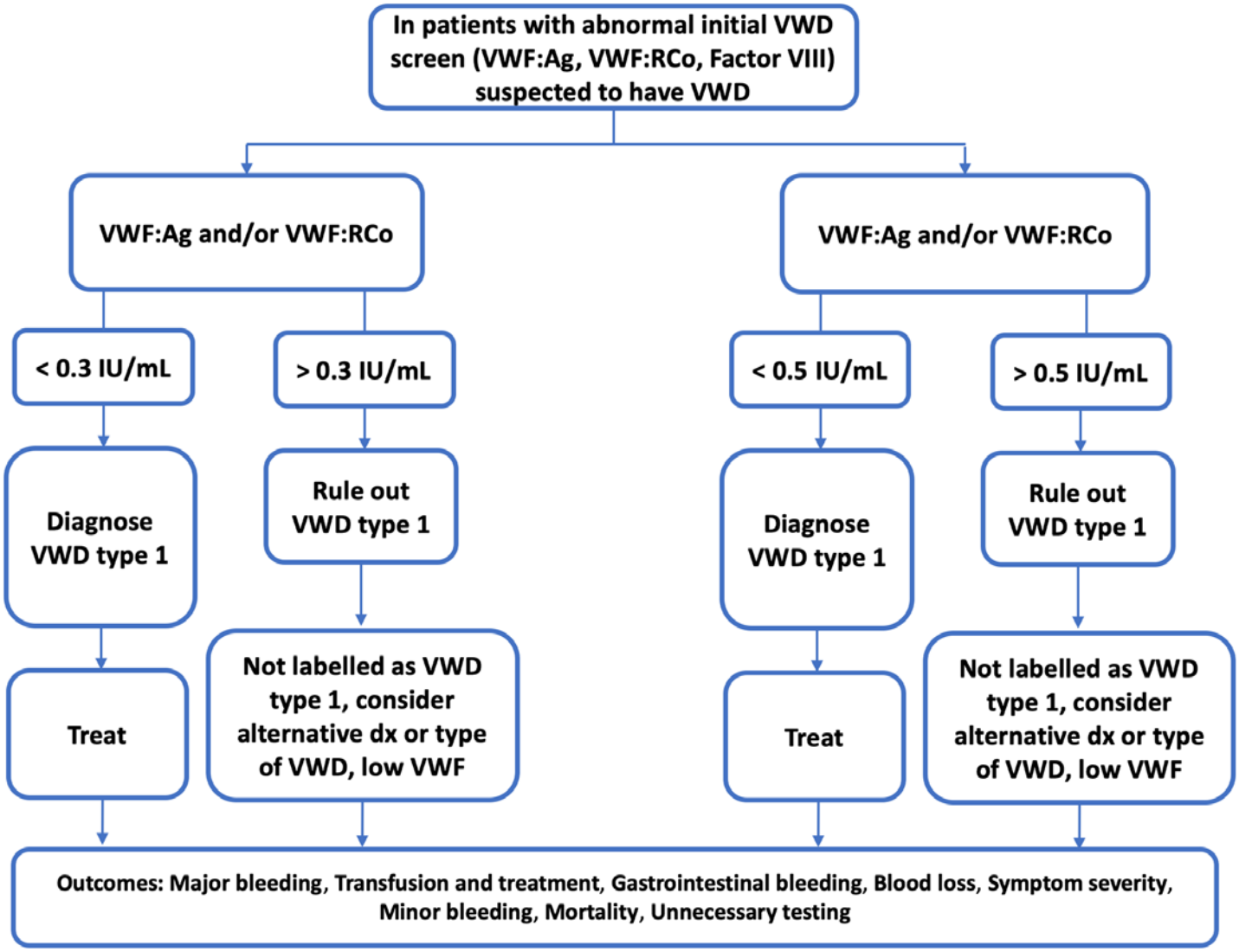
Question 5

Should VWF factor <30 IU/dL vs. VWF factor <50 IU/dL be used for diagnosing von Willebrand disease type 1?	
POPULATION:	Patients suspected of von Willebrand Disease type 1
INTERVENTION:	VWF factor <30 IU/dL
COMPARISON:	VWF factor <50 IU/dL
MAIN OUTCOMES:	Mutation detection; Likelihood ratios (LRs) of von Willebrand disease (VWD) ; VWF level and Bleeding score correlation; Bleeding tendency;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. Type 1 vWD is frequently difficult to be diagnosed because of the limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and vWD patients (Pathare, 2018). Type 1 VWD is responsible for a vast majority of cases (>75%) (Lavin 2017). It presents with mild to moderate mucosal bleeding symptoms, typically associated with a family history of bleeding and a quantitative reduction in von Willebrand factor (VWF) protein (Flood, 2016).
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. Robert Montgomery was recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are	This question was judged to be a priority among many candidate

○ Probably yes ● Yes ○ Varies ○ Don't know	never diagnosed. VWD diagnosis and classification require numerous laboratory tests. Type 1 VWD is frequently difficult to be diagnosed because of the limitations in laboratory diagnostic tests as well as overlapping nonspecific mild bleeding symptoms between healthy individuals and VWD patients (Pathare, 2018). Type 1 VWD is responsible for a vast majority of cases (>75%) (Lavin 2017). It presents with mild to moderate mucosal bleeding symptoms, typically associated with a family history of bleeding and a quantitative reduction in von Willebrand factor (VWF) protein (Flood, 2016).	questions to address in these guidelines. The 0.3 diagnostic threshold was set historically based on expert consensus.
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 1 and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 1 and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 1 and not suffer the side effects of treatment but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 1 but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders or labeled as low VWF. **False Positive:** These are patients who did not have VWD type 1 but they will be labeled as having VWD and receive unnecessary treatment. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. (this group is relevant for a cut-off of <0.5).	The importance for the patient is whether they have the diagnosis, and will they be able to access the appropriate management. Diagnostic thresholds are important because they clearly outline the diagnosis and direct patients towards treatments. Prevent bleeding: Defining false positive and false negative for type 1 VWD is not the priority, it is a question of who is bleeding, and if they are bleeding because of their VWF levels or because of another reason. Treating patients: patients with negative test results may have other bleeding disorders that may benefit from treatment with desmopressin even if they don't have VWD.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 1 and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 1 and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 1 and not suffer the side effects of treatment but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 1 but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders or labeled as low VWF. **False Positive:** These are patients who did not have VWD type 1 but they will be labeled as having VWD and receive unnecessary treatment. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. (this group is relevant for a cut-off of <0.5).	Denied treatment to patients with VWD that were undiagnosed (false negative). Overdiagnosis
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	While a clear-cut diagnosis is easy in severe von Willebrand factor reductions, the advantage of pursuing a definite diagnosis in mild or dubious cases should be weighed against the risk of over-medicalization. Identifying patients with VWD type 1 will help to give a treatment that will correct the defect of hemostasis caused by the abnormal/reduced von Willebrand factor. (Castaman, 2013).	The VWF gene is very highly susceptible to mutation so there are novel mutations causing VWD Type 1 that have not yet discovered, leading to a lack of agreed-on reference standard to define type 1 VWD.
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important		While patients are interested in the results of the antigen and activity assays but frequently have little understanding of the tests and diagnostic thresholds, they desire an

uncertainty or variability ○ No important uncertainty or variability		accurate diagnosis that will lead to proper treatment. Patients value clear and consistent guidelines on the reasons for different test choices and the diagnostic thresholds used, as patients are frustrated when they are not able to determine if they definitively do or do not have VWD. In speaking with others who have VWD, patients may desire the same testing regardless of need so they may compare results to each other. As an example, If a patient has bleeding symptoms and levels <50 they would think it is relevant to have the diagnosis by placing a higher value on avoiding bleeding compared to unnecessary treatment, costs, and risks of adverse reaction; however they might not be happy if the diagnosis was only restricted to levels <30. So, the cut-off values should not be applied in a stringent manner. The VWF antigen and activity are continuous variables with a continuous increase in bleeding risk with lower levels. The clinical phenotype is determined by more than the levels only. Results may confirm or exclude a prior diagnosis which may impact the patient's understanding of their bleeding and its treatment and could provoke fear of bleeding (or thrombosis) if treatment is changed.
Balance of effects		

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considers the bleeding phenotype in patients as the most important factor to drive the decision. Mutations are more likely to be detected in patients with baseline levels <30 but patients with levels 30-50 may also bleed because of their low levels. The panel is placing a high value on not missing the diagnosis especially in those patients who bleed. The panel also places a high value on avoiding overdiagnosis in patients who do not bleed.

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There is no effect on changing the ratio on costs.

		VWF:Ag	VWF:RCo	VWF:Gp1bR	VWF:Gp1bM
USA	$	25-30	25-30	80	
Canada	$	25-30	25-30		25-30
Australia	$	80-120	250	160-220	
New Zealand	$	12	20	15	
Europe	€	25-30	25		25
UK	£	8-20	30		

There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates. The data for required resources for some of the assays are not available because of lack of availability of the assay in different countries.

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention		

○ Varies ● No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Not all tests are accessible to all patients. Therefore, a thorough and proper investigation may be limited due to the high cost and lack of exams with appropriate quality control. Insurance coverage for these tests is variable based on location and funding model. In the United States of America, most private insurance will cover VWF antigen and activity assays, but some patients may have a large deductible. Sometimes the reimbursed value does not cover the overall cost of the test, especially in public services. In New Zealand specifically, all residents get blood tests for free. This is also applicable in the United Kingdom, since there is no practical restriction on requesting these tests. In Italy, they are partly covered by insurance. In Australia, a limited number of antigen and activity assays are covered by

		insurance - above 3 assays the cost is not covered. In the Netherlands, all assays are covered by insurance. The VWF:RCo is potentially less useful in the African American population given the higher frequency of the D1472H variant in this population. Because of the higher rate of the benign variants that affect the VWF:RCo giving false positively low results, the VWF:GPIbM testing can be used in follow-up testing in Hispanic and African American populations more than Caucasian. The aforementioned populations may be less likely to have easy access to larger centers.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Generally, all patients accept the blood tests in question
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies		Antigen and activity assays have limited availability – available in most larger population centers will have centralized testing in specialist centers. It is usually not found in

○ Don't know		resource-poor countries and non-primary care hospitals even in high-income setting countries, specifically the activity assays. VWF:GPIbm or GPIbR is not available in most centers in the United States of America, but VWF:Ag and VWF:RCo are more readily available. VWF:Ag is only available in hospitals with special coagulation labs, and special coagulation labs usually only run either the VWF:RCo or one of the newer assays. Countries differ in the challenges to access the testing (referrals within the system and logistic issues like traveling hundreds of kilometers), so testing is often sent out reference laboratories (with all the issues of pre-analytical variables, including sample collection and transport that can affect the reliability of results) outside of medium to large academic centers in the United States. Even when the tests are available in smaller non-academic centers, results may differ when compared to those from large referral centers. Depending on where patients are allowed to undergo testing, there could be variation in results (e.g., in California, insurers may not reimburse repeat testing of VWF:Ag and VWF:RCo or VWF:GPIbm to be done at the respective academic center if performed already at private commercial laboratories).

		Often repeat testing is needed particularly if obtained at a time of stress (following a procedure) or in times of significant anemia. This issue is illustrated with teenage girls undergoing evaluation during an episode of heavy menstrual bleeding. Levels may be elevated over baseline and obscure the diagnosis of VWD or its subtype. It may be possible to say that one or two activity measures are not accurate and reduce their use, but many labs are bound by managed service contracts and performing all labs as a single 'best' assay is often not feasible. Another feasibility issue assay availability and turnaround time in the perioperative setting. Some of the tests, such as the VWF:RCo, have a considerable coefficient of variation, which may influence laboratory research. In addition, the physiological or induced variations of VWF plasma levels also may affect the diagnosis of borderline cases, especially of type 1 VWD and low levels of VWF.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF	Very low	**Low**	Moderate	High			No included

	JUDGEMENT						
EVIDENCE							studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The panel recommends a VWF level of <30 IU/dL, and in patients with abnormal bleeding, a VWF level of 30-50 IU/dL, to confirm the diagnosis of Type 1 VWD. (Strong recommendation based on low certainty in the evidence)

Remarks:

- VWF level(s) refers to VWF:Ag and/or VWF activity
- Patients with a family history of Type 1 VWD in a first degree relative and VWF levels of 30-50 IU/dL should be diagnosed with Type 1 VWD.
- A concomitant bleeding disorder should be considered in patients with VWF levels of 30-50 IU/dL.

Justification

With this recommendation, the panel is placing high value on not missing the diagnosis especially in those patients who bleed. The panel also places a high value on avoiding overdiagnosis in patients who do not bleed.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Detailed data about levels 30-60 and their relation to bleeding symptoms.
- Information about family members of patients with VWD.

APPENDIX

1. Risk of bias:

Author, year	Patient selection Risk of bias	Index test Risk of bias	Reference standard Risk of bias	Flow and timing Risk of bias
Lavin, 2017	Low	Moderate	Low	Low
Flood, 2016	Low	Moderate	Low	Low
Bucciarelli, 2015	Low	Moderate	Low	Low
Quiroga, 2014	Low	Low	Moderate	Low
Bowman, 2009	Low	Low	Low	Low
Tosetto, 2007	Low	Moderate	Low	Low
James, 2007	Low	Moderate	Low	Low
Goodeve, 2007	Low	Moderate	Low	Low
Eikenboom, 2006	Low	Moderate	Low	Low

2. Outcomes:

Certainty assessment							Impact	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Mutation detection								
3 [1,2,3]	observational studies	not serious	not serious	not serious	not serious	none	· for VWF:Ag <0.3 mutations were detected in 75-82% of patients in 2 studies · for VWF:Ag 0.3-0.5 mutations were detected in 44-60% of patients in 3 studies	⊕⊕◯◯ LOW
Likelihood ratios (LRs) of von Willebrand disease (VWD)								
2 [4,5]	observational studies	not serious	not serious	not serious	not serious	none	. Tosetto 2007 et al (MCMDM-1VWD), in patients with VWD and family history of VWD: Level <20, LR = 374 (52.2–2677). Level 20-40, LR = 95.1 (39.1–232). Level 40-60, LR = 1.82 (1.28–2.58). Level >60, LR = 0.10 (0.06–0.16). . Bucciarelli et al, in patients who were investigated for bleeding episodes: Levels 30-40 dL, LR of having VWD= ∞ (in all of them, VWD was confirmed by second-level tests), Levels 41-50 dL, LR = 0.73 (0.41–1.30), Levels 51-60 dL, LR = 0.33 (0.18–0.62).	⊕⊕◯◯ LOW

VWF level and Bleeding score correlation

2 [1,2]	observational studies	not serious	serious [a]	not serious	not serious	none	in Lavin, 2017 the majority of patients with low VWF had significant bleeding histories, as determined using either the ISTH BAT or the Condensed MCMDM-1 VWD score, respectively. In Flood, 2016, there was no difference between BS and VWF levels because the BS used was after patients were recruited in the study and were receiving treatment. Data from unpublished work showed a continuum, with a higher BS in those with lower VWF at the time of enrollment/diagnosis.	⊕◯◯◯ VERY LOW

Bleeding tendency

1 [5]	observational studies	not serious	not serious	not serious	not serious	none	In Bucciarelli, 2015, 70/93 (75%) with borderline VWF (0.3-0.5) were investigated after a bleeding episode: mucocutaneous bleeding was present in 35, 25 bled after surgery, and 10 bled after dental procedures. Ten patients experienced more than one symptom.	⊕⊕◯◯ LOW

CI: Confidence interval

Explanations

a. Results from the 2 studies are not consistent with each other

References

1. Lavin, . . 2017.
2. Flood, . . 2016.
3. James, . . 2007.
4. tosetto, . . 2007.
5. Bucciarelli, . . 2015.

- *Mutations detection:*

Author, year	**Mutations detection**
Lavin, 2017	VWF gene sequence variations in 60.3% of the LoVIC cohort. Importantly, previously described damaging VWF variants, or sequence variations predicted to be damaging, were observed in only 39.7% of patients with low VWF levels.
Flood, 2016	VWF sequence variations with VWF:Ag <30 IU/dL (82%), whereas subjects with type 1 VWD and VWF:Ag >30 IU/dL had an intermediate frequency of variants (44%).
James, 2007	in 32 index cases with level <0.30, mutations within the VWF gene were found in 24 (75%). In 91 index cases with level >0.30, mutations within the VWF gene were found in 45 (49%). (P = .114, Pearson chi-square) 3 index cases with VWF:Ag levels less than 0.20 IU/mL for whom VWF gene mutations were not identified
Eikenboom, 2006	Logarithm of the odds (LOD score): In genetics, the LOD score is a statistical estimate of whether two genes, or a gene and a disease gene, are likely to be located near each other on a chromosome and are therefore likely to be inherited. - Clinical practice diagnosis: Ag<30 - 17.4. Ag>30 - 8.41 - Stringent diagnosis: Ag<30 - 2.51, Ag>30 - 0 - Bleeding diathesis: Ag<30 - 1.99, Ag>30 0.21

- *Likelihood ratios:*

Author, Year	Outcome	Likelihood ratios
Bucciarelli, 2015	Likelihood ratios (LRs) of von Willebrand disease (VWD) diagnosis according to von Willebrand factor ristocetin cofactor activity (VWF:RCo) plasma levels	In 45 of the 93 individuals with borderline VWF plasma levels (48%), the diagnosis of VWD was confirmed with second-level tests. Of these, 38 (84%) were found to be type 1 and seven (16%) type 2. Levels 30-40 dL, LR = ∞ (in all of them, VWD was confirmed by second-level tests) Levels 41-50 dL, LR = 0.73 0.73 (0.41–1.30) Levels 51-60 dL, LR = 0.33 (0.18–0.62)
Tosetto, 2007	Diagnostic positive likelihood ratios (LR) for von Willebrand factor antigen (VWF:Ag) and VWF ristocetin cofactor (VWF:RCo) in 204 subjects considered as affected in the present study in comparison to 1155 healthy controls	Level <20, LR = 374 (52.2–2677) Level 20-40, LR = 95.1 (39.1–232) Level 40-60, LR = 1.82 (1.28–2.58) Level >60, LR = 0.10 (0.06–0.16). These results are consistent when splitting the patients into subgroups of abnormal multimers (except for level 40-60, LR = 0.65 (0.31-1.37)), normal multimers and mutation, normal multimers no mutation.
Goodeve, 2007	Association between the presence of mutations and VWF level in index cases	Level 0-15, OR = 23.0 (2.9-182.6) Level 16-30, OR = 5.0 (1.8-14.0) Level 31-45, OR = 2.2 (0.90-5.3) Level >45, OR = 1
Eikenboom, 2006	Association between co-segregation of the clinical practice diagnosis and categories of VWF in index cases	Level 0-15, OR 1 Level 16-30, OR 0.73 (0.20–2.68) Level 31-45, OR 0.67 (0.19–2.32) Level >45, OR 0.24 (0.07–0.82)

- *Bleeding tendency:*

Author, year	Outcomes	Results
Lavin, 2017	Bleeding history and low VWF	the majority of patients with low VWF had significant bleeding histories, as determined using either the ISTH BAT or the Condensed MCMDM-1 VWD score, respectively.

Bucciarelli, 2015	Bleeding tendency in borderline VWF	70/93 with borderline VWF (75%) were investigated after a bleeding episode: mucocutaneous bleeding was present in 35, 25 bled after surgery, and 10 bled after dental procedures. Ten patients experienced more than one symptom.

- *Diagnostic test accuracy:*

Author, Year	**Outcome**	**Results**
Quiroga, 2014	Diagnosis rate at different cut-off (<30, <40, <2.5th percentile). (i) NHLBI recommendation (VWF:Ag or VWF:RCo < 30 IU dL and measurements between 30 and 50 IU dL to qualify for 'possible type 1 VWD' or 'low VWF'); (ii) EUVWD criterion: plasma VWF:RCo or VWF:CB < 40 IU dL; and (iii) ZPMCBVWD preliminary criterion: plasma VWF:Ag or VWF:RCo < 40 IU dL.	The NHLBI recommendation allowed diagnosing 122 (2.8%) of 4298 patients, whereas the same data analyzed by the EUVWD, ZPMCBVWD, and 2.5th percentiles criteria led to 339 (7.9%), 357 (8.3%) and 280 (6.5%) patients with diagnosis of the disease, respectively, equivalent to 2.8-, 2.9-, and 2.3-fold increases in the diagnostic rate.
Bowman, 2009	DTA for different VWF levels	The sensitivity and specificity for VWF:RCo < 0.40 IU/mL are 80% and 100%, respectively. The sensitivity for VWF:RCo < 0.30 IU/mL is 75% (this is lower than the higher cut-off values because of the small sample size; specificity cannot be calculated below 0.40) and that for VWF:RCo < 0.20 IU/mL is 100%.

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1. Lavin M, Aguila, S., Schneppenheim, S., Dalton, N., Jones, K. L., O'Sullivan, J. M., O'Connell, N. M., Ryan, K., White, B., Byrne, M., Rafferty, M., Doyle, M. M., Nolan, M., Preston, R. J. S., Budde, U., James, P., Di Paola, J., O'Donnell, J. S. Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels. Blood. 2017;130(21):2344-2353.
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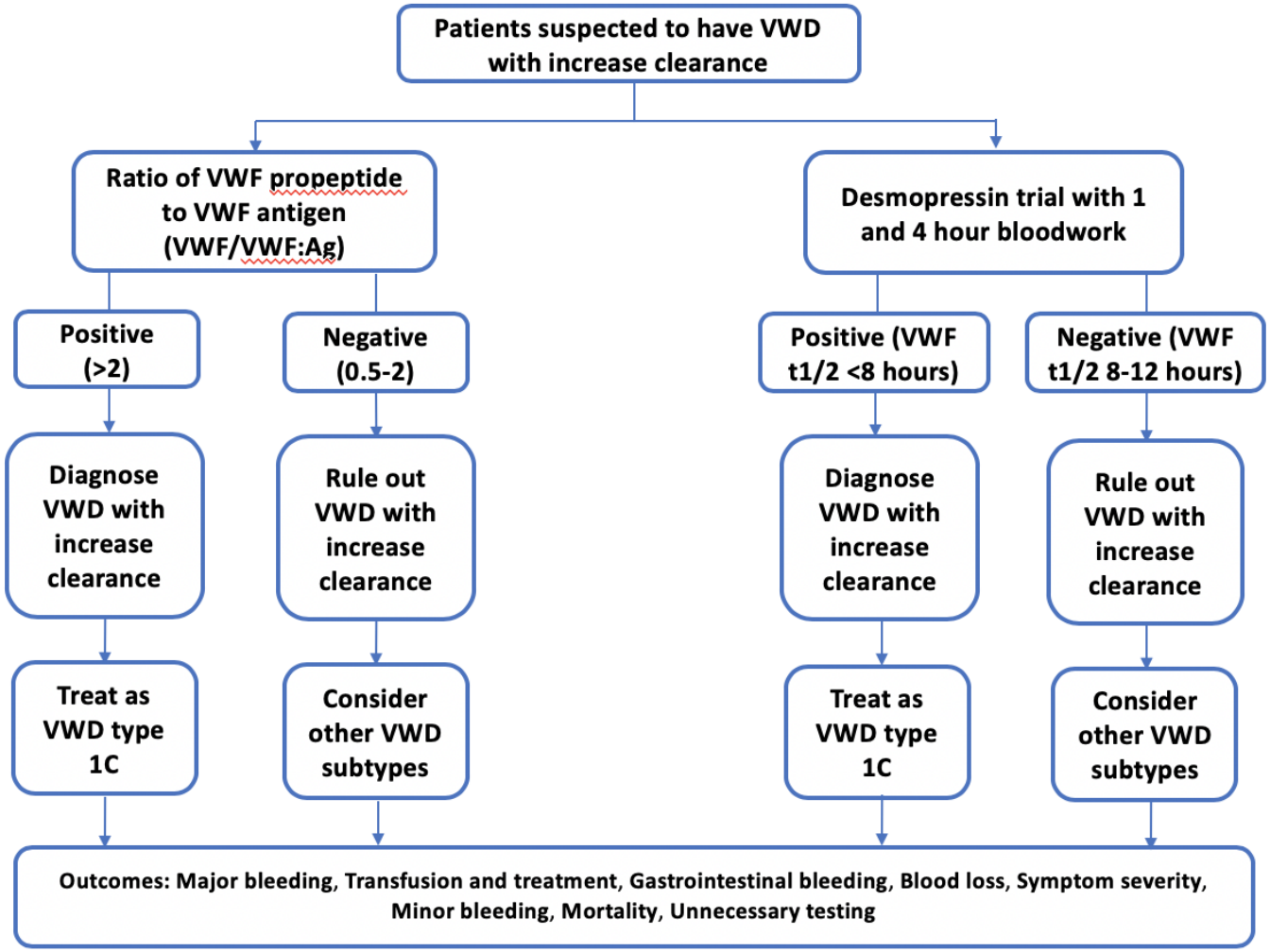
Question 6

Should the VWF propeptide to VWF:Ag ratio vs. a desmopressin trial (with 1 and 4 hour levels) be used to diagnose VWD type 1C in patients with suspected VWD type 1C?	
POPULATION:	patients with suspected VWD type 1C
INTERVENTION:	VWF propeptide to VWF:Ag ratio
COMPARISON:	desmopressin trial (with 1 and 4 hour levels)
PURPOSE OF THE TEST:	Identify VWD type 1C patients
ROLE OF THE TEST:	Identify VWD type 1C patients
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	VWFpp/Ag – False positive, VWFpp/Ag – False negative, VWFpp/Ag – True positive, VWFpp/Ag – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed (Pathare, 2018). A shorter VWF survival has been suggested as a mechanism behind VWD (Casonato, 2002; Brown, 2003). A greater VWF clearance from the plasma was first described in type Vicenza VWD (Casonato et al, 2002) and a shorter VWF survival has also been reported in type 1 VWD (Brown et al, 2003). Haberichter et al (2006) claimed that a shorter VWF survival can be predicted from the ratio of VWFpp to VWF concentrations in the plasma.
SUBGROUPS:	
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, James O'Donnell, Claire McLintock, Simon McRae, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. Barbara Konkle, Robert Sidonio Jr, and Robert Montgomery were recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed (Pathare, 2018). A	This question was judged to be a priority among many candidate questions to address in these guidelines.

● Yes ○ Varies ○ Don't know	shorter VWF survival has been suggested as a mechanism behind VWD (Casonato, 2002; Brown, 2003). A greater VWF clearance from the plasma was first described in type Vicenza VWD (Casonato et al, 2002) and a shorter VWF survival has also been reported in type 1 VWD (Brown et al, 2003). Haberichter et al (2006) claimed that a shorter VWF survival can be predicted from the ratio of VWF propeptide to VWF antigen concentrations in the plasma. Based on unpublished data, the VWF level cut-off for testing patients suspected of type 1C VWD is <30 IU/dL (Haberichter), and the levels are lower than expected to see from the bleeding phenotype for type 1C, in which bleeding is less severe than the type 3, even with the very low levels.	

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ● Don't know	No test accuracy results were presented in the studies because of the lack of an agreed-on reference standard to define type 1 C VWD, desmopressin trial was used in some papers to determine the increased clearance and the propeptide ratio was used in other papers. However, an inverse correlation between VWFpp/VWF:Ag and VWF antigen half-life was shown in 3 studies. The results indicate that the steady-state ratio of plasma VWFpp and VWF can be used to easily identify patients with type 1 VWD with an increased plasma VWF clearance phenotype.	

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
VWFpp/VWF:Ag ratio correlation with VWF:Ag half life	In Sztukowska, 2008, a pronounced drop in VWF survival in the type Vicenza VWD patients was reported: mean t1/2 significantly lower than in controls (1.3 ± 0.2 h, P < 0.0001). A dramatic increase in VWFpp ratio in the type Vicenza VWD cases was shown: VWFpp ratio from 7.14 to 17.7, mean 13.02 ± 0.49 – 10 times higher than in the control group (P < 0.001). In Haberichter, 2008, s substantially increased VWFpp/VWF:Ag ratio was predictive of a significantly decreased VWF half-life in 7 individuals who had a >2-fold desmopressin response and an initial VWF:Ag less than 30 IU/dL. 3 individuals had a decreased VWF half-life that was not predicted by an increased VWFpp/VWF:Ag ratio. Individuals who had a substantially increased VWFpp/VWF:Ag ratio and significantly reduced VWF:Ag level were also found to have an enhanced response to desmopressin (greater than 4-fold increase). The	(2 observational studies)	⊕◯◯◯ VERY LOW[a,b]

	VWFpp/VWF:Ag ratio (r =0.92, P < .001)		
Correlation of the VWFpp/VWF:Ag ratio with the presence or absence of a VWF gene mutation	In Haberichter, 2006, all affected individuals harbored a VWF gene mutation and showed an increased ratio, whereas no mutation was detected in unaffected individuals. In Eikenboom, 2013, the increased VWFpp/ VWF:Ag ratio was particularly raised (median 4.3) in patients with slightly abnormal multimers and mutations. An increased VWFpp/ VWF:Ag ratio was a good predictor of VWD patients with mutations in the VWF gene: a VWFpp/VWF:Ag >3 had a positive predictive value for the presence of a VWF mutation of 98% with a specificity of 99% in the entire cohort of patients and family members. In Stufano, 2019, the genetic analysis of the mutation at codon 1205 in the group (n= 14) with the markedly increased VWF clearance distinguished between VWD type 1 Vicenza (characterized by the presence of the mutation p.R1205H) and AVWS (absence of this mutation).	(3 observational studies)	⊕⊕◯◯ LOW

a. The reference test in determining patients with VWD type 1 C is poorly defined
b. Studies do not present the number of patients with increased clearance

Refer to the Appendix at the end of the document

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**True Positive:** These are patients who have VWD type 1C and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 1C and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 1C and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD type 1C but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are patients who did not have VWD type 1C but they will be labeled as having VWD but will be identified as not having VWD on blood testing. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	

	Refer to the Appendix at the end of the document	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**True Positive:** These are patients who have VWD type 1C and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 1C and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 1C and not suffer the side effects of treatment. **False Negative:** These are patients who have VWD type 1C but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. **False Positive:** These are patients who did not have VWD type 1C but they will be labeled as having VWD but will be identified as not having VWD on blood testing. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. Refer to the Appendix at the end of the document	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	The way we look at the test is affected by the definition of what is considered to have increased clearance: the increased clearance is a phenotypic characteristic and when it is defined genotypically, different mutations will have different phenotypes that are not well defined (because the mutations were

		identified based on increased propeptide ratio, so they are non-validated mutations), making mutation analysis a poor reference standard test.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Both interventions are blood tests that do not have any test's direct effects.	The panel discussed that a propeptide to antigen ratio assessment is not a replacement for desmopressin trial, because sometimes the propeptide is normal and the desmopressin trial is abnormal. However, the propeptide ratio can still be used if the patient cannot receive desmopressin (e.g. in pediatrics due to logistic difficulty in serial blood draws) or the patient refuses the desmopressin challenge test.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		Both interventions are needed, not only to identify patients with increased clearance (propeptide ratio), but also to determine the treatment plan (Desmopressin might not be the optimal treatment option for those patients because of very short half-life, but can be used for minor bleeding even with the short half-life). Currently, the desmopressin trial is still done because the response to desmopressin cannot be predicted without the trial, whereas propeptide may be informative but cannot answer the question on which treatment will benefit the patient.
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Refer to the Appendix at the end of the document.	
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		VWFpp/VWF:Ag ratio is preferred by the majority because of convenience in avoiding the adverse effects of desmopressin, especially with the multiple blood draws (pediatric population) and the four hour fall off which is less convenient, seeing the patient availability and time commitment. However, some patients may desire to know if they will respond to desmopressin especially with the limited availability of VWFpp/VWF:Ag (only available in 2-3 sites in the US). The possibility to avoid plasma products may be valued; some patients prefer to learn about a test that is "new" (since the 2008 NIH: NHLBI VWD guideline) such as VWF propeptide, which is possibly the easiest alternative from the patient's point of view, as it consists of a single blood draw.

		In a patient affected by VWF Type 1 whose insurance would not cover the cost of a desmopressin 4-hr trial, patients wonder whether a propeptide ratio assay would be a logical step in a diagnostic workup, especially if a family member was known to have Type 1C VWD.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	VWF propeptide cost: Europe €50. Desmopressin trial cost: • Australia $400-500 • USA $1000 (nursing time, lab costs, costs of IV tubing, and cost to have a patient in an outpatient clinic included). • Europe €300. There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		VWF propeptide is not always covered by insurance. However, in the UK it could be covered, possibly with an explanation for conducting the test, with most of these tests being done under NHS cost. Desmopressin trials are covered by insurance but may have a very high deductible. Patients with access problems and people with

		no health insurance are disadvantaged (including transportation issues in poorer patients). Also, taking a day off from work/school and travel for the desmopressin trial would be a definite barrier for some. The interpretation of the results in each alternative has differences and therefore may influence the correct diagnosis if both options are not available.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Patients usually accept having desmopressin trial once the rationale is explained and that it is a test that is conducted once. So, good communication, counseling on how the test is done and possible side effects and symptoms are required. Some patients who carry a diagnosis and have had desmopressin before, but have never had their levels appropriately checked before/after, may be reluctant. The reasons not to accept the test include side effects and available time (Batty, 2017)	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		VWFpp/VWF:Ag is not available in all hospitals. It is usually available in research-active departments and specialized laboratories, which are few around the world, but has a limited availability otherwise. One of the potential outcomes of this question is that it might prompt more labs to start offering the test. The desmopressin trial is done differently between different centers with different timeframes considered. The desmopressin trial is used in different ways too, it will let treating

		physicians look at the difference between the 4 hours and the peak, to check if desmopressin or factor are to be used: if there is >50% decrease in levels at 4 hours, there is concern about increased clearance and factor would be more helpful to treat that patient (absolute level decrease at 4 hours vs % decrease after an initial increase at 1 hour). Most hospitals can perform the desmopressin challenge test unless there are supply chain-related shortages that do happen in the U.S. It might not be feasible from the standpoint of specialized suites of the medical center for which other types of patients compete. This is especially true if patients must stay for the 4-hour blood draw. The 0-time point is recommended as baseline fluctuations present in VWF levels and to calculate a CR would need to understand the fold increase. Testing at the 4-hour mark is difficult unless there is a dedicated nurse for the bleeding disorder patients, thus the test was moved to baseline, 1 and 3-hour testing in some settings. The free intranasal desmopressin program has to be set up with the pharmacy to avoid inducement concerns with government insurance. Smaller centers may use intravenous desmopressin if they cannot get this program up and running. It is suggested that desmopressin 1 and 4-hour trials to be done when VWF levels are < 20%, and if rapid clearance, a sample should be sent to a reference laboratory for VWF propeptide level and genotyping.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	**Don't know**
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the	Probably favors	Does not favor	Probably favors	Favors the	Varies	**No included**

	JUDGEMENT						
	comparison	the comparison	either the intervention or the comparison	the intervention	intervention		**studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The panel suggests against using the VWFpp/VWF:Ag (ratio of VWF propeptide to antigen), and rather using a desmopressin trial with 1 and 4-hour post-infusion blood work, to confirm diagnosis in patients with VWD suspected of Type 1C.
(Conditional recommendation based on low certainty in the evidence)

Good practice statement:

- Desmopressin responsiveness should be confirmed before it is used clinically in the management of patients with VWD.

Justification

The guideline panel determined that there is low certainty in the evidence for a net health benefit from using the desmopressin trial with a 1 and 4-hour bloodwork in patients suspected of type 1C VWD over using propeptide ratio. Other EtD criteria were generally in favor of using desmopressin trial with 1 and 4-hour bloodwork, so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Data about the Propeptide/antigen ratio
- Data about desmopressin trial with bloodwork at 4 hours.

APPENDIX

1. **Risk of bias:**

Author	Risk of bias population selection	Risk of bias index test	Risk of bias reference test[a]	Flow and timing Risk of bias
Sztukowska, 2008	High	Low	Low	Low
Haberichter, 2006	Low	Low	High	Low
Eikenboom, 2013	Low	Low	High	Low
Haberrichter, 2008	Low	Low	High	Low
Stufano, 2019	Low	Low	Low	Low

a. Reference test determining patients with increased clearance not clearly defined.

2. **Outcomes:**
   - *Correlations:*

Certainty assessment							Impact	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
VWFpp/VWF:Ag ratio correlation with VWF:Ag half life								

2	observational studies	serious [a]	not serious	serious [b]	not serious	none	In Sztukowska, 2008, a pronounced drop in VWF survival in the type Vicenza VWD patients was reported: mean t1/2 significantly lower than in controls (1.3 ± 0.2 h, P < 0.0001). A dramatic increase in VWFpp ratio in the type Vicenza VWD cases was shown: VWFpp ratio from 7.14 to 17.7, mean 13.02 ± 0.49 – 10 times higher than in the control group (P < 0.001). In Haberichter, 2008, s substantially increased VWFpp/VWF:Ag ratio was predictive of a significantly decreased VWF half-life in 7 individuals who had a >2-fold desmopressin response and an initial VWF:Ag less than 30 IU/dL. 3 individuals had a decreased VWF half-life that was not predicted by an increased VWFpp/VWF:Ag ratio. Individuals who had a substantially increased VWFpp/VWF:Ag ratio and significantly reduced VWF:Ag level were also found to have an enhanced response to desmopressin (greater than 4-fold increase). The desmopressin response was found to correlate with the VWFpp/VWF:Ag ratio (r =0.92, P < .001)	⊕◯◯◯ VERY LOW

Correlation of the VWFpp/VWF:Ag ratio with the presence or absence of a VWF gene mutation

3	observational studies	not serious	not serious	not serious	not serious	none	In Haberichter, 2006, all affected individuals harbored a VWF gene mutation and showed an increased ratio, whereas no mutation was detected in unaffected individuals. In Eikenboom, 2013, the increased VWFpp/ VWF:Ag ratio was particularly raised (median 4.3) in patients with slightly abnormal multimers and mutations. An increased VWFpp/ VWF:Ag ratio was a good predictor of VWD patients with mutations in the VWF gene: a VWFpp/VWF:Ag >3 had a positive predictive value for the presence of a VWF mutation of 98% with a specificity of 99% in the entire cohort of patients and family members. In Stufano, 2019, the genetic analysis of the mutation at codon 1205 in the group (n= 14) with the markedly increased VWF clearance distinguished between VWD type 1 Vicenza (characterized by the presence of the mutation p.R1205H) and AVWS (absence of this mutation).	⊕⊕◯◯ LOW

CI: Confidence interval

Explanations

a. The reference test in determining patients with VWD type 1 C is poorly defined
b. Studies do not present the number of patients with increased clearance

- *Test accuracy results:*

VWFpp/VWF:Ag	Desmopressin trial with 1 and 4 hour bloodwork

Prevalences	1%	3%	50%

Sensitivity	0.88 to 1.00	Sensitivity	0.99 to 1.00
Specificity	0.92 to 1.00	Specificity	0.70 to 0.70

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested						Test accuracy CoE
								pre-test probability of 1%		pre-test probability of 3%		pre-test probability of 50%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWFpp/VWF:Ag	Desmopressin trial with 1 and 4 hour bloodwork	VWFpp/VWF:Ag	Desmopressin trial with 1 and 4 hour bloodwork	VWFpp/VWF:Ag	Desmopressin trial with 1 and 4 hour bloodwork	
True positives (patients with VWD type 1C)	3 studies 68 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	not serious	none	9 to 10	10 to 10	26 to 30	30 to 30	440 to 500	495 to 500	⨁⨁◯◯ LOW
								1 fewer to 0 fewer TP in VWFpp/VWF:Ag		**4 fewer to 0 fewer TP in VWFpp/VWF:Ag**		**55 fewer to 0 fewer TP in VWFpp/VWF:Ag**		
False negatives (patients incorrectly classified as not having VWD type 1C)								0 to 1	0 to 0	0 to 4	0 to 0	0 to 60	0 to 5	
								1 more to 0 fewer FN in VWFpp/VWF:Ag		**4 more to 0 fewer FN in VWFpp/VWF:Ag**		**55 more to 0 fewer FN in VWFpp/VWF:Ag**		
True negatives (patients without VWD type 1C)	3 studies 193 patients	cross-sectional (cohort type accuracy study)	serious [a]	serious [b]	not serious	not serious	none	911 to 990	693 to 693	892 to 970	679 to 679	460 to 500	350 to 350	⨁⨁◯◯ LOW
								218 more to 297 more TN in VWFpp/VWF:Ag		**213 more to 291 more TN in VWFpp/VWF:Ag**		**110 more to 150 more TN in VWFpp/VWF:Ag**		
False positives (patients incorrectly classified as having VWD type 1C)								0 to 79	297 to 297	0 to 78	291 to 291	0 to 40	150 to 150	
								218 fewer to 297 fewer FP in VWFpp/VWF:Ag		**213 fewer to 291 fewer FP in VWFpp/VWF:Ag**		**110 fewer to 150 fewer FP in VWFpp/VWF:Ag**		

Explanations

a. Not all studies describe how the reference standard was conducted and interpreted

b. The 2 interventions are not compared together in the included studies. the desmopressin trial was not done at 1 and 4 hours. VWF:Ag half-life results from the desmopressin trial were used to calculate test accuracy results

c. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).

d. Typically seen in patients investigated for VWD because of a personal history of bleeding symptoms (e.g., mucocutaneous bleeding). - Quiroga, 2007.
e. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD.

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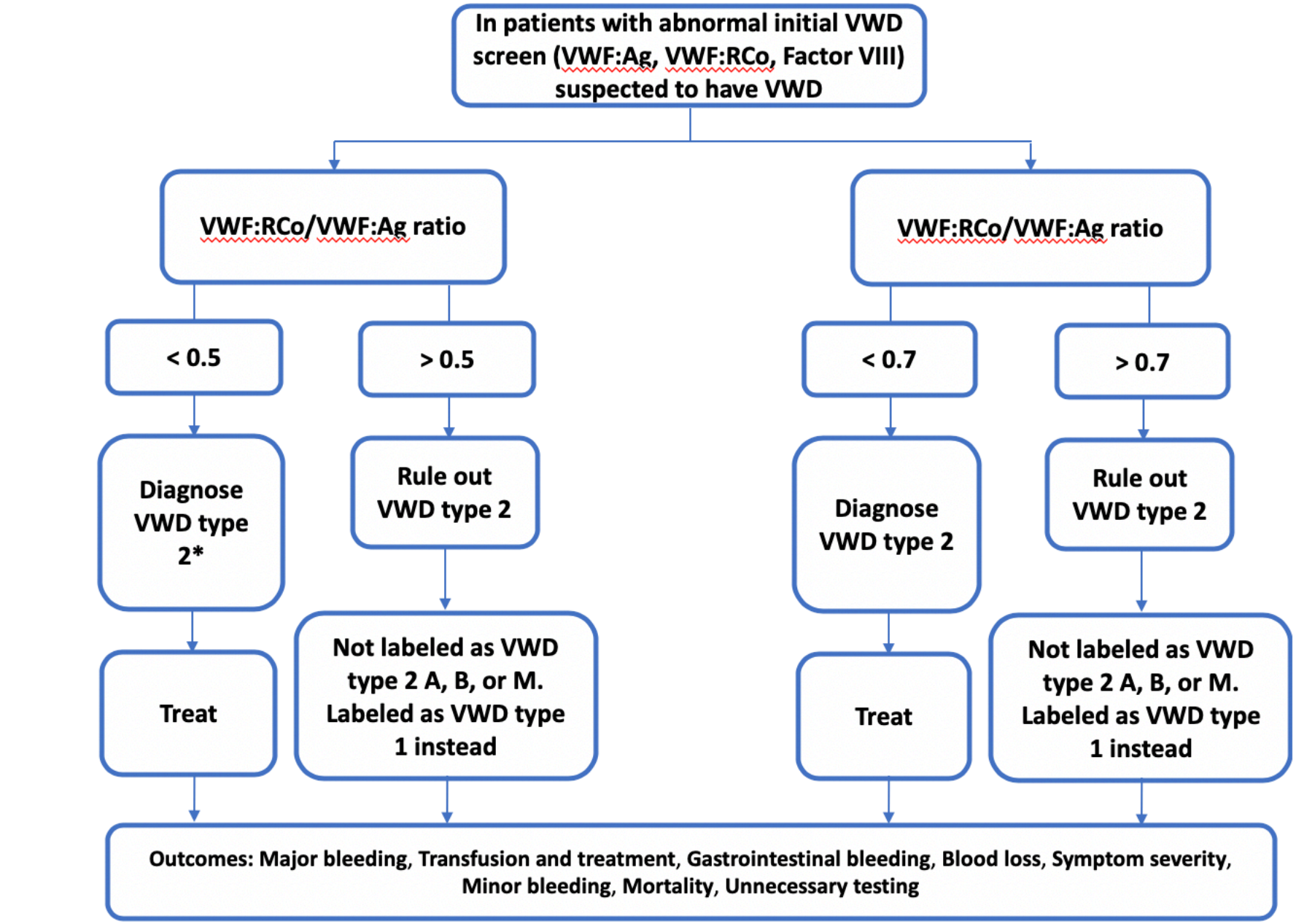
Question 7

Should VWF:RCo/Ag <0.5 vs. VWF:RCo/Ag <0.7 be used to diagnose VWD type 2 in Patients suspected of VWD type 2?	
POPULATION:	Patients suspected of VWD type 2
INTERVENTION:	VWF:RCo/Ag <0.5
COMPARISON:	VWF:RCo/Ag <0.7
PURPOSE OF THE TEST:	Identify patients with VWD type 2
ROLE OF THE TEST:	Identify patients with VWD type 2
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	VWF:RCo/Ag <0.5 – False positive, VWF:RCo/Ag <0.5 – False negative, VWF:RCo/Ag <0.5 – True positive, VWF:RCo/Ag <0.5 – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient setting
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD requires correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types.
SUBGROUPS:	
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



* Polymorphism should be considered if the patient has an abnormal VWF:RCo

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require a correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. While a clear-cut diagnosis is easy in severe von Willebrand factor reductions, the advantage of pursuing a definite diagnosis in mild or dubious cases should be weighed against the risk of over-medicalization. Identifying patients with VWD type 2 will help to give a treatment that will correct the dual defect of hemostasis caused by the abnormal/reduced von Willebrand factor and the concomitant deficiency of factor VIII. (Castaman, 2013).	This question was judged to be a priority among many candidate questions to address in these guidelines.

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ● Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	At <0.5, sensitivity was between 0.58 to 0.79 in 3 studies with 95 patients, and specificity was assumed to be 1. At <0.6, sensitivity was between 0.68 to 0.97 in 3 studies with 97 patients and specificity was 0.87 in 1 study with 97 patients. At <0.7, pooled sensitivity was 0.90 (95% CI: 0.83 to 0.94) in 5 studies with 204 patients and specificity was 0.91 (95% CI: 0.76 to 0.97) in 4 studies with 994 patients.	

Test result	Number of results per 1000 patients tested (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 30%			
	VWF:RCo/Ag <0.5	VWF:RCo/Ag <0.7		
True positives patients with VWD type 2	205 (161 to 249)	270 (249 to 282)	299 (6)	
	65 fewer TP in VWF:RCo/Ag <0.5			

False negatives patients incorrectly classified as not having VWD type 2	95 (51 to 139)	30 (18 to 51)		⊕◯◯◯ VERY LOW[a,b,c]
	65 more FN in VWF:RCo/Ag <0.5 IU/dL			
True negatives patients without VWD type 2	700 (693 to 700)	637 (532 to 679)	994 (4)	⊕◯◯◯ VERY LOW[a,c,d]
	63 more TN in VWF:RCo/Ag <0.5 IU/dL			
False positives patients incorrectly classified as having VWD type 2	0 (0 to 7)	63 (21 to 168)		
	63 fewer FP in VWF:RCo/Ag <0.5			

a. Case control design lead to serious patient selection bias
b. The studies are not comparative
c. There is high unexplained heterogeneity
d. The studies are not comparative and the specificity was assumed to be 100% at the 0.5 cut-off

Refer to the Appendix at the end of the document

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2 A, B, or M and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2 A, B, or M and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2 A, B, or M and not suffer the side effects of treatment, but may benefit from treatment for VWD type 1 or 2N. **False Negative:** These are patients who have VWD type 2 A, B, or M but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be labeled as VWD type 1 or 2N, and may receive inappropriate treatment (Desmopressin) and may be incorrectly counseled about the risk in their children. **False Positive:** These are patients who did not have VWD type 2 A, B, or M but they will be labeled as having VWD type 2 A, B, or M and receive unnecessary treatment. These patients actually have VWD type 1 or 2N. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	There is not much harm to have high false positives as there is a tendency to use genetic testing in the few coming years when the testing becomes cheaper. False negatives are considered more relevant to this question by patients and clinical experts.

Undesirable Effects
How substantial are the undesirable anticipated effects?

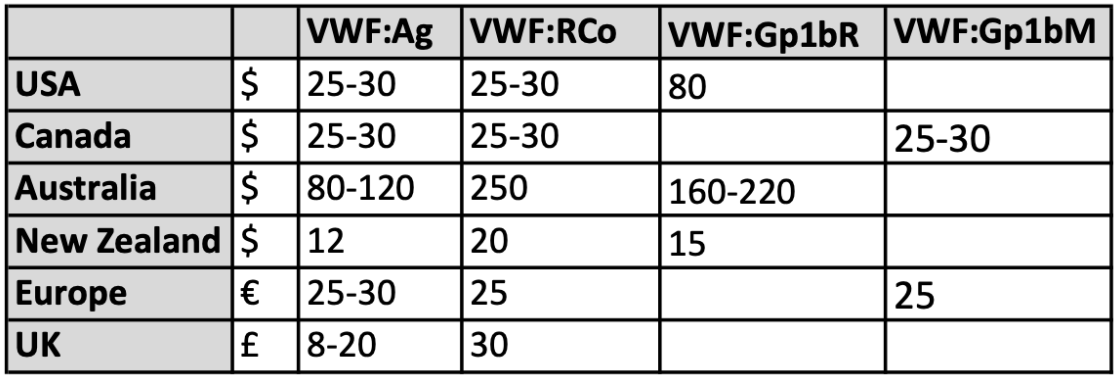
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2 A, B, or M and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2 A, B, or M and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2 A, B, or M and not suffer the side effects of treatment, but may benefit from treatment for VWD type 1 or 2N. **False Negative:** These are patients who have VWD type 2 A, B, or M but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be labeled as VWD type 1 or 2N, and may receive inappropriate treatment (Desmopressin) and may be incorrectly counseled about the risk in their children. **False Positive:** These are patients who did not have VWD type 2 A, B, or M but they will be labeled as having VWD type 2 A, B, or M and receive unnecessary treatment. These patients actually have VWD type 1 or 2N. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	Higher false negative when using the 0.5 diagnostic threshold. Potentially inappropriate treatment.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence for test accuracy is very low and that is due to case-control design leading to serious population selection bias. Also, issues around labeling as type 2M were noted. The studies do not compare the 2 tests cut-offs directly and there is serious unexplained heterogeneity.	
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High	Test's effects are not applicable since the intervention consists of a blood test that has no important direct benefits, adverse effects or burden.	

● No included studies		
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The cut off between types 1 and 2 is for classification only. It is not a crucial issue when deciding on treatment. Desmopressin is more likely not to work for type 2 A and 2 M, and is relatively contraindicated for type 2 B. However, if the choice of treatment is not desmopressin, the labeling will not have an effect
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included	Refer to the Appendix at the end of the document	

studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Patients are very familiar with having blood drawn for lab testing for any reason. Well-trained phlebotomists at blood disorder treatment centers are efficient and have a good technique which means little or no bruising from blood draws for specialized hematology laboratory tests (Aschman, 2014). Actually, patients care to have assays that can be trusted and don't have to be repeated on multiple occasions. So, patient concerns or preferences that are specific to these specialized labs are not different than other blood testing techniques, but concerns arise regarding the cut-off value used. (Baker, 2019).	Patients are interested in the results of the antigen and activity assays but frequently have no understanding of the tests and cut-offs, they desire an accurate diagnosis that will lead to proper treatment. Patients value clear and consistent guidelines on the reasons for different test choices and the cut-off used, as patients are frustrated when they are not able to determine if they certainly have or do not have VWD. In addition to getting the diagnosis right, patients place value in getting the diagnosis in a timely matter. The quality of life and counseling are the concern for patients when they are mislabeled. Some pregnant women were refused epidural anesthesia because they are labeled as type 2, but that would not be a problem if they are labeled as type 1. For patients, it is very important to understand the difference in treatment between the different types of VWD. Patients guidelines with educational material is needed.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There is no effect on changing the ratio on costs.

		VWF:Ag	VWF:RCo	VWF:Gp1bR	VWF:Gp1bM
USA	$	25-30	25-30	80	
Canada	$	25-30	25-30		25-30
Australia	$	80-120	250	160-220	
New Zealand	$	12	20	15	
Europe	€	25-30	25		25
UK	£	8-20	30		

There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates. The data for required resources for some of the assays are not available because of lack of availability of the assay in different countries.

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The cost and difficulty of good quality control of these tests make these tests less accessible. There is difficulty in running multiple assays due to cost considerations, and reimbursement only available for a limited number of tests in an individual patient. Physicians should choose the assays that have basic requirements and then identify those that could be of use in settings where the resource is not so much of an issue.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention	In a Markov decision analytic model taking a societal perspective and costs expressed in 2007 US dollars, the cost of testing adolescents with menorrhagia for VWD was $1790, versus $1251 for not testing for VWD. The effectiveness of not testing in quality-adjusted life-years (QALYs) gained (14.237 QALYs) was similar to the VWD testing strategy (14.246 QALYs). Compared with not testing for VWD, screening for VWD had an incremental cost-effectiveness ratio of $62 791 per QALY, a value typically considered economically reasonable (Sidonio, 2010).	

or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Not all tests are accessible to all patients. Therefore, a thorough and proper investigation may be limited due to the high cost and lack of exams with appropriate quality control. Insurance coverage for these tests is variable based on location and funding model. In fact, in the US most good private insurance cover antigen assay and activity assay, but some people have a large deductible. However, sometimes the value does not cover the overall cost of the test, especially in public services. In New Zealand specifically, all residents get blood tests for free. This is also applicable in the UK, since there is no practical restriction on requesting these tests. In Italy, they are partly covered by insurance. In Australia, a limited number of antigen and activity assays are covered by insurance - above 3 assays the cost is not covered. In the Netherlands, all assays are covered by insurance.

		The VWF:RCo is potentially less useful for the African American population given the higher frequency of the D1472H variant in this group. Because of the higher rate of the benign variants that affect the VWF:RCo giving false positively low results the VWF:GPIbm testing is used in followup testing in Hispanic and African American groups more than Caucasian. The aforementioned populations are less likely to have easy access to larger centers.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Generally, all patients accept the blood tests in question
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Antigen and activity assays have limited availability – available in most larger population centers will have centralized testing in specialist centers. It is usually not found in resource-poor countries and tertiary care centers even in high-income setting countries, specifically the activity assays. VWF:GPIbm or GPIbR is not available in most centers in the United States of America, but VWF:Ag and VWF:RCo are more readily

		available. VWF:Ag is only available in hospitals with special coagulation labs, and special coagulation labs usually only run either the VWF:RCo or one of the newer assays. Countries differ in the challenges to access the testing (referrals within the system and logistic issues like traveling hundreds of kilometers), so testing is often sent out reference laboratories (with all the issues of pre-analytical variables, including sample collection and transport that can affect the reliability of results) outside of medium to large academic centers in the United States. Even when the tests are available in smaller non-academic centers, results may differ when compared to those from large referral centers. Depending on where patients are allowed to undergo testing, there could be variation in results (e.g., in California, insurers may not reimburse repeat testing of VWF:Ag and VWF:RCo or VWF:GPIbm to be done at the respective academic center if performed already at private commercial laboratories). Often repeat testing is needed particularly if obtained at a time of stress (following a procedure) or in times of significant anemia. This issue is illustrated with teenage girls undergoing evaluation during an episode of heavy menstrual bleeding. Levels may be elevated over baseline and obscure the diagnosis of VWD or its subtype. It may be possible to say that one or two activity measures are not accurate and reduce their use, but many labs are bound by managed service contracts and performing all

		labs as a single 'best' assay is often not feasible. Another feasibility issue assay availability and turnaround time in the perioperative setting. Some of the tests, such as the VWF:RCo, have a considerable coefficient of variation, which may influence laboratory research. In addition, the physiological or induced variations of VWF plasma levels also may affect the diagnosis of borderline cases, especially of type 1 VWD and low levels of VWF.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	**Inaccurate**	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**

CERTAINTY OF EFFECTS	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

The panel suggests against a VWF activity/VWF:Ag (ratio of VWF activity to antigen) <0.5 as a cut-off value, and rather using a higher cut-off value of <0.7 to confirm the diagnosis of Type 2 VWD (2A, B, or M) in patients with an abnormal initial VWD screen (e.g.VWF:Ag and/or VWF activity), or a low VWF activity/VWF:Ag ratio.
(Conditional recommendation based on low certainty in the evidence)

Justification

The guideline panel determined that there is low certainty in the evidence for a net health benefit from using a VWF:RCo/Ag cut-off of <0.7 over a lower cut-off of <0.5 in patients suspected of type 2 VWD. Other EtD criteria were generally in favor of using a cut-off of <0.7 so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Variability in VWF:RCo assay in different ethnic groups.

Appendix

1. Risk of bias:

Author	Year	Population selection risk of bias	Index test risk of bias	Reference test risk of bias	Flow and timing risk of bias
Vangenechten, K	2018	High	Low	Low	Low
de Maistre, E	2014	High	Low	Low	Low
Chen, D.	2011	Low	Low	Low	Low
James, P	2007	High	Low	Low	Low
Caron, C	2006	High	Low	Low	Low
Adcock, D	2006	Low	Low	Low	Low

2. Outcomes:

- *Diagnostic test accuracy:*

  - VWF:RCo/Ag<0.5 versus VWF:RCo/Ag<0.6:

VWF:RCo/Ag <0.5 IU/dL		VWF:RCo/Ag <0.6 IU/dL	
Sensitivity [e]	0.68 (95% CI: 0.54 to 0.83)	Sensitivity [e]	0.85 (95% CI: 0.71 to 0.99)
Specificity [f]	1.00 (95% CI: 0.99 to 1.00)	Specificity	0.88 (95% CI: 0.87 to 0.88)

Prevalences	30%[d]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
								pre-test probability of 30%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWF:RCo/Ag <0.5	VWF:RCo <0.6	
True positives (patients with VWD type 2)	4 studies 145 patients	cohort & case-control type studies	serious [a]	serious [b]	serious [c]	not serious	none	204 (162 to 249)	256 (212 to 299)	⊕◯◯◯ VERY LOW
								52 fewer TP in VWF:RCo/Ag <0.5		
								96 (51 to 138)	44 (1 to 88)	

False negatives (patients incorrectly classified as not having VWD type 2)								**52 more FN in VWF:RCo/Ag <0.5**		
True negatives (patients without VWD type 2)	1 studies 87 patients	cohort & case-control type studies	serious [a]	serious [b]	not serious	not serious	none	700 (693 to 700)	616 (609 to 616)	⊕⊕◯◯ LOW
								84 more TN in VWF:RCo/Ag <0.5		
False positives (patients incorrectly classified as having VWD type 2)								0 (0 to 7)	84 (84 to 91)	
								84 fewer FP in VWF:RCo/Ag <0.5		

Explanations

a. Case Control design leading to serious population selection bias. Also, issues around labeling as type 2M noted.
b. The studies do not compare the 2 tests cut-offs directly
c. There is serious unexplained heterogeneity
d Typically seen in patients investigated for VWD type 2 because of an low VWF:Rco/Ag ratio.
e. Pooled in proportion, not enough studies to pool as test accuracy results
f. Specificity assumed to be 100% at a <0.5 cut-off

- VWF:RCo/Ag<0.5 versus VWF:RCo/Ag<0.7:

VWF:RCo/Ag <0.5 IU/dL		VWF:RCo/Ag <0.7 IU/dL	
Sensitivity [f]	0.68 (95% CI: 0.54 to 0.83)	Sensitivity [f]	0.90 (95% CI: 0.83 to 0.94)
Specificity [g]	1.00 (95% CI: 0.99 to 1.00)	Specificity [g]	0.91 (95% CI: 0.76 to 0.97)

Prevalences	30%[e]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested pre-test probability of 30%		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWF:RCo/Ag <0.5	VWF:RCo/Ag <0.7	
True positives (patients with VWD type 2)	6 studies 299 patients	cohort & case-control type studies	serious [a]	serious [b]	serious [c]	not serious	none	205 (161 to 249)	270 (249 to 282)	⊕◯◯◯ VERY LOW
								65 fewer TP in VWF:RCo/Ag <0.5		
False negatives (patients incorrectly classified as not having VWD type 2)								95 (51 to 139)	30 (18 to 51)	
								65 more FN in VWF:RCo/Ag <0.5		

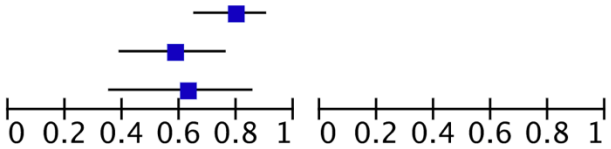
True negatives (patients without VWD type 2)	4 studies 994 patients	cohort & case-control type studies	serious [a]	serious [d]	serious [c]	not serious	none	700 (693 to 700)	637 (532 to 679)	⨁◯◯◯ VERY LOW
								63 more TN in VWF:RCo/Ag <0.5		
False positives (patients incorrectly classified as having VWD type 2)								0 (0 to 7)	63 (21 to 168)	
								63 fewer FP in VWF:RCo/Ag <0.5		

Explanations

a. Case control design lead to serious patient selection bias. Also, issues around labeling as type 2M noted.
b. The studies are not comparative
c. There is high unexplained heterogeneity
d. The studies are not comparative and the specificity was assumed to be 100% at the 0.5 cut-off
e. Typically seen in patients investigated for VWD type 2 because of an low VWF:Rco/Ag ratio.
f. Pooled in proportion, not enough studies to pool as test accuracy results
g. Specificity assumed to be 100% at a <0.5 cut-off

- VWF:RCo/Ag <0.5:

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Adcock, 2006	38	0	10	0	0.79 [0.65, 0.90]	Not estimable
Caron, 2006	18	0	13	0	0.58 [0.39, 0.75]	Not estimable
James, 2007	10	0	6	0	0.63 [0.35, 0.85]	Not estimable



Sensitivity	0.58 to 0.79
Specificity	0.99 to 1.00[c]

Prevalences	30%[b]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%	
True positives (patients with VWD type 2)	3 studies 95 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	174 to 237	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having VWD type 2)								63 to 126	
True negatives (patients without VWD type 2)	0 studies patients							693 to 700	-

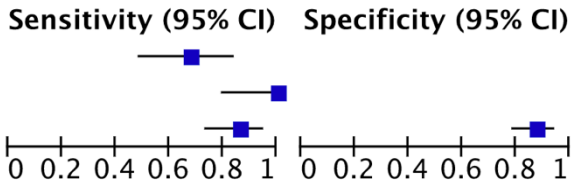
False positives (patients incorrectly classified as having VWD type 2)								0 to 7	

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, issues around labeling as type 2M noted.
b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).
c. Specificity assumed to be 100% with a <0.5 ratio cut-off.

- VWF:RCo/Ag <0.6:

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Caron, 2006	21	0	10	0	0.68 [0.49, 0.83]	Not estimable
James, 2007	16	0	0	0	1.00 [0.79, 1.00]	Not estimable
Vangenechten, 2018	43	11	7	76	0.86 [0.73, 0.94]	0.87 [0.79, 0.94]



Sensitivity	0.68 to 0.97
Specificity	0.87 to 0.88

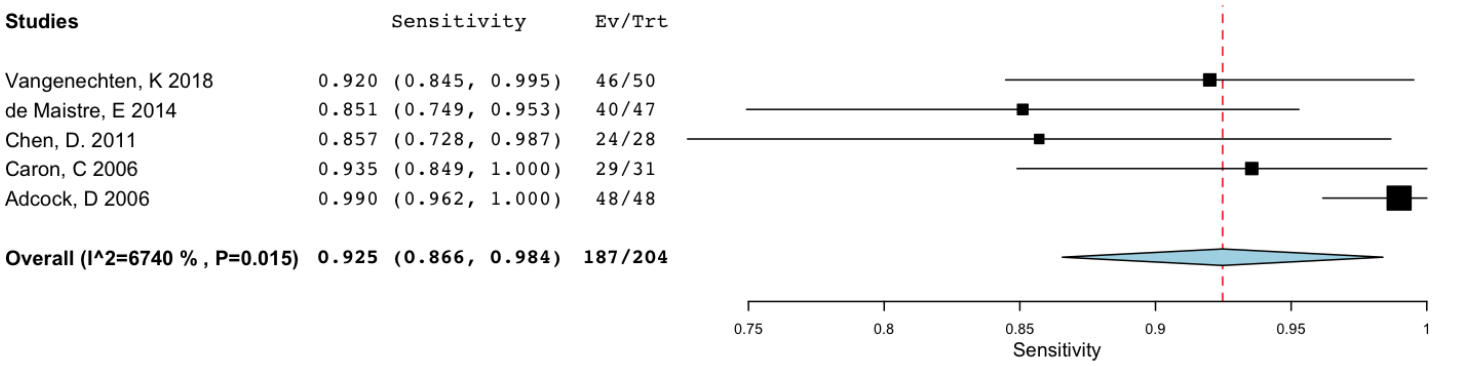
Prevalences	30%[c]

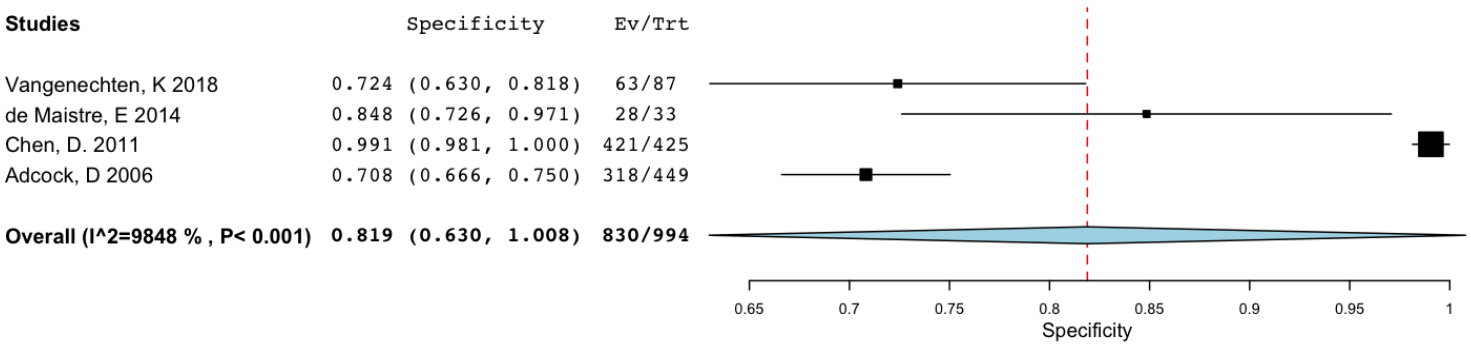
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%	
True positives (patients with VWD type 2)	3 studies 97 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	203 to 291	⊕⊕◯◯ LOW
False negatives (patients incorrectly classiiied as not having VWD type 2)								9 to 97	
True negatives (patients without VWD type 2)	1 studies 87 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	612 to 612	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having VWD type 2)								88 to 88	

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, issues around labeling as type 2M noted.
b. Confidence intervals do not cross the effect estimates of different studies
c. Typically seen in patients investigated for VWD type 2 because of an low VWF:Rco/Ag ratio.

- VWF:RCo/Ag <0.7:





Sensitivity [d]	0.90 (95% CI: 0.83 to 0.94)
Specificity [d]	0.91 (95% CI: 0.76 to 0.97)

Prevalences	30%[c]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%	
True positives (patients with VWD type 2)	5 studies 204 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	269 (249 to 281)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having VWD type 2)								31 (19 to 51)	
True negatives (patients without VWD type 2)	4 studies 994 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	serious [c]	none	573 (441 to 700)	

False positives (patients incorrectly classified as having VWD type 2)								127 (0 to 259)	⊕◯◯◯ VERY LOW

Explanations

a. Serious patient selection risk of bias due to case-control design. Also, issues around labeling as type 2M noted.
b. Considering the upper versus the lower boundary of the estimate effect would may lead to different clinical decision
c. Typically seen in patients investigated for VWD type 2 because of an low VWF:Rco/Ag ratio.
d. Pooled in proportion, not enough studies to pool as test accuracy results

https://gdt.gradepro.org/presentations/#/isof/isof_8e790c07-29f2-4ced-8bbd-9647785c4e60-1573056703410

- *Mutation detection:*

Author, year	**Study type**	**Outcomes**	**Results**
James, 2007	Cross sectional Case control	VWF:Rco and mutation correlation	identified 8 different missense mutations (R854Q, T1054M, R1315C, R1374C, R1374H, L1382P, S2179F, and T2647M) within these 16 families. it was significantly more likely to identify a VWF mutation in cases with RCo/Ag ratios < 0.50 (P < 0.05, chi- squared test). Importantly, every index case with an RCo/Ag ratio < 0.40 (4/4 index cases) had a mutation identified within the A1 domain, in contrast to 1/12 cases with an RCo/Ag ratio > 0.40.

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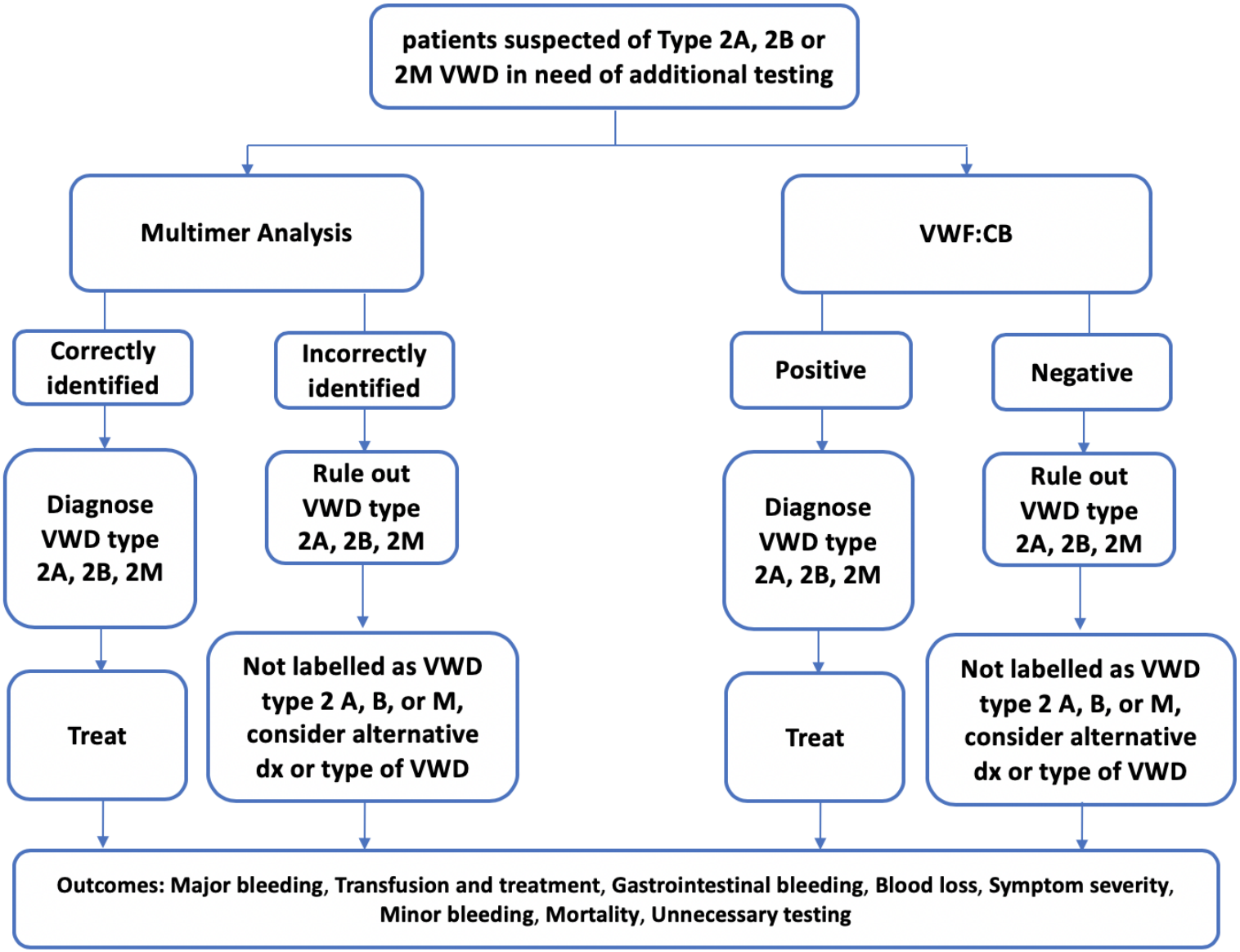
QUESTION

Should VWF multimer analysis vs. VWF:CB/Ag ratio be used to diagnose patients with VWD type 2 in Patients suspected of VWD type 2?	
POPULATION:	Patients suspected of VWD type 2 (Rec)
INTERVENTION:	VWF multimer analysis
COMPARISON:	VWF:CB/Ag ratio
PURPOSE OF THE TEST:	Identify subtype of VWD in VWD type 2 patients
ROLE OF THE TEST:	Identify subtype of VWD in VWD type 2 patients
LINKED TREATMENTS:	Desmopressin, Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	VWF:CB – False positive, VWF:CB – False negative, VWF:CB – True positive, VWF:CB – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD requires correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. More tests like multimer analysis and VWF:CB are used to characterize the subtypes of the disease.
SUBGROUPS:	
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members were recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. More tests like multimer analysis and VWF:CB/Ag are used to characterize the subtypes of the disease.	This question was judged to be a priority among many candidate questions to address in these guidelines.

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	Data presented in some studies for all type 2 VWD patients together, and in other studies separated by subtypes (2A, 2B, 2M). Some studies have a case-control design and others have a cohort design. Data about VWF:CB/Ag is presented with different cut-offs in different studies (<0.5, <0.6, <0.7) that were pooled.	The good results in the multimer analysis evaluations in the different studies are due to the high quality control standards under which the test was performed, as all were done in centers of excellence. Very low VWF antigen levels (<0.15) will lead to unreliable VWF:CB/Ag and VWF:RCo/Ag ratios. The panel agreed that 2M is defined by the multimers results, making this assay as the reference standard for type 2M VWD.

Test result	Number of results per 1000 patients tested (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 80%			
	VWF multimer analysis	VWF:CB/Ag		
True positives patients with patients with VWD type 2	720 (720 to 792)	720 (624 to 768)	476 (9)	⨁◯◯◯ VERY LOW[a,b]
	0 fewer TP in VWF multimer analysis			
False negatives patients incorrectly classified as not having patients with VWD type 2	80 (8 to 80)	80 (32 to 176)		
	0 fewer FN in VWF multimer analysis			
	194 (188 to 198)	190 (178 to 196)	948 (9)	

True negatives patients without patients with VWD type 2	4 more TN in VWF multimer analysis			
False positives patients incorrectly classified as having patients with VWD type 2	6 (2 to 12)	10 (4 to 22)		⊕◯◯◯ VERY LOW[a,b]
	4 fewer FP in VWF multimer analysis			

a. Case-control design makes patient selection bias serious. Different cut-offs were used in the VWF:CB/Ag ratios (0.5 in Popov versus 0.7 in Flood)
b. A different clinical decision would be considered if the upper versus lower boundary of the pooled effect estimate was used

Refer to the Appendix at the end of the document

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2A, 2B, 2M and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2A, 2B, 2M and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2A, 2B, 2M and not suffer the side effects of treatment but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2A, 2B, 2M but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2A, 2B, 2M but they will be labeled as having VWD type 2A, 2B, 2M and receive unnecessary treatment. They do not benefit from the treatment for type 2A, 2B, 2M. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	

	Refer to the Appendix at the end of the document	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2A, 2B, 2M and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2A, 2B, 2M and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2A, 2B, 2M and not suffer the side effects of treatment but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2A, 2B, 2M but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2A, 2B, 2M but they will be labeled as having VWD type 2A, 2B, 2M and receive unnecessary treatment. They do not benefit from the treatment for type 2A, 2B, 2M. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. Refer to the Appendix at the end of the document	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low ○ Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	It is important to note that the collagen-binding corresponds to more than one assay depending on the collagen type: type 3 is generally used because type 4 is not very sensitive to multimers. Multimer testing is done after VWF:CB to capture abnormalities not captured by VWF:CB to allow for further characterization.
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Test's effects are not applicable since the intervention consists of a blood test that has no important direct benefits, adverse effects or burden.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	While a clear-cut diagnosis is easy in severe von Willebrand factor reductions, the advantage of pursuing a definite diagnosis in mild or dubious cases should be weighed against the risk of over-medicalization. Identifying patients with VWD type 2 will help to give a treatment that will correct the dual defect of hemostasis caused by the abnormal/reduced von Willebrand factor and the concomitant deficiency of factor VIII. (Castaman, 2013).	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The cut off between types 1 and 2 is mostly for classification purposes. It is not a critical factor when deciding on treatment. Desmopressin is more likely not to work for type 2 A and 2 M, and is relatively contraindicated for type 2 B.

		However, if the choice of treatment is not Desmopressin, the labeling will not have an effect
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		Patients are very familiar with having blood drawn for lab testing for any reason. Well-trained phlebotomists at blood disorder treatment centers are efficient and often have a good technique, which means little or no bruising from blood draws for specialized hematology laboratory tests. Patients care to have assays that can be trusted that will lead to an accurate diagnosis, and don't have to be repeated on multiple occasions. So, patient concerns or preferences that are specific to these specialized labs are not different than other blood testing.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	<table><tr><th></th><th></th><th>VWF:CB</th><th>Multimer analysis</th></tr><tr><td>USA</td><td>$</td><td>30</td><td>200-300</td></tr><tr><td>Canada</td><td>$</td><td></td><td>100</td></tr><tr><td>Australia</td><td>$</td><td>150</td><td>500</td></tr><tr><td>New Zealand</td><td>$</td><td>30</td><td>180</td></tr><tr><td>Europe</td><td>€</td><td>50</td><td>200</td></tr><tr><td>UK</td><td>£</td><td>15-20</td><td>30</td></tr></table> There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	The cost and difficulty of good quality control of these tests make these exams less accessible. There is difficulty in running multiple assays due to cost considerations, and reimbursement being only available for a limited number of tests in an individual patient. Physicians should choose the assays that have basic requirements and then identify those that could be of use in settings where the resource is not so much of an issue.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Insurance coverage for VWF:CB/Ag and multimer testing tests are variable based on location and funding model. In fact, in the United States of America, most private insurance will cover these assays, but some people have a large deductible. Sometimes the reimbursed value does not cover the overall cost of the test, especially in public services.

		In New Zealand specifically, all residents get blood tests for free. This is also applicable in the United Kingdom, since there is no practical restriction on requesting these tests. In Italy, the Netherlands, Canada, and Australia, they are covered by insurance. People with access problems and people with no health insurance are disadvantaged, specifically in regards to the multimer analysis testing. In fact, if insurance does not cover one test, but covers another and the latter is still a good option (even if not the best), the patient tends to go with the more cost-effective assay.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Generally, patients accept the blood tests in question.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Classic multimer analysis is labor-intensive, time-consuming and requires expertise for interpretation (Luchtman-Jones, 2019). Overall, VWF:CB/Ag is more widely available than multimer analysis and of more practical use. National or international reference centers that coordinate quality assurance exercises are required. However, it is difficult to recommend one over the other as labs will have different assays and expertise available to them. In fact, there is some practical value in pursuing a detailed characterization of the disease but it is possible to manage patients reasonably well without that.	VWF:CB/Ag is generally available in research-active departments and specialized centers. Multimer analysis is a very cumbersome test for the lab to perform and takes multiple days to complete, thus some labs try to use VWF:CB/Ag to replace the need for multimer analysis. It is not a widely available test in all hospitals and is usually sent out to specialized centers. For instance, it is available in a single national center in Australia, and expertise is

		waning due to lack of referrals. The extent of training of personnel to perform the test is at the discretion of the clinical laboratory director.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	**Very low**	Low	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the**	Probably favors the intervention	Favors the intervention	Varies	Don't know

	JUDGEMENT						
			intervention or the comparison				
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The panel suggests using either VWF multimer analysis or VWF:CB/VWF:Ag (ratio of VWF collagen binding to antigen) to diagnose Type 2 VWD in patients suspected of Type 2A, 2B or 2M VWD in need of additional testing.
(Conditional recommendation based on low certainty in the evidence)

Remarks:

- Different vascular collagens interact with VWF; Types I and III interact with the A3 domain and Type IV and VI interact with the A1 domain. Although not widely available, if labs perform a VWF:CB assay, they will most often use Type I and/or III Collagen. Binding to Types I or III is known to be a surrogate for the presence of high molecular weight VWF.
- Type 2M VWD is defined by a normal VWF multimer profile, including the presence of high molecular weight VWF.

Justification

The guideline panel determined that there is low certainty in the evidence for neither a health benefit nor a harm from using multimer analysis over VWF:CB in patients with type 2 VWD in need for additional testing for classification. Other EtD criteria were generally not favor of using either assays for classification so that the desirable consequences were equal to the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

- Diagnostic test accuracy for doing multimers in VWD patients that already had abnormal collagen binding.

APPENDIX

1. **<u>Risk of bias:</u>**

Author	Risk of bias population selection	Risk of bias index test	Risk of bias reference test	Flow and timing Rsk of bias
Perez-Rodriguez, 2018	Moderate	Low	Low	Low
Vangenechten, 2018	High	Low	Low	Low
Jousselme, 2018	High	Low	Low	Low
Bowyer, 2018	High	Low	Low	Low
Casonato, 2017	Low	Moderate	Low	Low
Ni, 2013	Low	Low	Low	Low
Flood, 2013	High	Low	Moderate	Low
Popov, 2006	Low	Low	Low	Low
Adcock, 2006	Low	Low	Low	Low
Riddell, 2002	High	Low	High	Low
Federici, 2000	High	Moderate	Low	Low

2. Outcomes:

- *Diagnostic test accuracy VWD type 2A 2B:*

Author, Year	Study Design	PICO arm	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI	Comments
Ni, 2013	Cross sectional, Cohort	VWF:CB/VWF:Ag	47	2	7	45	0.959	0.851	0.99	0.865	0.744	0.934	at 0.5 cutoff
Popov, 2006	Cross sectional, Cohort	Multimer	36	0	135	2715	0.986	0.818	0.999	0.952	0.944	0.96	
		VWF:CB/VWF:Ag	30	6	16	75	0.833	0.675	0.923	0.824	0.732	0.889	at 0.5 cut off
Adcock, 2006	Cross sectional, Cohort	VWF:CB/VWF:Ag	47	0	21	428	0.99	0.854	0.999	0.952	0.928	0.968	at 0.5 cut off
Perez-Rodriguez, 2018	Cross sectional, Case Control	VWF:CB/VWF:Ag	127	19	0	30	0.874	0.809	0.916	0.984	0.789	0.999	at 0.7 cutoff
		Multimer	132	14	0	30	0.904	0.836	0.938	0.984	0.789	0.999	
Vangenechten, 2018	Cross sectional, Case Control	VWF:CB/VWF:Ag	31	19	3	84	0.62	0.48	0.743	0.966	0.898	0.989	at 0.6 cut off
Jousselme, 2018	Cross sectional, Case Control	VWF:CB/VWF:Ag	17	22	0	21	0.437	0.294	0.592	0.977	0.723	0.999	at 0.6 cut of
Bowyer, 2018	Cross sectional, Case Control	Multimer	48	5	4	51	0.906	0.793	0.96	0.927	0.822	0.972	
Flood, 2013	Cross sectional, Case Control	Multimer	51	2	2	144	0.962	0.861	0.991	0.986	0.947	0.997	
		VWF:CB/VWF:Ag	44	9	1	145	0.83	0.705	0.909	0.993	0.953	0.999	at 0.7 cutoff
Riddell, 2002	Cross sectional, Case Control	VWF:CB/VWF:Ag	7	0	0	22	0.937	0.461	0.996	0.978	0.732	0.999	at 0.7 cutoff
Federici, 2000	Cross sectional, Case Control	VWF:CB/VWF:Ag	39	5	2	48	0.886	0.755	0.952	0.96	0.854	0.99	at 0.7 cutoff

- *VWF:CB/Ag vs multimer:*

VWF multimer analysis		VWF:CB/Ag	
Sensitivity	0.90 (95% CI: 0.90 to 0.99)	Sensitivity	0.90 (95% CI: 0.78 to 0.96)
Specificity	0.97 (95% CI: 0.94 to 0.99)	Specificity	0.95 (95% CI: 0.89 to 0.98)

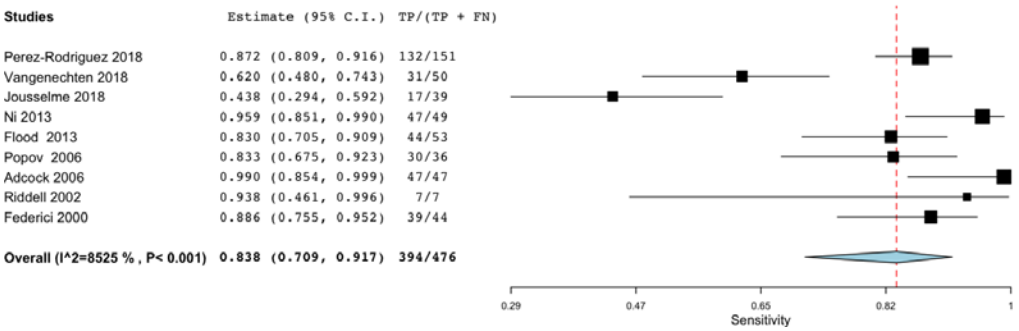
Prevalences	80%[c]

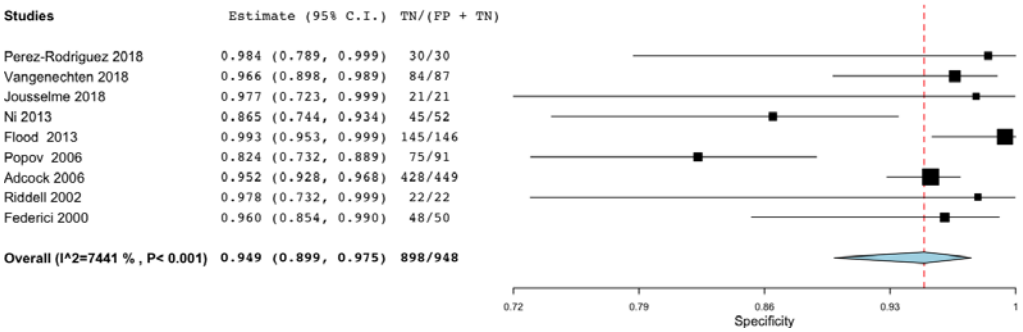
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
								pre-test probability of 80%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	VWF multimer analysis	VWF:CB/Ag	
True positives (patients with patients with VWD type 2)	9 studies 476 patients	cohort & case-control type studies	very serious [a]	not serious	not serious	serious [b]	none	720 (720 to 792)	720 (624 to 768)	⨁◯◯◯ VERY LOW
								0 fewer TP in VWF multimer analysis		
False negatives (patients incorrectly classified as not having patients with VWD type 2)								80 (8 to 80)	80 (32 to 176)	
								0 fewer FN in VWF multimer analysis		
True negatives (patients without patients with VWD type 2)	9 studies 948 patients	cohort & case-control type studies	very serious [a]	not serious	not serious	serious [b]	none	194 (188 to 198)	190 (178 to 196)	⨁◯◯◯ VERY LOW
								4 more TN in VWF multimer analysis		
False positives (patients incorrectly classified as having patients with VWD type 2)								6 (2 to 12)	10 (4 to 22)	
								4 fewer FP in VWF multimer analysis		

Explanations

a. Case-control design makes patient selection bias serious. Different cut-offs were used in the VWF:CB/Ag ratios (0.5 in Popov versus 0.7 in Flood)
b. A different clinical decision would be considered if the upper versus lower boundary of the pooled effect estimate was used
c. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.

- *VWF:CB/Ag:*





Question: Should VWF:CB be used to diagnose VWD type 2A and 2B in Patients suspected of VWD type 2?

Sensitivity	0.90 (95% CI: 0.78 to 0.96)
Specificity	0.95 (95% CI: 0.89 to 0.98)

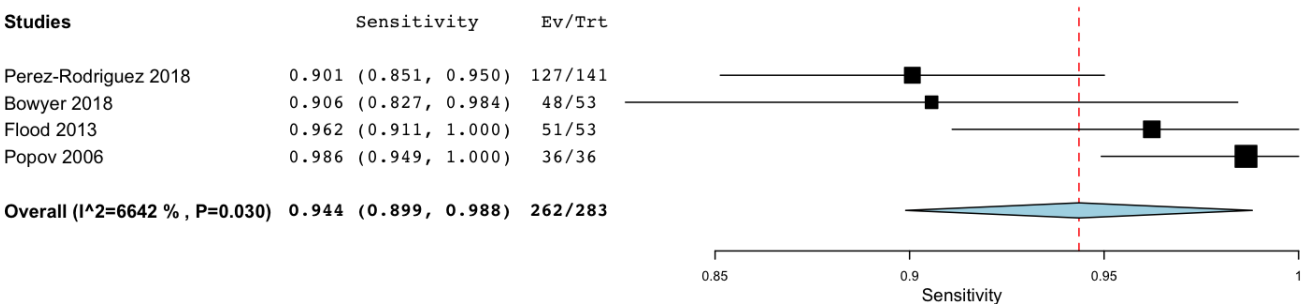
Prevalences	80%[c]

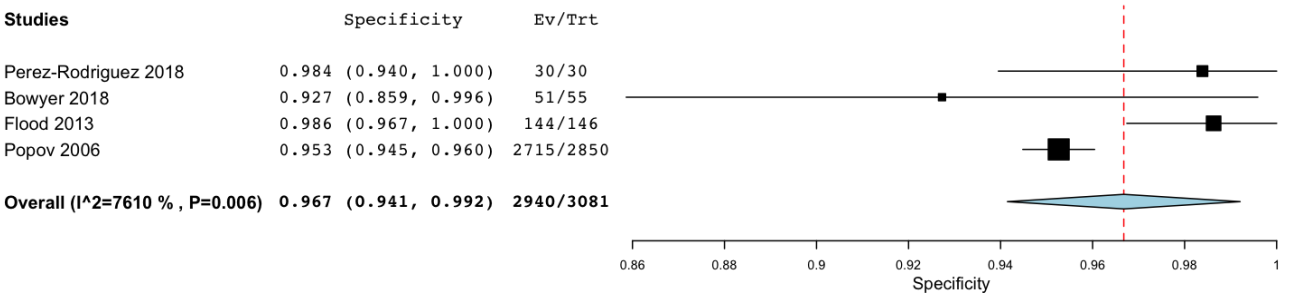
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 80%	
True positives (patients with VWD type 2A and 2B)	9 studies 476 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	670 (567 to 734)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having VWD type 2A and 2B)								130 (66 to 233)	
True negatives (patients without VWD type 2A and 2B)	9 studies 948 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	190 (180 to 195)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having VWD type 2A and 2B)								10 (5 to 20)	

Explanations

a. Case-control design makes patient selection bias serious
b. The confidence intervals of the single effect estimates do not overall with other effect estimates
c. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.

- *Multimer Analysis:*





Sensitivity [c]	0.90 (95% CI: 0.90 to 0.99)
Specificity [c]	0.97 (95% CI: 0.94 to 0.99)

Prevalences	80%[b]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 80%	
True positives (patients with VWD type 2A and 2B)	4 studies 283 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	721 (719 to 790)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having VWD type 2A and 2B)								79 (10 to 81)	
True negatives (patients without VWD type 2A and 2B)	4 studies 3081 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	193 (188 to 198)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having VWD type 2A and 2B)								7 (2 to 12)	

Explanations

a. Case-control design makes patient selection bias serious

b. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.

c. Pooled in proportion since the number of studies does not allow for diagnostic test accuracy pooling.

- *Diagnostic test accuracy VWD type 2M:*

Author, Year	Study Design	PICO arm	TP	FN	FP	TN	Sens	Low CI	Up CI	Spec	Low CI	Up CI	Comments
Popov, 2006	Cross sectional, Cohort	Multimer	12	0	135	2715	0.962	0.597	0.998	0.952	0.944	0.96	
Perez-Rodriguez, 2018	Cross sectional, Case Control	VWF:CB/VWF:Ag	26	13	0	30	0.667	0.829	0.999	0.984	0.789	0.999	At 0.7 cutoff
		Multimer	39	0	0	30	0.663	0.999	0.791	0.984	0.789	0.999	
Jousselme, 2018	Cross sectional, Case Control	VWF:CB/VWF:Ag	7	0	0	21	0.937	0.461	0.996	0.977	0.723	0.999	at 0.6 cutoff
Bowyer, 2018	Cross sectional, Case Control	Multimer	28	6	4	51	0.824	0.659	0.919	0.927	0.822	0.972	
Flood, 2013	Cross sectional, Case Control	Multimer	17	1	2	144	0.944	0.693	0.992	0.986	0.947	0.997	
		VWF:CB/VWF:Ag	18	0	1	145	0.974	0.69	0.998	0.99	0.951	0.998	at 0.7 cutoff
Riddell, 2002	Cross sectional, Case Control	VWF:CB/VWF:Ag	25	0	0	22	0.981	0.756	0.999	0.978	0.732	0.999	at 0.7 cutoff

- *VWF:CB/Ag vs Multimer analysis:*

multimer analysis		VWF:CB	
Sensitivity	0.86 (95% CI: 0.73 to 0.98)	Sensitivity	0.98 (95% CI: 0.96 to 1.00)
Specificity	0.97 (95% CI: 0.94 to 0.99)	Specificity	0.99 (95% CI: 0.98 to 1.00)

Prevalences	80%[c]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
								pre-test probability of 80%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	multimer analysis	VWF:CB	
True positives (patients with VWD type 2M)	4 studies 103 patients	cohort & case-control type studies	very serious [a]	not serious	not serious	serious [b]	none	686 (588 to 784)	786 (765 to 800)	⊕◯◯◯ VERY LOW
								100 fewer TP in multimer analysis		
False negatives (patients incorrectly classified as not having VWD type 2M)								114 (16 to 212)	14 (0 to 35)	
								100 more FN in multimer analysis		
True negatives (patients without VWD type 2M)	4 studies 3081 patients	cohort & case-control type studies	very serious [a]	not serious	not serious	not serious	none	193 (188 to 198)	198 (196 to 200)	

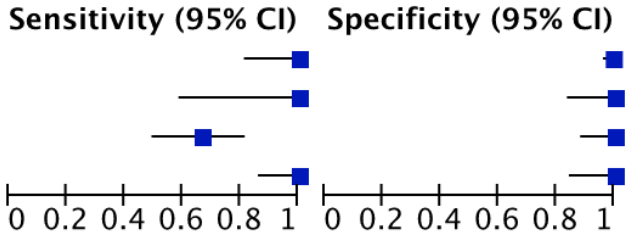
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE
								pre-test probability of 80%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	multimer analysis	VWF:CB	
								5 fewer TN in multimer analysis		⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having VWD type 2M)								7 (2 to 12)	2 (0 to 4)	
								5 more FP in multimer analysis		

Explanations

a. Case-control design makes patient selection bias serious. Different cut-offs were used in the VWF:CB/Ag ratios (0.5 in Popov versus 0.7 in Flood)
b. A different clinical decision would be considered if the upper versus lower boundary of the pooled effect estimate was used
c. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.

- *VWF:CB/Ag:*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flood 2013	18	1	0	145	1.00 [0.81, 1.00]	0.99 [0.96, 1.00]
Jousselme 2018	7	0	0	21	1.00 [0.59, 1.00]	1.00 [0.84, 1.00]
Perez-Rodriguez 2018	26	0	13	30	0.67 [0.50, 0.81]	1.00 [0.88, 1.00]
Riddel 2002	25	0	0	22	1.00 [0.86, 1.00]	1.00 [0.85, 1.00]



Sensitivity [c]	0.98 (95% CI: 0.96 to 1.00)
Specificity [c]	0.99 (95% CI: 0.98 to 1.00)

Prevalences	80%[d]

a. Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 80%	
True positives (patients with VWD type 2M)	4 studies 89 patients	cohort & case-control type studies	serious [a]	not serious	not serious	serious [b]	none	786 (765 to 800)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having VWD type 2M)								14 (0 to 35)	
True negatives (patients without VWD type 2M)	4 studies 219 patients	cohort & case-control type studies	serious [a]	not serious	not serious	serious [b]	none	198 (196 to 200)	

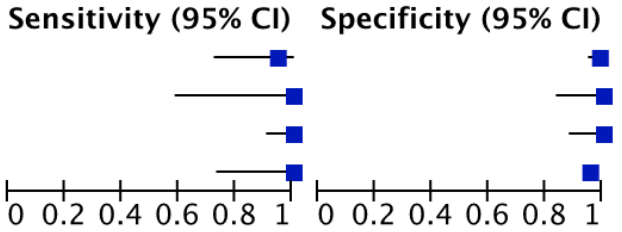
a. Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 80%	
False positives (patients incorrectly classified as having VWD type 2M)								2 (0 to 4)	⊕⊕◯◯ LOW

Explanations

b. Case-control design makes patient selection bias serious
c. Very few number of events.
d. Pooled in proportion since the number of studies does not allow for diagnostic test accuracy pooling.
e. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.

- *Multimer Analysis:*

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flood 2013	17	2	1	144	0.94 [0.73, 1.00]	0.99 [0.95, 1.00]
Jousselme 2018	7	0	0	21	1.00 [0.59, 1.00]	1.00 [0.84, 1.00]
Perez-Rodriguez 2018	39	0	0	30	1.00 [0.91, 1.00]	1.00 [0.88, 1.00]
Popov 2006	12	135	0	2715	1.00 [0.74, 1.00]	0.95 [0.94, 0.96]



Sensitivity [d]	0.86 (95% CI: 0.73 to 0.98)
Specificity [d]	0.97 (95% CI: 0.94 to 0.99)

Prevalences	80%[c]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 80%	
True positives (patients with VWD type 2M)	4 studies 103 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	none	686 (588 to 784)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having VWD type 2M)								114 (16 to 212)	
True negatives (patients without VWD type 2M)	4 studies 3081 patients	cohort & case-control type studies	serious [a]	not serious	not serious	not serious	none	193 (188 to 198)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having VWD type 2M)								7 (2 to 12)	

Explanations

a. Case-control design makes patient selection bias serious
b. The confidence intervals of the single effect estimates do not overalap with other effect estimates
c. Typically seen in patients with VWD type 2 in need for additional testing for subtype classification.
d. Pooled in proportion since the number of studies does not allow for diagnostic test accuracy pooling.

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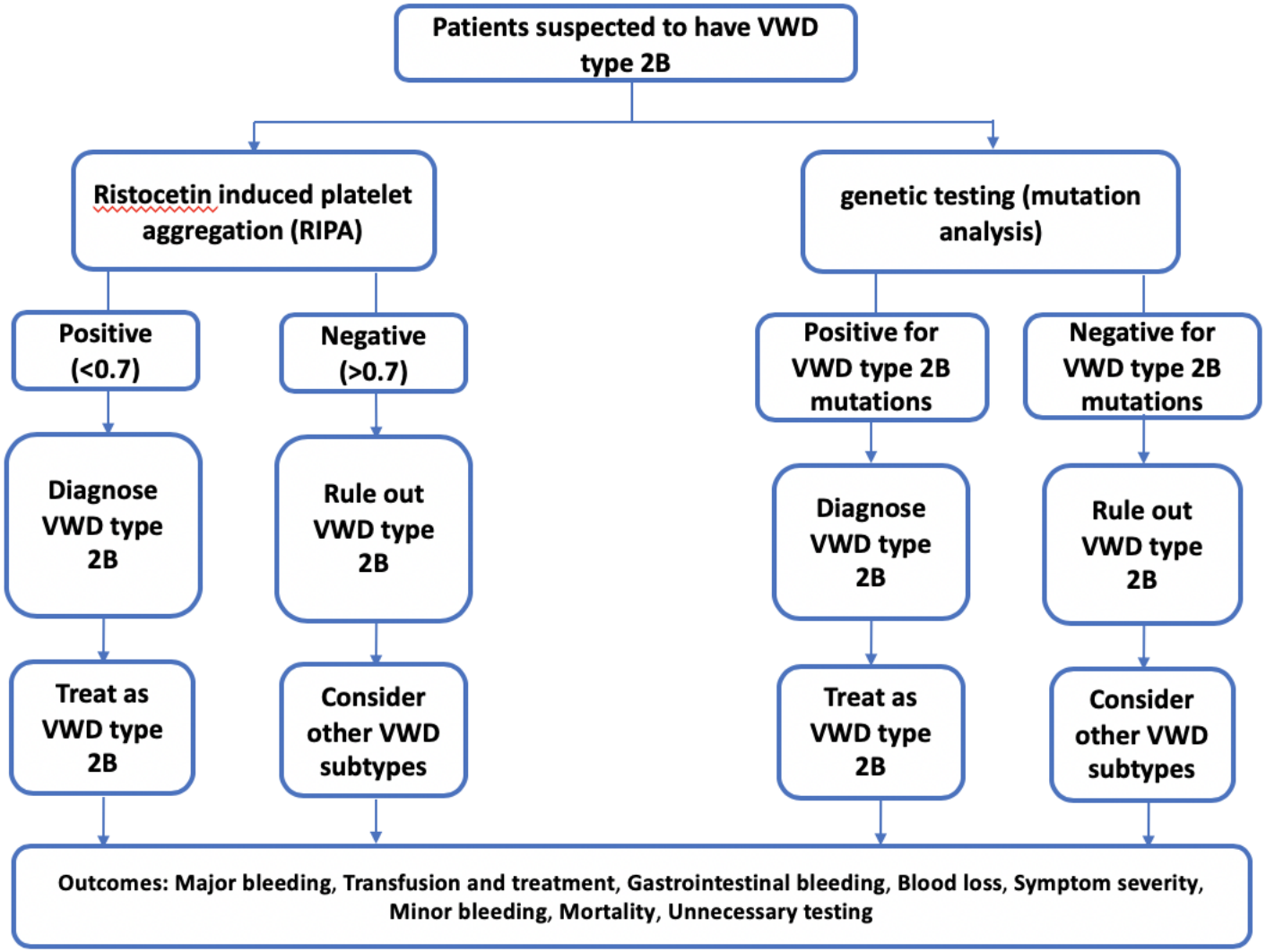
Question 9

Should genetic testing vs. ristocetin-induced platelet aggregation (RIPA) be used to diagnose VWD type 2B in patients suspected of VWD type 2?	
POPULATION:	patients suspected of VWD type 2B
INTERVENTION:	genetic testing
COMPARISON:	ristocetin-induced platelet aggregation (RIPA)
PURPOSE OF THE TEST:	Identify VWD type 2B patients
ROLE OF THE TEST:	Identify VWD type 2B patients
LINKED TREATMENTS:	Tranexamic acid, Factor replacement
ANTICIPATED OUTCOMES:	RIPA – False positive, RIPA– False negative, RIPA – True positive, RIPA – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. More tests like multimer analysis, RIPA, genetic testing and VWF:FVIII are used to characterize the subtypes of the disease. Sometimes, different workers ascribe the same mutation to differing types of VWD, and different types of VWD will seemingly arise from mutations in close proximity on the VWF gene. Genetic testing for VWD is not fool-proof, is likely to be very costly, and has not as yet been shown to be cost-effective in the diagnostic setting. VWD can arise from genetic events unrelated to the VWF gene, and the expression of VWF and the clinical severity in individual patients can be influenced by several epigenetic events. Most of these additional complexities currently remain unknown (Favaloro, 2008).
SUBGROUPS:	
CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell.

Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr were recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. More tests like multimer analysis, RIPA, genetic testing and VWF:FVIII are used to characterize the subtypes of the disease.	This question was judged to be a priority among many candidate questions to address in these guidelines.

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ● Accurate ○ Very accurate ○ Varies ○ Don't know	Different studies report different RIPA concentrations. The higher the concentration the higher the sensitivity, and the lower the concentration the higher the specificity. Genotype was considered to be the reference standard and correlation was made with RIPA results, providing the sensitivity of RIPA. The methods used in selecting patients led to the difference in the frequency (around 60%, unlike the majority that has 100%). It can also be due to some genotypes being more common and more picked up than others.	Many mutations for type 2B VWD are known, but not all of them. In fact, type 2B reflects a gain of function mutation so there would be less mutations that can create this gain of function unlike loss of function mutation in other subtypes (e.g. type 2N VWD) leading to the certainty about genetic testing for type 2B to be higher.

Test result	Number of results per 1000 patients tested (95% CI)						№ of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence 1%		Prevalence 50%		Prevalence 0%			
	Genetic testing	RIPA	Genetic testing	RIPA	Genetic testing	RIPA		
True positives patients with VWD	10 (10 to 10)	10 (6 to 10)	500 (500 to 500)	495 (300 to 500)	0 (0 to 0)	0 (0 to 0)	296 (9)	⨁⨁◯◯ LOW[a]

type 2B	0 fewer TP in Genetic testing		5 more TP in Genetic testing		0 fewer TP in Genetic testing			
False negatives patients incorrectly classified as not having VWD type 2B	0 (0 to 0)	0 (0 to 4)	0 (0 to 0)	5 (0 to 200)	0 (0 to 0)	0 (0 to 0)		
	0 fewer FN in Genetic testing		5 fewer FN in Genetic testing		0 fewer FN in Genetic testing			
	990 fewer FP in Genetic testing		500 fewer FP in Genetic testing		1000 fewer FP in Genetic testing			

a. Serious study population bias because of Case-Control design, and serious reference standard and/or index test bias in 9 studies

Refer to the Appendix at the end of the document.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2B, and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2B, and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2B, and not suffer the side effects of treatment, but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2B, but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2B, but they will be labeled as having VWD type 2B and receive unnecessary treatment. They do not	RIPA: get the results fast, and picks up platelet type VWD Genetics: chance of getting a more definitive answer, counseling

	benefit from the treatment for type 2B. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. Refer to the Appendix at the end of the document	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**True Positive:** These are patients who have VWD type 2B, and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2B, and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2B, and not suffer the side effects of treatment, but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2B, but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2B, but they will be labeled as having VWD type 2B and receive unnecessary treatment. They do not benefit from the treatment for type 2B. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. Refer to the Appendix at the end of the document	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document	
Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Test's effects are not applicable since the intervention consists of a blood test that has no important direct benefits, adverse effects or burden.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		The cut off between types 1 and 2 is mostly for classification purposes. It is not a critical factor when deciding on treatment. Desmopressin is more likely not to work for type 2 A and 2 M, and is relatively contraindicated for type 2 B. However, if the choice of treatment is not Desmopressin, the labeling will not have an effect
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High	Refer to the Appendix at the end of the document	

○ No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		Some individuals may be concerned regarding the impact of genetic testing on the determination of parentage (if family testing performed), along with normal privacy issues around genetic testing, as patients may have fears of what the sample may later be used to test for. Patients want to know that their genetic information is secure and anonymized. It is usually more complex to understand genetic testing. Anxiety might emerge for patients who have a mutation and information availability can impact other generations, who do not get consented in the process of diagnostic genetic testing. Patients want a test that is the most reliable. One concern is whether genetic testing will affect future ability to obtain health insurance (pre-existing condition). On the other hand, some patients find it very rewarding to know if they have a VWF mutation, especially when taking part in a study that would be published and help others. Regarding RIPA, the test must be done on a fresh sample, so the patient has to go to the lab performing the test since the sample can't be shipped. Time and need to travel to a specialized laboratory is a patient concern in some instances, as opposed to genetic testing where the sample can be sent out. Also, testing may require the patient to reattend the clinic

		more than once. Patients are very familiar with having blood drawn for lab testing for any reason. Well-trained phlebotomists at blood disorder treatment centers are efficient and have a good technique which means little or no bruising from blood draws for specialized hematology laboratory tests. Patients care to have assays that can be trusted that will lead to an accurate diagnosis and don't have to be repeated on multiple occasions.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Refer to the Appendix at the end of the document	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	* Genetic testing cost depends on how many exons have to be sequenced, and the sequencing is usually targeted to specific exons. There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates.	

		Genetic testing	RIPA
USA	$	350-2000	300-500
Australia	$	500	500
Europe	€	1000	100

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Taylor, 2015 used for genetic diagnosis.	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Genetic testing is not always covered by insurance, most insurance companies require prior authorization for genetic testing in the US, and decisions are made by insurance companies on a case-by-case basis. In many instances, research studies offer free genetic testing. RIPA are covered by insurance but may have a very high deductible. In New Zealand, all residents get blood tests for free. This is also applicable in the UK since there is no practical restriction on requesting these tests. RIPA and genetic testing is covered in Canada. Patients with access problems and those without health insurance are disadvantaged. Genetic testing is becoming more accessible and gives the confirmatory diagnosis.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Generally, patients accept having genetic testing and prefer it over other assays if they believe it could impact their personal diagnosis and/or management by providing definite answers. However, some patients believe that genetic testing is not necessary to make the diagnosis. It will not change management and is costly; also it is difficult to perform and may not always reveal a mutation/known mutation. Rarely the testing is turned down because of concern over privacy and if there is a genetic counselor available to discuss the test with them. Appropriate counseling and education are required, in addition to confirmation of results privacy.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Although genetic testing is not available in all hospitals, most patients have access to it as it can be sent out to reference labs. However, the process of genetic testing may take much longer, so patients will have to wait longer for results. So patient access to the hospital may be a feasibility issue, considering rural and remote patients and repeated visits required to diagnose, which is important when testing is needed to guide treatment for active bleed. To note, more data on genotype-phenotype correlation is needed. Relying on genetic testing alone is not safe - it may reveal a variant whose significance is completely unknown - then functional testing would be needed anyway in such a case.

		RIPA is not available in all hospitals since a fresh sample and platelet aggregation studies are needed to perform the test, which is considered to be difficult. It is usually available in research-active departments and specialized laboratories but limited availability otherwise. When available, the test is performed at specific times and days only, which creates feasibility issues around this test.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	**Probably yes**	Yes		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	**Accurate**	Very accurate		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	**Low**	Moderate	High			No included studies
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF EFFECTS	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important**	Possibly	Probably no	No important			

	JUDGEMENT						
	uncertainty or variability	important uncertainty or variability	important uncertainty or variability	uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

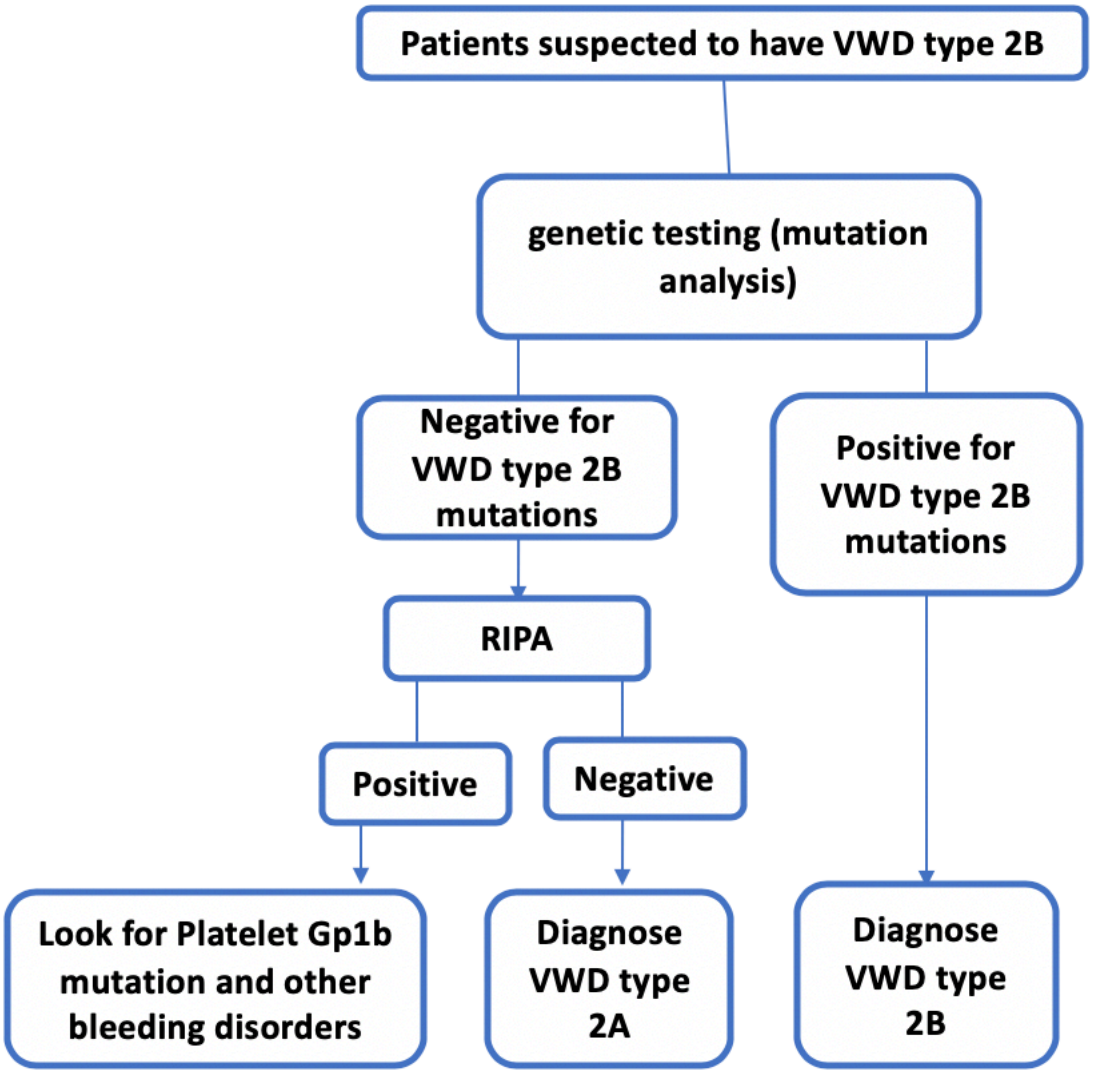
CONCLUSIONS

Recommendation

The panel suggests targeted genetic testing, when available, over RIPA (ristocetin induced platelet agglutination) to diagnose Type 2B VWD in patients suspected of Type 2A or 2B in need of additional testing. (Please see Diagnostic algorithm xxx)
(Conditional recommendation based on low certainty in the evidence)

Remark:

- Confirmatory testing with the other assay (or additional assays) is commonly performed.



Justification

The guideline panel determined that there is low certainty in the evidence for a net health benefit from using genetic testing over RIPA in patients suspected of VWD type 2A, 2B in need for additional testing. Other EtD criteria were generally in favor of using genetic testing so that the desirable consequences were greater than the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Diagnostic test accuracy for RIPA

APPENDIX

1. **Risk of bias:**

Author	Risk of bias population selection	Risk of bias index test	Risk of bias reference test	Flow and timing risk of bias

Woods, 2017	High	Low	Low	Low
Borras, 2017	Low	Low	High	Low
Veyradier, 2016	High	Low	High	Low
Shen, 2016	Low	High	Low	Low
Batlle, 2016	Low	Low	High	Low
Laderas, 2015	Low	High	High	Low
Kaur, 2014	High	High	High	Low
Hamilton, 2011	High	High	Low	Low
Federici, 2009	High	Low	Low	Low
Caron, 2006	High	Low	Low	Low
Facey, 2000	High	Low	Low	Low
Casana, 1998	High	High	Low	Low
Wood, 1996	Low	Low	High	Low
Cooney, 1991	High	Low	High	Low

2. **Outcomes:**
   - *Identified mutations:*

Studies	**Mutations Identified**
Freitas, 2019	Arg1341Gln, Arg1308Cys and Pro1266Leu
Woods, 2017	p.Y1258C, p.P1266L, p.M1304V, p.R1306W, p.R1308C, p.S1310F, p.V1316M
Borras, 2017	p.Arg1306Trp, p.Arg1308Arg, p.Val1316Met, p.Pro1266Leu and p.Pro1266Gln, p.Arg1306Gln
Veyradier, 2016	M1304dup, R1306Q/P/W, R1308C, I1309V, S1310F/P, V1316M, P1337L, R1341L/Q/W, I1372S, L1360F/P, A1461V, P1266L/Q, H1268D/N/Q
Shen, 2016	p.Arg1306Trp, p.Val1316Met and p.Arg1308Cys
Batlle, 2016	p.Arg1308Cys, p.Arg1306Trp, p.Val1316Met, p.Pro1266Leu, p.Arg1306Gln, p.Pro1266Gln
Laderas, 2015	p.R1306Q, p.R1306W, p.R1308C, p.R1315H and p.R1341Q
Kaur, 2014	Arg1341Gln, His1268Asn, Val1316Met, Arg1306Trp
Federici, 2009	P1266Q/L, H1268D, R1306W, R1308C/L, I1309V, V1316M, P1337L, R1341Q/W
Caron, 2006	H1268D, R1306W, R1306Q, R1306L, R1308C, V1316M, R1341Q and A1461V

Facey, 2000	Arg543Trp, Arg545Cys, Arg543Leu
Casana, 1998	R1308C, V1316M, P1337L, R1306W, R1341W
Wood, 1996	Arg543Trp, Val553Met, Ser547Phe, Arg578Gln
Cooney, 1991	Arg543Trp, Arg545Cys, Val553Met, and Arg578Gln

- *Phenotype genotype correlations:* The correlation between genotype and phenotype was assessed by experts from central laboratories who contrasted the results of the phenotypic test panel and the genetic analysis on the basis of the effect and localization of mutations and previous descriptions in the literature and/or databases.

Author, year	RIPA	Genotype	Frequency/Sensitivity
Borras, 2017	12	35	34%
Veyradier, 2016	112	112	100%
Laderas, 2015	3	5	60%
Federici, 2009	67	67	100%
Caron, 2006	31	31	100%
Facey, 2000	13	13	100%
Wood, 1996	7	7	100%

Genetic testing		RIPA	
Sensitivity	1.00 (95% CI: 1.00 to 1.00)	Sensitivity	0.99 (95% CI: 0.60 to 1.00)

Prevalences	1%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested				Test accuracy CoE
								pre-test probability of 1% [b]		pre-test probability of 50% [c]		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Genetic testing	RIPA	Genetic testing	RIPA	
True positives (patients with VWD type 2B)	9 studies 296 patients	cohort & case-control type studies	very serious [a]	not serious	not serious	not serious	none	10 (10 to 10)	10 (6 to 10)	500 (500 to 500)	495 (300 to 500)	⨁⨁◯◯ LOW
								0 fewer TP in Genetic testing		**5 more TP in Genetic testing**		
False negatives (patients incorrectly classified as not having VWD type 2B)								0 (0 to 0)	0 (0 to 4)	0 (0 to 0)	5 (0 to 200)	
								0 fewer FN in Genetic testing		**5 fewer FN in Genetic testing**		

Explanations

a. Serious study population bias because of Case-Control design, and serious reference standard and/or index test bias in 9 studies
b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).
c. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD type 2N.

Studies	Correlation
Woods, 2017	p.P1266L, 100% at 0.4 mg/ml p.M1304V, 66.6% at 0.5 and 33.4% at 0.4 p.R1306W, 20% at 0.6, 0.5, 0.4 and 40% at 0.3 p.R1308C, 25% at 0.7, 50% at 0.6, 12.5% at 0.4, 12.5% at 0.2 p.S1310F, 33.3% at 0.7 and 66.6% at 0.4 p.V1316M, 10% at 0.7, 0.6, 0.3, and 50% at 0.5, and 20% at 0.2 p.Y1258C, 100% at 0.3
Borras, 2017	- 35 patients were diagnosed as having type 2B VWD by molecular diagnosis. - A good phenotype-genotype correlation could be established **for all patients**, as most showed a loss of high- molecular-weight multimers and discordance between VWF:Ag and VWF:RCo levels (mean ratio=0.51; range 0.19-1.1) and a classical type 2B mutation.
Veyradier, 2016	100% correlation for 112 (17%) that exhibited type 2B VWD including 95 patients with a ‘‘classical’’ type 2B and 17 patients with a type 2B ‘‘New York’’
Batlle, 2016	- 35 patients were diagnosed as having type 2B VWD by molecular diagnosis. - A good phenotype-genotype correlation could be established for all patients, as most showed a loss of high- molecular-weight multimers and discordance between VWF:Ag and VWF:RCo levels (mean ratio=0.51; range 0.19-1.1) and a classical type 2B mutation.
Laderas, 2015	RIPA was positive in 3 of 5 mutations identified p.R1306Q, p.R1306W, and p.R1308C
Hamilton, 2011	48/110 had A1 domain mutations consistent with type 2B VWD. Seventeen cases carried platelet GP1BA mutations consistent with PT-VWD. In both the Australian and UK cases, apart from normal family members, there has not been any case where the phenotypic diagnosis has not matched the genotype finding, and ultimately making either a correct type 2B VWD, or its alternative PT-VWD, diagnosis possible. In Brazil, RIPA was performed in 14/18 cases, showing an enhanced response in 12, yet genetic analysis identified 2B VWD mutations in only three cases. In Canada, Apart from two normal family members, 9/40 were mutation negative for both VWF and GP1BA and only two cases showed GP1BA mutations. In the three cases from Switzerland, the 2B VWD phenotype matched the genetic analysis identifying known 2B VWD mutations. In Sweden, one case had a VWF mutation R1308P coinciding with 2B VWD and enhanced RIPA, but both parents of this index cases were completely normal, both phenotypically and genotypically with respect to the VWF gene.
Federici, 2009	All mutations were captured at a mean RIPA concentration of 0.6 (0.3-0.8)

Caron, 2006	All 31 cases displayed a positive RIPA at 0.5 mg/ml ristocetin concentration.
Facey, 2000	In all cases, RIPA occurred at concentrations of 0.5 mg/ml of ristocetin, while in one individual it occurred at 0.25 mg/ml of ristocetin. The RIPA results demonstrated increased platelet sensitivity to reduced levels of ristocetin, a finding consistent with type 2B VWD.
Wood, 1996	RIPA was increased in all 7 patients studied, but the concentration is not indicated in the study.
Cooney, 1991	All mutations were captured were captured as patients had enhanced RIPA at a low concentration of ristocetin (0.2-0.6mg/ml)

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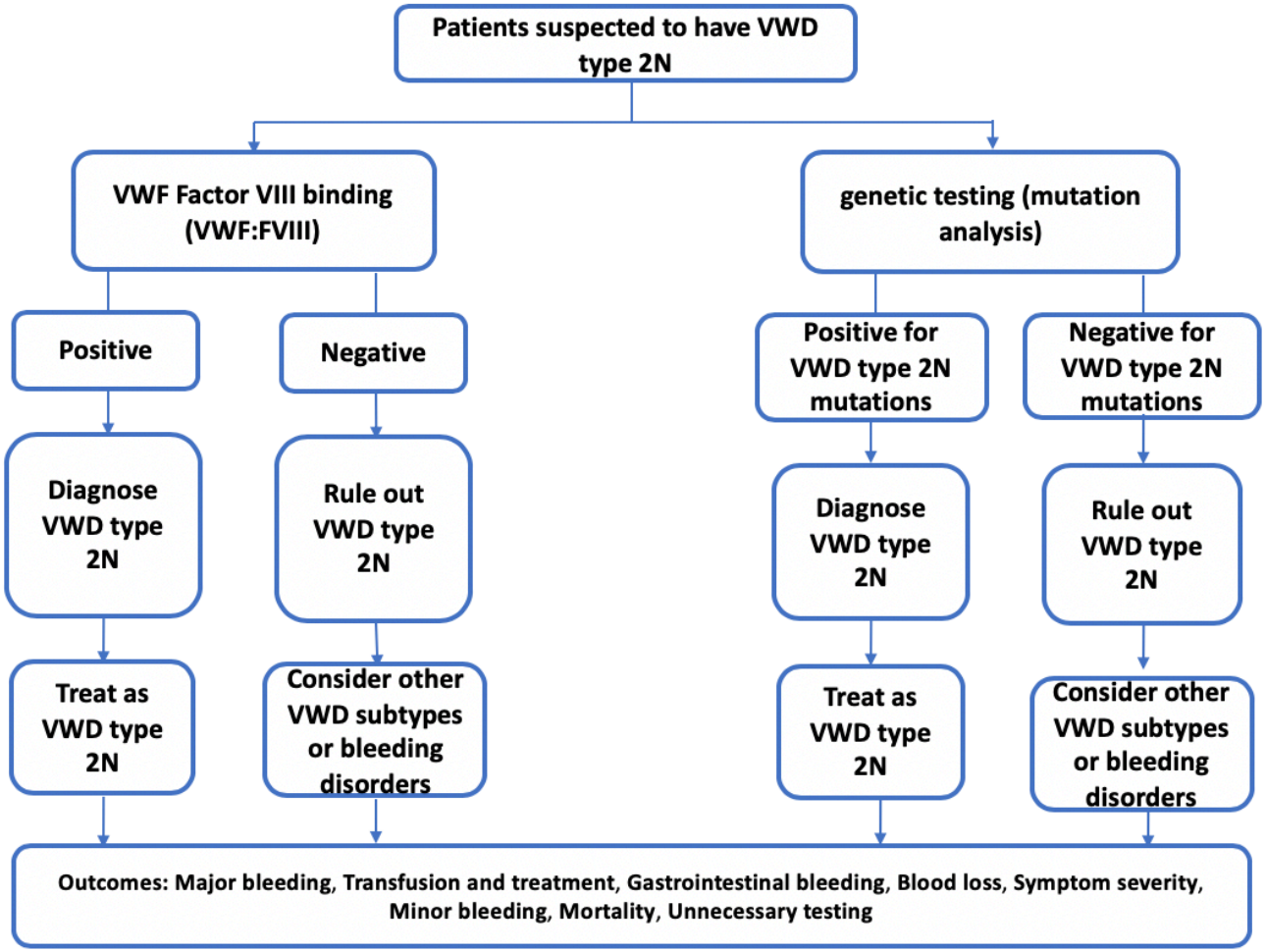
Question 10

Should genetic testing vs. FVIII:VWF binding be used to diagnose VWD type 2N in patients suspected of VWD type 2N?	
POPULATION:	Patients suspected of VWD type 2N
INTERVENTION:	Genetic testing
COMPARISON:	FVIII:VWF binding
PURPOSE OF THE TEST:	Identify VWD type 2N patients
ROLE OF THE TEST:	Identify VWD type 2N patients
LINKED TREATMENTS:	Tranaxemic acid, factor replacement
ANTICIPATED OUTCOMES:	VWF:FVIII – False positive, VWF:FVIII– False negative, VWF:FVIII – True positive, VWF:FVIII – True negative Major bleeding, transfusion and treatment, blood loss, gastrointestinal bleeding, symptom severity, minor bleeding, mortality.
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – population perspective
BACKGROUND:	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). The ratio of VWF:RCo/VWF:Ag is used to distinguish type 2 from other VWD types. More tests like multimer analysis, RIPA, genetic testing and VWF:FVIII are used to characterize the subtypes of the disease. Type 2N von Willebrand disease is a rare subtype of VWD in which a mutation (mostly in exons 18-20) of the VWF gene leads to impaired binding of the VWF molecule to FVIII, and consequent shortened half-life of FVIII. Routine laboratory assays will show reduced FVIII levels, but normal VWF, mimicking a diagnosis of haemophilia A. Differences in the clinical approach to management of patients with type 2N VWD and Haemophilia A, together with the implications for genetic counselling for this autosomal defect, reinforce the need to differentiate these disorders with reliable FVIII binding assays (Jennings, 2015). Sometimes, different workers ascribe the same mutation to differing types of VWD, and different types of VWD will seemingly arise from mutations in close proximity on the VWF gene. Genetic testing for VWD is not fool-proof, is likely to be very costly, and has not as yet been shown to be cost-effective in the diagnostic setting. VWD can arise from genetic events unrelated to the VWF gene, and the expression of VWF and the clinical severity in individual patients can be influenced by several epigenetic events. Most of these additional complexities currently remain unknown (Favaloro, 2008).
SUBGROUPS:	

CONFLICT OF INTERESTS:	ASH conflict of interest declaration and management policies were applied, and the following panel members were voting panel members (determining the direction and strength of the recommendation): Sandra Haberichter, Jeroen Eikenboom, Barbara Konkle, Robert Sidonio Jr, Simon McRae, Robert Montgomery, James O'Donnell, Claire McLintock, Barbara Ameer, Nicolas Giraud, Nikole Scappe, Vicki Jacobs-Pratt, Paula James, Nathan Connell. No panel members recused as a result of risk of conflicts of interest.



ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Von Willebrand disease (VWD) is the most common inherited bleeding disorder known in humans: while estimated to affect between 0.1 and 1% of the general population, many are never diagnosed. VWD diagnosis and classification require numerous laboratory tests. (Pathare, 2018). Type 2 VWD accounts for 25% of cases and results from the expression of a functionally abnormal VWF molecule (Lavin 2017). Diagnosis and classification of VWD require correlation between clinical findings and laboratory results. Recommended initial laboratory tests include measurements of plasma VWF antigen (VWF:Ag), VWF-platelet GP Ib binding activity (e.g. VWF:RCo) and FVIII:C (Chenn, 2011). Type 2N von Willebrand disease is a rare subtype of VWD in which a mutation (mostly in exons 18-20) of the VWF gene leads to impaired binding of the VWF molecule to FVIII, and consequent shortened half-life of FVIII. Routine laboratory assays will show reduced FVIII levels, but normal VWF (or low), potentially mimicking a diagnosis of hemophilia A. Differences in the clinical approach to management of patients with type 2N VWD and Haemophilia A, together with the implications for genetic counseling for this autosomal defect, reinforce the need to differentiate these disorders with reliable FVIII binding assays (Jennings, 2015).	This question was judged to be a priority among many candidate questions to address in these guidelines.
Test accuracy How accurate is the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ● Don't know	There is not test accuracy results due to the lack of agreed-on reference standard for type 2N VWD. In all studies, homozygous type 2N VWD patients had binding ratios <0.12, heterozygous carriers had intermediate binding ratios of 0.44–0.61, and healthy control subjects had ratios of 0.73–1.42. Refer to the Appendix at the end of the document.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**True Positive:** These are patients who have VWD type 2N, and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2N, and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2N, and not suffer the side effects of treatment, but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2N, but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2N, but they will be labeled as having VWD type 2N and receive unnecessary treatment. They do not benefit from the treatment for type 2N. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects. Refer to the Appendix at the end of the document	Counseling. Picking up unknown mutations.
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	**True Positive:** These are patients who have VWD type 2N, and who received preventive and appropriate treatment. They benefit from decreasing the risk of bleeding with treatment and they suffer the side effects of treatment. **True Negative:** These are patients who did not have VWD type 2N, and who were correctly identified as not having the disease. They will appropriately not receive treatment for VWD type 2N, and not suffer the side effects of treatment, but may benefit from treatment for other bleeding disorders. **False Negative:** These are patients who have VWD type 2N, but the diagnosis was missed and will be sent home without appropriate treatment. They face the risks of prolonged and heavy bleeding due to not receiving treatment. They will be considered for other bleeding disorders. **False Positive:** These are patients who did not have VWD type 2N, but they will be labeled as having VWD type 2N and receive unnecessary treatment. They do not benefit from the treatment for type 2N. They may benefit from the treatment if they have other bleeding disorders, but they suffer side effects.	Missing the diagnosis in 2N. Serious implications for family counseling Serious implications on treatment; wrong ineffective treatment so the patients will bleed.

	Refer to the Appendix at the end of the document	

Certainty of the evidence of test accuracy What is the overall certainty of the evidence of test accuracy?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	Refer to the Appendix at the end of the document	The reference standard was considered to be mutation analysis, however, sometimes the mutation captured was never defined as VWD type 2N, in that case the phenotype that is defined by binding deficiency needs to be done to identify type 2N. Some patients would have antibodies to VWF that prevents its binding to FVIII and those patients would have a positive VWF:FVIII but no VWD type 2N.

Certainty of the evidence of test's effects What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		Genetic testing will help counseling patients and will help pick up other mutations. Given this condition is an autosomal recessive disease, counseling would be different than other subtypes. Doing only VWF:FVIII will indicate the presence of the type 2N phenotype, in that case the patient might be homozygous (meaning their child can only be heterozygous for type 2N), but the patient can also be heterozygous with the second allele indicating VWD type 1 (the child can have VWD type 1 in that case or be heterozygous for type 2N). Having said that, VWF:FVIII is not enough for counseling.

Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the test results?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	While a clear-cut diagnosis is easy in severe von Willebrand factor reductions, the advantage of pursuing a definite diagnosis in mild or dubious cases should be weighed against the risk of over-medicalization. Identifying patients with VWD type 2 will help to give a treatment that will correct the dual defect of hemostasis caused by the abnormal/reduced von Willebrand factor and the concomitant deficiency of factor VIII. (Castaman, 2013).	
Certainty of the evidence of test result/management How certain is the link between test results and management decisions?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		If the choice of treatment is not desmopressin, the labeling will not have an effect. In fact, there is a limitation of using desmopressin in VWD type 2N because the levels of FVIII would drop quickly after administering the drug because the circulating VWF would not be carrying FVIII appropriately, that is why factor and tranexamic acid are more used in this particular group of patients.
Certainty of effects What is the overall certainty of the evidence of effects of the test?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Refer to the Appendix at the end of the document	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		Some individuals may be concerned regarding the impact of genetic testing on the determination of parentage (if family testing performed), along with normal privacy issues around genetic testing, as patients may have fears of what the sample may later be used to test for. Patients want to know that their genetic information is secure and anonymized. It is usually more complex to understand genetic testing. Anxiety might emerge for patients who have a mutation and information availability can impact other generations, who do not get consented in the process of diagnostic genetic testing. Patients want a test that is the most reliable. One concern is whether genetic testing will affect future ability to obtain health insurance (pre-existing condition) or life insurance if they have no bleeding disorder but had a genetic mutation identified. On the other hand, some patients find it very rewarding to know if they have a VWF mutation, especially when taking part in a study that would be published and help others. Patients are very familiar with having blood drawn for lab testing for any reason. Well-trained phlebotomists at blood disorder treatment centers are efficient and have a good technique which means little or no bruising from blood draws for specialized hematology laboratory tests. Patients care to have assays that can be trusted that will lead to an accurate diagnosis and don't have to be repeated on multiple occasions. So, patient concerns or preferences that are specific to VWF:FVIII binding are not different than other blood tests.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

<table>
<tr><td>○ Favors the comparison
○ Probably favors the comparison
● Does not favor either the intervention or the comparison
○ Probably favors the intervention
○ Favors the intervention
○ Varies
○ Don't know</td><td>Refer to the Appendix at the end of the document</td><td>The panel agreed that these tests can be complimentary: FVIII:VWF is a straightforward laboratory test, however genetic counseling is better when doing genetic testing as opposed to the phenotypic testing.</td></tr>
<tr><td colspan="3">Resources required
How large are the resource requirements (costs)?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
<tr><td>○ Large costs
● Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know</td><td>*Genetic testing cost depends on how many exons have to be sequenced, and the sequencing is usually targeted to specific exons.

<table><tr><td></td><td></td><td>Genetic testing</td><td>VWF:FVIII</td></tr><tr><td>USA</td><td>$</td><td>350-2000</td><td>150</td></tr><tr><td>Australia</td><td>$</td><td>500</td><td>240</td></tr><tr><td>Europe</td><td>€</td><td>1000</td><td>100</td></tr></table>
There is considerable variability in cost among different jurisdictions. Cost is also affected by different factors including insurance plans. The estimate provided are based on the clinical experts best estimates.</td><td></td></tr>
<tr><td colspan="3">Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?</td></tr>
<tr><td>JUDGEMENT</td><td>RESEARCH EVIDENCE</td><td>ADDITIONAL CONSIDERATIONS</td></tr>
</table>

○ Very low ○ Low ● Moderate ○ High ○ No included studies	Kaylor, 2015 used for genetic diagnosis.	
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced		Genetic testing is not always covered by insurance, most insurance companies require prior authorization for genetic testing in the US, and

○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		decisions are made by insurance companies on a case-by-case basis. In many instances, research studies offer free genetic testing. VWF:FVIII are covered by insurance but may have a very high deductible. In New Zealand, all residents get blood tests for free. This is also applicable in the UK since there is no practical restriction on requesting these tests. All assays are covered in Canada. Genetic testing is paid for in Australia. People with access problems and people with no health insurance are disadvantaged. Genetic testing is becoming more accessible and gives the confirmatory diagnosis.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Generally, patients accept having genetic testing and prefer it over other assays if they believe it could impact their personal diagnosis and/or management by providing definite answers. However, some patients believe that genetic testing is not necessary to make the diagnosis. It will not change management and is costly; also it is difficult to perform and may not always reveal a mutation/known mutation. Rarely the testing is turned down because of concern over privacy and if there is a genetic counselor available to discuss the test with them. Appropriate counseling and education are required, in addition to confirmation of results privacy.
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No	VWF:FVIII binding requires very trained staff with experience with the assay.	Although genetic testing and VWF:FVIII binding are

○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	(Jennings, 2015)	not available in all hospitals, but most patients have access to it as they are sent out tests. However the process of genetic testing may take much longer, so patients will have to wait longer for results. So patient access to the hospital may be a feasibility issue, considering rural and remote patients and repeated visits required to diagnose, which is important when testing is needed to guide treatment for active bleed. To note, more data on genotype-phenotype correlation is needed. Relying on genetic testing alone is not safe - it may reveal a variant whose significance is completely unknown - then functional testing would be needed anyway in such a case.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	**Don't know**
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	Low	Moderate	High			**No included studies**
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
CERTAINTY OF EFFECTS	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

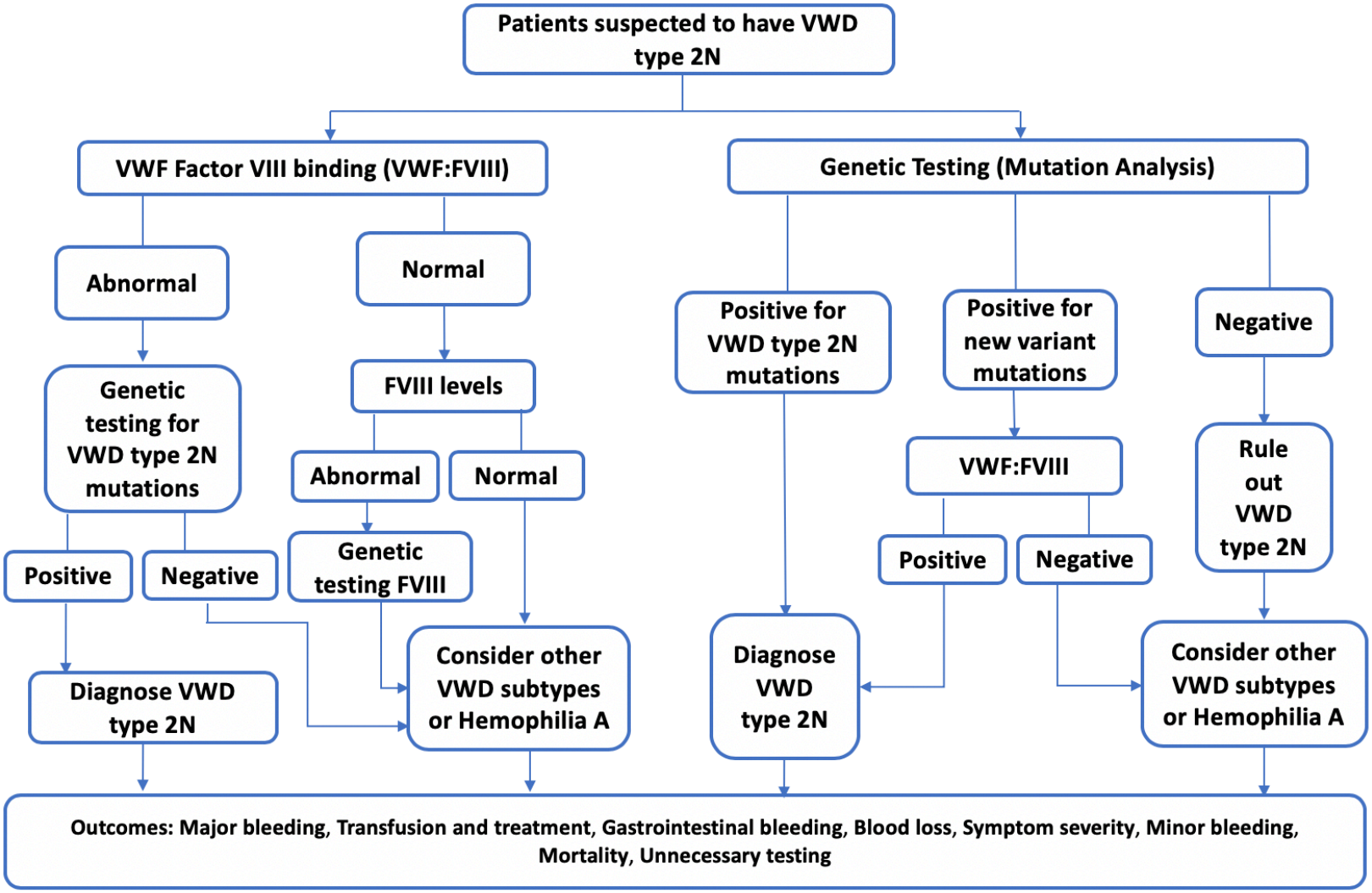
TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

The panel suggests using either VWF:FVIIIB (VWF FVIII binding assay) or targeted genetic testing, in patients with suspected Type 2N VWD in need of additional testing. (Please see Diagnostic algorithm xxx).
(Conditional recommendation based on low certainty in the evidence)



Justification

The guideline panel determined that there is low certainty in the evidence for either a health benefit or harm from using FVIII:VWF assay over genetic testing in patients with suspected type 2N VWD in need for additional testing for classification. The panel agreed that these tests can be complementary: FVIII:VWF is a straightforward laboratory test, however genetic counseling is better when doing genetic testing as opposed to the phenotypic testing. Other EtD criteria were generally not favor of using either assays for classification so that the desirable consequences were equal to the undesirable consequences.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Research around a reference standard for type 2N VWD.

APPENDIX

1. **Risk of bias:**

Author	Risk of bias population selection	Risk of bias index test	Risk of bias reference test	Flow and timing Rsk of bias
Batlle, 2006	High	Low	High	Low
Borras, 2017	High	Low	High	Low

Casonato, 2018	Low	Low	High	Low
Veyradier, 2016	High	High	Low	Low
Costa Pinto, 2014	High	High	Low	Low
Wang, 2013	Low	High	Low	Low
Hamoshire, 2013	High	High	Low	Low
Veyradier, 2011	High	Low	High	Low
Zhukov, 2009	High	Low	High	Low
Corrales, 2009	High	High	High	Low
Casanato, 2007	High	Low	High	Low
Taylor, 2002	Low	Low	High	Low
Rodgers, 2002	High	High	Low	Low
Caron, 2002	High	Low	Low	Low
Casonato, 1998	High	Low	High	Low
Bowen, 1998	Low	High	High	Low
Schneppenheim, 1996	Low	Low	High	Low

2. Outcomes:

- *Mutation detection:*

Article	**Mutations**
Borras, 2017	p.Arg816Trp, p.Arg854Gln
Batlle, 2016	p.Arg816Trp and p.Arg854Gln
Casonato, 2018	p.R854Q, p.P812Rfs*31, p.G2352_2360del or the new p.C524Y, p.R760C
Veyradier, 2016	R768Q, C788Y, T791M, L809P, R816W, R854Q, G887R, C1060R
Costa Pinto, 2014	R816W, R854Q
Wang, 2013	P812L, R854Q, R924Q,
Hamoshire, 2013	(p.C788R, p.C1225G)
Veyradier, 2011	Arg854Gln, Arg816Trp, Cys788Tyr, Cys1070Arg, Thr791Met, Leu884PhefsX19, Cys1060Arg
Zhukov, 2009	R854Q, H817Q, H817Q/R1342C
Corrales, 2009	R816W
Casanato, 2007	R854Q, R760C
Taylor, 2002	R53W, R91Q
Rodgers, 2002	R854Q
Caron, 2002	R816W, R854Q, C858F, C804F,
Casonato, 1998	R53W, R91Q
Bowen, 1998	R854Q, R952Q, R816W, H817Q, C858F

Schneppenheim, 1996	E24K, T28M, R91Q

- *Correlation results:*

Author, year	**Results: In all studies homozygous VWD2N patients had binding ratios <0.12, heterozygous carriers had intermediate binding ratios of 0.44–0.61, and healthy control subjects had ratios of 0.73–1.42**
Batlle, 2016 Borras, 2017	9 patients were type 2N VWD and 11 patients were carriers of type 2N VWD. Regarding the 2N VWD patients, five were homozygous for a 2N mutation, and four were compound heterozygous in trans for p.Gln895His and a nonsense or missense mutation.
Casonato, 2018	Genetic analysis demonstrated that all the patients with VWF:FVIIIB ratios below 0.3 were carrying the p.R854Q mutation at homozygous or compound heterozygous level with a quantitative VWF defect. There were also 51 patients with a VWF:FVIIIB ratio below 0.74, but above 0.3. 34/51 (67%) were heterozygous for the p.R854Q mutation, and one was carrying the p.R760C mutation at heterozygous level; two of the 34 patients were also haemophilia A carriers, and one suffered from haemophilia A. The other 16 patients revealed no mutations in the main FVIII binding domain of VWF.
Veyradier, 2016	100% correlation for the 81 type 2N VWD patients. in type 2N, 22 truncating mutations leading to a silent allele were also found (type 2N/3 patients) including one-third also found in our type 3 VWD patients
Costa Pinto, 2014	All type 2N VWD patients (n = 5) showed normal VWF:RCo/VWF:Ag ratios and VWF:FVIIIB <0.8.
Hamoshire, 2013	When compared against normal plasma (100%), patient plasma had reduced FVIII binding capacity (VWF:FVIIIB) similar to that observed in plasma from a known type 2N patient homozygous for p.T791M (p.C788R homozygote 0% (heterozygote 49%) vs. 1.3%; p.C1225G homozygote 7.1% vs. 7.1%)
Veyradier, 2011	The mean FVIII:C/VWF:Ag ratio is 0.26 which is mainly representative of the homozygous Arg854Gln subgroup (mean FVIII:C/ VWF:Ag ratio at 0.27). The values range between 0.04 and 0.47. 9 heterozygous carriers for a 2N mutation includes 8 subjects with a Arg854Gln mutation and 1 subject with a Cys1060Arg mutation. In all of them, the FVIII:C/VWF:Ag ratio is normal, higher than 0.6. All patients with type 2N VWD exhibit a severely decreased VWF:FVIIIB with values lower than 15%, and No control subject (healthy subjects, haemophilia A, haemophilia carriers or VWD patients other than type 2N) exhibit a markedly decreased VWF:FVIIIB.

Zhukov, 2009	All samples from subjects with homozygous or heterozygous mutation showed abnormal VWF- FVIII binding, and three distinct ratio ranges were observed: homozygous VWD2N patients had binding ratios <0.12, heterozygous carriers had intermediate binding ratios of 0.44–0.61, and healthy control subjects had ratios of 0.73–1.42 Special precautions must be taken when reporting patient results in the 0.65–0.72 range, which is probably the assay's true equivocal zone; rare outliers of both normal and heterozygous individuals occasionally fall in this range, as do results from compromised samples.
Casanato, 2007	all the type 2N carriers identified in the present study had a reduced VWF:FVIIIB to VWF:Ag ratio, regardless of the FVIII/VWF:Ag ratio or VWF:FVIIIB values. The mean VWF:FVIIIB ratio was 0.56±0.10 vs nor- mal >0.75 and no relationship was demonstra- ble between VWF:FVIIIB and FVIII/VWF:Ag.
Taylor, 2002	The homozygous R53W sample exhibited minimal FVIII binding activity, whilst the heterozygous R91Qr gave a result of 0.43 compared with the PNP reference plasma value of 1.0
Rodgers, 2002	patients with very low factor VIII binding were clearly identified, and all control subjects with hemophilia were clearly identified as having normal factor VIII binding.
Caron, 2002	A total of 15 unrelated patients were diagnosed as being affected with type 2N VWD because their VWF:FVIIIB was found to be markedly decreased (9.65 ± 2.75%, n = 14) or nul (n = 1). 5 patients exhibited intermediate FVIII binding capacity (VWF:FVIIIB = 57.2 ± 6.8%), similar but slightly greater (P = 0.015) than that obtained with the NP/2N mixture.
Schneppenheim, 1996	All 5 patients and their families (total of 68) with VWD type 2N homogenous and heterogenous mutations had a VWF:FVIII level of <60, (if homogenous <8) except for 1 patient with WT|R91Q genotype had a level of 63.

Genetic testing		FVIII:VWF binding	
Sensitivity	1.00 (95% CI: 1.00 to 1.00)	Sensitivity	1.00 (95% CI: 1.00 to 1.00)

Prevalences	1%	50%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested				Test accuracy CoE
								pre-test probability of 1%[b]		pre-test probability of 50%[c]		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Genetic testing be used	FVIII:VWF binding	Genetic testing be used	FVIII:VWF binding	
True positives (patients with VWD type 2N)	10 studies 178 patients	cohort & case-control type	very serious [a]	not serious	not serious	not serious	none	10 (10 to 10)	10 (10 to 10)	500 (500 to 500)	500 (500 to 500)	⊕⊕◯◯ LOW
								0 fewer TP in Genetic testing be		**0 fewer TP in Genetic testing be**		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested				Test accuracy CoE
								pre-test probability of 1%[b]		pre-test probability of 50%[c]		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Genetic testing be used	FVIII:VWF binding	Genetic testing be used	FVIII:VWF binding	
		studies						**used**		**used**		
False negatives (patients incorrectly classified as not having VWD type 2N)								0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
								0 fewer FN in Genetic testing be used		**0 fewer FN in Genetic testing be used**		

Explanations

a. Serious patient selection bias due to case-control study design and serious bias with the reference standard and/or index test in all studies
b. Typically seen in patients investigated for VWD because of a personal history of abnormal laboratory test (e.g., increased PTT).
c. Typically seen in patients investigated for VWD as a first degree relative for a patient with VWD type 2N.

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