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ORIGINAL ARTICLE

Von Willebrand disease

An international survey to inform priorities for new guidelines on von Willebrand disease

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Abstract

Introduction: von Willebrand disease (VWD) is an inherited bleeding disorder caused by a quantitative or qualitative dysfunction of von Willebrand factor. Clinicians, patients and other stakeholders have many questions about the diagnosis and management of the disease.

Aim: To identify topics of highest importance to stakeholders that could be addressed by guidelines to be developed by the American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF) and the World Federation of Hemophilia (WFH).

Methods: A survey to determine and prioritize topics to be addressed in the collaborative development of guidelines for VWD was distributed to international stakeholders including patients, caregivers and healthcare providers (HCPs). Representatives of the four organizations coordinated the distribution strategy. The survey focused on both diagnosis and management of VWD, soliciting 7-point Likert-scale responses and open-ended comments, in English, French and Spanish. We conducted descriptive analysis with comparison of results by stakeholder type, gender and countries' income classification for the rating questions and qualitative conventional content data analysis for the open-ended responses.

Results: A total of 601 participants responded to the survey (49% patients/caregivers and 51% healthcare providers). The highest priority topics identified were diagnostic criteria/classification, bleeding assessment tools and treatment options for women and surgical patients. In contrast, screening for anaemia and differentiating plasma-derived therapy versus recombinant therapies received lower ratings.

Conclusion: This survey highlighted areas of importance to a diverse representation of stakeholders in the diagnosis and management of VWD, providing a framework for future guideline development and implementation.

KEYWORDS

bleeding disorders, guidelines, multidisciplinary, patient engagement, stakeholders, survey, von Willebrand disease

The authors presented in 'For the VWD working group' are placed in Appendix A.

1 | INTRODUCTION

von Willebrand disease (VWD) is the most common inherited bleeding disorder, due to abnormalities of the haemostatic protein, von Willebrand factor (VWF).[1] VWF binds and stabilizes coagulation factor VIII (FVIII) in the circulation and plays a crucial role in platelet adhesion and aggregation.[2-5] Patients with VWD may experience excessive, mainly mucocutaneous bleeding including easy bruising, epistaxis, oral cavity bleeding, heavy menstrual bleeding, gastrointestinal bleeding and abnormal bleeding after dental work, childbirth and surgery. In the most severe cases, musculoskeletal bleeding may be seen. The bleeding symptoms vary in severity between patients, and the pattern of bleeding within an individual also can vary over time.[6] These bleeding symptoms have implications for daily living and are associated with a reduced quality of life in VWD patients.[7]

There is considerable variation in the published prevalence of VWD. The prevalence based on patients who present to tertiary care centres with clinical symptoms is reported to be 0.01%[8,9]; symptomatic VWD in primary care clinics is described to be at least 0.1%[8-10]; and VWD can affect up to 1% of the general population based on epidemiological studies.[11,12] This prevalence is even higher among women with chronic heavy menstrual bleeding, ranging from 11% to 16% in different reports.[13,14] There are three types of VWD: type 1 and 3 are partial and complete quantitative deficiencies of VWF, respectively, while type 2 is comprised of four qualitative variants (type 2A, 2B, 2M and 2N).[5,12,13] The subtype variations and the different clinical phenotypes contribute to the complexity of the diagnosis and management of VWD.[15]

Additionally, there is a limited awareness of VWD, even within the healthcare community, leading to further challenges for patients and healthcare providers (HCPs) including delays in diagnosis and uncertainty about optimal management.[16] In an effort to address these issues, The American Society of Hematology (ASH), the International Society on Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF) and the World Federation of Hemophilia (WFH) are collaborating with the University of Kansas Medical Center (KUMC) to develop clinical practice guidelines on the diagnosis and management of VWD. These guidelines will inform all stakeholders on essential issues where there is variation or uncertainty in clinical practice and will support decision-making in the context of patients' values and preferences.[17]

Medical organizations encourage patient and clinician engagement in clinical practice guideline development internationally, but research to inform mechanisms for active engagement is limited.[18,19] International medical societies and organizations recognize the importance of meticulous and thorough processes for guideline development to ensure the best available evidence is utilized with input from different stakeholders.[20] While this is true for all guidelines,

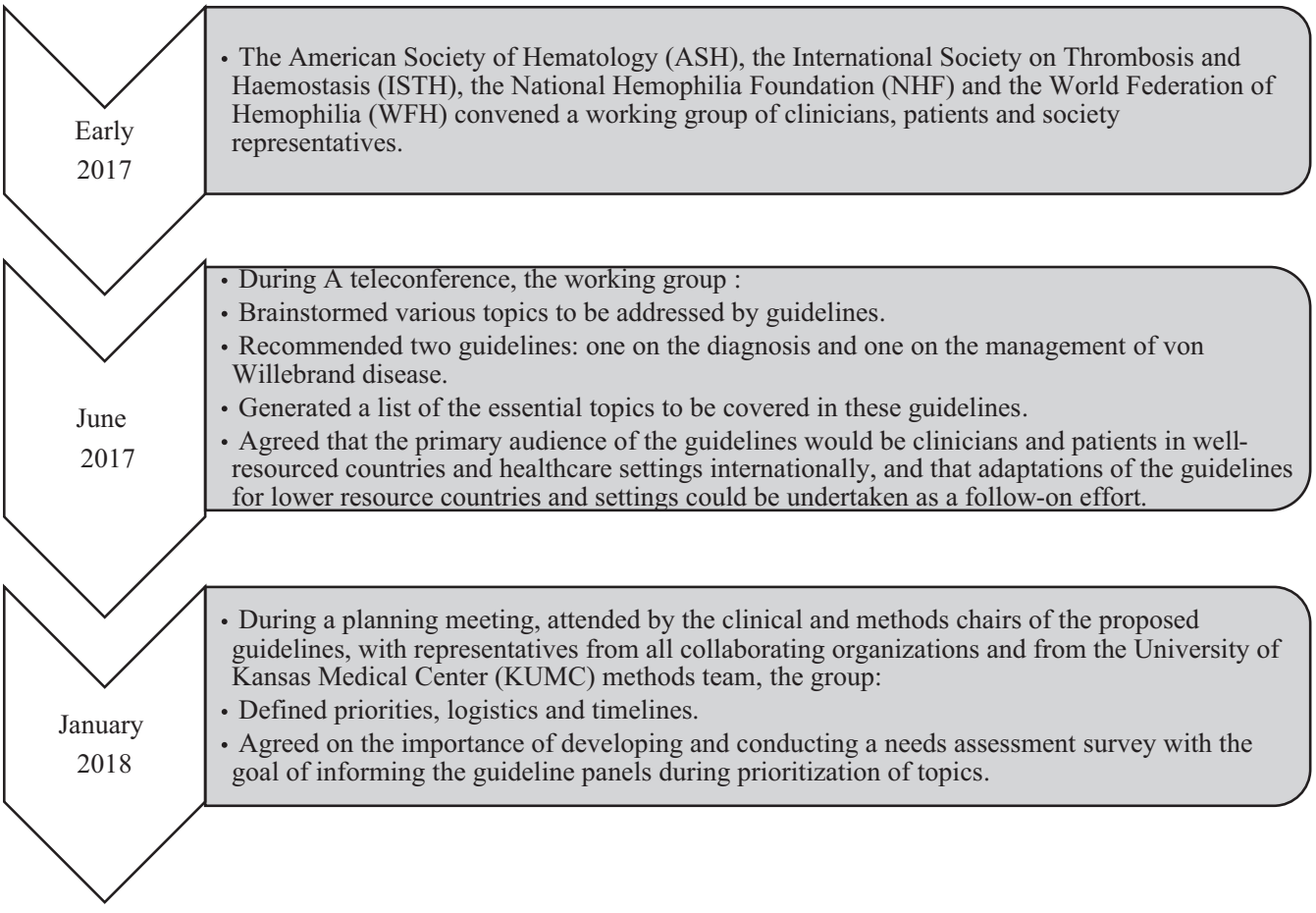


FIGURE 1 Identification of topics to be addressed in the survey

it is undoubtedly even more critical in uncommon and phenotypically variable diseases like VWD. Collaborating organizations agreed that there is a need to update and augment published VWD guidelines.[1,21] In this study, we identified and prioritized the main topics to be covered in a collaborative guideline development effort for the diagnosis and management of VWD.

2 | MATERIALS AND METHODS

2.1 | Survey development

The KUMC methods team developed a survey based on the topics identified by the working group (Figure 1). The survey underwent an iterative process of review and feedback from the guideline chairs, clinicians, patients and representatives from all collaborating organizations until no further important modifications were needed. The survey was pilot-tested by patient and clinician panel members before distribution. The SurveyMonkey platform[22] was used to conduct the survey.

The survey (Appendix S1) included two sections: a diagnosis section (with seven topics) and a management section (with eight topics) (see Table 1). We asked respondents to rate each of the topics using a 7-point Likert scale, in which the anchors were [1]—the topic is important but can be addressed at a later stage; and [7]—it is important to address this topic in the current guideline. The survey also included open-ended questions to collect comments (qualitative data) about the proposed topics, additional topics and the most important health-related outcomes for people with VWD. The survey was available in three languages: English, French and Spanish. The survey was developed in English and translated into French and Spanish by professional translators with experience translating VWD medical texts, and the translations were verified by VWD clinicians who are native speakers of French and Spanish, respectively. Professional translators translated comments provided by respondents in French and Spanish to English. A third party who is fluent in all three languages and experienced in bleeding disorders medical education verified these translations.

2.2 | Ethics statement

The University of Kansas Medical Center Institutional Review Board reviewed the study protocol and approved it. Participation in the survey was voluntary, and data collected did not include any patient or HCP identifiers. All respondents consented to participate before accessing the survey.

2.3 | Respondents and survey distribution

We used purposeful sampling and aimed to obtain as many responses as possible from a variety of stakeholders, including patients, caregivers, allied health professionals (eg nurses and care coordinators) and clinicians. The guideline chairs and representatives of the collaborating organizations coordinated the survey distribution to a broad range of international stakeholders. These stakeholders are the same as those targeted in the guidelines.

The survey was announced during large international meetings, including the WFH 2018 World Congress in Glasgow, Scotland in May 2018 and the ISTH Scientific and Standardization Committee meeting in Dublin, Ireland in July 2018. To elicit maximal participation, the investigators and collaborators used social media outreach and emails to collaborating organizations' members and stakeholders, in English, French and Spanish, with at least one email reminder sent to each organization recipients set. Moreover, we used a 'snowballing' sampling technique, by requesting survey respondents to further distribute the survey to others affected by or caring for people with VWD including reaching out to organizations representing important stakeholders like VWDConnect. The survey opened on 7 June 2018 and closed on 7 August 2018. To avoid response duplication, we limited each Internet Protocol (IP) address to a single entry.

TABLE 1 VWD topics in the survey

Topics	Diagnosis	Management
1	Bleeding assessment tools	Desmopressin trials
2	Diagnostic journey	Plasma-derived therapies vs. recombinant therapies
3	Diagnostic criteria/classification	Prophylaxis
4	Comparing phenotypic vs. genotypic diagnosis	Appropriate models of care delivery
5	Laboratory cut-offs (thresholds) for type 1 VWD	Management of bleeding or laboratory testing prior to invasive procedures when VWD diagnosis is uncertain
6	Standards for assessing a laboratory's test results and quality	Treatment options for patients with specific VWF levels
7	Screening for anaemia and iron deficiency	Treatment options for surgical patients
8		Treatment options for women and girls with VWD

2.4 | Statistical analyses

The primary analysis was based on the rating exercise with a descriptive analysis of the demographic characteristics of respondents. The secondary analysis compared means by stakeholders' type (patients/caregivers and HCPs), by gender and by countries' income classification (low/middle-income (LMI) and high-income (HI)). In all analyses, we grouped clinicians and allied health professionals as 'healthcare providers (HCPs)' and patients and caregivers as 'patients/caregivers'. In order to determine the geographical distribution of the responses, we extracted and analysed IP addresses and categorized them into countries that meet the definition of LMI versus HI classification, as defined by the World Health Organization (WHO).[23] SPSS V23 was used to perform the statistical analysis. We compared results between groups using the t test for equality of means and considered a *P*-value of <.05 to be statistically significant.

We performed an enhanced exploration of the range of concepts from the survey respondents using a qualitative descriptive approach.[24,25] Qualitative comments were subjected to conventional content data analysis via a data coding system corresponding to the data collection[26] and reviewed in their entirety. Using a combination of deductive and inductive coding processes, two investigators (MK and MA) coded all data independently and in duplicate, generating codes that captured key concepts.

3 | RESULTS

3.1 | Demographics

Six hundred and one participants responded to the survey. Table 2 summarizes the stakeholders' distribution by language. The survey reached 71 countries in six continents, with 18.3% of respondents from countries that meet the definition of LMI classification, and 81.7% from countries that meet the definition of HI classification (Figure 2). Of the 601 respondents, 49% self-identified as patients and caregivers (34% and 15% respectively), whereas 51% were HCPs. Males constituted 21% of the respondents while female respondents were 54%, and 25% elected not to indicate gender. Additionally, 59% of the respondents received or provided care at a comprehensive care centre (CCC), whereas 17% did not provide or receive care at a CCC, and 24% elected not to answer.

3.2 | Quantitative analysis

3.2.1 | Diagnosis of VWD

We observed statistically significant differences when we analysed responses by participant subtype, likely reflecting the specific challenges experienced by each group (Figure 3). In stratified analyses, we have not seen a significant difference between male and female patients/caregivers, except for 'screening for anaemia and iron deficiency', which was rated higher by female respondents but still had the lowest score overall (*P*-value = .04) (Figure S1). Similarly, there was no statistically significant difference between responses from countries classified as LMI vs. HI, for any topic (Figure S3).

3.2.2 | Management of VWD

We observed statistically significant differences between HCPs and patients/caregivers responses (Figure 4). When female and male patients/caregivers were compared, both rated 'treatment options for women with VWD' highest, whereas female patients/caregivers rated 'management of bleeding or laboratory testing prior to invasive procedures' higher (*P*-value = .00) (Figure S2). There was no statistically significant difference between responses from countries classified as LMI vs. HI, for any topic (Figure S4).

3.3 | Qualitative analysis

The respondents demonstrated a high level of interest and engagement with the survey which was revealed by the discrete comments, of which over 9500 were submitted and analysed. The comments showed additional topics of interest in the management and diagnosis of VWD, as well as important sub-populations, interventions and outcomes, and were summarized accordingly in Table 3. Additional analyses are presented in Appendix S2 and S3.

Of note, we considered all age groups by respondents, with a large number of comments referencing 'children' or 'parents'. In fact, respondents mentioned vulnerable populations (female, paediatric, geriatric and low-income setting) in almost every topic. In the diagnosis section, respondents were highly interested in accurate and specific diagnosis by limiting false-positive and false-negative results but there was no mention of the potential trade-off between different accuracy results. In the management section, respondents were mostly interested in quality of life subsequent to receiving different treatment modalities. One additional common theme that emerged was that of patients'/caregivers' concerns about the safety and side effects of desmopressin use.

4 | DISCUSSION

This study represents a large collaborative effort between the haematology organizations involved in the VWD guideline development project: ASH, ISTH, NHF and WFH. The investigators capitalized upon this collaboration to seek a deeper understanding of diverse stakeholders' views (patients, caregivers, clinicians and allied healthcare professionals) from around the world on the most important topics to be addressed in the development of clinical practice guidelines for the diagnosis and management of VWD. Prior guidelines did not incorporate such input from patients/caregivers and HCPs.

TABLE 2 Stakeholders distribution by language (%)

	Stakeholders (n)				
Language (n)	Patients (201)	Caregivers (85)	Clinicians (197)	Allied Health team (98)	Missing (20)
English (505)	149 (74%)	81 (95%)	172 (87%)	88 (90%)	15 (75%)
French (56)	42 (21%)	0 (0%)	10 (5%)	2 (2%)	2 (10%)
Spanish (40)	10 (5%)	4 (5%)	15 (8%)	8 (8%)	3 (15%)

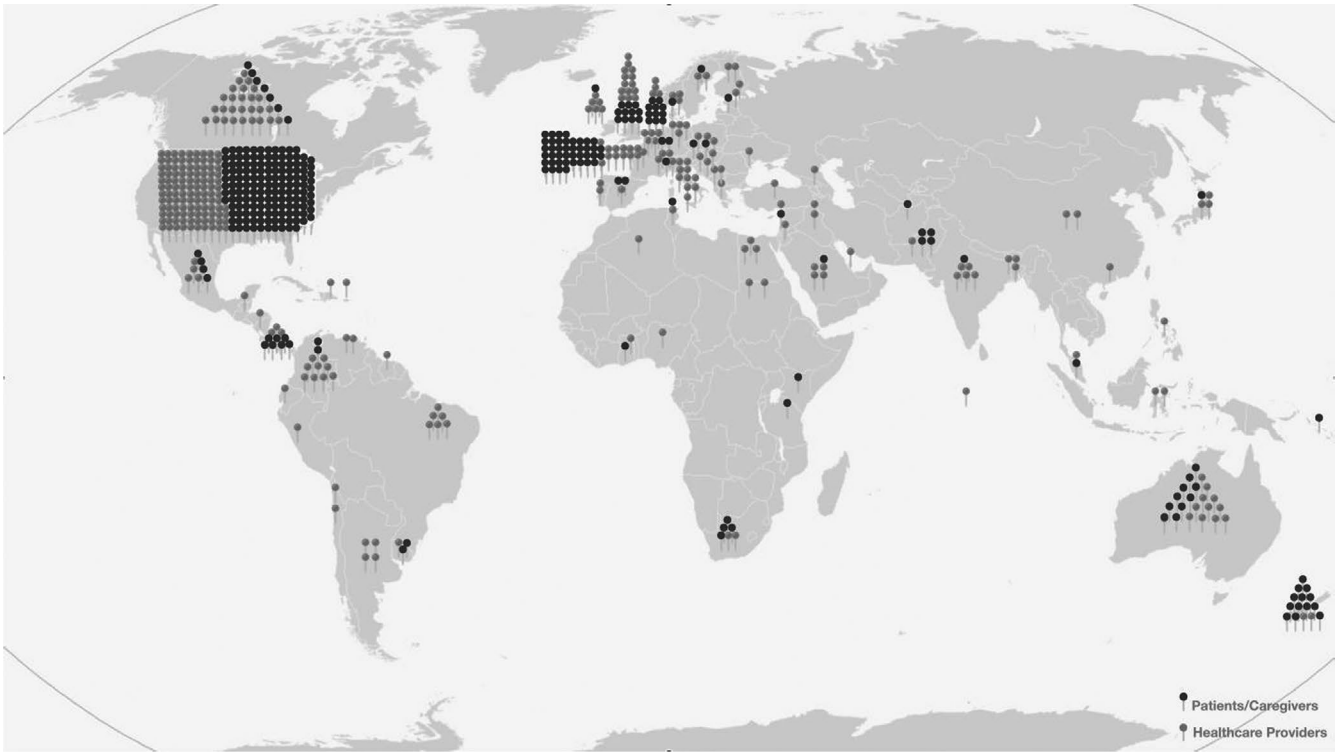
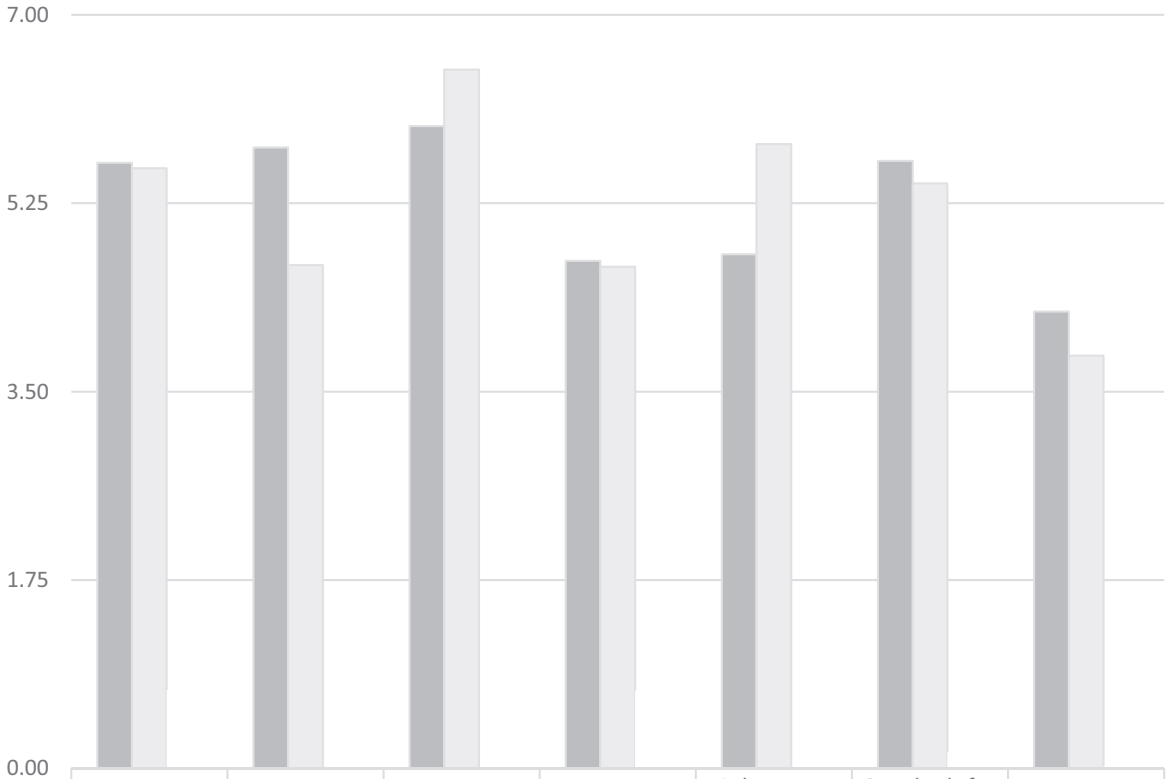


FIGURE 2 Distribution of survey respondents around the world. Each dot represents one participant (red for healthcare providers, blue for patients/caregivers). The location of each dot represents the country and not the actual city or state in the country

Six hundred and one participants (49% patients/caregivers and 51% healthcare providers). responded to the survey. The highest priority topics identified were diagnostic criteria/classification, bleeding assessment tools, and treatment options for women and surgical patients. The survey results highlighted areas of importance in the diagnosis and management of VWD across different groups of stakeholders and will guide future guideline efforts. While the threshold for significance was set a priori at <0.05, statistical significance was not the sole determinant to drive decisions about topics to be covered in the guidelines. Attention was given to areas of convergence of opinion between patients/caregivers and HCPs.

The comments of the respondents underscored the importance of developing recommendations suitable for specific patient subgroups such as women, children, elderly patients and those with comorbidities. Additionally, screening, counselling and education were emphasized as important topics to be addressed. While the views of patients/caregivers and HCPs were mostly consistent, patients/caregivers rated 'diagnostic journey' higher than HCPs. This difference may indicate variability in the path taken to obtain an accurate diagnosis by haematologists and/or general practitioners. The difference also highlights the negative impact on the quality of life and outcomes of patients whose diagnosis is delayed, as opposed to the professional frustration of a HCP unable to reach a conclusive diagnosis for their patient. These results highlight the importance of the physician-patient partnership to reduce suffering due to the disease and to provide patient-centred care, a finding that is consistent with evidence from other studies in haematology.[27] Additionally, discussions among the VWD community continue regarding the most appropriate diagnostic algorithms including access to genetic testing which is part of the topic of diagnostic journey in this survey. As general practitioners are typically the first point of entry into the healthcare system, these results



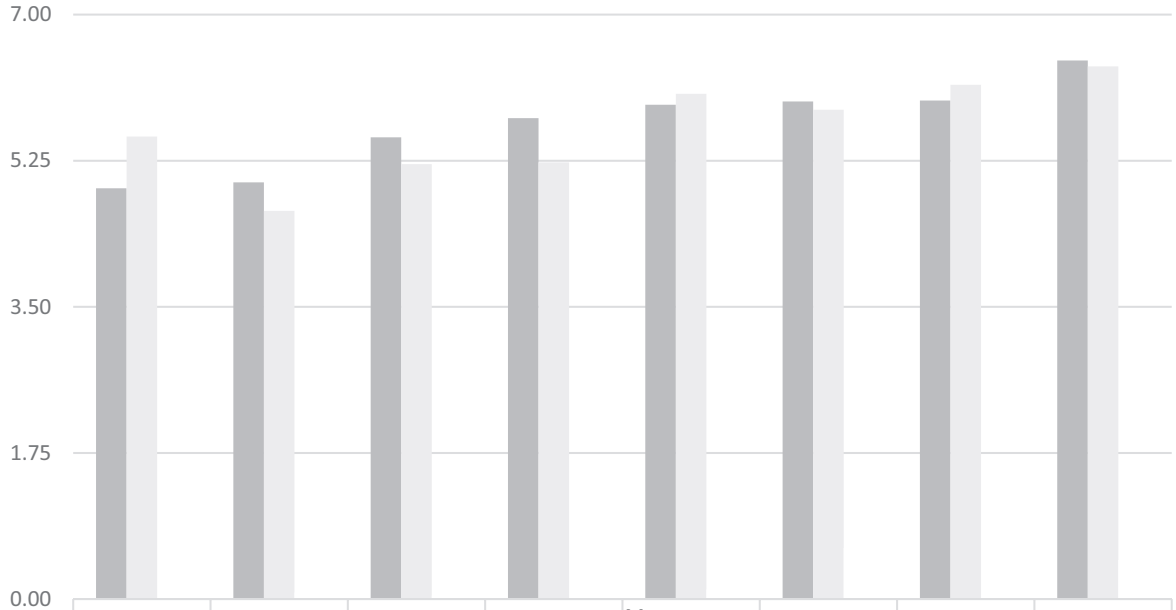
	Bleeding assessment tools	Diagnostic journey	Diagnostic criteria/ classification	Comparing phenotypic vs genotypic diagnosis	Laboratory cutoffs (thresholds) for type 1 VWD	Standards for assessing a laboratory test results and quality	Screening for anemia and iron deficiency
Patients/Caregivers	5.63	5.77	5.97	4.72	4.78	5.64	4.24
Healthcare providers	5.58	4.68	6.49	4.66	5.80	5.43	3.83
P-Value	0.73	0.00	0.00	0.72	0.00	0.15	0.02

FIGURE 3 Patients/Caregivers versus healthcare providers rating for diagnosis topics. All mean numbers are out of a 7-point Likert scale, *P*-value measures the level of statistical significance comparing the means ofresponses for patients/caregivers vs healthcare providers, the threshold of significance is $P < .05$. Although there was a statistically significant difference between patients/caregivers and HCPs for "diagnostic criteria/classification" and "screening for anemia and iron deficiency", both groups rated them as the highest and lowest priorities, respectively

also highlight the need for education and outreach to primary care providers about VWD and other uncommon bleeding disorders. Regarding 'laboratory cut-offs for VWD-type 1', HCPs rated this topic higher than patients/caregivers. This finding is consistent with other studies which emphasize the dilemmas physicians face when making a VWD diagnosis and their desire to have well-defined diagnostic thresholds.[28] Patients, however, are perhaps more concerned about the burden of their disease as highlighted by Salek et al,[27] than the lack of a well-defined threshold in the diagnosis of VWD. Our results underscore differences in the awareness among different stakeholders regarding the lack of standardized diagnostic threshold for VWD. We also note that patients/caregivers were less interested in 'desmopressin trials' compared to HCPs. Our finding that patients express a desire to avoid desmopressin as a treatment modality is consistent with the findings of Ozgönenel et al[29] The comments showed the reasons for patients'/caregivers' responses in the qualitative part of the survey where respondents explicitly discussed safety concerns associated with the use of desmopressin (Appendix S3).

Patients/caregivers rated 'appropriate models of care' higher than HCPs. This finding is important to consider in the need for a patient-centred care approach when treating people with VWD. There is a vital need for reporting patient-related outcomes, as highlighted by the European Hematology Association, as an initiative for improving quality of life in patients with haematological disorders.[30]

In the diagnosis section of the survey, we did not observe a significant difference between male and female patients/caregivers apart from the 'screening for anaemia and iron deficiency' topic, which was rated higher by female patients/caregivers. Interestingly, both male and female patients/caregivers rated 'treatment options for women with VWD' highest in the management section. Female respondents rated 'the management of bleeding or laboratory testing prior to invasive procedures' higher than male respondents. These results may be explained by the higher symptomatology



	Desmopressin trials	Plasma derived therapies vs recombinant therapies	Prophylaxis	Appropriate models of care delivery	Management of bleeding or laboratory testing prior to invasive procedures	Treatment options for patients with specific VWF levels	Treatment options for surgical patients	Treatment options for women with VWD
Patients/Caregivers	4.92	4.99	5.53	5.76	5.92	5.96	5.97	6.45
Healthcare providers	5.54	4.65	5.21	5.23	6.05	5.86	6.16	6.38
P-value	0.00	0.08	0.04	0.00	0.12	0.61	0.23	0.47

FIGURE 4 Patients/Caregivers versus healthcare providers rating for the management topics. All mean numbers are out of a 7-point Likert scale, *P*-value measures the level of statistical significance comparing the means of responses for patients/caregivers vs healthcare providers, the threshold of significance is $P < .05$

and bleeding complications (eg heavy menstrual bleeding) experienced by women with VWD.[31,32] The fact that both male and female respondents rated 'treatment options for women with VWD' highest could be explained by men valuing the symptomatology of their female relatives, given the hereditary nature of the disease. Additionally, we did not observe a difference between respondents in countries classified as LMI and those classified as HI. These results support the generalizability of the survey findings and confirm that these findings are robust and representative of different settings. Although responses from countries classified as LMI and HI were similar, we would like to highlight that the considerable diversity in resources and access that exists within countries could have affected the applicability of the results.

This study has multiple strengths. First, 601 participants from 71 countries responded to the survey, including countries representing a wide variety of socioeconomic classifications. Additionally, the survey was conducted in three languages, which contributes to an increased applicability of the results. Patients/caregivers and HCPs were almost equally represented in the respondents. The number of responses and the volume of comments appear to reflect a commitment to the importance of VWD among respondents and an eagerness of the VWD community to engage with consultative initiatives. The level of response was unexpected considering the uncommon nature of VWD. The survey was developed through an intentional process including several meetings to incorporate the input of HCPs and patients, to thoroughly assess the needs in this area. This study consisted of a mixed-methods survey that not only collected quantitative data about stakeholders' views, but also respondents' comments about the topics, additional themes, and outcomes. Finally, stratified analyses were conducted to ensure that the results are robust for the different stakeholders.

This study has few limitations. The survey was conducted electronically, which would have excluded stakeholders without Internet or computer access. Additionally, stakeholders who do not speak English, French or Spanish are not represented. As highlighted by Baethge et al,[33] it is very likely that the language limitation impacted patients/caregivers more than HCPs, as HCPs are more likely to be able to answer a survey in English. Although we did not collect data regarding the age of respondents, it was clear from the comments that respondents did consider all age groups, which indicates that respondents took into account their own burden of disease and that of their children and other relatives. The number of female respondents was higher than male respondents, which may have influenced the results. However, this is consistent with the published demographics of diagnosed VWD, as females are more commonly diagnosed.[31] Finally, while we administered the survey globally, most

TABLE 3 Results from analysis of qualitative comments

	Subthemes	
Themes	**Diagnosis**	**Management**
Additional topics of interest	• Screening for VWD • Counselling about genetic testing in patients at risk for VWD • Counselling about family planning in patients with VWD • Monitoring tools, specifically for bleeding assessment	• Counselling about family planning for women with VWD
Populations and subgroups	• Women (pregnancy, labour, postpartum, breast-cancer, women using hormone replacement therapy) • Infants and children • Geriatric population • Different races and ethnicities	• Patients undergoing dental procedures • Patients with positive family history • Patients with VWD with coexisting disease (eg Ehlers Danlos syndrome, angiodysplasia)
Interventions	• Validation of standardized international test • Self-management and efficacy • Pharmacologic stressor test to add confirmatory information to the VWD diagnosis • New tests such as Glycoprotein IbM (GPIbM) binding activity, the role of ristocetin cofactor (VWF:RCo) testing, use of propeptide analysis and collagen binding, molecular studies, VWF collagen binding (VWF: CB), VWF Factor VIII binding (VWF: FVIIIB) • VWF function immunoassays, circulating antibodies that cause the disease, and functional and immunological tests for diagnosis • Multimer testing • Using platelet aggregation studies for guiding different subtypes treatment	• Adjunctive therapies • Blood components such as cryoprecipitate • Antiplatelet or anticoagulation in patients with VWD • Fluid restriction with Desmopressin (DDAVP) • Other options (eg tranexamic acid) • Co-administration of recombinant factor VIII (rFVIII) with rVWF. • Prophylaxis standardization nationally, and globally • Physical therapy • Optimal VWF level to be reached before procedures • Preoperative preparation for surgery (eg thromboprophylaxis) • Peri-procedure management • Monitoring during the perioperative period • Dual use of the tranexamic acid with oral contraceptive (OCP) pills for women with heavy menstrual bleeding (HMB)
Outcomes	• Quality of life • Musculoskeletal complications • Control of gingival bleeding • Mortality • Psychological effects • Access to treatment • The ability to restore and maintain haemostasis • Avoiding over or under treatment • VWD effect on employment opportunity • Rehabilitation needs • Prevention of bleeding especially peripartum and postpartum bleeding	

of the responses came from countries classified as HI settings (North America and Europe). Our stratified analysis showed no significant difference between responses from countries classified as LMI and HI. However, the survey is underpowered to detect a difference.

The geographically and socioeconomically diverse respondents along with the large numbers of completed surveys with open-field comments suggest a broad-based desire for increased attention to VWD guidelines. The analysis of the survey responses informed the panels as they formulated questions for the forthcoming guidelines. Involving the broader stakeholder community from an early stage in guideline development will ensure that the different values and priorities are well represented in the development of recommendations. This is recognized as important by several studies such as Bovenkamp et al.[34-36] In fact, this study recognizes the rights of different stakeholders in health policy development and emphasizes that patients are experts. We hope this effort will emphasize the importance of developing trustworthy guidelines for VWD and will eventually facilitate shared decision-making based on the best available evidence.

This study represents a real-world example of the feasibility of engaging diverse stakeholders and different organizations to ensure a high-quality guideline development process. It is important for future research to further explore differences between LMI and HI settings, as well as stakeholders with no Internet access, and different gender values including a focus on male patients' views. Additionally, acknowledging the different stakeholders' values and needs will help inform setting priorities and derivation of appropriate shared decision-making tools, interactive learning, training and educational resources, as well as guiding global development initiatives in the diagnosis and management of VWD.

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Angela Weyand is a member of advisory board for Bayer, has received research funding from Shire and NovoNordisk, is a co-investigator on clinical trials funded by Roche/Genentech, BMS/Pfizer and Shire and was a consultant to Shire and Kedrion.

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AUTHOR CONTRIBUTIONS

RAM, PJ, VF, NC, CC, ER, MS, RP, FR, ES, MK and MA, designed and conducted the study. MK and RAM did the initial writing. NC, VF, PJ, RBP, CC, JC, ER, FR and MS approved the design. NC, VF, PJ and RBP contributed to the writing of the paper. All authors reviewed and distributed the survey, discussed the results, performed critical revision and approved the manuscript. JC, JG, SH, RK, RP, ER, FR and MS helped with dissemination and worked on translation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

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