Evidence-based diagnosis of type 1 von Willebrand disease: a Bayes theorem approach

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The diagnosis of type 1 von Willebrand disease (VWD) is based on the presence of bleeding symptoms, reduced von Willebrand factor (VWF) levels, and autosomal inheritance of the phenotype. To better appreciate the contribution of clinical and laboratory data to the final diagnosis of VWD, we computed the likelihoods of having VWD as a function of the bleeding score (LRscore), of VWF level (LRVWF), and of number of first-degree family members with reduced VWF levels (LRfamily). The 3 likelihoods were therefore combined using the Bayes theorem, giving the final probability (odds) of having VWD. LRfamily and LRVWF were the 2 factors mostly influencing the final probability of having VWD. Data from the present study provide an evidence-based description of the minimal criteria for the diagnosis of type 1 VWD. As an example, presence of VWF levels lower than 40 IU/dl in at least 2 family members (including the proband) and a bleeding score of at least 1 were found to be required for a final odd of VWD higher than 2.0 (false-positive rate less than one-half).

Validation of this approach and of its clinical utility is, however, required by analysis in other cohorts of well-characterized type 1 VWD patients. (Blood. 2008;111:3998-4003)

Introduction

The last decade has witnessed an increasing interest in the diagnosis of von Willebrand disease (VWD). Much of this interest stems from the high prevalence of VWD in the population, ranging from 0.1% to 1%,1,2 making VWD the most frequent inherited bleeding disorder, and therefore its diagnosis relevant for a clinician. The most common variant of VWD is represented by type 1 VWD, a quantitative deficiency of von Willebrand factor (VWF) without overt abnormalities of the circulating molecule, as detected by sensitive immunoelectrophoretic techniques.3,4 Type 1 VWD is transmitted as an autosomal dominant (heterozygous) disease, and a substantial overlap of both clinical and laboratory phenotype is usually present between VWD patients and healthy subjects, particularly in mild cases of VWD.3 In view of the difficulties for an appropriate diagnosis of type 1 VWD, provisional criteria have been recently formulated.5 These criteria rest on the presence of bleeding symptoms and reduced VWF levels in the patient, together with an autosomal inheritance of the phenotype. Unfortunately, these provisional criteria are essentially based on experts’ consensus rather than on evidence.

A different approach to the diagnosis of VWD may be to estimate the final probability of type 1 VWD based on the combination of the likelihood of having VWD as a function of bleeding severity, VWF levels, and first-degree relatives sharing a deficiency of VWF. This approach, based on the well-known Bayes theorem, allows the estimation of the probability (odds) of having VWD as a function of an individual patient phenotype, including inheritance.5 Such an approach has become feasible since the recent availability of large, multicenter studies on different cohorts of type 1 VWD patients.8-10 In this paper, we present the development of a Bayesian model for the diagnosis of VWD as a tool for evidence-based diagnostic criteria.

Methods

Development of the model

According to the Bayes theorem, the odds of a disease could be computed as the a priori probability of a disease multiplied by the likelihood ratio (LR) supporting or opposing that diagnosis. LRs are essentially the ratio between the probabilities of being affected or not for any specific phenotype, such as a particular clinical finding or a specific value of a laboratory test. Thus, in the Bayes theorem, the baseline prior probability of a disease (eg, the prevalence of VWD) is multiplied by the LR given by a clinical or laboratory finding to obtain a posterior probability of that disease in the studied subject. In turn, this latter probability could be further refined by further multiplication by the LR given by another observation (thus posterior probabilities could always be used as better priors probabilities for another LR, provided that all LRs are independent and unbiased11). LRs could be considered as independent and unbiased when their estimates are obtained from different datasets (independent) and their effect is not influenced by other LRs (unbiased). Therefore, under the hypothesis of a low disease prevalence, the model could be written as

\[ \text{odds}_{\text{disease}} = \text{prevalence} \times \text{LR}_1 \times \text{LR}_2 \times \ldots \times \text{LR}_n \]

where LRn is the likelihood ratio of having the disease for 1 to n different clinical or laboratory tests.7 Thus, computing the final odds of VWD requires appreciation of VWD prevalence and of the LR of having VWD for each involved test as a function of the individual phenotype. For type 1 VWD, we computed the odds of being VWD as a function of bleeding symptoms (LRscore), plasma VWF levels (LRVWF), and number of first-degree family members having reduced VWF levels (LRfamily). The choice of these 3 LRs (LRscore, LRVWF, and LRfamily) was consequent to the definition of VWD as an inherited bleeding disorder with reduced VWF.6


An Inside Blood analysis of this article appears at the front of this issue.

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Prevalence of VWD was conservatively estimated to be 0.1% in the general population.1,2,12

**Likelihood ratios of VWD as a function of bleeding severity (LR-score)**

We evaluated data from an international, multicenter study on type 1 VWD patients (hereafter referred as IMS-VWD).8 In the IMS-VWD, 42 obligatory carriers of type 1 VWD were selected on the basis of inheritance, subjects being considered as obligatory carriers (OCs) if they had at least an affected offspring and at least another affected first-degree relative (either father/mother or brother/sister). Thus, the IMS-VWD study selected VWD patients independently from their bleeding history and from their plasma VWF level; therefore, LR-score derived from the IMS-VWD study could be considered as independent from LRVWF. Two hundred fifteen subjects without history of bleeding disease were considered as a control group, as previously described.13 Using a publicly available standardized questionnaire,13 bleeding symptoms were collected through a physician-driven interview and summarized in a bleeding score (BS).8,14 The BS is generated by summing the severity of all bleeding symptoms reported by a subject, and graded according to an arbitrary scale ranging from 0 (complete absence of symptom) to 3. Grade 1 was given when a patient reported presence of bleeding, grade 2 if the symptom required evaluation by a physician but no active intervention, and grade 3 if there was some kind of intervention by the physician. Based on the original study dataset, we computed for the present study the LR of VWD as the ratio between the percentages of type 1 VWD OCs versus control subjects with that particular BS value. Computations of LRs and their 95% confidence intervals were carried out according to Pepe15 using the Stata “diagt” procedure (Stata Statistical Software: Release 10.0; StataCorp, College Station, TX).

**Likelihood ratios of VWD as a function of VWF level (LRVWF)**

We used data from the MCMDM-1VWD study, a multicenter European study that enrolled 154 families with von Willebrand disease and 1166 healthy controls.15 Likelihood ratios in type 1 VWD have been recently reported,16 and were computed for those subjects that in addition to having been diagnosed historically as VWD by the enrolling center (either index case or affected family member) belonged to a family showing clear linkage of the VWD phenotype with the VWF locus (totaling 204 subjects belonging to 64 families). This latter requirement allowed to base the computation of LRVWF on those patients for whom the level of measured VWF was of less importance for their diagnosis. Furthermore, families enrolled in the MCMDM-1VWD study are different from those enrolled in the IMS-VWD study. Thus, computation of both LRscore and LRVWF could be considered as unbiased (ie, LRscore is not based on diagnoses contingent on bleeding, and LRVWF is largely not based on the VWF level actually measured in the MCMDM-1VWD study) and independent (because they are based on independent datasets). Therefore, LRscore and LRVWF could be used multiplicatively for the calculation of the final probability of having VWD. It should be noted that the LRVWF does assume that no factor potentially influencing VWF levels (eg, pregnancy, inflammatory states) is present in the considered proband. Sampling and computation of LRVWF should be withheld until resolution of the influencing conditions when present.

**Likelihood ratios of VWD as a function of family members with reduced VWF levels (LRfamily)**

Within a family of size s, the probability of finding n family members with reduced VWF levels (n possibly ranging from 0 to s, 0 ≤ n ≤ s) depends on the presence of the disease gene within the family and on the sensitivity and specificity of the test, these latter being the probabilities of finding an abnormal VWF level conditional to the presence or absence of an abnormal disease gene, respectively. On the basis of a previous study, we assumed a sensitivity of 0.8 and a specificity of 0.975 for VWF measurement, corresponding to the sensitivity and specificity given by the 2.5 percentile reference limit.16 The probability of having a low VWF conditional to belonging to a healthy or VWD family is reported in Table 1, under the hypothesis of an autosomal disease with low frequency in the population (for this reason, in this model we assumed that only one parent could be a carrier of VWD).17 In healthy families, the final probabilities of finding n subjects with reduced VWF (with probability = 1-Specificity) from s are computed using the binomial distribution. In VWD families, the probability of finding nparents (0 ≤ nparents ≤ 2) with reduced VWF should be summed with the probability of finding nsibs (0 ≤ nsibs ≤ s-2) with reduced VWF; this latter quantity being computed using the binomial distribution with probability 0.5 × (1 + sensitivity – specificity). LRfamily is finally computed for each value of n as the ratio of the probabilities obtained in VWD and in healthy families. Likelihood ratios derived by this theoretic model completely predicted the results obtained by a computer simulation using the Stata “simpred” procedure (Stata Statistical Software). Since LRfamily was computed following the theoretic assumption of an autosomal dominant model, LRfamily could be considered as valid and independent from LRVWF and LRscore and could therefore also be used as the third LR in our model.

The study protocols of the IMS-VWD study and of the MCMDM-1VWD study were submitted and approved by local Internal Review Boards, according to the rules present in each country of the participating centers (see refs 8 and 9 for a list of participating centers). Informed signed consent was obtained from each patient in accordance with the Declaration of Helsinki.

**Results**

**Likelihood ratios of VWD as a function of bleeding severity**

The likelihoods of having VWD as a function of the BS in obligatory carriers of VWD are reported in Table 2. Bleeding scores equal or lower than 2 were all associated with an LR lower than 1, hence lowering the final probabilities of being a VWD patient, whereas a substantial increase in the final probability was observed for BS equal or greater than 5.

**Likelihood ratios of VWD as a function of family members with reduced VWF levels (LRfamily)**

As expected, the likelihood of VWD increased almost exponentially as the number of family members with reduced VWF

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**Table 1. Probability of having low VWF levels in parents and offspring given presence (VWD families) or absence (healthy families) of a disease gene transmitted as an autosomal dominant trait**

<table>
<thead>
<tr>
<th>Family Structure</th>
<th>Healthy families</th>
<th>VWD families</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation, parents</td>
<td>1 – Spec = 0.025</td>
<td>Sens if carrier = 0.80;</td>
</tr>
<tr>
<td></td>
<td>1 – Spec if not carrier = 0.025</td>
<td></td>
</tr>
<tr>
<td>Second generation, offspring</td>
<td>1 – Spec = 0.025</td>
<td>0.5 × Sens if carrier;</td>
</tr>
<tr>
<td></td>
<td>0.5 × (1 – Spec) if not carrier</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.5 × Sens + 0.5 × (1 – Spec) =</td>
<td>0.5 × (1 + Sens – Spec) = 0.4125</td>
</tr>
</tbody>
</table>

**Table 2. Likelihood ratios for VWD at different levels of bleeding score**

<table>
<thead>
<tr>
<th>Bleeding score</th>
<th>No. of investigated subjects</th>
<th>OCs</th>
<th>Controls</th>
<th>Likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>158</td>
<td></td>
<td>0.097 (0.03-0.29)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
<td></td>
<td>0.51 (0.12-2.11)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>14</td>
<td></td>
<td>0.73 (0.17-3.10)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>9</td>
<td></td>
<td>2.28 (0.73-7.05)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>11</td>
<td></td>
<td>2.79 (1.09-7.13)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
<td></td>
<td>12.8 (2.57-63.8)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>1</td>
<td></td>
<td>20.5 (2.35-179)</td>
</tr>
<tr>
<td>6 or more</td>
<td>20</td>
<td>1</td>
<td></td>
<td>102 (14.1-742)</td>
</tr>
</tbody>
</table>

OC indicates obligatory carrier.
increased within a family (Table 3; Figure 1). Although the actual LR varied as a function of the family size, the slope and shape of the likelihood profiles was remarkably similar (Figure 1). As a general rule, however, a family without any family member with VWF levels lower than the 2.5 percentile (corresponding to a VWF:Ag or VWF:RCo lower than 47 IU/dL in a large cohort of healthy subjects16) is highly unlikely to have VWD. On the contrary, finding 2 members with reduced VWF levels strongly suggests the presence of VWD. It should be noted that \( L_{R_{\text{family}}} \) is computed either including or excluding the proband depending on his/her VWF values. For instance, if the proband and another sibling have VWF levels lower than 40 IU/dL, then the proband will get the same \( L_{R_{\text{family}}} \) of a proband with normal VWF but with 2 other siblings with VWF lower than 40 IU/dL. In subjects without family data available (ie, with information coming only from the proband), \( L_{R_{\text{family}}} \) is assumed to be 16.5 (0.4125, probability of low VWF in VWD family, divided by 0.025, probability of low VWF in a healthy family, Table 1) if the proband has reduced VWF; \( L_{R_{\text{family}}} \) is assumed to be 0.60 (0.5875, probability of normal VWF in VWD family, divided by 0.975, probability of low VWF in a healthy family, Table 1) otherwise. In families with incomplete familial investigation, computation of \( L_{R_{\text{family}}} \) could be derived assuming as the family size the total number of subjects actually investigated.

Final odds of VWD

Tables 4, 5, and 6 report, respectively, the final odds of VWD in subjects without a family investigation available and in subjects with 4 and 5 investigated family members.

Discussion

Although type 1 VWD is the most prevalent hemorrhagic disorder,2 its diagnosis still remains a clinical challenge.5,18 Provisional diagnostic criteria have been published, based on the presence of bleeding symptoms, reduced VWF levels, and inheritance of the phenotype within the family.6,19 Unfortunately, the contribution of each of these 3 factors to the final diagnosis is unknown, as is unknown the proportion of truly affected patients among all those subjects fulfilling the criteria (ie, the positive predictive value of the proposed criteria). Furthermore, current proposed criteria do not exploit all the clinically available information, since data are dichotomized into normal/abnormal values. For instance, an individual with borderline VWF levels (eg, lower than 40 IU/dL) would be considered abnormal just as an individual with severely reduced VWF (eg, lower than 20 IU/dL), even if the latter subject is obviously more likely to have VWD than the former one.

In this study, we aimed at appreciating the different contribution of bleeding symptoms, reduced VWF levels, and inheritance of the phenotype to the diagnosis of type 1 VWD and to quantitatively estimate the diagnostic accuracy of a VWD diagnosis based on the clinical and laboratory phenotype. For this purpose, we combined clinical and laboratory data using the Bayes theorem, an approach that has never been used before for the diagnosis of bleeding disorders. This methodology has the benefits of exploiting both qualitative and quantitative information (eg, VWF levels) and of providing the clinician the final probability (odds) of having VWD against being healthy. For instance, final odds of 2.0 means that every 3 evaluated subjects, 2 will have VWD and 1 will not (or a 2/3 = 66.6% positive predictive value); final odds of 10.0 means a 10:1 ratio of true-false positives (or 10/11 = 90.9% positive predictive value). Odds could be readily converted into probabilities of disease with the formula probability = odds/(odds + 1).

Thus, the clinician may have an immediate perception of the degree of certainty of the diagnosis, with final odds lower than 2.0 possibly having a high risk of misdiagnosis (since probability of VWD in this case would be 2/3 = 66%). In fact, in subjects with final odds lower than 2.0, reduction of circulating VWF may be better considered as a risk factor for bleeding rather than causative of a disease, as has already been proposed.3 Application of the Bayes theorem to VWD was made possible by the recent availability of data coming from studies on large cohorts of VWD (the IMS-VWD...
and MCMMDM-1VWD studies).9,10,16 Since the IMS-VWD and MCMMDM-1VWD enrolled different patient populations and used different selection criteria, combination of data from these 2 studies was possible, thus avoiding as much as possible circular reasoning for a disease without an independent diagnostic gold standard. The IMS-VWD was used to compute LR for the BS since in this study patients were selected independently from the presence of bleeding symptoms, therefore allowing unbiased estimation of LRscore. As a consequence, the questionnaire and the BS used by the IMS-VWD were used for this study.14 We used LRVWF recently reported in the MCMMDM-1VWD study since VWF was measured in a core laboratory from a large cohort of patients and controls.10 VWF:Ag was chosen as the reference method instead of VWF:RCo, given its better intralaboratory and interlaboratory reproducibility.16,20 Finally, we conservatively assumed a low prevalence of VWD (0.1% or 1 per 1000) in the population, since it possibly better reflects the prevalence of VWD as an autosomal dominant disease, with both proband and family members having VWF levels lower than the 2.5 percentile, as requested in our model. Given the properties of the Bayes theorem, however, changing the prevalence to 1 per 100 or 1 per 10 000 would mean multiply (or divide) by 10 the final odds of at least 5.4 (Table 5).

The study demonstrates first that the most important clue to the diagnosis of VWD is inheritance of the phenotype, followed by reduced VWF and bleeding symptoms in the proband. This could be easily appreciated by the very steep increase of LRfamily (and hence, of final odds) as a function of the number of family members found to have reduced VWF. On the contrary, the absolute contribution of LRscore and LRVWF to the final odds is much lower. In subjects without family data available, final odds of VWD higher than 2.0 are obtained only for very low VWF values together with very high BS (Table 4).

Second, the study shows that no single clinical or laboratory criterion reaches final odds higher than 2.0 (apart from the very unlikely situation of a family where almost everyone has reduced VWF levels). This study therefore confirms that at least a clinical and a laboratory positive finding need to be present for VWD diagnosis. For instance, having VWF levels lower than 20 IU/dL together with another family member with reduced VWF is highly likely to be associated with VWD, since combination of these 2 criteria results in final odds of at least 4.06 (Table 5). In patients with less severe reduction of VWF, however, the contribution of bleeding symptoms is always required to reach a sensible diagnosis. Hence, in the more frequent case of patients with VWF levels ranging from 20 to 40 IU/dL, a bleeding score of at least 1 together with another family member with reduced VWF are required for a final odds of at least 5.4 (Table 5).

Table 4. Final odds of VWD based on the combination of LR from bleeding score and VWF:Ag level

<table>
<thead>
<tr>
<th>VWF:Ag, IU/dL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>6 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20</td>
<td>0.59</td>
<td>3.14</td>
<td>4.50</td>
<td>14.06</td>
<td>17.21</td>
<td>78.98</td>
<td>126.50</td>
<td>629.44</td>
</tr>
<tr>
<td>20 to 40</td>
<td>0.15</td>
<td>0.80</td>
<td>1.14</td>
<td>3.57</td>
<td>4.37</td>
<td>20.08</td>
<td>32.16</td>
<td>160.05</td>
</tr>
<tr>
<td>40 to 47</td>
<td>0.00</td>
<td>0.01</td>
<td>0.02</td>
<td>0.07</td>
<td>0.08</td>
<td>0.38</td>
<td>0.61</td>
<td>3.09</td>
</tr>
<tr>
<td>47 to 60</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>60 or more</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
</tr>
</tbody>
</table>

No family investigation was available.
Final odds from 2.0 to 10.0 in italic; final odds higher than 10 in bold. Odds could be converted into probabilities of disease with the formula probability = odds/(odds + 1).

Table 5. Final odds of VWD based on the combination of LR from bleeding score, VWF: Ag level, and number of family members with VWF lower than the 2.5 percentile

<table>
<thead>
<tr>
<th>VWF:Ag, IU/dL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>6 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20</td>
<td>0.15</td>
<td>0.79</td>
<td>1.14</td>
<td>3.55</td>
<td>4.34</td>
<td>19.91</td>
<td>31.89</td>
<td>158.70</td>
</tr>
<tr>
<td>20 to 40</td>
<td>0.04</td>
<td>0.20</td>
<td>0.29</td>
<td>0.90</td>
<td>1.10</td>
<td>5.06</td>
<td>8.11</td>
<td>40.35</td>
</tr>
<tr>
<td>40 to 60</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.10</td>
<td>0.16</td>
<td>0.77</td>
</tr>
<tr>
<td>60 or more</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Less than 20</td>
<td>4.06</td>
<td>21.36</td>
<td>30.58</td>
<td>95.50</td>
<td>116.87</td>
<td>536.17</td>
<td>858.70</td>
<td>4272.58</td>
</tr>
<tr>
<td>20 to 40</td>
<td>1.03</td>
<td>5.43</td>
<td>7.78</td>
<td>24.28</td>
<td>29.72</td>
<td>136.34</td>
<td>218.35</td>
<td>1086.42</td>
</tr>
<tr>
<td>40 to 60</td>
<td>0.02</td>
<td>0.10</td>
<td>0.15</td>
<td>0.46</td>
<td>0.57</td>
<td>2.61</td>
<td>4.18</td>
<td>20.79</td>
</tr>
<tr>
<td>60 or more</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0.03</td>
<td>0.03</td>
<td>0.14</td>
<td>0.23</td>
<td>1.14</td>
</tr>
<tr>
<td>Less than 20</td>
<td>76.73</td>
<td>403.42</td>
<td>577.44</td>
<td>1803.50</td>
<td>2206.92</td>
<td>10124.93</td>
<td>16215.71</td>
<td>80683.02</td>
</tr>
<tr>
<td>20 to 40</td>
<td>19.51</td>
<td>102.58</td>
<td>146.83</td>
<td>458.59</td>
<td>561.17</td>
<td>2574.55</td>
<td>4123.30</td>
<td>20515.92</td>
</tr>
<tr>
<td>40 to 60</td>
<td>0.02</td>
<td>0.11</td>
<td>0.15</td>
<td>0.48</td>
<td>0.59</td>
<td>2.71</td>
<td>4.34</td>
<td>21.57</td>
</tr>
<tr>
<td>60 or more</td>
<td>0.07</td>
<td>0.39</td>
<td>0.56</td>
<td>1.74</td>
<td>2.13</td>
<td>9.76</td>
<td>15.63</td>
<td>77.75</td>
</tr>
</tbody>
</table>

Final odds from 2.0 to 10.0 in italic; final odds higher than 10 in bold. Odds could be converted into probabilities of disease with the formula probability = odds/(odds + 1).
*Total family size = 4. Proband included.
The results of the present study could be compared with the provisional criteria recently published,\textsuperscript{6} classifying type 1 VWD patients as “definite” and “possible.” Definite type 1 include significant mucocutaneous bleeding (at least 2 symptoms or one requiring blood transfusion, totaling a BS possibly ranging from 2 to 4), reduced VWF levels (> 2 SD lower than the mean), and at least another family member with reduced VWF. Accordingly, in a nuclear family of 4, the final odds of VWD according to the conservative criteria should be used assuming a more complex monogenic, autosomal dominant disease with incomplete penetrance). Even on this simple assumption, our study suggests that the appreciation of the odds of being affected could be useful both for clinical and research purposes. Second, our approach could also be useful for the exclusion of healthy individuals in particular situations. First, most cases of VWD come from families with mild reduction of VWF levels, where considerable overlap exists even with healthy subjects. In this case, a quantitative appreciation of the odds of being affected could be useful both for clinical and research purposes. Second, our approach could also be useful for the exclusion of the VWD diagnosis. For instance, a negative bleeding history (BS less than 3, as found in healthy subjects) is invariably associated with an LR\textsubscript{family} lower than 1, hence dramatically lowering the final odds of VWD. A strong negative value could be attributed also to lack of inheritance (ie, no family member with reduced VWF or none other than the proband) and to VWF values higher than 60 IU/dL. As an example, our approach could be useful for the exclusion of healthy individuals in families with severe VWD, since in this setting finding a low BS or LR\textsubscript{family} to VWF values higher than 60 IU/dL. Even with healthy subjects. In this case, a quantitative approach to VWD diagnosis adds little information in severe type 1 VWD and could confirm only an otherwise easy diagnosis. Our approach could be particularly useful for the clinician in 2 less clear-cut, but more frequent, situations. First, most cases of VWD come from families with mild reduction of VWF levels, where considerable overlap exists even with healthy subjects. In this case, a quantitative appreciation of the odds of being affected could be useful both for clinical and research purposes. Second, our approach could also be useful for the exclusion of the VWD diagnosis. For instance, a negative bleeding history (BS less than 3, as found in healthy subjects) is invariably associated with a LR\textsubscript{family} lower than 1, hence dramatically lowering the final odds of VWD. A strong negative value could be attributed also to lack of inheritance (ie, no family member with reduced VWF or none other than the proband) and to VWF values higher than 60 IU/dL. As an example, our approach could be useful for the exclusion of healthy individuals in families with severe VWD, since in this setting finding a low BS or intermediate VWF levels may considerably lower the high LR\textsubscript{family}. Finally, it should be noticed that the results of this study rest on the assumption that VWD is based on a clear-cut genetic model (a monogenic, autosomal dominant disease with incomplete penetrance). Even on this simple assumption, our study suggests that extreme caution should be used for the diagnosis of VWD in subjects with mild reduction of VWF and, therefore, even more conservative criteria should be used assuming a more complex genetic background of VWD (eg, allowing for the presence of phenocopies, epistasis, and multigenic effects). In this respect, this study aims at providing a quantitative assessment of the magnitude of diagnostic uncertainties of VWD diagnosis.

Several questions remain unanswered, however, and will need further investigation. First, it is presently difficult to establish a cutoff for an optimal diagnosis of VWD. The appreciation of the diagnostic sensitivity and of the unavoidable trade-offs for various

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
\textbf{Bleeding score} & \textbf{0} & \textbf{1} & \textbf{2} & \textbf{3} & \textbf{4} & \textbf{5} & \textbf{6} or more \\
\hline
\textbf{VWF:Ag, IU/dL} & \textbf{0.02} & \textbf{0.08} & \textbf{0.12} & \textbf{0.37} & \textbf{0.45} & \textbf{0.63} & \textbf{0.69} \\
\hline
\hline
\textbf{1 family member with VWF lower than 2.5 pctl*} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 40} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 60} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{60 or more} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\hline
\textbf{2 family members with VWF lower than 2.5 pctl*} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 40} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 60} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{60 or more} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\hline
\textbf{3 family members with VWF lower than 2.5 pctl*} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 40} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 60} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{60 or more} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\hline
\textbf{4 family members with VWF lower than 2.5 pctl*} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 40} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 60} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{60 or more} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\hline
\textbf{5 family members with VWF lower than 2.5 pctl*} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 40} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{20 to 60} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\textbf{60 or more} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} & \textbf{0.00} \\
\hline
\end{tabular}
\caption{Final odds of VWF based on the combination of LR from bleeding score VWF:Ag level and number of family members with VWF lower than the 2.5 percentile}
\end{table}
cutoffs will necessarily require the validation against a new set of patients independently diagnosed as having VWD. Second, it could be postulated that higher final odds of VWD could correlate with severity of disease and hence with bleeding risk, but this will also require validation by large, prospective surveys on VWD patients. Prospective surveys will also be needed to evaluate which one of the 3 components used to compute the final odds is the stronger predictor of the bleeding risk in VWD patients. Finally, the clinical utility of our proposed algorithm should be tested in prospective series of bleeding patients, without a previous diagnosis of VWD.

The study has some limitations; in particular, it is limited to the adult population and it does not take into account variables such as sex or age that have been previously demonstrated to be associated with an increased BS. Thus, the results of the present study should be applied with great caution to pediatric patients, and specific studies in children should be awaited. It should also be noted that, due to the relatively small numbers of available subjects, there is a wide variation of the confidence intervals around some LR estimates, and the true final odds may be refined once additional data from other ongoing projects are available.

In conclusion, the present data provide evidence that the diagnosis of VWD, particularly in patients with modestly reduced VWF levels and few bleeding symptoms, could be very uncertain. Sound diagnostic criteria should be based on laboratory data, personal bleeding history, and family data, and a quantitative approach could be useful to exploit all the gathered information. Analysis of other cohorts of patients is, however, required to test the predictive value and clinical usefulness of this approach for diagnostic and prognostic purposes.

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Authorship

Contribution: A.T. designed the research, performed statistical analysis, and drafted the paper; G.C. and F.R. designed the research, interpreted data, and revised the paper.

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References

Evidence-based diagnosis of type 1 von Willebrand disease: a Bayes theorem approach

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