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COMMENTARY

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Classification of von Willebrand disease in the context of modern contemporary von Willebrand factor testing methodologies

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von Willebrand disease (VWD) is reportedly the most common inherited bleeding disorder, potentially affecting up to 1% of the population according to epidemiologic data, although numbers based on presentation to clinics are closer to 0.1%.[1] VWD arises from defects and/or deficiency of von Willebrand factor (VWF), and laboratory testing assists clinical exclusion or diagnosis.[2–5] Contemporary laboratory assays comprise VWF antigen (VWF:Ag), markers of VWF activity, and factor VIII activity (FVIII:C),[2–7] using various methods. There are many VWF activity assays, especially those reflective of glycoprotein Ib (GPIb) binding (including classical ristocetin cofactor [VWF:RCo]), and for which the VWF/VWD Scientific Standardisation Committee (SSC) of the ISTH has recommended revised nomenclature.[5,7] VWF:RCo assays using platelets, ristocetin, and native GPIb remain *VWF:RCo*, but those using other solid-phase particles and recombinant GPIb are termed *VWF:GPIbR*.[5,7] Additional gain-of-function VWF assays using recombinant GPIb mutations reflect VWF:GPIb binding assays similar to VWF:RCo and VWF:GPIbR but that do not employ ristocetin are termed *VWF:GPIbM*.[5,7–9] Another distinct category of VWF activity assay is the collagen binding assay (VWF:CB).[5,10] Assessment of VWF multimers by gel electrophoresis also has a place in VWD diagnosis, although classical methods are nonstandardized, complex, time consuming, and subject to high error rates in diagnostic practice.[11,12]

As previously described by the VWD ISTH SSC,[2] and supported by geographically placed expert groups,[3,4] VWD is currently classified within 6 types, dependent on presenting VWF phenotype. Types 1 and 3 VWD respectively define partial and total quantitative deficiency of VWF, whereas type 2 VWD defines qualitative VWF disorders comprising 2A, 2B, 2M, and 2N.[2] 2A VWD categorizes patients with loss of the most adhesive VWF forms (as represented by high-molecular-weight [HMW] multimers [HMWMs]). Type 2B identifies "hyper-adhesive" VWF forms as also usually associated with HMW VWF loss.[2] Type 2N VWD identifies defective VWF:FVIII binding.[2] Finally, type 2M VWD represents a rather heterogenous ("residual") group of VWF binding defects that cannot be classified into 2A, 2B or 2N, but ultimately reflecting VWF dysfunction not associated to ("substantial") loss of HMW VWF.

One main purpose of the 2006 VWD classification[2] was to provide a minimum (n = 6) set of VWD types to facilitate patient management. Prior to these guidelines, there were over 20 "different" VWD types; although of clear academic interest, well-defined clinical utility for such distinctions were lacking. There are 2 major therapeutic options in VWD: desmopressin (1-desamino-8-d-arginine vasopressin [DDAVP]) and VWF replacement.[3,4] DDAVP promotes release of endogenous stored VWF and is effective for most clinical needs for most patients with type 1 VWD, and some patients with type 2 VWD. VWF replacement is otherwise the main alternate or supplementary treatment (most patients with type 2 VWD, all patients with type 3 VWD, and all patients with extended needs such as major surgery or protracted treatment).

Superficially, the simplification of classification into six groups[2–4] should now streamline patient diagnosis, as should the growth in modern contemporary VWF test methodologies.[5–10] However, there remains some diagnostic "subjectivity" that may prevent clear determination of VWD type. One pragmatic example is type 2M VWD, which some laboratories hardly ever identify, whereas others

TABLE 1 Main classifications with anticipated test patterns in different types of von Willebrand disease (VWD)

VWD type	Classification description	VWF:Ag	VWF:GPIb binding[a]	VWF:CB	FVIII:C	Multimers	GPIb binding/ Ag[b]	CB/Ag[b]	FVIII/ VWF[b]	Comments/additional testing
1	Partial quantitative deficiency of VWF	↓ to ↓↓	↓ to ↓↓	↓ to ↓↓	N to ↓↓	Normal pattern but reduced intensity	>(0.5-0.7)	>(0.5-0.7)	>(0.5-0.7)	VWF levels between ~30-50 U/dL will generally not be associated with *VWF* mutations and can be considered as representing "low" VWF as a risk factor for bleeding. VWF levels below ~30 U/dL will often be associated with *VWF* mutations and can be considered as representing "true" VWD
2A	Decreased VWF-dependent platelet adhesion and a selective deficiency of HMW VWF multimers	N to ↓↓	↓↓ to ↓↓↓	↓↓ to ↓↓↓	↓ to ↓↓	Loss of HMW VWF	<(0.5-0.7)	<(0.5-0.7)	>(0.5-0.7)	2A and 2B VWD can only be distinguished by means of RIPA. Platelet type (PT) VWD phenotypically resembles 2B VWD; these can be distinguished by means of RIPA mixing studies, or by genetic analysis of *VWF* and/or platelet *GPIb* genes. Some atypical 2B VWD cases will not show these patterns, but will still express elevated RIPA responsiveness as well as a *VWF* mutation
2B	Increased affinity of VWF for platelet glycoprotein Ib	N to ↓↓	↓ to ↓↓↓	↓ to ↓↓↓	N to ↓↓	Loss of HMW VWF	<(0.5-0.7)	<(0.5-0.7)	>(0.5-0.7)	
2N	Markedly decreased binding affinity for factor VIII	N to ↓↓	N to ↓↓	N to ↓↓	↓↓ to ↓↓↓	Normal pattern	>(0.5-0.7)	>(0.5-0.7)	<(0.5-0.7)	Phenotypically similar to hemophilia A; distinguish using VWF:FVIII binding assay or genetic analysis of *FVIII* and/or *VWF* genes
2M	Decreased VWF-dependent platelet adhesion without a selective deficiency of HMW VWF multimers	N to ↓↓	(↓ to ↓↓↓)	(↓ to ↓↓↓)	↓ to ↓↓	No significant loss of HMW VWF; some multimer defects may however be observed	<(0.5-0.7) (platelet-binding defect) or >(0.5-0.7) (collagen binding defect)	<(0.5-0.7) (collagen-binding defect) or >(0.5-0.7) (platelet binding defect)	>(0.5-0.7)	2A and 2M VWD can only be distinguished by comprehensive or composite panel testing, including VWF:Ag, GPIb binding assay,[a] *plus* VWF:CB and/or multimer analysis. Platelet binding dysfunction 2M VWD is more common than collagen binding defect variants
3	Virtually complete deficiency of VWF	↓↓↓ (absent)	↓↓↓ (absent)	↓↓↓ (absent)	↓↓↓ (<10 U/dL)	No VWF present	NA	NA	NA	Type 3 VWD can only be identified when VWF tests are performed and these are sensitive to very low levels of VWF. The parents of affected patients should also be tested for VWF levels

Note: Table is intended to provide a practical guide to current identification of different types of VWD. ↓ to ↓↓ to ↓↓↓ are "grades" representing increasing loss.

Ag, antigen; CB, collagen binding; FVIII, factor VIIII; GPIb, glycoprotein Ib (platelet VWF receptor); GPIbM, GPIb mutation-based assay; GPIbR, recombinant GPIb–based assay; HMW, high-molecular-weight (VWF); N, normal; NA, not applicable; RCo, ristocetin cofactor; RIPA, ristocetin-induced platelet aggregation; VWD, von Willebrand disease; VWF, von Willebrand factor.

[a]For the purpose of this commentary, VWF:GPIb binding assays include classical VWF:RCo assays plus VWF:GPIbM and VWF:GPIbR assays.

[b]Assay ratios used as cutoff for type 1 vs 2 VWD discrimination generally range in the region of 0.5-0.7 (viz, 0.5, 0.6, or 0.7). Different assays and different laboratories will use different cutoffs based on local evaluation but a generic cutoff of 0.6 is often applied. Type 2N VWD patients yield FVIIIB/VWF:Ag ratios around 0.5 (0.3-0.7) for heterozygous mutations, and <0.3 for more severe genetic changes (including homozygous, double heterozygous, or combined heterozygous 2N mutation with second null allele).

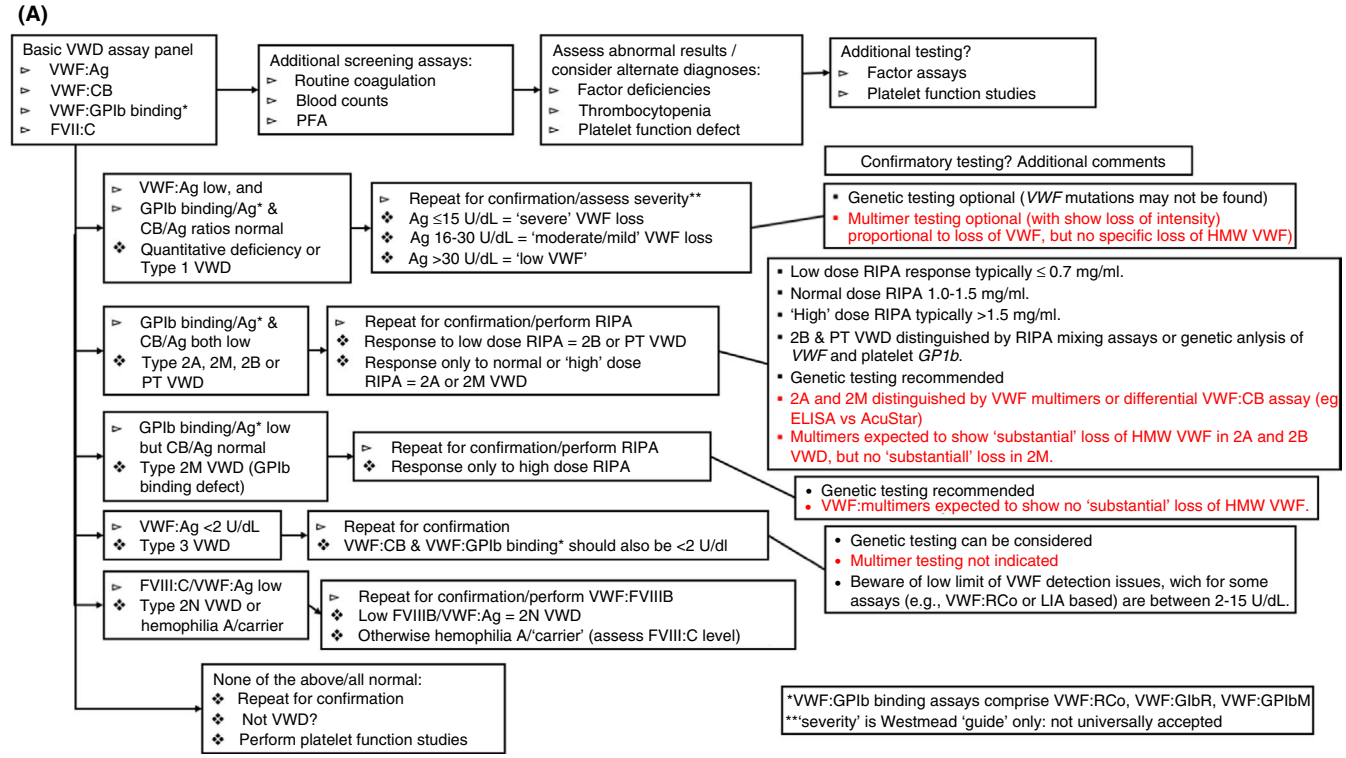

FIGURE 1 F (A) Algorithm that describes a diagnostic process for VWD that takes into account the differential utility of different VWF:CB methods, as well as VWF multimers, from the author's experience and perspective. Ag, antigen; CB, collagen binding; FVIII, factor VIIII; GPIb, glycoprotein Ib (platelet VWF receptor); GPIbM, GPIb mutation-based assay; GPIbR, recombinant GPIb–based assay; HMW, high-molecular-weight (VWF); LIA, latex immunoassay; N, normal; NA, not applicable; PFA, platelet function analyzer; RCo, ristocetin cofactor; RIPA, ristocetin-induced platelet aggregation; VWD, von Willebrand disease; VWF, von Willebrand factor. (B) Summary of ranges for percentage of low-molecular-weight multimers (LMWMs), intermediate-molecular-weight multimers (IMWMs), and high-molecular-weight multimers (HMWMs), for different sample groupings for previously published studies with comparable sample numbers.[15,18,23] Of interest, the publications from Bowyer et al[23] and Favaloro et al[18] seem to more closely align with one another, showing more overlaps between VWD groups (ie, less definitive discrimination) than findings reported by Vangenechten and Gadisseur.[15] This is likely to be reflective of test sample cohorts, with those of Vangenechten and Gadisseur[15] reflecting well-characterized genetically confirmed cases from a VWD biobank. In contrast, cases from the prior publications reflect those arising in "real-world diagnostic test practice." In other words, most laboratories applying the methodology to diagnostics are unlikely to achieve the clear separations reported by Vangenechten and Gadisseur[15] (Note: SHP=standard human plasma [=pooled normal plasma])

(including us) assert comprises upwards of 50% of all type 2 VWD cases.[13] Moreover, there remains great general misunderstanding about the utility of individual VWF test methods, as well as their interchangeability (or not).[14]

The clinical utility of one VWF test method, multimer analysis, is featured in this issue of the journal.[15] Considered essential for VWD diagnosis and classification by some experts, the methodology as often employed in general diagnostic laboratories instead greatly compromises correct VWD diagnosis, with higher diagnostic error rates (20%-50%)[11,12] than classical phenotypic assays (around 10%).[16] VWF multimer analysis assesses the distribution and structure of VWF according to size, given that VWF forms multimers of increasing size with increasing overall adhesiveness or function. Thus, absence of the largest (HMW) multimers is characteristic of types 2A and 2B VWD, and usually an indication for clinical management by VWF factor replacement. In theory, all other VWD forms (excepting type 3) should retain HMW VWF, although reduction in HMW VWF in parallel with general reduction in VWF will be apparent in type 1 VWD.

Table 1 provides a summary of the classification description and what may be expected in terms of VWF test findings, including multimers, for VWD. It should be recognized that although this table will in general hold true for most cases of VWD, there are always exceptions, given the great heterogeneity in both VWD (on a case-by-case basis) and VWF defects (as highlighted by the large number of "mutations" evident in both the VWF database and published literature[17]).

In practical terms, all assays reflective of platelet GPIb binding (ie, VWF:RCo, VWF:GPIbR, VWF:GPIbM) should provide similar information, and are essentially "interchangeable" from a VWD diagnosis standpoint.[5,6,9,14] This does not infer that these tests are identical, but rather that for VWD cases, they should provide similar data to one another. Other assays, such as VWF:CB, and VWF:FVIIIB (VWF:FVIII binding assay for 2N VWD) provide disparate data, although for most cases of VWD, findings will be still be similar to those of GPIb binding assays. This can be identified in Table 1 but confuses many clinicians. Indeed, it is when data is disparate between assays,

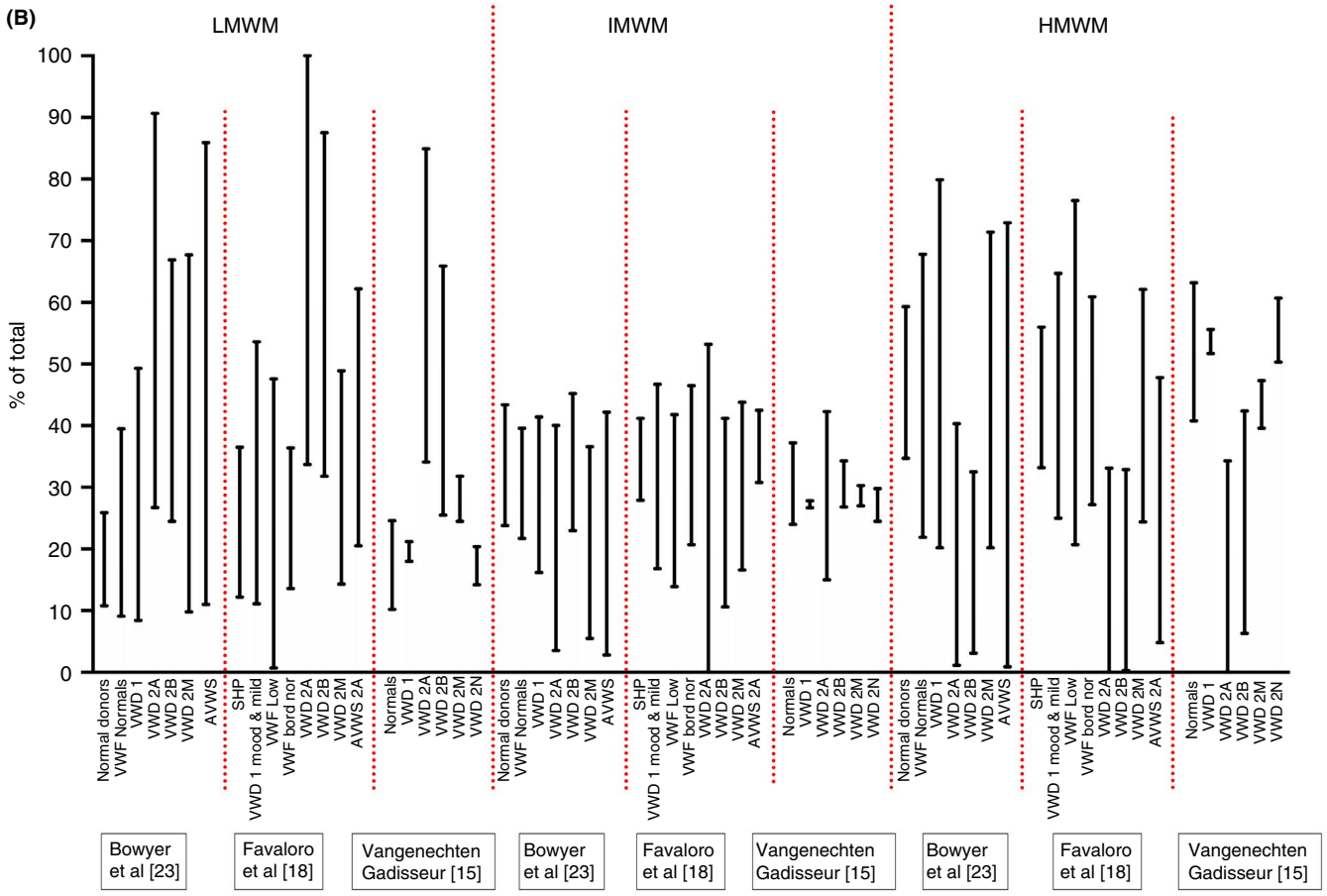

FIGURE 1 Continued

for example between platelet GPIb binding vs VWF:CB, that certain VWD types (eg, 2M) become apparent. Thus, absence of VWF:CB in a test repertoire, as currently performed by most diagnostic laboratories outside of Australia and Europe, leads to a potential absence of identification of 2M VWD, and instead these cases may be reported as either type 2A or type 1 VWD.[13]

As noted, VWF multimer analysis should aid in VWD diagnosis and classification. However, most laboratories continue to use non-standardized in-house assays, with high diagnostic error rates. In one report, this averaged 15%, with some laboratories (5%) reporting loss of HMW VWF in normal samples, many laboratories (18%) reporting loss of HMW VWF in type 1 VWD samples, and many (18%) reporting a normal multimer pattern in type 2A or 2B VWD.[11] Nevertheless, this was overshadowed by a previous report, with errors of up to 23% in normal samples and 52% in type 1 VWD.[12] Thus, a standardized VWF multimer assay holds great promise for reducing such errors, and thus improving VWD diagnosis/classification. The assay evaluated by Vangenechten and Gadisseur,[15] as reported in this issue of *RPTH*, reflects one such assay. Currently available in 5-gel and 11-gel formats, the Hydrasys VWF multimer assay has high interassay consistency.[18] In the *RPTH* report,[15] the method compared well to the in-house comparator; indeed, it performed well enough to convince the authors to subsequently use the commercial method as their first-line VWF multimer method. This report used an impressive number of VWD cases, and a 2-pronged evaluation approach of testing and validation.

The main strengths of the new methodology include high reproducibility, ability for same-day test results, automation of many test steps, and ability to "accurately" identify loss or retention of HMW VWF by both visual and quantitative methods (densitometry). Nevertheless, there are also some limitations, as summarized in another recent publication.[18] One main limitation is the current single agarose gel concentration, limiting identification of VWF structural changes, including an absence of any triplet banding. Thus, specialized VWF multimer methods will still retain a clear place in VWD diagnostics; however, the new method should be able to find a home in many diagnostic laboratories and otherwise lead to a reduction in diagnostic error rates. Notably, Vangenechten and Gadisseur[15] also suggested that data with the new methodology could be used as a surrogate for identifying cases typically identified on triplet banding patterns.

Irrespective, VWD types with loss of HMW VWF (namely, 2A and 2B [at least typical cases of 2B with evident loss of HMW VWF and low VWF:Activity/Ag ratios]) should be clearly separable from VWD cases not showing such loss (ie, types 1, 2N, and, at least in theory, 2M). As this separation comprises a major distinction, this has value in triaging patients for subsequent targeted testing. Figure 1 provides an additional perspective on

the relative place of multimer testing in VWD from this author's perspective. The diagnostic value of VWF multimers is somewhat dependent on the initial test panel, sometimes called first-line tests. If the panel only comprises the often standard 3-test panel of FVIII:C, VWF:Ag, and a VWF GPIb binding assay (VWF:RCo, VWF:GPIbR, or VWF:GPIbM), then assessment of VWF multimers is more important compared to use of a 4-test panel also including VWF:CB.[3,5] This is because use of a "good" VWF:CB provides additional information on likely VWD type (see Table 1), namely, an additional test confirmation and/or discriminator for type 2 VWD. Vangenechten and Gadisseur[15] also identified the added value of VWF:CB testing.

The Hydrasys VWF multimer system has undergone additional evaluation by our laboratory and several other groups.[18–24] Results in general reflect positively for the methodology, albeit with already-noted limitations.[18,20] Nevertheless, the method, on its own, is not definitive, and does not replace VWF phenotypic testing. There is overlap in test data on relative absence/retention of HMW VWF between VWD types, with these potentially reflecting continuous rather than discrete variables (Figure 1B). For example, type 2A and 2B cases will overlap, and thus ristocetin-induced platelet aggregation analysis remains the key to diagnosis/exclusion of 2B VWD.[25] Another example is 2M VWD. In the original classification,[2] the onus was on retention of HMW VWF despite apparent loss of VWF activity detected by functional VWF assays (VWF GPIb binding usually, sometimes also VWF:CB). This is sometimes erroneously identified as meaning that no loss of HMW VWF is ever evident in 2M VWD. In the original classification, the "weighting" was on no "significant" loss. Unfortunately, this is a subjective concept. Thus, in 2M VWD, sometimes multimers will show no loss, and other times will show "minor" loss and/or structural changes (generally not evident with the commercial method upon visual inspection[21]). Thus, sometimes patients with "minor" loss of 2M VWD may instead be identified as 2A VWD. A simple way of thinking about this is to suggest that loss of HMW VWF represents a main driver for bleeding risk in 2A VWD, whereas in 2M VWD, the main driver for bleeding risk is likely to be VWF dysfunction per se (be it reduction in GPIb binding and/or collagen binding), rather than any "minor" loss of HMW VWF. This is not to say that VWF dysfunction in 2A VWD is not also an important risk factor for bleeding, or that "minor" loss of HMW VWF in 2M VWD does not itself also contribute to bleeding risk.

Our laboratory identifies prevalence of 2M VWD as being similar to that of 2A VWD,[13] largely based on phenotypic characterization (low VWF:Activity/Ag ratio by VWF GPIb binding assay but normal VWF:CB/Ag ratio, thereby in main part reflecting VWF GPIb binding defects).[13] In large part, these cases will show no loss in HMW VWF by visual inspection[21] but may evidence some "minor" loss of HMW VWF by densitometry.[15,18] Although recommended, genetic testing does not always provide clarity, given the same or close proximity *VWF* "variants" are sometimes classified as 2M, and sometimes as 2A, and indeed also sometimes as type 1.[26]

We can only await further clarification of this fascinating story with additional study, in particular with emerging newer contemporary VWF methodologies, including VWF:GPIbR and VWF:GPIbM, as well as novel VWF:CB methods by chemiluminescence procedures.[6,16,18,27] I also look forward to increasing recognition of 2M VWD, and reduction in 2M VWD misdiagnosis.[13,26–28]

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RELATIONSHIP DISCLOSURE

The author has declared nothing to report.

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