



Building the foundation for a community-generated national research blueprint for inherited bleeding disorders: research priorities for mucocutaneous bleeding disorders

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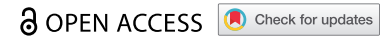


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ORIGINAL RESEARCH



Building the foundation for a community-generated national research blueprint for inherited bleeding disorders: research priorities for mucocutaneous bleeding disorders

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ABSTRACT

Background: Excessive or abnormal mucocutaneous bleeding (MCB) may impact all aspects of the physical and psychosocial wellbeing of those who live with it (PWWMCB). The evidence base for the optimal diagnosis and management of disorders such as inherited platelet disorders, hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD), Ehlers-Danlos syndromes (EDS), and von Willebrand disease (VWD) remains thin with enormous potential for targeted research.

Research design and methods: National Hemophilia Foundation and American Thrombosis and Hemostasis Network initiated the development of a National Research Blueprint for Inherited Bleeding Disorders with extensive all-stakeholder consultations to identify the priorities of people with inherited bleeding disorders and those who care for them. They recruited multidisciplinary expert working groups (WG) to distill community-identified priorities into concrete research questions and score their feasibility, impact, and risk.

Results: WG2 detailed 38 high priority research questions concerning the biology of MCB, VWD, inherited qualitative platelet function defects, HSD/EDS, HHT, bleeding disorder of unknown cause, novel therapeutics, and aging.

Conclusions: Improving our understanding of the basic biology of MCB, large cohort longitudinal natural history studies, collaboration, and creative approaches to novel therapeutics will be important in maximizing the benefit of future research for the entire MCB community.

Plain Language Summary

More people experience mucocutaneous bleeding (MCB), affecting tissues like skin and gums, than have hemophilia A or B. MCB is not understood as well as hemophilia. Common types of MCB include nosebleeds, bleeding gums, heavy menstrual bleeding, and digestive tract bleeding. Mucocutaneous inherited bleeding disorders include inherited platelet disorders, hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD) and Ehlers-Danlos syndromes (EDS), von Willebrand Disease (VWD), and others. Diagnosing and treating MCB is complicated and sometimes medical providers dismiss the bleeding that patients report when they cannot find a medical explanation for it. Many people with mucocutaneous bleeding (PWWMCB) do not receive the care they need; for example, women with VWD live with symptoms for, on average, 16 years before they are diagnosed in the US. This struggle to obtain care has important negative impacts on patients' physical and psychological health and their quality-of-life. The National Hemophilia Foundation (NHF), a large US bleeding disorders patient advocacy organization, set out to develop a National Research Blueprint for

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Inherited Bleeding Disorders focused on community priorities. They brought together a group of patients, providers, and researchers with MCB expertise to identify the research that would most improve the lives of PWMCB through targeted and accessible diagnostics and therapies. We report in this paper that research is needed to better understand the biology of MCB and to define the mechanisms of disease in these disorders. We also describe high priority research questions for each of the main disorders, novel therapeutics, and aging.

1. Introduction

1.1. Mucocutaneous inherited bleeding disorders

Clotting factor VIII (FVIII) and factor IX (FIX) deficiency, hemophilia A and B, respectively, are the best known and studied inherited bleeding disorders (BD) with their characteristic musculoskeletal bleeding, and associated long-term sequelae. However, excessive or abnormal bleeding of mucocutaneous tissues (MCB), and mucocutaneous inherited bleeding disorders (MCIBD) have a higher prevalence (up to $\leq 1:33$, **Supplementary Table S1**) [1–19].

These disorders include, but are not limited to, inherited platelet disorders (IPD), hereditary hemorrhagic telangiectasia (HHT), hypermobility spectrum disorders (HSD) and Ehlers-Danlos syndromes (EDS), and the most common inherited BD, von Willebrand disease (VWD). A large proportion of people with MCB (PWMCB) are eventually diagnosed with a bleeding disorder of unknown cause (BDUC) [1,20], or left without a diagnosis. Typical symptoms include epistaxis, easy bruising, gingival bleeding, prolonged bleeding from cuts, gastrointestinal (GI) bleeding, heavy menstrual bleeding (HMB), and post-partum hemorrhage (PPH) [21–24]. A lack of standardized methodology to evaluate the severity of most MCB combined with a poor correlation between laboratory results and clinical phenotype complicate diagnosing MCIBD [20,25,26]. A historic focus on hemophilia may have influenced study designs to the detriment of MCB research. Studies often prioritize outcomes well characterized in hemophilia research [27], but which may not accurately reflect the pathobiology of individual MCIBDs or the priorities of people living with them [20,26,28,29].

1.1.1. Impact of inadequate understanding of mucocutaneous bleeding

Typical laboratory investigations of clotting factors, platelet function, and bleeding time are normal in many PWMCB, complicating their diagnosis and access to treatment [25,30]. BDUC, defined as a clear bleeding tendency in the presence of normal hemostatic tests, may facilitate access and offer important validation of their lived experiences to PWMCB, but remains a challenging and unstandardized diagnosis [26]. As many as 10% of those seen in some hemophilia treatment centers (HTC), most notably women with HMB or PPH, are diagnosed with BDUC, and their bleeding assessment tool (BAT) scores indicate MCB phenotypes comparable to those of people with VWD or IPDs [1,20,31–34].

Undiagnosed and sub-optimally managed MCB may negatively impact many aspects of a person's life, through the physiological sequelae of bleeds; financial sequelae with loss

of time from work and school from repeated and extensive lab tests and doctor visits; and psychosocial and mental health sequelae of the uncertainty, limitations on normal physical and social activities, and in some cases not being believed or taken seriously by healthcare professionals (HCP). Stigmatization of menstruation and the long-standing issue of sexism in BDs contribute to decreased awareness and a failure to recognize the legitimacy of reported symptoms [35]. A recent study suggests a higher prevalence of depression and anxiety in young adults with HMB than the general population [36,37]. Conflicting perceptions, between HCP and PWMCB, regarding the clinical importance of symptoms exacerbate diagnostic challenges and the lack of standardized care [1,26,29].

1.1.2. Von Willebrand disease

VWD is autosomally inherited equally by men and women. The estimated prevalence of a laboratory diagnosis of VWD is 1:100 while the prevalence of symptomatic VWD is 1:1000 [15–19]. It is caused by a dysfunction or deficiency in von Willebrand factor (VWF), a multimeric glycoprotein with multiple roles in hemostasis including as a chaperone for FVIII, and in the adhesion and aggregation of platelets at the site of blood vessel injury [19]. VWF is also involved, through interactions with multiple cellular and extracellular proteins, in thrombosis, inflammation, and the regulation of angiogenesis [38,39]. The most common symptoms include HMB, epistaxis, easy bruising, prolonged bleeding from minor wounds and in the oral cavity, GI bleeding, and bleeding following dental procedures or tooth exfoliation, childbirth, and surgery. There are three general types of VWD, based on the nature of the VWF deficiency or dysfunction, with type 2 further subtyped by specific functional deficiency [40–42].

Accurate diagnosis can be complex, requiring specialized laboratory assays [43]; available data suggest VWD remains largely underdiagnosed around the world [44]. Women in the US report the passage of, on average, 16 years between their first VWD symptoms and a clinical diagnosis [17]. Management of VWD is best tailored to type and symptoms, and consists primarily of antifibrinolytic treatments, such as tranexamic acid; the vasopressin analog, desmopressin (often referred to as DDAVP); and recombinant or plasma-derived VWF replacement therapy [43]. Hormonal therapies are often effective in controlling HMB, while prophylaxis with replacement factor is sometimes appropriate [43,45–47].

1.1.3. Inherited platelet disorders

IPDs that cause abnormal or excessive bleeding can be quantitative, qualitative, or both, in nature. Qualitative platelet

disorders may be caused by defects in the cytoskeleton, cell surface receptors, signal transduction pathways, secretory granules, or other aspects of platelet structure and/or function [48]. Accurate determination of the causative platelet problem is not always adequately achieved with the widely available assays [49]. Advances in molecular diagnosis underscore the multifactorial, polygenic complexity of many IPDs [49,50]. Clinical presentation and bleeding symptoms, mostly mucocutaneous, are highly variable, ranging from mild or no bleeding to life-threatening hemorrhages [24]. Transfusion of platelet concentrates, infusion of recombinant activated FVII, desmopressin, and antifibrinolytics, constitute the primary therapeutic options for IPDs with management often focused on achieving adequate hemostasis in contexts of acute bleeding risk such as surgery and childbirth [51]. Optimal management remains elusive for many people with IPDs.

1.1.4. Hereditary hemorrhagic telangiectasia

HHT is an autosomal dominant disorder that causes abnormal blood vessel formation manifesting in mucocutaneous telangiectasias, arteriovenous malformations (AVM), and bleeding with resulting secondary iron deficiency anemia [52–54]. Though this multisystemic disorder is often omitted from discussions of inherited BDs, common complications of AVMs include epistaxis, GI bleeding, iron deficiency, iron deficiency anemia, hemorrhagic stroke, and increased risk of thrombosis making the involvement of a hematologist in the HHT multidisciplinary care team essential [52,54]. Diagnosis is primarily clinical and based on the presence of three to four of the following: spontaneous and recurrent epistaxis; multiple telangiectasias at characteristic sites (lips, oral cavity, fingers, nose); GI telangiectasias, pulmonary, hepatic, cerebral, or spinal AVMs; a first degree relative with HHT [55,56].

A number of genetic variants associated with HHT have been well characterized; genetic testing can be a useful diagnostic tool, particularly in the detection of clinically silent but complication-prone pulmonary and cerebral AVMs in asymptomatic family members [57]. Treatment of HHT is patient- and symptom-specific consisting primarily of mitigating epistaxis and GI bleeding, including the use of antifibrinolytic and antiangiogenic agents, supportive iron supplementation for anemia, and ablation of bleeding sites and AVMs [52,54,55,57–59].

1.1.5. Hypermobility spectrum disorder and Ehlers-Danlos syndromes

HSD and EDS represent a clinically and genetically heterogeneous group of conditions often omitted from considerations of inherited BDs, but typified by easy bruising and bleeding [60]. Thirteen clinical EDS subtypes have been classified; classical (cEDS) and hypermobile EDS (hEDS) are the most common [61], vascular EDS (vEDS) manifests the most severe bleeding phenotypes and worst prognosis [14,30]. Definitive diagnosis, complicated by clinical overlap between subtypes and with other heritable connective tissue disorders, relies heavily on confirmation of causative genetic variants, except in the case of hEDS where no such signature has been identified [61]. Individuals with HSD share many of the clinical findings of EDS including associated bleeding symptoms [62], but do not meet formal EDS diagnostic criteria [61].

Multidisciplinary teams are key to the management of HSD and EDS [63–65]. The focus is on awareness and avoidance of activities, such as contact sports, or conditions, such as high blood pressure, that may exacerbate vessel and tissue fragility with urgent repair of arterial rupture and pain control [14,66,67]. People with EDS may struggle to obtain disease-centered coordinated multidisciplinary care (as provided at an HTC) as they tend to be seen in a variety of community and clinical settings, and lack a designated specialty provider or medical home [68].

1.2. People with mucocutaneous bleeding at the center of research

The mission of the NHF, the largest US patient advocacy organization serving people with inheritable blood disorders, is to find cures and to address and prevent the complications of these disorders through research, education, and advocacy enabling people and families to thrive [69]. NHF recognizes that this vision starts with research and that the people who live with these disorders are true lived experience experts (LEE) with unique and valuable expertise [70,71]. In 2014 NHF brought together VWD LEEs and research, care, policy, clinician, payer, industry, and federal agency stakeholders. This VWD Summit prioritized raising awareness, improving access to care, the development of evidence-based clinical practice guidelines, and a recommitment to collaborative efforts to improve VWD research [72]. In 2021, the American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), NHF, and World Federation of Hemophilia (WFH) World Federation of Hemophilia (WFH) developed clinical guidelines on the diagnosis and management of VWD [45,73]. This precedent-setting extensive international collaboration was motivated by the joint LEE-clinician identified need; the clinical questions it addressed were prioritized through a trilingual stakeholder survey with equal proportions of LEE and HCP respondents [74], and approximately one quarter of the expert guideline development panel members were LEEs [75]. The valuable contributions of LEEs to all aspects of the evidence base are increasingly being recognized and capitalized upon.

1.3. Community-identified areas of priority research

In 2020 NHF, in collaboration with the American Thrombosis and Hemostasis Network (ATHN), launched an initiative to establish the research needs of the community culminating in a State of the Science Research Summit (SOSRS) [70,76]. They conducted extensive consultations with all stakeholders to identify the priorities of people with inherited bleeding disorders (PWIBD) and the people who care for them, and recruited expert working groups (WG) to distill these into concrete research questions. WG2 Research Priorities for VWD, Platelet Dysfunction and Other Mucocutaneous Inherited Bleeding Disorders was challenged with the key question: What is needed to engender more targeted and accessible diagnostics and therapies for all people with these disorders [70]? The NHF SOSRS Steering Committee charged

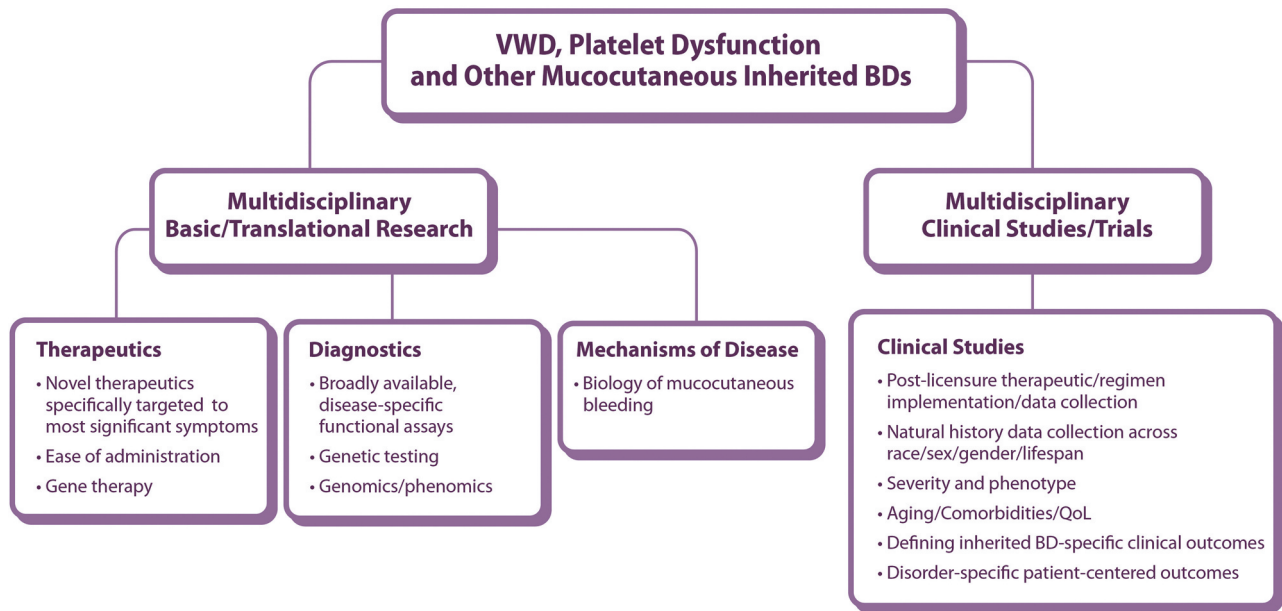


Figure 1. Working Group 2 VWD, platelet dysfunction and other mucocutaneous inherited bleeding disorders schematic of community-identified areas for priority research framework.

BD: bleeding disorder, QoL: quality-of-life, VWD: von Willebrand disease

WG2 with investigating multidisciplinary opportunities to address the issues prioritized in the community consultations through both basic and translational research and clinical studies (Figure 1).

We report the response of WG2 to this challenge: priority research questions for VWD, platelet dysfunction, and other

MCIBDs, and how we arrived at them. These proposals were presented to the inherited BD community at the NHF SOSRS in September 2021; ensuing discussions contributed to refinement of the WG's conclusions. Advancing VWD, platelet dysfunction, and other MCIBD research is essential to bringing health equity within reach of all PWIBDs. WG2 offers these

Table 1. Members of working group 2.

Member	Stakeholder Group	Affiliation
Veronica H. Flood, MD (Co-chair)	Pediatric hematologist	Pediatric Hematology/Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin
Robert F. Sidonio, Jr., MD, MSc (Co-chair)	Pediatric hematologist	Aflac Cancer and Blood Disorders; Hemophilia of Georgia Center for Bleeding and Clotting Disorders, Atlanta, Georgia
Paulette C. Bryant, MD	Pediatric hematologist; NHF Board member	St. Jude Affiliate Clinic at Novant Health Hemby Children's Hospital, Charlotte, North Carolina; NHF
Jorge Di Paola, MD	Pediatric hematologist	Pediatrics, Hematology/Oncology, Washington University in St. Louis, Missouri
Sarah Hale	Industry	Takeda Pharmaceuticals U.S.A., Lexington, Massachusetts
Meadow Heiman, LCGC	Genetic counselor	Indiana Hemophilia and Thrombosis Center, Indianapolis, Indiana
G Shellye Horowitz, MA	LEE	Hemophilia Federation of America
Christi Humphrey, LCSW	Social worker	Hemophilia of Georgia, Atlanta, Georgia
Julie Jaffray, MD	Pediatric hematologist	Children's Hospital Los Angeles; University of Southern California; Keck School of Medicine, California
Lora C. Joyner, MS, PT, PCS	Physical therapist	East Carolina University Hemophilia Treatment Center, Greenville, North Carolina
Raj Kasthuri, MD	Medical hematologist	UNC Hemophilia and Thrombosis Center, University of North Carolina at Chapel Hill, North Carolina
Barbara A. Konkle [†] , MD	Medical hematologist	Washington Center for Bleeding Disorders, Seattle, Washington
Peter A. Kouides, MD	Medical hematologist	Mary M. Gooley Hemophilia Center, Rochester, New York
Cindy Leissing, MD	Medical hematologist	Louisiana Comprehensive Hemophilia Center, Tulane University Medical Center, Louisiana
Robert Montgomery, MD	Medical hematologist	Blood Research Institute, Versiti; Medical College of Wisconsin, Milwaukee, Wisconsin
Keith Neeves, PhD	Researcher	Hemophilia and Thrombosis Center, University of Colorado Denver; Anschutz Medical Center, Colorado
Anna M. Randi, MD, PhD	VWF and vascular biology researcher	National Heart and Lung Institute, Imperial College, London, UK
Nikole Scappe	LEE; NHF staff	NHF
Cristina Tarango, MD	Pediatric hematologist	Department of Pediatrics, University of Cincinnati College of Medicine; Cincinnati Children's Hospital Medical Center, Ohio
Kelly Tickle, MSN, APN, PCNS-BC, PPCNP-BC	Advanced practice practitioner	Aflac Cancer and Blood Disorders; Children's Healthcare of Atlanta; Hemophilia of Georgia Center for Bleeding and Clotting Disorders, Atlanta, Georgia
Pamela Trapane, MD	Pediatrician	Pediatric Genetics, University of Florida, Jacksonville, Florida
Michael Wang, MD	Pediatric hematologist	Hemophilia and Thrombosis Center, University of Colorado Denver; Anschutz Medical Center, Colorado
Brittany Waters, DMD	Dentist	Children's Healthcare of Atlanta, Georgia

[†]NHF SOSRS Steering Committee

LEE: lived experience expert, NHF: National Hemophilia Foundation, SOSRS: State of the Science Research Summit, VWF: von Willebrand factor

prioritized research questions, and the themes that they underscore, to the development of a National Research Blueprint for Inherited Bleeding Disorders [77].

2. Methods

2.1. Working Group 2 composition

The makeup of WG2 reflected the breadth of their charge (Table 1). The co-chairs worked with the NHF SOSRS Steering Committee to recruit the expertise necessary to develop the community-prioritized issues into concrete research questions with the greatest potential to improve the lives of people with VWD, platelet dysfunctions, and other MCIBDs. Central to the group were several LEEs, contributing the unique expertise of people who live with these disorders daily [71]. The WG also benefited from experts in adult and pediatric hematology; basic biology including systems biology, microfluidics, angiogenesis, genomics, vascular and platelet biology; connective tissue disorders including EDS; HHT; and multidisciplinary care for PWBD including social work, genetic counseling, advanced practice nursing, dentistry, physical therapy, and patient education and advocacy, as well as an industry partner. All WG members had equal standing; the co-chairs actively solicited input from everyone including the lived experiences and perspectives of LEEs. An NHF support person accompanied the LEEs throughout with multiple individual and group consultations designed to empower their participation.

2.2. Ways of working

WG2 met virtually, via the Microsoft Teams platform, twice a month from May to August 2021. They subdivided their focus area into six topics; the entire group worked together to identify specific priority research questions concerning:

- Biology of mucocutaneous bleeding
- Von Willebrand disease
- Inherited qualitative platelet function defects
- Hypermobility spectrum disorders/Ehlers-Danlos syndromes, hereditary hemorrhagic telangiectasia, and bleeding disorder of unknown cause
- Novel therapeutics
- Aging

The WG developed each topic individually, then reviewed all questions generated, collapsing any redundancy and assigning cross-over questions to a single topic. Areas of investigation better suited to other WGs were offered to their chairs. Potential ambiguities were resolved through discussions between co-chairs, for example the WG3 Research Priorities for Ultra-Rare Inherited Bleeding Disorders co-chairs agreed to include Glanzmann thrombasthenia and Bernard Soulier Syndrome in their work [78]. WG2 focused on qualitative platelet function defects, often classified as mild inherited BDs, but whose impact on the lives of PWMCB can be very significant [24].

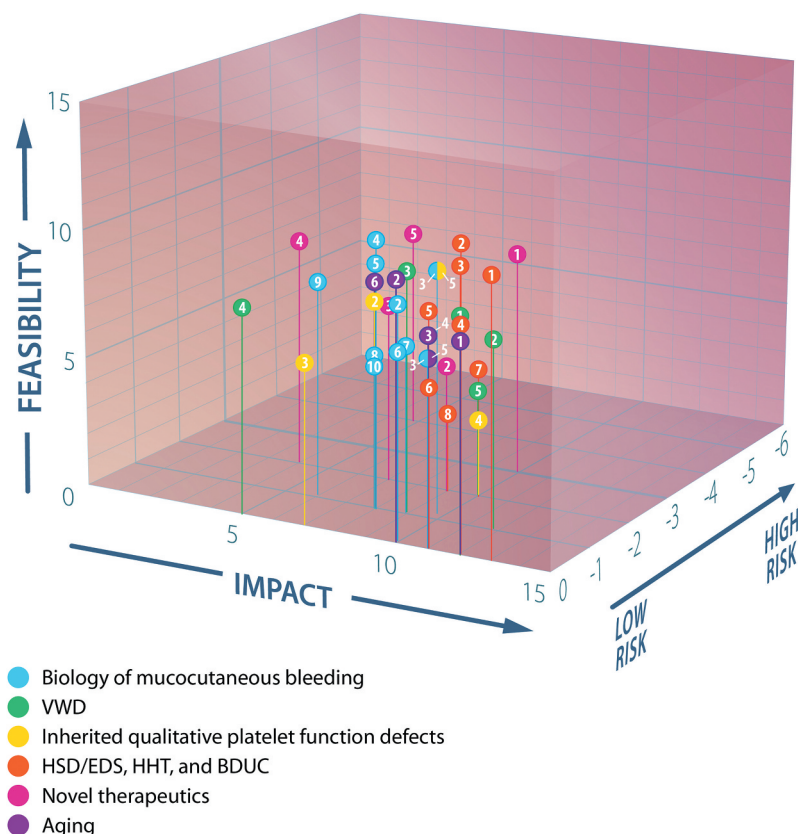


Figure 2. Plot of feasibility, impact, and risk scores of prioritized questions in WG2 subgroup subject areas.

Label numbers correspond to those in Tables 2–7, segmented circles indicate data points from different topics with identical coordinates. BDUC: bleeding disorder of unknown cause, EDS: Ehlers-Danlos syndromes, HHT: hereditary hemorrhagic telangiectasia, HSD: hypermobility spectrum disorders, VWD: von Willebrand disease

Table 2. Feasibility-impact-risk scored highest priority research questions concerning the biology of mucocutaneous bleeding.

#	Research Question	F-I-R Score
1	Can we define the differences in the biology of the various components of distinct mucocutaneous locations (i.e. environmental differences between the GI tract, nasal tissue, and uterus; presence of different mucins, rheology etc.)?	19
2	In people with VWD, is there an inherent defect in wound healing, and if so in which tissues?	19
3	What is the role of hormones (including gender), menstruation, pregnancy, and the perimenopausal context on the blood vessel environment as it relates to MCB?	18
4	Can we characterize the pathways mediating the interaction of platelets and plasma proteins with the different, tissue-specific vascular beds and extravascular space?	18
5	What is the role of vascular mural cells (e.g. pericytes) in the control of hemostasis and MCB?	17
6	Does VWF have any function(s) in regulating vascular integrity, and/or any other function(s) that are not currently measurable which could contribute to MCB?	17
7	What are the contributions of blood vessel associated pathways, the extracellular matrix, and the microenvironment to MCB?	16
8	How do we develop better animal and in vitro (e.g. organ and blood vessel on a chip, ECFC/personalized) models to capture the contribution of the microenvironment to MCB?	14
9	What is the role of the interaction between VWF and various proteins (e.g. ECM proteins, growth factors) in the regulation of hemostasis and vascular integrity?	14
10	What is the biologic difference in the distinct microenvironments (GI tract, nasal tissue and uterus) of EDS and HHT compared to VWD?	13

ECFC: endothelial colony forming cells, EDS: Ehlers-Danlos syndromes, F-I-R: feasibility-impact-risk, GI: gastrointestinal, HHT: hereditary hemorrhagic telangiectasia, MCB: mucocutaneous bleeding, VWD: von Willebrand disease, VWF: von Willebrand factor

Table 3. Feasibility-impact-risk scored highest priority research questions concerning von Willebrand disease.

#	Research Question	F-I-R Score
1	Can we longitudinally characterize joint health in people with VWD? (Including bone and joint changes, physical therapy assessment, pain symptoms, and clinical function for all VWD subtypes)	21
2	Can we improve diagnostic VWD testing such that it does not rely on specialized coagulation laboratories?	19
3	Can emicizumab be used effectively as subcutaneous therapy (prophylaxis) for people with severe VWD?	18
4	What can be done to better understand the male journey with VWD?	13
5	How can we use anti-angiogenesis agents for management of certain bleeding symptoms in people with severe VWD?	12

F-I-R: feasibility-impact-risk, VWD: von Willebrand disease

Table 4. Feasibility-impact-risk scored highest priority research questions concerning inherited qualitative platelet function defects.

#	Research Question	F-I-R Score
1	What is the natural history in people with qualitative platelet function defects? (Including QoL and the evolution of bleeding symptoms as people age)	19
2	How can we optimize the management of qualitative platelet function defects?	15
3	What is the relationship between certain medications and some qualitative platelet function defects?	13
4	How can we improve and standardize platelet function testing beyond platelet aggregation, and standardize diagnostic testing for IPDs?	13

F-I-R: feasibility-impact-risk, IPD: inherited platelet disorder, QoL: quality-of-life

Table 5. Feasibility-impact-risk scored highest priority research questions concerning hypermobility spectrum disorders/Ehlers-Danlos syndromes, hereditary hemorrhagic telangiectasia, and bleeding disorder of unknown cause.

#	Research Question	F-I-R Score
1	Can we define a cohort of PWBUDC and characterize them longitudinally? (Requires definition of BUDC, and standardization of workup to exclude other causes)	24
2	Can we develop a collaborative effort in longitudinal evaluation and surveillance of HSD/EDS, HHT, and BUDC within the HTC network?	24
3	How does iron deficiency affect the bleeding and thrombotic risk in HHT?	23
4	What is the risk of thrombosis in HHT and why? Can we determine the prevalence of thrombosis in people with HHT?	21
5	What is the mechanism of the coagulation defect in HHT?	20
6	What is the appropriate hemostatic evaluation for PWBUDC, particularly rare fibrinolytic defects and TFPI disorders?	17
7	Can we develop a national biorepository for samples from people without a diagnosis including those with BUDC?	13
8	Is there a molecular signature that can confirm a diagnosis of hypermobile EDS?	10

BUDC: bleeding disorder of unknown cause, EDS: Ehlers-Danlos syndromes, F-I-R: feasibility-impact-risk, HHT: hereditary hemorrhagic telangiectasia, HSD: hypermobility spectrum disorders, HTC: hemophilia treatment center, PWBUDC: person with a bleeding disorder of unknown cause, TFPI: tissue factor pathway inhibitor

2.3. Feasibility-impact-risk scoring

NHF provided a scoring matrix for comparative evaluation of priority research questions which assigned pre-specified scores to distinct characteristics across the three dimensions of feasibility, impact, and risk (F-I-R) [70,76,79]. Summing the three dimensions allowed comparison of questions with diverse associated opportunities and challenges. The WG scored the six sets of research questions individually, and

then reconvened to discuss, and adjust if necessary, the scores of all of the questions. Deliberations were constructive, collaborative, and respectful reaching consensus on all scores.

2.4. NHF State of the Science Research Summit

The WG sought community input from the >880 LEEs, physicians, researchers, multidisciplinary care team professionals,

Table 6. Feasibility-impact-risk scored highest priority research questions concerning novel therapeutics.

#	Research Question	F-I-R Score
1	Is it possible to develop aptamer-based treatments for the hemostatic management of mild MCB disorders?	16
2	Can VWF be modified to be given subcutaneously to treat people with VWD?	12
3	Are there other drugs with cross-over potential that could be used to treat BDUC and inherited qualitative platelet function defects?	12
4	Do genetic differences in endothelial cells affect response to desmopressin?	11
5	Can desmopressin be optimized for the management of bleeding in VWD?	9

BDUC: bleeding disorder of unknown cause, F-I-R: feasibility-impact-risk, MCB: mucocutaneous bleeding, VWD: von Willebrand disease

Table 7. Feasibility-impact-risk scored highest priority research questions concerning aging.

#	Research Question	F-I-R Score
1	Do people with mild MCB disorders develop joint damage and does this change with age (including how this affects activities of daily living and venous access)?	20
2	Does QoL change with age in people with mild MCB disorders?	20
3	Is there an effect on bone and joint health in mild MCB disorders (including VWD and platelet defects) and does it accelerate over time?	19
4	How can we optimize antiplatelet therapy in older patients with cardiovascular disease and mild MCB disorders including VWD?	19
5	Does the surgical bleeding risk change with age in patients with mild MCB disorders?	18
6	What happens to VWF levels over the lifespan? (Including determination of, for any given age, normal VWF values and the level needed to prevent bleeding) Can one outgrow (mild) VWD?	16

F-I-R: feasibility-impact-risk, MCB: mucocutaneous bleeding, QoL: quality-of-life, VWD: von Willebrand disease, VWF: von Willebrand factor

and federal and industry partners at the (virtual) NHF SOSRS, September 12–15, 2021 [70]. Nikole Scappe presented her personal perspective on the importance of MCB LEEs contributing to research agenda setting, James O'Donnell, MD, delivered a plenary on the diagnosis and treatment of phenotypically variable VWD, and the co-chairs presented a summary of WG2's work and conclusions. Barbara A. Konkle, MD, moderated a live panel discussion engaging the co-chairs, plenary speaker, presenting LEE, and several WG2 members with questions and comments from SOSRS delegates. This panel discussion informed the Discussion and Conclusions of this paper.

3. Results

Whole-group discussions of the community priorities outlined in Figure 1 produced many research questions in the six high priority research areas (Suppl Table S2). Questions were refined and consolidated into shortlists, and evaluated against the F-I-R matrix (for complete component scores see Suppl Table S3, summarized in Figure 2 and Tables 2–7), further detailed below.

Several topics generating considerable discussion fell more suitably within the remit of other WGs. Questions regarding HMB and perimenopausal concerns, while highly relevant to PWMCB, were re-directed to Working Group 4 Research Priorities for the Health of People Who Have or Had the Potential to Menstruate [80]. Barriers to accessing testing and home care, delivery of services to people with HSD/EDS, and access to mental health care for PWIBD were referred to Working Group 5 Diversity, Equity and Inclusion, Health Services Research, and Implementation Science [81]. Several advocacy issues also surfaced repeatedly in WG2 discussions including access to genetic testing for HHT and qualitative platelet function defects, empowering PWMCB and their families to be heard during the workup of their bleeding disorder(s), and retaining people with BDUC (PWBDUC) in hematology clinics/HTCs.

Three other worthy lines of inquiry spanned the breadth of inherited BDs:

- How does needle aversion affect diagnosis and treatment of mild BDs?
- Might it be possible to develop a cost-efficient and equitable treatment with antifibrinolytics alone for mild BDs?
- Post-approval surveillance data collection for new drugs is important to the community.

3.1. Biology of mucocutaneous bleeding

WG2 set out to formulate the most important research questions concerning the diagnosis and treatment of MCB, however they found themselves severely restricted by the limited current understanding of the basic biology underlying these disorders. Detailing this knowledge gap generated the greatest number of high priority research questions of the six areas (Table 2). The questions seek to elucidate the interactions of plasma proteins and blood cells with mucocutaneous proteins and cells, and how these interactions vary between tissues in the healthy state and in specific inherited BDs. The differences between distinct microenvironments (GI tract, nasal tissue, uterus) must first be better understood, to then question how they are impacted by individual MCIBDs (e.g. EDS, HHT, VWD). The potentially multigenic nature of these disorders, and how this might be used to better diagnose and manage them, was discussed, but the low feasibility of this research avenue precluded it from the final shortlist. Similarly, questions about the potential differences between platelet and plasma VWF populations, how these might explain some MCB, and whether changes in these characteristics with age are not being captured by current functional assays were deemed of great interest, but not currently sufficiently feasible to prioritize. Much work remains to understand the interactions between blood vessels, the extracellular matrix, and the tissue microenvironment and their contributions to MCB.

Some of the proposed studies are more immediately feasible, others will be more challenging to perform, however the potential impact on the lives of PWMCB of even the more difficult questions is so high that they must be addressed, with urgency.

3.2. Von Willebrand disease

The five top scoring VWD research questions are presented in [Table 3](#). The highest priority question addresses the longitudinal joint health of people with VWD, an area where significant advances have been made in hemophilia [82], while VWD has lagged behind. Careful joint assessment by qualified physical therapists is typical for hemophilia but less common for other inherited BDs. Other high priority questions include the development of diagnostic tests that require less specialized equipment and technical expertise than currently, and to consider the potential benefits of a novel US Food and Drug Administration (FDA) approved hemophilia non-factor therapy (emicizumab) in preventing bleeding in VWD. WG2 prioritized research into opportunities that anti-angiogenesis agents might offer for the management of certain severe VWD symptoms, and into the specific experiences of males with VWD. Multigenic contributions to the pathobiology of VWD and the investigation of multiple potentially causative variants was discussed, the feasibility concluded to be limited. Improving genetic testing and the overall understanding of test results for people with type 1 VWD were considered, but rated poorly on feasibility and impact criteria. While intellectually inviting, pursuit of gene therapy for VWD returned low feasibility and highly negative risk scores, yielding a very low total score. Priority research questions pertaining to VWD and aging are reported below.

3.3. Inherited qualitative platelet function defects

The differentiation of the highest scoring question in this topic ([Table 4](#)) versus the other top priority questions reflects the dearth of data on qualitative platelet function defects, likely due to diagnostic challenges and the extensive heterogeneity in the precise defect between individuals, and the need to better understand how these defects impact the lives of individuals with IPDs. Such investigations must include quality-of-life outcomes and how symptoms evolve throughout the lifespan, including with aging. The second question, investigating optimal management of these platelet defects, may lend itself well to a combined study with the first. Examining how medications helpful for other conditions might exacerbate qualitative platelet function defects, or even be beneficial, received a relatively high priority score, again reflecting the poor current understanding of many fundamental management aspects. Inadequacies of existing platelet function assays (primarily whole blood impedance or light transmission aggregometry) and their susceptibility to pre-analytic variables informed the prioritization of standardizing diagnostic testing. Investigating genetic sequence variations in the diagnosis of IPDs was discussed, but scored too low on feasibility. Recall that Glanzmann thrombasthenia and Bernard Soulier

Syndrome fell within the remit of WG3 Research Priorities for Ultra-Rare Inherited Bleeding Disorders [78].

3.4. Hypermobility spectrum disorders/Ehlers-Danlos syndromes, hereditary hemorrhagic telangiectasia, and bleeding disorder of unknown cause

WG2 was tasked with examining research priorities for VWD and IPDs, but also for several MCIBDs often omitted from discussions of inherited BDs: hypermobility spectrum disorders (HSD)/Ehlers-Danlos syndromes (EDS) and hereditary hemorrhagic telangiectasia (HHT). Upon reflection, WG2 added bleeding disorder of unknown cause (BDUC), also sometimes referred to as bleeding of unknown cause (BUC) or unclassified bleeding disorder (UBD). In the pursuit of health equity for all PWIBD, WG2 felt it was essential that none of these groups be excluded from the setting or execution of this community-centered research agenda ([Table 5](#)). The top ranked resulting question proposes a logical starting point: the definition of a cohort of PWBDUC which can then be characterized longitudinally. Doing so requires defining BDUC and standardizing how a PWMCB would be screened into the cohort, through exclusion of known causes. This longitudinal study should be a collaborative multi-center effort and include evaluation and surveillance of people with HSD/EDS and HHT. Such a study would inform, in time, the optimal hemostatic management for PWMCB including those with BDUC. Other highly prioritized HHT research questions seek to elucidate the impact of iron deficiency on bleeding and thrombotic risk and to characterize the risk and prevalence of thrombosis in the different HHT genetic mutation types. Investigations of the mechanism of the underlying coagulation defect of HHT, including how a specific genotype might impact phenotype and bleeding severity, was also prioritized, as a key to mitigation strategies. The final few questions concerning BDUC and HSD/EDS did not score as highly in the F-I-R matrix, but WG2 would like to stress the importance of investing in them. The first highlights the need to determine the appropriate hemostatic evaluation for PWBDUC, particularly how best to investigate a rare fibrinolytic or tissue factor pathway inhibitor (TFPI) defect. The group also proposes the establishment of a national biorepository of samples from PWBDUC. Continued research advancing our understanding of MCB should generate novel opportunities to test these samples and determine the cause of bleeding for some individuals. The development of targeted therapies for HHT and HSD/EDS was discussed but did not make the final shortlist of current highest priority research questions.

3.5. Novel therapeutics

Excitement around novel therapeutics in inherited BDs is most pronounced in the hemophilia treatment landscape, but WG2 prioritized a number of research avenues concerning novel therapeutics for PWMCB ([Table 6](#)). The highest scoring of these focused on the potential for aptamer-based treatments in the management of mild MCB disorders. WG2 would like to see investigations into modifications of VWF permitting subcutaneous administration, despite a feasibility score lowered

by the current absence of the appropriate technology. The WG also highlighted the opportunity, potentially in combination with other priorities listed above, to pursue benefits of therapeutics currently in use in other inherited BDs in the management of BDUC and qualitative platelet function defects. Several novel therapy avenues that have demonstrated considerable success in the management of hemophilia were discussed but deemed to incur relatively high risk compounded by low feasibility. These included the creation of an extended half-life recombinant VWF product for intravenous administration, the subcutaneous administration of a non-factor product that mimics the function of VWF to treat and prevent bleeding in VWD, and the utilization of other existing or pipeline non-factor products to treat and prevent bleeding in mild MCIBDs. Elucidating practical aspects of the optimal management of bleeding with desmopressin, commonly used to treat VWD, was prioritized by the WG, along with investigations into the potential impact of any genetic differences in endothelial cells on responsiveness.

3.6. Aging

WG2 prioritized six questions regarding understanding BDs across the lifespan, particularly how they impact people as they age (Table 7). The top prioritized questions reflect community concerns addressing how joint health and joint damage, venous access, activities of daily living, and quality-of-life are affected by mild MCIBDs, including VWD and platelet dysfunction, with age. As PWMCB encounter the common comorbidities of aging, the WG felt it important to investigate whether antiplatelet therapy could be safely used to treat their cardiovascular disease. They also prioritized characterizing their risk of bleeding with surgery over time. Finally, they highlighted understanding how VWF levels change with time, including determining age-appropriate normal levels, and the minimal level required to prevent bleeding at any given age. While VWF levels appear to increase with age, it is not clear why that happens and whether it is possible to 'outgrow' VWD clinically when laboratory normalization of VWF levels occurs. Furthermore, whether those individuals require prophylaxis for subsequent invasive procedures is unclear.

4. Discussion

The inherited BD community prioritized multiple issues concerning MCB disorders in the NHF consultations (Figure 1). As WG2 distilled these into actionable research questions across six topics (Tables 2–7) their discussions coalesced around several themes. The basic biology of MCB is very poorly understood and absolutely must be investigated as a high priority. This lack of understanding contributes to the long, potentially costly, and unsatisfactory diagnostic journey of many PWMCB, and to inadequate treatment [1,20,25]. The innovative application of therapeutics previously characterized in other disorders, informed by a better understanding of the basic biology, may offer important opportunities to improve that treatment. Building the evidence base for better diagnosis and management of PWMCB hinges upon quality data collection starting with the natural history of the disorders throughout the lifespan, including a focus on

hemostatic changes with aging. The overarching theme is one of health equity for all PWIBD. There is a passionate commitment to leave no one with MCB without support, validation, advocacy, a medical home, consistency of care, a diagnosis or the collection of data to contribute to an eventual diagnosis, and the best treatment available which must improve with an evolving understanding of MCIBDs. Given the predominance of gingival bleeding, a dental home is also critical for optimal care. WG2 underscores the importance of conducting the research that will inform improvements in diagnosis and care for PWMCB.

4.1. Basic biology of mucocutaneous bleeding

Our understanding of the basic biology of mucocutaneous milieu, in the healthy state and in the context of the BDs with which WG2 was primarily concerned (IPD, EDS, HHT, BDUC, and even VWD) lags well behind the hemophilia diagnosis and management evidence base. As a result, the ability to accurately diagnose MCIBDs is extremely limited and the treatment goals of PWMCB fall far short of envisaging a lifestyle unimpacted by disease limitations [29,83]. MCB research has tended to follow the hemophilia model, characterizing plasma protein levels. Understanding MCB requires first understanding how the many relevant proteins and cells interact with one another and the cellular and protein components of the vascular bed, the extracellular matrix, mucosa, and the entire blood vessel microenvironment. We must learn how these interactions differ between tissues, organs, and throughout the lifespan including periods of hormonal variation and aging, prerequisite to effectively querying what goes wrong in each specific MCIBD. For example, we need a better understanding of the multiple roles of platelets in response to injury, and regulation of those activities. Combined with improved microfluidic and organ-on-chip models to assay PWMCB samples in an environment mimicking the blood vessel, this new knowledge will greatly enhance characterization of an individual's platelet dysfunction.

The MCB biology research agenda proposed by WG2 is ambitious, but essential to meaningful progress in the diagnosis and management of PWMCB.

4.2. Diagnostic journey of people with mucocutaneous bleeding

PWMCB without a diagnosis face multiple challenges. They live with the limitations and physiological sequelae of a bleeding tendency, as well as important psychosocial stresses [20,26]. HCPs may even dismiss the experiences they report if the results of standard bleeding disorder laboratory tests are negative [29], while insurers may not reimburse the cost of 'negative' diagnostic testing or semi-empiric treatment. The resulting lack of specific treatment leaves them susceptible to future bleeding events and the long-term morbidity associated with repeated bleeding. It is the experience of some of the authors that some LEEs report feeling isolated, abandoned, and disrespected. Some may choose not to return to seek further medical help. It is important that PWBDUC are not dismissed or their disorder minimized, that they are

offered continued surveillance and assistance and that their concerns are taken into consideration and addressed in a supportive manner [29]. Improvements in diagnostic techniques, largely dependent upon advances in understanding basic mucocutaneous microenvironment biology, MCB, and specific pathophysiology of individual MCIBDs, stand to dramatically positively impact the lives of many PWMCB.

VWD is perhaps the best studied MCIBD, yet the VWD diagnostic journey remains challenging [43,84]. Existing diagnostic tests, especially for subtype determination, require highly specialized laboratory equipment and expertise only available in larger urban academic centers [73]. This restricts access to accurate and timely diagnosis – essential to optimal management. Development of tests that can be performed by a greater number of less specialized laboratories has the potential to reduce time to diagnosis, and the number of undiagnosed people with VWD. Most types of VWD are inherited equally by males and females [84]. Females, through menstruation and childbirth, usually encounter diagnostic opportunities more categorically than males [85]. While the diagnostic and management journey of females with VWD is often neither simple nor optimal, the experiences of males are even less well characterized. WG2 is concerned that males with VWD may be unaware and/or hesitant to seek health care; a better understanding of their experiences could help prevent many from going without care.

Advancing molecular and genetic determinations offer important diagnostic opportunities. Classical EDS (cEDS) can usually be established through clinical examination and family history, with confirmation through genetic testing, however, no such helpful molecular signature has been identified for hypermobile EDS (hEDS) [61,86]. Less is known about genetic alterations in HSD. Misdiagnosis and diagnostic frustration are common experiences for people with EDS, which may negatively impact trust in providers and likelihood of seeking care [68]. The lack of a comprehensive framework to organize and respond to the physical and mental health needs of people with complex chronic or rare disorders [87] underscores the importance of providing a medical home for these PWMCB.

It is important to confirm, through functional assays, that novel molecular signatures correspond to physiological or functional hemostatic abnormalities. A number of diagnostic opportunities lie in the standardization of definitions and existing techniques. Characterization of platelet function, or dysfunction in IPDs, currently relies largely on whole blood impedance or light transmission aggregometry, both of which are plagued by preanalytical and analytical variables that affect the results [88,89]. Light transmission aggregometry is favored by many, however despite significant recent efforts to standardize its methodology and interpretation [90–92], in the absence of international reagent standardization or a quality assessment program, standardization between laboratories remains a challenge [93].

The ultimate opportunity to improve the lives of PWMCB through standardization of definitions lies with BDUC. While an increasing number of PWBDUC are being diagnosed [1,26,33], diagnostic criteria vary widely [26,29,94]. Often a diagnosis of exclusion, it is difficult to characterize identifying features of bleeding that cannot (currently) be explained. Leaving people with a bleeding tendency without a diagnosis leads to

unintended harms. It may deny them access to treatment, insurance coverage, and even consultation with a specialist [20,29]. Determining the cause of bleeding must be the end goal for PWBDUC, but in the absence of this capability PWBDUC need a medical home, validation of their experiences, the best treatment available based on what can be determined about their bleeding, and a commitment to continue to follow them and collect their data. Failing to diagnose, register, and accompany PWBDUC also deprives the already scant knowledge base the contribution of their data. This opportunity lies within reach, requiring neither extensive financial resources nor technological advances. WG2 calls upon leaders in this domain to come together and propose a single set of diagnostic definitions and protocols, and the whole community to work constructively to reach a functional consensus. Further diagnostic standards (e.g. appropriate hemostatic evaluation regarding rare fibrinolytic defects and TFPI disorders) may then also be advanced. Such a consensus should also pave the way for a biorepository of samples from PWBDUC, constituting a wealth of material upon which hypotheses may be tested and ultimately individual diagnoses elucidated, as understanding of underlying pathophysiology advances.

HCP education about MCIBDs, BDUC, and how to respond should common coagulation laboratory tests return normal results for a person reporting abnormal bleeding, constitute another important opportunity. Hematologists, other specialists, and primary care physicians must be made aware of the existence and common presentations of lesser known and mild to moderate BDs, and educated to take reported symptoms seriously. They must know how to refer PWMCB to specialist care and why it is important to do so. Inherited BD patient organizations such as the NHF and Hemophilia Federation of America (HFA) will be invaluable in educating HCPs on PWIBD perspectives, the impact of a difficult diagnostic journey, and the life-changing potential of multidisciplinary care. They will also be key in reaching PWMCB not currently accessing such care or outside the HTC network. The capacity of telehealth to extend networks across geographic and transportation challenges may prove very valuable.

People experiencing excessive MCB may not recognize it as abnormal or know where to turn for help. Especially, in the absence of a known family history, they may not be connected to established inherited BD networks, necessitating public awareness raising campaigns extending well beyond these networks. Creativity is required to meet these people where they are, and invite them into the inherited BD community, mutually benefiting their personal health and research initiatives.

4.3. Large cohort longitudinal natural history studies

WG2 proposes large cohort longitudinal natural history studies to address the multifaceted knowledge gap concerning MCIBDs and their natural history throughout the lifespan, including aging and periods of hormonal changes. With the standardization of BDUC definitions, a cohort of PWBDUC can be defined and followed longitudinally. Similarly, for VWD, HHT, HSD/EDS, and IPD; collecting samples and data from large cohorts of individuals throughout their lives will provide substantial information about their joint and bone health, surgical bleeding risk, thrombotic

prevalence and risks, potential disease modifiers, inheritance patterns, quality-of-life and mental health, and how these evolve. Extensive characterization harnessing all the omics (genomics, epigenomics, transcriptomics, proteomics, glycomics, etc.) would multiply these endeavors.

Up to 50–70% of people investigated for a mild or moderate bleeding tendency will not receive a diagnosis of a known bleeding disorder, despite comprehensive laboratory testing [32,94]. Large collaborative long-term observational studies will demonstrate the benefits of treatments that do work for PWMCB and for which specific disorders, expanding the evidence base upon which to optimize and harmonize the standard of care. These investigations will require creative approaches, differing from traditional efforts that design a solution to a well characterized target. They will also demonstrate the amplitude of the community that stand to benefit from treatment innovations and that, contrary to some commercial concerns, does constitute a significant therapeutic population.

4.4. Collaboration

The recently published ASH ISTH NHF WFH 2021 Guidelines for Diagnosis and Management of VWD constitute an important advancement in evidence-based MCB clinical guidelines, though the vast majority of the recommendations were conditional given the paucity of a robust evidence base [45,73]. MCB studies are often constrained by small numbers of participants, inadequately powered to draw robust conclusions, the heterogeneity of parameters and definitions between studies precluding meta analyses of results. WG2 recognizes that large cohort longitudinal natural history studies are impossible without multidisciplinary, cross-specialty, national and even international collaboration. Thoughtful research is required to maximize the impact of each participating PWMCB.

Several collaborative data collection efforts and opportunities already exist. ATHN partners with over 140 US HTC to build a safe, secure national database – the ATHNdataset – offering an opportunity to efficiently initiate novel collaborative inclusive research within an established network [95]. ATHN9 is a current natural history cohort study of the safety, effectiveness, and practice of treatment for people with severe VWD [96], which will form the severe VWD natural history arm of ATHN Transcends: A Natural History Study of the Safety, Effectiveness, and Practice of Treatment in People with Non-Neoplastic Hematologic Disorders [97]. The US Centers for Disease Control and Prevention (CDC) Community Counts Public Health Surveillance of Bleeding Disorders project (Community Counts) gathers and shares data on people with BDs, including some PWMCB, who receive care at US HTCs [98]. NHF's Community Voices in Research initiative is a community-powered registry facilitating direct access for researchers to PWIBD and their data [99]. A network of 26 HHT Centers of Excellence (CoE) spans Canada and the US with several additional centers around the world [100]. The international von Willebrand Disease Prophylaxis Network (VWD PN) united 20 centers from 10 countries to conduct an important retrospective study of prophylaxis

in people with severe VWD [101]; efforts are underway to revive and extend this collaboration. WG2 recognizes that establishing the nature, logistics, infrastructure, and financing of these collaborations requires considerable effort and thanks WG6 Facilitating Priority Research in the Inherited Bleed Disorder Community for their deliberations [102].

Some simpler collaborations also offer significant impact. HHT is a multisystem disorder whose diagnosis requires multidisciplinary collaboration [103]. Recent recognition as an inherited BD, by CDC and ATHN, opened the door to collaborative data collection, however, few people with HHT are under the care of a hematologist. Simply connecting HHT CoEs and HTCs, to share expertise and treatments, has the potential to greatly improve the quality-of-life of many individuals. Similar opportunities exist for HSD/EDS.

4.5. Creative approaches to novel therapeutics

Modern day treatment goals for people with hemophilia include an annualized bleeding rate (ABR) of zero, a functional cure, and freedom from lifestyle and medical restrictions caused by hemophilia [83]. Such health equity is unimaginable for most PWMCB. The inadequate understanding of the basic biology underpinning the disorders combined with limited exploration of therapeutic options leaves PWMCB, and those that treat them, settling for suboptimal treatment goals. In addition to basic research and large cohort longitudinal studies, novel therapeutics constitute an exciting avenue to explore. Some evidence suggest it may be possible to extend some of the benefits of new strategies to rebalance hemostasis in hemophilia [104–106] to other inherited BDs [107]. Roles for emicizumab in severe VWD treatment, recombinant VWF modification for effective subcutaneous administration or to prolong its half-life, and optimization of the management of bleeding in mild VWD with desmopressin are just three such possibilities. Capitalizing on cross-specialty collaborations, studies of anti-angiogenesis agents in the management of certain severe VWD bleeding symptoms where angiodysplasia may contribute to bleeding (e.g. GI bleeding) constitute another.

Therapeutics that have been approved for use in other disorders, and whose mechanisms of action target proteins or processes relevant to MCB, should be tested in collaboration with experts in their established fields. A deeper understanding of the basic biology of MCB should increase such opportunities, particularly for BDUC. There may be some initial reluctance, industry may not recognize the value of investing to expand a well-established market to include a few rare disorders, however with the data generated by more inclusive registries and cohort characterization studies, the MCB community can demonstrate this value. A large number of PWMCB experience significant morbidity and the currently available treatments are woefully inadequate. WG2 highlights this opportunity to advocate to industry the potential benefits of including MCB in their research, and the deliberations of WG3 Research Priorities for Ultra-Rare Inherited Bleeding Disorders on countering reluctance [78].

LEE Perspective

Lived experience experts (LEE) were actively included throughout the entire process reported in this paper. We collaborated with our WG to develop and prioritize the research questions that had the most significant potential to improve the lives of people with VWD, platelet dysfunctions, and other MCIBDs.

We brought forward our lived experiences and shared community stories relevant to the conversation. The LEE role was not a “sit there and listen” role. The co-chairs and other members would constantly pause and ask, “What do the LEEs think? Do you have any questions?”

Some of the most critical points that the LEEs emphasized included that validating and treating bleeding symptoms is essential regardless of the individual’s diagnosis, gender, and age. We felt those who cannot find a specific diagnosis should still have access to treatment and be prioritized in the research realm. We also advocated for males with VWD who are often undiagnosed or not until a traumatic experience occurs. Finally, we felt that categorization as mild, moderate, and severe is irrelevant when doing certain types of research as every affected individual with bleeding symptoms matters, regardless of severity. We challenged the group to research all severities.

This project is so crucial for the future of those with VWD, platelet disorders, and other MCIBDs. Often research is driven by the healthcare providers or researchers. Having the opportunity to walk through the research questions and provide patient experiences and feedback was instrumental in addressing the community's needs.

5. Conclusions

Research into MCB offers many opportunities to advance the pursuit of health equity for all PWIBD. The NHF community consultations revealed myriad ways undiagnosed and/or inadequately treated MCB impacts the physical, mental, financial, and social wellbeing of LEEs living with VWD, platelet dysfunctions, and other MCB every day. Upon this foundation, WG2 built shortlists of prioritized research questions with the greatest potential to positively impact those lives, in six MCB subject areas: biology of MCB; VWD; inherited qualitative platelet function defects; HSD/EDS, HHT, and BDUC; novel therapeutics; and aging (Tables 2–7). A passionate recurring refrain in their discussions was the commitment to leave no person with MCB behind. This means fully welcoming HSD/EDS, HHT, and BDUC into the inherited BD community, ensuring their inclusion in research and data collection, sharing expertise with and inviting it from specialists from other disciplines, educating HCPs and other stakeholders within the inherited BD community, and proactively seeking to provide a medical home for all PWMCB within the HTC network. It means dedicated outreach beyond the established inherited BD community to PWMCB, and all the HCPs they may encounter, ensuring their symptoms are recognized and validated, that they receive the best diagnosis and treatment available, and their potential contributions to advancing research are capitalized upon.

WG2 calls for a commitment to create the conditions and conduct the research that will lead to the transformation of diagnosis and care for PWMCB. A vital component in creating these conditions is to instill in LEEs a sense of the importance of their contributions, the potential of the research, and confidence in the people and institutions conducting it [71]. The NHF SOSRS exemplified the passion, dedication, and desire to collaborate that characterize the inherited BD community. Exchanges between individuals with specialized knowledge of HSD/EDS, HHT, BDUC, VWD, IPD, basic mucocutaneous biology, federal agencies, industry, and living with MCB were constructive and productive. Together we can spur greater interest and investment in MCB research, contributing participant recruitment, cross-specialty multidisciplinary collaboration, institutional support, industry involvement, and regulatory engagement to the realization of the research prioritized by the community. WG2, energized and inspired by this experience, counts on NHF and the National Research Blueprint for Inherited Bleeding Disorders [77] to operationalize these initiatives, capitalize upon the engagement of so many partners, and insistently move everyone steadily toward realizing the prioritized research.

List of abbreviations

ABR	Annualized bleeding rate
ASH	American Society of Hematology
ATHN	American Thrombosis and Hemostasis Network
AVM	Arteriovenous malformations
BAT	Bleeding assessment tool
BD	Bleeding disorder
BDUC	Bleeding disorder of unknown cause
BUC	Bleeding of unknown cause
CDC	US Centers for Disease Control and Prevention
cEDS	Classical Ehlers-Danlos syndrome
CoE	Centers of Excellence
ECFC	Endothelial colony forming cells
ECM	Extracellular matrix
EDS	Ehlers-Danlos syndrome
FVIII	Factor VIII
FIX	Factor IX
F-I-R	Feasibility-impact-risk
GI	Gastrointestinal
HCP	Healthcare professional
hEDS	Hypermobile Ehlers-Danlos syndrome
HFA	Hemophilia Federation of America
HHT	Hereditary hemorrhagic telangiectasia
HMB	Heavy menstrual bleeding
HSD	Hypermobility spectrum disorder
HTC	Hemophilia treatment center
IPD	Inherited platelet disorder
ISTH	International Society on Thrombosis and Haemostasis
LEE	Lived experience expert
MCB	Mucocutaneous bleeding
MCIBD	Mucocutaneous inherited bleeding disorders
NHF	National Hemophilia Foundation
PPH	Post-partum hemorrhage
PWBUC	Person with a bleeding disorder of unknown cause
PWIBD	Person with an inherited bleeding disorder
PWMCB	Person with mucocutaneous bleeding
QoL	Quality-of-life
SOSRS	State of the Science Research Summit
TFPI	Tissue factor pathway inhibitor
US	United States
vEDS	Vascular Ehlers-Danlos syndrome
VWD	Von Willebrand disease
VWD PN	Von Willebrand Disease Prophylaxis Network

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VWF	Von Willebrand factor
WFH	World Federation of Hemophilia
WG	Working Group

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Declaration of interest

The authors are integrated members of the inherited bleeding disorders community: people with inherited bleeding disorders, their family members, healthcare providers and researchers (including physicians, nurses, physical therapists, pharmacists, social workers/psychologists, geneticists/genetic counselors, etc.), industry partners, government officials/regulators, local community organization representatives, and others.

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Author contributions

RF Sidonio Jr and VH Flood led the working group recruitment, organization, discussions, and analysis. All authors contributed to analysis and deliberations. RF Sidonio Jr and VH Flood led manuscript preparation, all authors offered input and contributed to revisions of the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work. GS Horowitz and N Scappe led writing of the Plain Language Summary and LEE Perspective sections.

Presentation of content

RF Sidonio Jr and VH Flood presented highlights of the deliberations of Working Group 2 at the National Hemophilia Foundation State of the Science (virtual) Research Summit (SOSRS), September 12–15, 2021. Summit discussions informed the Discussion and Conclusions of this paper.

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