



HAL
open science

Big picture initiatives in bleeding disorders

Antoine Rauch, Leonard A Valentino, Kevin Mills, Michelle L Witkop, Maria E Santaella, Donna Dimichele, Michael Recht, Sophie Susen

► **To cite this version:**

Antoine Rauch, Leonard A Valentino, Kevin Mills, Michelle L Witkop, Maria E Santaella, et al.. Big picture initiatives in bleeding disorders. *Haemophilia*, 2022, 28 (S4), pp.53-60. 10.1111/hae.14532 . hal-04357416

HAL Id: hal-04357416

<https://hal.science/hal-04357416>

Submitted on 3 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Big picture initiatives in bleeding disorders

Journal:	<i>Haemophilia</i>
Manuscript ID	HAE-00020-2022
Manuscript Type:	Supplement Abstracts
Date Submitted by the Author:	14-Jan-2022
Complete List of Authors:	Rauch, Antoine; Lille University Hospital Center, Hemostasis and Transfusion Recht, Michael; American Thrombosis and Hemostasis Network, ; Oregon Health & Science University, Mills, Kevin; National Hemophilia Foundation Witkop, Michelle L ; National Hemophilia Foundation Santaella, Maria E ; National Hemophilia Foundation Valentino, Leonardo; National Hemophilia Foundation; Rush University DiMichele, Donna ; National Hemophilia Foundation Susen, Sophie; Lille University Hospital Center, Hemostasis and Transfusion
Keywords:	inherited bleeding disorders, heavy menstrual bleeding, pregnancy, postpartum haemorrhage, health equity

Unit 1011: Nuclear Receptors, Metabolic and Cardiovascular Diseases – Pr Bart Staels
Team 2 “Heart disease, flow disturbances and haemostasis” – Pr Sophie Susen

To: Prof. Cedric Hermans
Editor-in-Chief
Haemophilia

MS title: **“Big picture initiatives in bleeding disorders”**

Dear Prof. Hermans,

Please find enclosed, our State-of-the-Art manuscript reflecting the content of the medical session “Big picture initiatives in bleeding disorders” to be featured in the WFH 2022 Congress supplement of the Haemophilia Journal. Two of the three topics scheduled into this session are covered by the manuscript (“NHF research agenda” by Dr Len Valentino, USA; and “Principles of care for management of women with bleeding disorders” by Pr Sophie Susen, France) since Dr Mrinal Gounder did not have time to contribute to this manuscript due to the last COVID-19 wave.

On behalf of all the authors, the work has not been published and is not being considered for publication elsewhere.

Thank you for your consideration.

Sincerely yours,

Antoine Rauch, M.D., Ph.D.

Sophie Susen, M.D., Ph.D.

Types of articles: State-of-the-Art manuscript

Word counts; Abstract: 248, Text: 3597, References: 51, Figure: 1, Tables: 2

Sophie Susen,
Department of Hematology and Transfusion
CHU Lille
59037 Lille Cedex
France

tel +33 3 20 44 59 37
fax +33 3 20 44 69 89
sophiesusen@aol.com

Big picture initiatives in bleeding disorders

Authors: Antoine Rauch¹, Leonard A. Valentino^{2,3}, Kevin Mills², Michelle L Witkop², Maria E Santaella², Donna DiMichele², Michael Recht⁴, Sophie Susen¹

¹CHU Lille, Hematology Transfusion, LILLE, France

²National Hemophilia Foundation, New York, NY USA

³Rush University, Chicago, IL USA

⁴American Thrombosis and Hemostasis Network, Rochester, NY USA

Corresponding author:

Sophie Susen, MD, PhD, Heart and Lung Institute, Hemostasis Department, Bd du Pr Leclercq, CHU Lille, 59037 Lille Cedex, France. Email: sophie.susen@chru-lille.fr

1. Abstract

The inherited bleeding disorders (IBD) community has witnessed significant therapeutic advances in recent years, yet important gaps persist, particularly for those with rare disorders and historically underserved populations. An ambitious initiative underway aims to create an actionable national research blueprint enhancing patient-centric principles to address the priorities of the IBD community. Furthermore, this initiative will accelerate research progress and address important gaps in care. Led by the National Hemophilia Foundation (NHF), this effort is defined by input from across the community, including patients and caregivers who bring lived experiences and are considered subject matter experts (SMEs) of their disorder, research leaders, allied health professionals and specialists, and representatives of the biopharmaceutical industry. Two foundational principles of the blueprint are: 1) it must deliver on key issues that significantly impact the lives of those affected by IBDs, and 2) the priorities defined are relevant and actionable aimed to achieve health equity among all those affected by IBDs. NHF will develop the national research blueprint, to be prepared and issued in 2022. Women and girls with IBDs, who face specific challenges associated with reproduction and the menstrual cycle, are an illustration of critical gaps that remain to be addressed. A multidisciplinary approach is necessary for an optimal management of puberty, transition to adulthood and pregnancy. Recent studies show that even if strict guidelines are followed, these women are still facing a high bleeding burden suggesting a specific research agenda is needed to further improve their management and quality of life.

Key words : inherited bleeding disorders, heavy menstrual bleeding, pregnancy, postpartum haemorrhage.

2. National Hemophilia Foundation research agenda

The inherited bleeding disorders (IBD) community has witnessed significant therapeutic advances in recent years, yet important gaps persist, particularly for those with rare disorders and historically underserved populations. An ambitious initiative underway in the IBD community aims to create an actionable national research blueprint enhancing patient-centric principles to address the priorities of the IBD community. Furthermore, this initiative will accelerate research progress and address important gaps in care. Led by the National Hemophilia Foundation (NHF), this effort is defined by input from across the community, including patients and caregivers who bring lived experiences and are considered subject matter experts (SMEs) of their disorder, research leaders, allied health professionals and specialists, and representatives of the biopharmaceutical industry. Two foundational principles of the blueprint are: 1) it must deliver on key issues that significantly impact the lives of those affected by IBDs, and 2) the priorities defined are relevant and actionable aimed to achieve health equity among all those affected by IBDs. NHF will develop the national research blueprint, to be prepared and issued in 2022.

To ensure the national research blueprint accurately reflects the most pressing needs from across the community, NHF has enlisted the support of diverse segments of the population throughout the process. NHF coordinated a comprehensive, community-wide listening exercise, including focus groups, virtual listening sessions, and consumer and professional surveys, to collect insights shaping and guiding the blueprint development. Representatives from across the IBD community were enlisted to participate in the development process through enrollment in 1 of 6 interdisciplinary working groups (WGs), each focusing on broad themes raised during the listening exercises. The key themes to be addressed by multidisciplinary groups included the use of new technologies for therapeutic advancements, such as application of precision medicine, genetic testing, and point of care diagnostics, as well as continued pursuit of novel therapies for underserved disease populations. In addition, community input raised the need for improvements in comprehensive care, such as mental health, diagnosis, and supportive care; rare IBDs and health disparities; and infrastructure, resource planning and workforce development (see Table 1). In total, 15 individuals participated as a steering committee and 164 in the WGs, inclusive of chapter representatives, allied healthcare providers, researchers, federal partners, and other IBD research organizations. Each WG also featured experts outside the IBD community who introduced innovations from other fields and SMEs who provided personal perspectives on the value and potential impact of the proposed research priorities. NHF actively supported these groups with regular engagement, guidance, and recommendations while encouraging robust dialogue to distill critical priority research areas.

1
2
3 NHF devised a rigorous development and refinement process in order that the blueprint is
4 clearly defined and actionable. Together with expert advisers, NHF has defined a set of
5 feasibility criteria to help the WGs address potential opportunities based on three key areas.
6 Feasibility assesses the difficulty in answering the proposed question, including required
7 expertise, infrastructure, and resources. Impact estimates the change we can foster through
8 the priority. Risk assessment considers the challenges of the research question, such as the
9 technical feasibility for novel strategies and any ethical considerations (see Figure 1). Each
10 research priority or model was scored based on these areas, and the combined evaluation
11 will determine how they are included and prioritized by each WG for ultimate inclusion in the
12 blueprint.

13
14
15
16
17
18
19 Upon the completion of the WG assessments, NHF brought the community together for a
20 virtual State of the Science (SOS) Research Summit, held from September 12-15, 2021. The
21 WG Chairs summarized their recommendations in a live, interactive discussion. During each
22 session, panels discussed the recommendations and collected feedback from community
23 participants, as well as from remote participation groups (RPGs) comprised of
24 representatives from underserved segments of the population (see Table 2). NHLBI support
25 made the inclusion of the critical input from these groups possible (Award Number
26 R13HL158209). NHF's SOS Research Summit attracted 887 attendees who joined 21
27 sessions, led by 43 speakers, and totaled 2,279 unique session views. There was a total of 5
28 RPGs – more are planned in the future. When the SOS Research Summit social media
29 metrics were analyzed, there were demonstrable increases across all social media platforms
30 compared to our non-event averages. The voices of individuals affected by IBDs have been
31 the central drivers in this process, from the listening activities and WGs to the planned SOS.
32 The discussions from the working groups and Research Summit will be consolidated into a
33 series of manuscripts and published as a community-driven national research blueprint in
34 mid-2022. The community will continue to champion the efforts defined in the blueprint.

35
36
37
38
39
40
41
42
43
44 The emergent global themes from the collective efforts of the six WGs were: 1) the
45 importance of people-centricity in research; 2) the importance of multidisciplinary
46 collaboration; and 3) the need to strive for diversity, inclusion, and equity in research and
47 health care. There was an array of different recurring themes raised during the SOS
48 Research Summit. Such themes included: 1) new and inclusive research models, evolution
49 of HTCs to transform access, and realignment for more holistic care, 2) how essential
50 validated patient-centric outcomes are, 3) innovative clinical trial designs including
51 decentralization, adaptive strategies, and incorporation of real-world experience, and 4)
52 importance of data science and infrastructure in research and clinical practice. Furthermore,
53 there were needs that representatives from across the IBD community raised. Such needs
54 included: 1) patients' participation in research at all levels, 2) comprehensive and long-term
55
56
57
58
59
60

1
2
3 approach to workforce expansion, recruitment, career growth, retention, 3) standardized
4 protocols for the diagnosis of inherited platelet disorders, and 4) clinical trial network and
5 integrated infrastructure bringing funding, oversight, capabilities. Such themes,
6 needs/recommendations will serve to align and propel the community's research priorities.
7

8
9 Following the SOS Research Summit, we have initiated a comprehensive, community-driven
10 research blueprint planning effort. The blueprint planning and development process will
11 mirror that of the SOS Research Summit, leveraging defined working groups with cross-
12 cutting charges. Individually and collectively the blueprint working groups, together with a
13 steering committee, will define actionable research plans, including key research initiatives,
14 necessary infrastructure, potential funding agencies, recommended timelines and
15 milestones, and forward-looking plans for community engagement, data dissemination, and
16 progress evaluation. As a part of the blueprint development effort NHF will convene several
17 workshops, bringing together different groups of stakeholders to provide input into, and
18 assessment of, developing plans. These efforts will culminate in a follow-on National
19 Research Blueprint Summit during which the actionable plan will be detailed by participants
20 in the process and community feedback will be sought.
21

22
23 This initiative presents an opportunity to catalyze impactful change in the treatment of IBDs.
24 To ensure its success, NHF has methodically enlisted broad community involvement and
25 driven a rigorous prioritization process to identify specific and actionable topics that will help
26 guide research plans for the IBD community. Actively soliciting the community's views is
27 central in our process to advance research in IBDs. This blueprint will help to guide
28 community research that could fundamentally redefine the experience of living with these
29 disorders. Input and participation from the scientific research community will be key to ensure
30 the success of this process.
31
32

33 34 35 36 37 38 39 40 41 42 43 **3. Principles of care for management of women with bleeding disorders**

44
45
46 Women with IBDs are disproportionately affected, when compared to men, because of
47 specific bleeding challenges related to menstruations and childbirth [1]. Heavy menstrual
48 bleeding (HMB) is the most prevalent symptom in women with IBDs, whatever the underlying
49 diagnosis : von Willebrand disease (VWD), inherited platelet disorders (IPDs), hemophilia
50 carriers or other rare coagulation factor deficiencies [2-4]. These women can experience
51 hemorrhagic ovarian cysts resulting sometimes in hemoperitoneum [5], and are at higher
52 risk of early and late postpartum hemorrhage (PPH), as illustrated by a 2 to 10 fold increased
53 risk in women with VWD, the most frequent IBDs [6]. All these bleeding symptoms impair the
54 quality of life by creating significant physical, emotional, sexual, social, and financial burdens.
55
56
57
58
59
60

1
2
3 Accurate and timely diagnosis of women with IBDs is therefore important to prevent adverse
4 bleeding events and reduce potentially unnecessary surgical interventions such as
5 hysterectomy for HMB or PPH [7-8]. With recent studies showing that some knowledge gaps
6 persist, the impact of bleeding in women with IBDs is of increasing research focus.
7
8
9

10 11 **Screening of IBDs in adult and adolescent women with HMB**

12 Although HMB has been previously defined as >80 mL of menstrual blood per cycle, the last
13 definition proposed in 2018 by the Federation of International Gynecology and Obstetrics
14 (FIGO) relies on the women's self-experience : « excessive menstrual blood loss, which
15 interferes with the woman's physical, emotional, social and material quality of life, and which
16 can occur alone or in combination with other symptoms » [9]. HMB is commonly reported in
17 women of reproductive age and occurs most frequently during the years immediately
18 succeeding menarche and during the perimenopausal transition because these age ranges
19 have the highest prevalence of anovulatory cycles [9-10]. HMB in the setting of ovulatory
20 dysfunction relates to the absence of a predictable cyclic progesterone production from the
21 corpus luteum. The imbalance resulting from the lack of progesterone and the relative
22 excess of estrogen acting on the endometrium, leads to excessive menstrual bleeding.
23 Approximately 13% of women with HMB have an underlying IBDs, most often VWD [11].
24 Early referral, diagnosis, and treatment of HMB in women with IBDs is essential to prevent
25 anemia, need for transfusion of blood products, and hospitalization. According to current
26 international gynecologic or hematologic guidelines, IBDs should be systematically considered
27 in the differential diagnosis of adolescents or women presenting with HMB [12-13]. Of note, a
28 recent study indicates that screening for IBDs in adolescents with HMB should be performed
29 irrespective of the anovulatory or ovulatory pattern of menstrual bleeding [14]. Evaluation of
30 adolescents with HMB should include assessment for iron deficiency anemia, including
31 serum ferritin, the presence of an endocrine disorder leading to anovulation, and screening
32 for the presence of an IBD [10, 12].
33
34
35
36
37
38
39
40
41
42
43
44
45

46 A major challenge is achieving an accurate and timely diagnosis of women with IBDs. Recent
47 studies have shown that screening or referral for screening for IBDs is not routinely
48 performed in women with HMB [15-16]. Several reasons may account why many women with
49 IBDs are still left undiagnosed despite having HMB. The severity of HMB can be easily
50 overlooked when not using the Pictorial Blood Assessment Chart score [17] to provide an
51 objective quantification of menstrual blood loss. General practitioners or obstetrician
52 gynecologist, who are usually the first healthcare providers to encounter women with
53 menorrhagia, may not always consider an underlying IBDs if no other concurrent bleeding
54 symptom is present, given the high rate of anovulatory bleeding in healthy young women and
55 the lack of adequate bleeding challenges before menarche [18]. Use of self-reported
56
57
58
59
60

1
2
3 bleeding assessment tool available online, dedicated mobile period tracker apps and
4 telehealth initiatives for patients residing far from comprehensive care centers for bleeding
5 disorders have been proposed to improve IBDs diagnosis rate in women with HMB [19]. The
6 lack of an appropriate access to specialized laboratory testing or referral to an hematologist
7 with expertise to IBDs is another barrier to diagnosis. The biological exploration should not
8 be limited to routine coagulation assays (prothrombin time and activated partial
9 thromboplastin time). As VWD is the most prevalent IBD, the first level exploration should
10 include specific blood testing for VWD with measurements of von Willebrand factor (VWF)
11 antigen, VWF-platelet GPIIb/IIIa binding activity and factor VIII plasma levels [13]. If this first-line
12 exploration is normal, studies of platelet aggregation and platelet release should be
13 considered, since inherited platelet disorders may also be associated with HMB [20].
14
15
16
17
18
19
20
21

22 **Management of HMB in women with IBDs**

23 Once diagnosed, adolescents and women with IBDs who have HMB should be referred to
24 multidisciplinary clinics, in which gynecologists and hematologists see patients jointly to
25 provide a coordinated and proactive outpatient care [10, 12, 21]. Individuals with HMB have
26 shown high satisfaction rates of 90% with this multidisciplinary approach [22]. In girls with a
27 familial history of IBD, screening before menarche is of the utmost importance to deliver a
28 management plan, set in conjunction with the referent gynecologist and hematologist, if
29 menarche is associated with HMB [10]. Women with known IBD and HMB should also
30 undergo a standard gynecologic assessment to rule out common pelvic pathologies [9].
31 Management of women with IBDs having HMB has to be tailored individually. The goals of
32 HMB management are to reduce morbidity, prevent iron deficiency and improve quality of life
33 through reducing menstrual blood loss and attainment of a predictable pattern of
34 menstruation. Several haemostatic and hormonal options can be used either alone or in
35 combination depending on age, menstrual pattern, the need for contraception and patients
36 tolerability and acceptability of available treatment options [10, 21, 23]. Antifibrinolytic
37 treatment with tranexamic acid as first-line therapy can be efficient to reduce menstrual blood
38 loss in some women with IBDs [24-25].
39
40
41
42
43
44
45
46
47
48

49 Hormonal therapy is the other cornerstone of HMB management in women with IBDs [20,
50 26]. Combined hormonal contraceptives (CHCs) provide an estrogen (usually ethinyl
51 estradiol), helpful in adolescents to obtain more regular and predictable cycles, and a
52 progestin (a synthetic form of progesterone) which reduce menstrual blood loss by
53 downregulating endometrial estrogen receptors, thereby reducing glandular proliferation and
54 inducing endometrial atrophy. By suppressing ovulation, CHCs also reduce the risk of
55 hemorrhagic ovarian cysts. CHCs are available under different formulations (oral pills,
56
57
58
59
60

1
2
3 patches and vaginal rings) but only oral contraceptive pills have been included in randomized
4 trials of HMB [27]. Better outcomes are obtained with continuous as opposed to cyclic
5 administration and with pills containing more than 20 µg of ethinyl estradiol [28]. Progestin-
6 only contraceptives, available under different formulations and route of administrations, are
7 an alternative to CHCs for the reduction of menstrual blood flow. The use a levonorgestrel-
8 releasing intrauterine device (LNG-IUD) is now considered as a first-line alternative to CHCs
9 given it's efficiency in reducing menstrual blood flow in women with IBDs [29]. Expulsion of
10 LNG-IUD can sometimes occur, possibly because of increased menstrual bleeding during
11 first few periods after insertion [30]. Moreover, LNG-IUD can not prevent formation of
12 hemorrhagic ovarian cysts as it does not suppress ovulation. LNG-IUD indication
13 should be discussed in a multidisciplinary setting involving both hematologists and
14 gynecologists.

15
16 In women refractory to hormonal therapy, the use of specific hemostatic therapies should be
17 considered when available for the IBD in question. Desmopressin, a synthetic analog of
18 vasopressin promoting the release in plasma of stored VWF and FVIII from endothelial cells,
19 can be used intranasally or subcutaneously to treat or prevent HMB in women with type 1
20 VWD and some type 2 VWD, as well as in hemophilia A carriers with mild FVIII deficiency.
21 The prophylactic use of specific coagulation factor concentrates is a last option for the most
22 severe cases. Iron replacement therapy is indicated in all reproductive-aged women with
23 anemia related to bleeding at a dose of 60-120 mg per day. In case of poor tolerance and or
24 inefficacy, alternate day iron supplementation may be provided without loss of efficacy [31].
25 Women should also be reminded that nonsteroidal antiinflammatory drugs should not be
26 used routinely for dysmenorrhea.

43 **Management of pregnancy and post-partum in women with IBDs**

44 Women with IBDs have an increased risk of bleeding during pregnancy and delivery and their
45 unborn child may also be at risk of neonatal bleeding if also affected. They require a
46 multidisciplinary management in close relation with a comprehensive care center for bleeding
47 disorders [32-33]. When desiring to become pregnant, these woman should receive a
48 preconception counselling about the genetic transmission, the available options for prenatal
49 diagnosis (preimplantation or prenatal genetic screening, fetal sex determination) and the
50 management of her pregnancy and delivery. The couple should also be referred to a
51 pediatric hematologist to discuss the current therapeutic options for the IBD in question if
52 their child is affected. If this woman is on hormonal treatment because of HMB, she has to be
53 informed for the possibility of menstrual bleeding recurrence once hormonotherapy is
54
55
56
57
58
59
60

1
2
3 stopped. HMB prophylaxis should be discussed with her referent hematologist and both the
4 haemoglobin and ferritin levels should be checked before stopping hormonal treatment and
5 controlled if HMB occurs. A transient hemostatic treatment can be indicated during
6 pregnancy in case of early pregnancy loss or if invasives procedures (procedural abortion,
7 amniocentesis, cerclage...) are needed. In some circumstances, bleeding prophylaxis with
8 factor replacement therapy might be indicated throughout pregnancy to prevent either
9 antenatal bleeding or spontaneous miscarriage (e.g. in women with afibrinogenemia [34] of
10 factor XIII deficiency [35]).

11
12 Delivery should be managed in a facility with on-site access to factor replacement therapy,
13 blood transfusion and a specialized coagulation laboratory. A delivery plan for both the
14 mother and the child should be in place before 32 weeks of gestation, in case of preterm
15 delivery, and communicated to the mother and the other members of the multidisciplinary
16 team. This plan should inform on an eventual contra-indication of neuraxial anesthesia and
17 the need for factor replacement therapy to prevent PPH in the mother and measures to
18 prevent bleeding in affected neonates. As shown by current guidelines on perinatal
19 management of women with IBDs and of hemophilia carriers, the optimal mode of delivery in
20 this setting is still a matter of debate [36-37]. In a recent PedNet multicenter study,
21 instrumental vaginal delivery was associated with the highest risk of intracranial bleeding in
22 neonates with moderate or severe hemophilia while there was no significant difference
23 between vaginal delivery without instruments, cesarean section prior to or during labor. The
24 comparison of planned cesarean section to planned vaginal delivery also showed no
25 significant difference [38]. If the fetus is known or thought to be at risk for an IBD, both
26 vaginal and elective vaginal delivery should be discussed between the obstetrician, the
27 hematologist and the mother in the setting of shared decision making. Instrumental vaginal
28 delivery should be avoided, but if unavoidable, forceps delivery should be preferred to
29 ventouse delivery. Fetal scalp electrodes and scalp blood sampling are also contra-indicated.
30 Prevention of PPH has to be tailored to the nature and the severity of the underlying
31 maternal IBD. Tranexamic acid use should be considered systematically after vaginal or
32 cesarean delivery as it lowers the risk of PPH in women with IBDs without a concurrent
33 increase in the thrombotic risk [39]. In any case, women with IBDs should be followed for at
34 least 2-3 weeks or longer postpregnancy such that delayed bleeding is recognized early and
35 managed appropriately [33].

54 55 **Research agenda for women with IBDs : an evolving roadmap**

56 In recent years, more awareness is raised about sex-specific dilemmas in IBDs. Quality-of-
57 life studies are still revealing a high burden of IBDs in women [40-42]. Despite being more
58 often referred and treated because of sex-specific bleeding such as HMB or PPH, women
59
60

1
2
3 with autosomal IBDs have paradoxically larger diagnostic delay than men [1]. As shown by
4 recent studies [16, 43], there is still a lack of adherence to consensus guidelines. Although a
5 late diagnosis is particularly deleterious for an adequate anticipation of menarche, too few
6 clinicians consider IBDs in the differential diagnosis of adolescent and women with HMB [15-
7 16]. Recent studies have also emphasized that HMB continues to pose significant ongoing
8 management challenges following initial formal diagnosis of IBDs such as VWD [3] or IPDs
9 [44].
10
11
12
13

14
15 Some gender specific issues may have been overlooked in women with IBD. Adult
16 haemophilia A carriers exhibit more bleeding symptoms than normal women, irrespective of
17 their baseline FVIII level [4]. This intriguing observation could be related to an insufficient
18 FVIII response to haemostatic stress, which could be a better predictor of bleeding than
19 baseline FVIII levels in haemophilia A carriers [45]. To improve communication around the
20 issue of bleeding in hemophilia carriers, a new nomenclature has been endorsed recently by
21 the International Society on Thrombosis and Haemostasis. The term “hemophilia carrier”
22 should now be reserved for genetic counseling while terms such as
23 “symptomatic/asymptomatic hemophilia carrier” and “women and girls with hemophilia”
24 should be used in clinical management [46]. Despite pregnancy-related rise in plasma VWF
25 and FVIII levels, a high frequency of PPH is still observed in women with VWD [8] or in
26 hemophilia carriers [47].
27
28
29
30
31
32
33
34
35

36 The latest VWD international guideline endorsed by the American Society for Haematology
37 (ASH), the International Society for Thrombosis and Haemostasis (ISTH), the World
38 Federation of Haemophilia (WFH) and the NHF has reclassified patients with a bleeding
39 phenotype and a mild quantitative reduction in plasma VWF levels (range, 0.30-0.50 IU/mL)
40 as having VWD [13]. This decision is a significant change from the previous guideline which
41 classified these individuals as having “low VWF” and is still controversial [48] given it’s low
42 level of evidence and the risk of overmedicalisation of a large number of individuals, mostly
43 with blood group O who are likely to have levels < 0.50 IU/mL as a variation of normal [49]. A
44 high prevalence of HMB was indeed reported in women with low VWF level, either
45 adolescents [50] or adults [51]. In the latter study, PPH was also self-reported by 63% of
46 parous adult women, with 21% of them requiring transfusion or medical intervention [51],
47 leading to the hypothesis that although VWF plasma levels increase during pregnancy, they
48 may still be lower than expected for gestation in women with low VWF. However, these
49 studies were limited by recall and referral biases inherent to their retrospective design.
50 Further research is therefore needed to determine whether women with low VWF levels
51 should be classified and managed as having a VWD [33].
52
53
54
55
56
57
58
59
60

4. Acknowledgements

The authors wish to acknowledge Karina Lopez for her assistance in preparing the manuscript along with the all the participants who shared their time and insights during the process. The authors have no competing interests relative to this manuscript.

5. References

1. Atiq F, Saes JL, Punt MC, van Galen KPM, Schutgens REG, Meijer K, et al; WiN, RBiN and TiN study groups. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. *EClinicalMedicine*. 2021; 32:100726.
2. Leebeck FW, Eikenboom JC. Von Willebrand's disease. *N Engl J Med*. 2016. 375(21) : 2067-2080.
3. Punt MC, Ruigrok ND, Bloemenkamp KWM, Uitslager N, Urbanus RT, Groot E, et al; Trombocytopathy in the Netherlands (TiN) Study Group. Prevalence, burden and treatment effects of vaginal bleeding in women with (suspected) congenital platelet disorders throughout life: a cross-sectional study. *Br J Haematol*. 2022. 196(1): 215-223.
4. Paroskie A, Gailani D, DeBaun MR, Sidonio RF Jr. A cross-sectional study of bleeding phenotype in haemophilia A carriers. *Br J Haematol*. 2015; 170(2):223-8.
5. Radakovic B, Grgic O. Von Willebrand disease and recurrent hematoperitoneum due to the rupture of haemorrhagic ovarian cysts. *Haemophilia*. 2009; 15(2):607-9.
6. James AH, Jamison MG. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. *J Thromb Haemost*. 2007; 5(6):1165-9.
7. De Wee EM, Knol HM, Mauser-Bunschoten EP, van der Bom JG, Eikenboom JC, Fijnvandraat K, et al; WiN study group. Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease. *Thromb Haemost*. 2011; 106(5):885-92.
8. Punt MC, Waning ML, Mauser-Bunschoten EP, Kruij MJHA, Eikenboom J, Nieuwenhuizen L, et al. Maternal and neonatal bleeding complications in relation to peripartum management in women with Von Willebrand disease: A systematic review. *Blood Rev*. 2020 Jan;39:100633.
9. Munro MG, Critchley HOD, Fraser IS, Committee FMD; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet*. 2018;143(3):393-408.
10. Borzutzky C, Jaffray J. Diagnosis and Management of Heavy Menstrual Bleeding and Bleeding Disorders in Adolescents. *JAMA Pediatr*. 2020; 174(2):186-194.
11. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. *BJOG*. 2004; 111(7):734-40.
12. Screening and Management of Bleeding Disorders in Adolescents With Heavy Menstrual Bleeding: ACOG COMMITTEE OPINION, Number 785. *Obstet Gynecol*. 2019; 134(3):e71-e83.
13. James PD, Connell NT, Ameer B, Di Paola J, Eikenboom J, Giraud N, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv*. 2021; 5(1):280-300.
14. Zia A, Jain S, Kouides P, Zhang S, Gao A, Salas N, et al. Bleeding disorders in adolescents with heavy menstrual bleeding in a multicenter prospective US cohort. *Haematologica*. 2020; 105(7):1969-1976.
15. Byams VR, Anderson BL, Grant AM, Atrash H, Schulkin J. Evaluation of bleeding disorders in women with menorrhagia: a survey of obstetrician-gynecologists. *Am J Obstet Gynecol*. 2012; 207(4):269.e1-5.

16. Powers JM, Stanek JR, Srivaths L, Haamid FW, O'Brien SH. Hematologic Considerations and Management of Adolescent Girls with Heavy Menstrual Bleeding and Anemia in US Children's Hospitals. *J Pediatr Adolesc Gynecol*. 2018; 31(5):446-450.
17. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97(8):734-739.
18. Dkeidek A, Mattinson R, Grover SR. Bleeding disorders: Are gynaecologists testing women at risk? *Haemophilia*. 2021;27(4):e534-e536.
19. James PD. Women and bleeding disorders: diagnostic challenges. *Hematology Am Soc Hematol Educ Program*. 2020; 2020(1):547-552.
20. James AH. Heavy menstrual bleeding: work-up and management. *Hematology Am Soc Hematol Educ Program*. 2016 Dec 2;2016(1):236-242.
21. Mauser-Bunschoten EP, Kadir RA, Laan ETM, Elfvinge P, Haverman L, Teela L, et al. Managing women-specific bleeding in inherited bleeding disorders: A multidisciplinary approach. *Haemophilia*. 2021; 27(3):463-469.
22. Lee CA, Chi C, Shiltagh N, Pollard D, Griffioen A, Dunn N, et al. Review of a multidisciplinary clinic for women with inherited bleeding disorders. *Haemophilia*. 2009; 15(1):359-60.
23. Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021; 5(1):301-325.
24. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2018; 4(4):CD000249.
25. Kouides PA, Byams VR, Philipp CS, Stein SF, Heit JA, Lukes AS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. *Br J Haematol*. 2009; 145(2):212-20.
26. Ray S, Ray A. Non-surgical interventions for treating heavy menstrual bleeding (menorrhagia) in women with bleeding disorders. *Cochrane Database Syst Rev*. 2016; 11(11):CD010338.
27. Matteson KA, Rahn DD, Wheeler TL 2nd, Casiano E, Siddiqui NY, Harvie HSet al; Society of Gynecologic Surgeons Systematic Review Group. Nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstet Gynecol*. 2013; 121(3):632-643.
28. Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2013; 2013(8):CD003989.
29. Kingman CE, Kadir RA, Lee CA, Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. *BJOG*. 2004; 111(12):1425-8.
30. Rimmer E, Jamieson MA, James P. Malposition and expulsion of the levonorgestrel intrauterine system among women with inherited bleeding disorders. *Haemophilia*. 2013 Nov;19(6):933-8.
31. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood*. 2015;126(17):1981-9.
32. Van Galen K, Lavin M, Skouw-Rasmussen N, Fischer K, Noone D, Pollard D, et al; European Haemophilia Consortium (EHC) and the European Association for Haemophilia and Allied Disorders (EAHAD). European principles of care for women and girls with inherited bleeding disorders. *Haemophilia*. 2021; 27(5):837-847.
33. Leebeek FWG, Duvekot J, Kruip MJHA. How I manage pregnancy in carriers of hemophilia and patients with von Willebrand disease. *Blood*. 2020;136(19):2143-2150.
34. Casini A, de Moerloose P; Congenital Fibrinogen Disorders Group. Management of congenital quantitative fibrinogen disorders: a Delphi consensus. *Haemophilia*. 2016; 22(6):898-905.

- 1
- 2
- 3 35. Bouttefroy S, Meunier S, Milien V, Boucekine M, Chamouni P, Desprez D, et al; CoDeC
- 4 study group. Congenital factor XIII deficiency: comprehensive overview of the
- 5 FranceCoag cohort. *Br J Haematol.* 2020; 188(2):317-320.
- 6 36. Management of Inherited Bleeding Disorders in Pregnancy: Green-top Guideline No. 71
- 7 (joint with UKHCDO). *BJOG.* 2017; 124(8):e193-e263.
- 8 37. MASAC guidelines for perinatal management of women with bleeding disorders and
- 9 carriers of hemophilia A or B (document 251).
- 10 38. Andersson NG, Chalmers EA, Kenet G, Ljung R, Mäkipernaa A, Chambost H; PedNet
- 11 Haemophilia Research Foundation. Mode of delivery in hemophilia: vaginal delivery and
- 12 Cesarean section carry similar risks for intracranial hemorrhages and other major bleeds.
- 13 *Haematologica.* 2019; 104(10):2100-2106.
- 14 39. Kouides PA. Antifibrinolytic therapy for preventing VWD-related postpartum hemorrhage:
- 15 indications and limitations. *Blood Adv.* 2017 Apr 25;1(11):699-702.
- 16 40. Punt MC, Aalders TH, Bloemenkamp KWM, Driessens MHE, Fischer K, Schrijvers MH, et
- 17 al. The experiences and attitudes of hemophilia carriers around pregnancy: A qualitative
- 18 systematic review. *J Thromb Haemost.* 2020;18(7):1626-1636.
- 19 41. Arya S, Wilton P, Page D, Boma-Fischer L, Floros G, Winikoff R, et al. "Everything was
- 20 blood when it comes to me": understanding the lived experiences of women with inherited
- 21 bleeding disorders. *J Thromb. Haemost* 2020; 18(12):3211–21.
- 22 42. Arya S, Wilton P, Page D, Boma-Fischer L, Floros G, Winikoff R, et al. "They don't really
- 23 take my bleeds seriously": barriers to care for women with inherited bleeding disorders. *J*
- 24 *Thromb Haemost.* 2021; 19(6):1506–14.
- 25 43. O'Brien SH, Stanek JR, Kaur D, McCracken K, Vesely SK. Laboratory monitoring during
- 26 pregnancy and post-partum hemorrhage in women with von Willebrand disease. *J*
- 27 *Thromb Haemost.* 2020; 18(3):604-608.
- 28 44. Roberts JC, Malec LM, Halari I, Hale SA, Oladapo A, Sidonio RF Jr. Bleeding patterns in
- 29 patients before and after diagnosis of von Willebrand disease: Analysis of a US medical
- 30 claims database. *Haemophilia.* 2021. doi: 10.1111/hae.14448. Epub ahead of print.
- 31 45. Candy V, Whitworth H, Grabell J, Thibeault L, Harpell L, Bowman M, et al. A decreased
- 32 and less sustained desmopressin response in hemophilia A carriers contributes to
- 33 bleeding. *Blood Adv.* 2018; 2(20):2629-2636.
- 34 46. Van Galen KPM, d'Oiron R, James P, Abdul-Kadir R, Kouides PA, Kulkarni R, et al. A
- 35 new hemophilia carrier nomenclature to define hemophilia in women and girls:
- 36 Communication from the SSC of the ISTH. *J Thromb Haemost.* 2021; 19(8):1883-1887.
- 37 47. Punt MC, Waning ML, Mauser-Bunschoten EP, Kruij MJHA, Eikenboom J,
- 38 Nieuwenhuizen L, et al. Maternal and neonatal bleeding complications in relation to
- 39 peripartum management in hemophilia carriers: A systematic review. *Blood Rev.* 2021;
- 40 49:100826.
- 41 48. Makris M, Hermans C. The 2021 von Willebrand disease guidelines: Clarity and
- 42 controversy. *Haemophilia.* 2022; 28(1):1-3.
- 43 49. Gallinaro L, Cattini MG, Sztukowska M, Padrini R, Sartorello F, Pontara E, et al A shorter
- 44 von Willebrand factor survival in O blood group subjects explains how ABO determinants
- 45 influence plasma von Willebrand factor. *Blood.* 2008; 111(7):3540-5.
- 46 50. Srivaths L, Minard CG, O'Brien SH, Wheeler AP, Mullins E, Sharma M, et al. The
- 47 spectrum and severity of bleeding in adolescents with low von Willebrand factor-
- 48 associated heavy menstrual bleeding. *Blood Adv.* 2020;4(13):3209-3216.
- 49 51. Lavin M, Aguila S, Dalton N, Nolan M, Byrne M, Ryan K, et al. Significant gynecological
- 50 bleeding in women with low von Willebrand factor levels. *Blood Adv.* 2018; 2(14):1784-
- 51 1791.
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

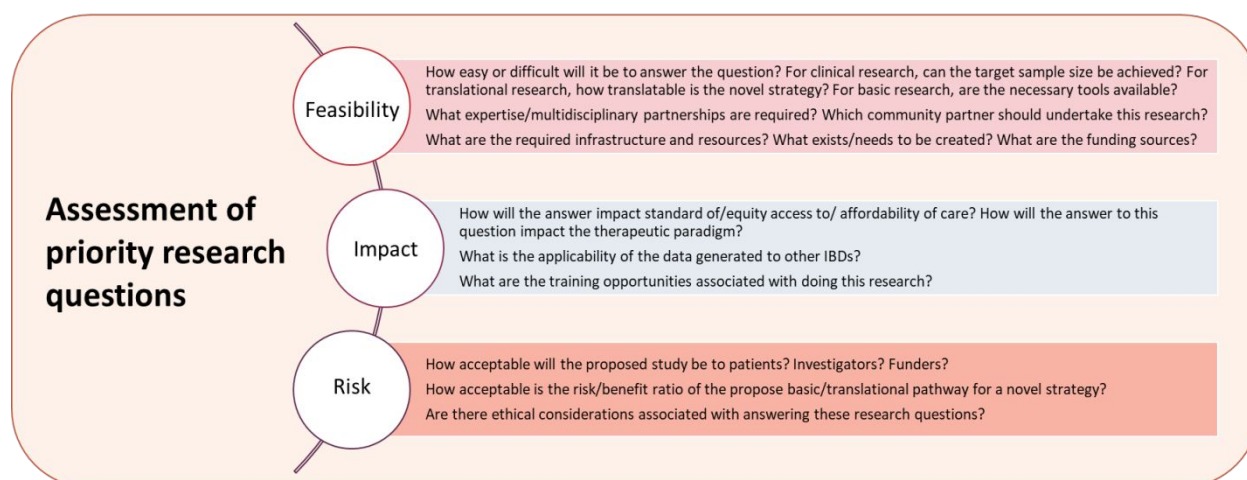
Table 1: State of the Science Research Summit Working Groups

Working Groups:	Priority Areas of Focus:
1. Research priorities for Hemophilia A and B	<ul style="list-style-type: none"> • Across the spectrum of disease • Understudied areas: women; non-severe disease
2. Research priorities for von Willebrand disease, platelet dysfunction, and other mucocutaneous IBDs	<ul style="list-style-type: none"> • Across genders and phenotypes • Diagnostics and therapeutics
3. Research priorities for ultra-rare IBDs	<ul style="list-style-type: none"> • Across genders and phenotypes • Diagnostics and therapeutics
4. Research priorities for health of women and girls and persons with the potential for menstruation	<ul style="list-style-type: none"> • Von Willebrand disease • Platelet disorders • Sex and gender-specific biology and IBD phenotype
5. Diversity, equity and inclusion, health services research and implementation science	<ul style="list-style-type: none"> • SOC implementation • DE&I health services research • Telehealth and delivery network development • Communications
6. Facilitating priority research in IBDs	<ul style="list-style-type: none"> • Infrastructure • Resource procurement/development • Workforce development

Table 2. Remote Participation Groups

Chapter/ Hemophilia Treatment Center	Priority Area	Focus	Format
Hemophilia of South Carolina	Hemophilia	Black/African American	In-person
New York City Hemophilia Chapter	Hemophilia	Aging	Virtual
Lone Star Bleeding Disorders Foundation	VWD or women, girls, and persons with the potential to menstruate	Hispanic women	Virtual
Virginia Hemophilia Foundation	Women and Girls, and Persons with the potential to menstruate	Women	Virtual
Bleeding Disorders Alliance of Illinois	Ultra-rare	LGBTQ	Virtual

1
2
3 **Figure 1. Questions Informing Feasibility Assessment**
4
5



National Hemophilia Foundation Research Agenda

Leonard A. Valentino^{1,2}, Kevin Mills¹, and Michael Recht³

¹National Hemophilia Foundation, New York, NY USA, ²Rush University, Chicago, IL USA, ³American Thrombosis and Hemostasis Network, Rochester, NY USA



Background: The inherited bleeding disorders (IBD) community has witnessed significant therapeutic advances in recent years, yet important gaps persist, particularly for those with rare disorders and historically underserved populations. An ambitious initiative underway in the IBD community aims to create an actionable national research blueprint enhancing patient-centric principles to address the priorities of the IBD community. Furthermore, this initiative will accelerate research progress and address important gaps in care. Led by the National Hemophilia Foundation (NHF), this effort is defined by input from across the community, including patients and caregivers who bring lived experiences and are considered subject matter experts (SMEs) of their disorder, research leaders, allied health professionals and specialists, and representatives of the biopharmaceutical industry. Two foundational principles of the blueprint are: 1) it must deliver on key issues that significantly impact the lives of those affected by IBDs, and 2) the priorities defined are relevant and actionable aimed to achieve health equity among all those affected by IBDs. NHF will develop the national research blueprint, to be prepared and issued in 2022.

Methods:
To ensure the blueprint accurately reflects the most pressing needs from across the community, NHF has enlisted the support of diverse segments of the population throughout the process.

Listening - NHF coordinated a comprehensive, community-wide listening exercise, including focus groups, virtual listening sessions, and consumer and professional surveys, to collect insights that have shaped and guided the blueprint development.

Engagement - Representatives from across the IBD community were enlisted to participate in the development process through enrollment in 1 of 6 interdisciplinary working groups (WGs), each focusing on broad themes raised during the listening exercises. The key themes to be addressed by multidisciplinary groups included the use of new technologies for therapeutic advancements, such as application of precision medicine, genetic testing, and point of care diagnostics, as well as continued pursuit of novel therapies for underserved disease populations. In addition, community input raised the need for improvements in comprehensive care, such as mental health, diagnosis, and supportive care; rare IBDs and health disparities; and infrastructure, resource planning and workforce development (see Table 1).

Assessment Tool: NHF devised a rigorous development and refinement process in order that the blueprint is clearly defined and actionable. Together with expert advisers, NHF has defined a set of feasibility criteria to help the WGs address potential opportunities based on three key areas. Feasibility assesses the difficulty in answering the proposed question, including required expertise, infrastructure, and resources. Impact estimates the change we can foster through the priority. Risk assessment considers the challenges of the research question, such as the technical feasibility for novel strategies and any ethical considerations (see Figure 1).

Summit: Upon the completion of the WG assessments, NHF brought the community together for a virtual State of the Science (SOS) Research Summit, held from September 12-15, 2021. The WG Chairs summarized their recommendations in a live, interactive discussion. During each session, panels discussed the recommendations and collected feedback from community participants, as well as from remote participation groups (RPGs) comprised of representatives from underserved segments of the population (see Table 2). NHLBI support made the inclusion of the critical input from these groups possible (Award Number R13HL158209).

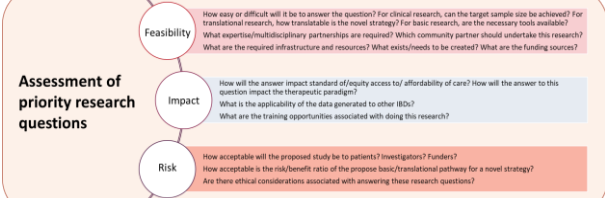
Table 1. Summit Working Groups

Working Groups:	Priority Areas of Focus:
1. Research priorities for Hemophilia A and B	<ul style="list-style-type: none"> Across the spectrum of disease Understudied areas: women; non-severe disease
2. Research priorities for von Willebrand disease, platelet dysfunction, and other mucocutaneous IBDs	<ul style="list-style-type: none"> Across genders and phenotypes Diagnostics and therapeutics
3. Research priorities for ultra-rare IBDs	<ul style="list-style-type: none"> Across genders and phenotypes Diagnostics and therapeutics
4. Research priorities for health of women and girls and persons with the potential for menstruation	<ul style="list-style-type: none"> Von Willebrand disease Platelet disorders Sex and gender-specific biology and IBD phenotype
5. Diversity, equity and inclusion, health services research and implementation science	<ul style="list-style-type: none"> SOC implementation DE&I health services research Telehealth and delivery network development Communications
6. Facilitating priority research in IBDs	<ul style="list-style-type: none"> Infrastructure Resource procurement/development Workforce development

Table 2. Remote Participation Groups

Chapter/ Hemophilia Treatment Center	Priority Area	Focus	Format
Hemophilia of South Carolina	Hemophilia	Black/African American	In-person
New York Cty Hemophilia Chapter	Hemophilia	Aging	Virtual
Lone Star Bleeding Disorders Foundation	WVD or women, girls, and persons with the potential to menstruate	Hispanic women	Virtual
Virginia Hemophilia Foundation	Women and Girls, and Persons with the potential to menstruate	Women	Virtual
Bleeding Disorders Alliance of Illinois	Ultra-rare	LGBTQ	Virtual

Figure 1. Questions Informing Feasibility Assessment



Results: NHF's SOS Research Summit attracted 887 attendees who joined 21 sessions, led by 43 speakers, and totaled 2,279 unique session views. There was a total of 5 RPGs – more are planned in the future. When the SOS Research Summit social media metrics were analyzed, there were demonstrable increases across all social media platforms compared to our non-event averages. The voices of individuals affected by IBDs have been the central driver in this process, from the listening activities and WGs to the planned SOS. The discussions from the working groups and Research Summit will be consolidated into a series of manuscripts and published as a community-driven national research blueprint in mid-2022. The community will continue to champion the efforts defined in the blueprint.

The emergent global themes from the collective efforts of the six WGs were (1) the importance of people-centricity in research; (2) the importance of multidisciplinary collaboration; and (3) the need to strive for diversity, inclusion, and equity in research and health care.

Following the SOS Research Summit, we have initiated a comprehensive, community-driven research blueprint planning effort. The blueprint planning and development process will mirror that of the SOS Research Summit, leveraging defined working groups with cross-cutting charges. Individually and collectively the blueprint working groups, together with a steering committee, will define actionable research plans, including key research initiatives, necessary infrastructure, potential funding agencies, recommended timelines and milestones, and forward-looking plans for community engagement, data dissemination, and progress evaluation. These efforts will culminate in a follow-on National Research Blueprint Summit during which the actionable plan will be detailed by participants in the process and community feedback will be sought.

Conclusion: This initiative presents an opportunity to catalyze impactful change in the treatment of IBDs. To ensure its success, NHF has methodically enlisted broad community involvement and driven a rigorous prioritization process to identify specific and actionable topics that will help guide research plans for the IBD community. Actively soliciting the community's views is central in our process to advance research in IBDs. This blueprint will help to guide community research that could fundamentally redefine the experience of living with these disorders.

Acknowledgement: The authors wish to acknowledge Karina Lopez for her assistance in preparing the manuscript and the collaboration of Michelle L Witkop and Maria E Santaella, all from the National Hemophilia Foundation and Donna DiMichele, and independent consultant to the National Hemophilia Foundation along with the all the participants who shared their time and insights during the process.