



NATIONAL
BLEEDING DISORDERS
FOUNDATION
Formerly NHF

NATIONAL RESEARCH BLUEPRINT RESEARCH PRIORITIES

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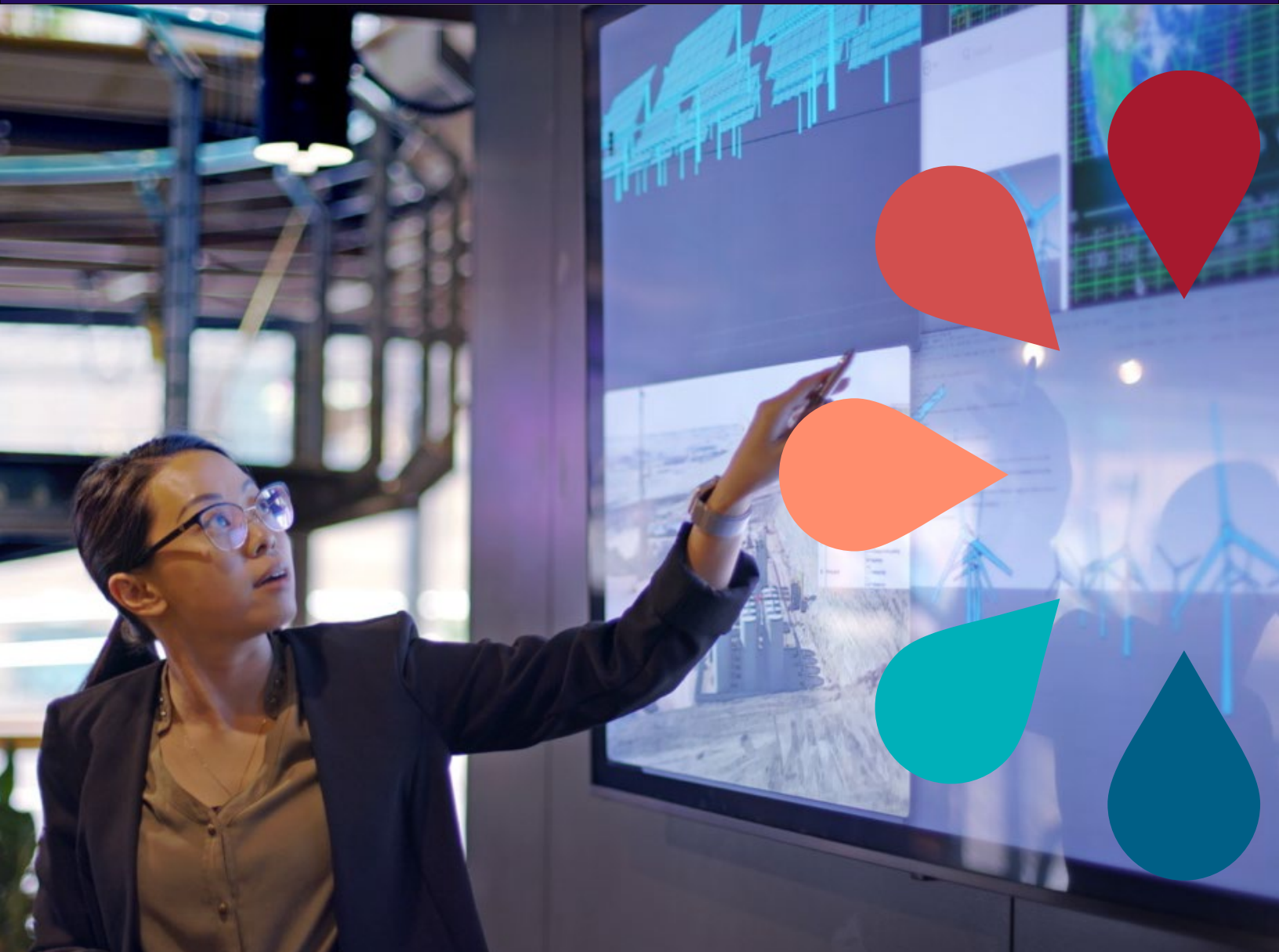
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***National Research Blueprint:
Research & Development
Research Priorities***



SPANNING TOPIC:

Lived Experiences

Lived Experiences: Scientific Areas of Interest

- ◆ Understand the barriers to and challenges in accessing healthcare for all individuals living with IBDs
- ◆ Study interventions to improve healthcare delivery for all individuals living with IBDs
- ◆ Determine and improve the financial burdens of living with an IBD
- ◆ How does living with a bleeding disorder impact meaningful outcomes and health-related quality of life?
- ◆ How can research efforts be designed to ensure inclusion and opportunities for meaningful involvement for all people living with bleeding disorders?
- ◆ How can we best understand and address the educational needs of people living with a bleeding disorder?

Lived Experiences: Research Priorities

Understand the barriers to and challenges in accessing healthcare for all individuals living with IBDs

- ◆ What inequities exist in experiences of care between non-marginalized and marginalized populations in the HTC setting?
- ◆ What is the definition of successful transition, what are the predictors, facilitators, and barriers to successful transition, and what specific metrics can be utilized in HTC and non-HTC care settings?
- ◆ What is the difference in comprehensive visit care, attendance, and outcomes between males and females with specific IBDs?
- ◆ Which physical (e.g., PCP referral, personal resources) or psychological (e.g., too busy being a caregiver, does not want to get worked up) factors impact access of care for females with hemophilia or other IBDs? What are other barriers?

LIVED EXPERIENCES

- ◆ For PWIBD, does identifying as being part of a marginalized or minoritized population* result in less frequent HTC comprehensive care visits and lower patient satisfaction, compared to PWIBD who do not identify as being part of a marginalized or minoritized population?
- ◆ Compare whether PWIBD who live in different settings (e.g. rural vs. urban, close to vs. far from an HTC in distance or time) who receive telemedicine vs. in-person care experience differences in terms of patient and/or HCP satisfaction, no-show rates, populations served, prophylaxis, adherence, outcomes (e.g. hospitalizations and/or ED visits, bleeds), and costs (e.g. time, travel).
- ◆ How many PWIBD have access to digital technologies (e.g. smart phones, text messaging, videoconferencing, downloadable apps, e-diary, internet access), and are there interventions that can increase access to digital technologies to improve participation in research and/or deliver health care?
- ◆ How do a person's language spoken at home, cultural environment, and faith tradition affect access to health care services?
- ◆ Do PWIBD born outside the U.S., seen at HTCs, experience the same number of HTC visits, same patient satisfaction for a comprehensive care visit, and same outcomes as PWIBD born in the U.S.?
- ◆ What policies and processes can identify, examine, and eliminate unconscious and conscious biases within HTCs and other healthcare institutions/organizations?
- ◆ Do PWIBD who identify as LGBTQIA+ receive the same care (e.g. PRO, comprehensive care visits, patient satisfaction) as PWIBD who do not identify as LGBTQIA+?

Study interventions to improve healthcare delivery for all individuals living with IBDs

- ◆ What are the most effective interventions to increase primary care and other HCP (e.g. dental, ENT, OB/GYN) awareness (e.g. screening, knowledge, referral) about IBDs, including female bleeding (e.g. HMB, PPH) and presentation of IBDs in marginalized populations?
- ◆ Do PWIBD who utilize telehealth tools or virtual visits experience the same satisfaction, PRO, and/or clinical outcomes (e.g. frequency or severity of bleeding episodes) as PWIBD that have in-person visits?
- ◆ What policies, processes, and practices can researchers and clinicians implement to mitigate identified biases, increase representation, and/or uplift voices of marginalized and minoritized populations in research and clinical care?
- ◆ How can clinical decision support tools be developed and/or refined to integrate social determinants of health and objectively identify higher risk patients (for which marginalized and minoritized populations may be disproportionately overrepresented)?
- ◆ Compare physical outreach, virtual outreach (e.g. telemedicine), and hybrid outreach of comprehensive care for PWIBD in terms of patient satisfaction, no-show rate, access to labs and diagnosis, access to treatment, prophylaxis (continuous, intermittent, on-demand), and adherence to treatment.



- ◆ How does care, treatment, and clinical and health-related QoL outcomes of those receiving specialized/integrated care differ between PWIBD at HTC compare to PWIBD receiving care outside HTCs?
- ◆ For PWIBD other than hemophilia, should integrated care vs. nonintegrated care be used?
- ◆ What care model(s) is/are most effective and feasible in caring for PWIBD across the lifespan, females with IBD, or PWIBD in marginalized groups?
- ◆ For LGBTQIA+ PWIBD, does regular access to the support resources of an HTC, as compared to standard hematology clinic resources, result in improved QoL?
- ◆ For transgender PWIBD undergoing gender-affirming care (including surgery), does management in an HTC improve outcomes? What are the QoL outcomes from uterine bleeding in trans-masculine people?
- ◆ Does HCP comprehensive sexual health training improve patient-reported satisfaction and QoL for LGBTQIA+ PWIBD?
What methods can be used to ensure that gene therapy and other curative therapies will be successful in providing health equity, affordability, and fairness for all stakeholders including society as a whole?

Determine and improve the financial burdens of living with a IBD

- ◆ Do PWIBD who have insurance that decreases/restricts access to HTC services (e.g. diagnostics, treatments, pharmacy services, PT, travel, other support) have worse outcomes?
- ◆ How does the cost effectiveness of care for PWIBD provided in managed care organizations compare to other models?
- ◆ For PWIBD that are underserved (e.g. rare and chronic, prevalent but underrecognized), what characteristics of insurance coverage (e.g. eligibility, benefits, network scope) are associated with increased wellness (e.g. physical, social, mental)?
- ◆ Is there a difference for PWIBD who are primarily insured through government health plans (e.g. Medicare/Medicaid) than PWIBD who have other insurance (e.g. private insurance plans, employer health plans, or transition to no insurance) in experiencing gaps (number, duration) in care (e.g. comprehensive or wellness visits), treatment (e.g. factor), or outcomes (e.g. ABR) as people transition from pediatric to adult care?
- ◆ How are health outcomes (e.g. number of visits, treatment, bleeding, PRO) impacted in PWIBD whose household income is less than a level (e.g. 138%) of the Federal Poverty Guideline (FPG) compared to PWIBD who have higher household incomes? How do outcomes compare with people with similar incomes without an IBD?
- ◆ Is there a difference for PWIBD whose household income is less than FPG if care is received at an HTC vs. non-HTC? Does household income influence use of shared decision-making by HCPs, prescribed treatment, adherence to treatment, or disease management self-efficacy?
- ◆ What are the costs of existing therapies, new factor therapies, non-factor therapies, gene therapy, and other curative therapies for different stakeholders, and what methods can be applied to



ensure health equity, affordability, and fairness for all stakeholders including individual PWIBD and society as a whole?

- ◆ What costs are associated with bleeding symptoms in females with IBDs? Does effective management of HMB reduce financial burden?
- ◆ Test the hypothesis that utilization of embedded psychosocial services (beyond the usual available in an HTC comprehensive visit) will decrease costs associated with IBD diagnosis and management.

How does living with a bleeding disorder impact meaningful outcomes and health-related quality of life?

- ◆ What quality of care indicators are important to PWIBD (e.g., shared decision-making, provider competence, provider communication, etc.)?
- ◆ In PWIBD, do disease-specific patient-reported outcome measures (PROs) offer advantages over generic (non-disease specific) PROs?
- ◆ What tools are currently available to assess QoL throughout the lifespan and what is missing? How does age impact QoL in PWIBD? Does IBD severity impact aging QoL in PWIBD?
- ◆ What is the correlation between QoL scores, pain assessments, and other outcomes (e.g., bleeding assessments, joint function, laboratory tests)?
- ◆ How does having an IBD or having specific bleeding-related symptoms (e.g. joint bleeding, HMB) affect QoL and mental health?
- ◆ How does the presence of an IBD or bleeding symptoms affect access to education, educational attainment, or occupational attainment?
- ◆ How does having an IBD affect intimacy, sexual function, and sexual relationships for PWIBD (and their partners)?
- ◆ How does pain (e.g. joint pain, female reproductive tract pain) impact QoL and clinical outcomes in PWIBD? What cultural considerations impact pain assessments in PWIBD?
- ◆ How do PWIBD and HCPs compare in ranking quality metrics of hemophilia and other IBD care?
- ◆ Can QoL metrics drive effective and safe personalized therapy?
- ◆ Does adherence to outcomes assessment measurement pre- therapy (e.g. new therapy, gene therapy) correlate with adherence to post- therapy follow-up regimen? What factors influence adherence?

How can research efforts be designed to ensure inclusion and opportunities for meaningful involvement for all people living with bleeding disorders?

- ◆ Identify best practices for participation of LEEs and other community members in research (e.g. research priorities, goals, design, operation, communications, community engagement)
- ◆ What data are available to measure social determinants of health and markers of health equity in the IBD population?



- ◆ What data still needs to be collected to ensure representation of marginalized and minoritized populations?
- ◆ How do we update our existing data infrastructure(s) to robustly capture meaningful data related to social determinants of health?
- ◆ What new types of data that are important and meaningful to members of marginalized and minoritized populations that are not currently being collected in current research studies (e.g. clinical studies, surveillance)?

How can we best understand and address the educational needs of people living with a bleeding disorder?

- ◆ What are the education needs of PWIBDs, families, and trainees/providers commensurate with recent clinical advances (e.g. non-coagulation factor replacement in hemophilia, potentially curative therapies, diagnostics)?
- ◆ Among agencies providing patient education, patient advocacy, or surveillance services, does using regional networks to organize services improve the effectiveness of these services compared to agencies who perform services outside of regional networks?
- ◆ How can knowledge and empowerment of PWIBDs be built to allow pathways of advocacy to help achieve health equity?
- ◆ What are the different lifespan educational needs for PWIBD (e.g. reproductive planning, neonatal and early life, puberty including menarche (first menstrual period), aging)?
- ◆ What are the most appropriate education and consenting methods for treatment (e.g. factor or non-factor therapy, gene therapy) for minors with IBDs?
- ◆ What are the best educational tools to facilitate medical independence during transition? Does access to a care navigator facilitate transition?
- ◆ What interventions can improve skill acquisition for PWIBD and caregivers (e.g. in early life, for successful transition, for PWIBD diagnosed later in life)?
- ◆ What are the most effective interventions to increase primary care awareness (screening, knowledge, referral) about the association of HMB and IBDs?
- ◆ How do hemophilia and gene therapy health literacy, psychosocial and clinical wellbeing, and educational interventions, influence decision making, compliance, psychosocial changes and other clinical outcomes following gene therapy?



SPANNING TOPIC:

Bleeding Assessments

Bleeding Assessments: Scientific Areas of Interest

- ◆ Improve existing tools and develop new methods to feasibly and accurately measure bleeding
- ◆ Apply electronic tools and home-based assessments to diagnose bleeding, track bleeding longitudinally, and understand the impact of bleeding on the individual
- ◆ Standardize measurements of bleeding and approaches to harmonize data from diverse sources to accurately and homogeneously assess bleeding across studies and in the real world
- ◆ Assess bleeding across the lifespan to better understand the natural history and evolution of bleeding with age in all IBDs

Bleeding Assessments: Research Priorities

Improve existing tools and develop new methods to feasibly and accurately measure bleeding

- ◆ Develop surveys and other tools to screen for individuals at risk for IBDs
- ◆ Develop tools to quantitate bleeding and identify patterns of bleeding in individuals diagnosed with IBDs
- ◆ Determine the utility and/or correlation of clinical and imaging joint assessment tools on outcomes (e.g., HJHS, Gilbert, ROM, total arc, gait, pain, MRI, X-ray, POC MSKUS)
- ◆ Correlate new measures of bleeding symptoms with existing validated tools, in vitro factor levels, biomarkers, imaging, QoL, and other metrics
- ◆ Assess existing methods and develop new tools for accurate assessment of menstrual blood loss and postpartum hemorrhage
- ◆ What tools can help providers and individuals with IBDs identify bleeding early on?

BLEEDING ASSESSMENT

- ◆ Identify characteristics of bleeding that should prompt investigation of a concomitant bleeding disorder

Apply electronic tools and home-based assessments to diagnose bleeding, track bleeding longitudinally, and understand the impact of bleeding on the individual

- ◆ Investigate how to engage and increase uptake of electronic tools to capture bleeding events (e.g. menstrual blood loss, bleeding scores)
- ◆ Use electronic tools and home-based assessments to study the impact of bleeding on the individual (QoL scores, mental health)
- ◆ Incorporate and validate existing and new tools into electronic and self-test formats
- ◆ Study the accuracy and feasibility of patient-reported menstrual blood loss measurements

Standardize measurements of bleeding and approaches to harmonize data from diverse sources to accurately and homogeneously assess bleeding across studies and in the real world

- ◆ Develop consensus definitions of excessive bleeding and bleeding quantification in large data sets and clinical studies (IBD and non-IBD cohorts)
- ◆ Standardize measures of bleeding (e.g. imaging, function scores) across research cohorts and in the real world
- ◆ Devise and validate quantitative and longitudinal assessments of bleeding in females (e.g. menstrual bleeding)
- ◆ Apply consensus definitions in clinical practice and survey real world bleeding rates in individuals with IBDs

Assess bleeding across the lifespan to better understand the natural history and evolution of bleeding with age in all IBDs

- ◆ Study the expected bleeding patterns in IBDs with and without therapies, including factor replacement, adjuvant therapies, and gonadal steroid hormone therapies
- ◆ Perform longitudinal assessments of bleeding, joint health, and functional (e.g. ultrasound, scores)
- ◆ Characterize the natural history of bleeding in qualitative platelet function defects and other rare IBDs
- ◆ Study development of joint damage in mild MCB and other non-severe bleeding disorders and determine if joint disease changes with age, affects activities of daily living, etc.
- ◆ Can bleeding disorder assessments be a mechanism for identification and long-term follow-up of mild mucocutaneous bleeding disorders (e.g. mild forms of VWD, platelet disorders, hemophilia, BDUC, HHT)



SPANNING TOPIC:

Female Bleeding

Female Bleeding: Scientific Areas of Interest

- ◆ Understand the biology of uterine bleeding (heavy menstrual bleeding, postpartum hemorrhage, and perimenopausal bleeding)
- ◆ Understand the biology of female hormones and their impact on IBDs
- ◆ Improve screening and diagnosis of females for risk for reproductive tract and other bleeding and determine approaches to improve implementation of treatment
- ◆ Determine the efficacy and safety of interventions for female reproductive tract bleeding

Females Bleeding: Research Priorities

Understand the biology of uterine bleeding (heavy menstrual bleeding, postpartum hemorrhage, and perimenopausal bleeding)

- ◆ Define the differences in the biology of the uterine lining and uterine bleeding vs. other mucocutaneous sites (e.g. GI, nasopharynx, oral, vaginal)
- ◆ Study the role of hormones (including biological sex), menstruation, pregnancy, and the perimenopausal context on the blood vessel environment as it relates to mucocutaneous bleeding
- ◆ Do defects in primary hemostasis have more of an effect on uterine bleeding compared to defects in secondary hemostasis?
- ◆ What are the symptom correlations of HMB in IBDs with dysmenorrhea (pain with menstruation) / pelvic pain?
- ◆ What is the pathophysiology and optimal management of endometriosis in IBDs?
- ◆ What are the risk factors for ovarian hemorrhage in IBDs?
- ◆ Are persons with IBDs at increased risk for excessive uterine or other bleeding in the presence of other conditions (e.g. COVID-19, connective tissue disorder, autoimmune disorder, PCOS)

FEMALE BLEEDING

- ◆ What are the QoL outcomes from uterine bleeding and HMB in trans-masculine people?

Understand the biology of female hormones and their impact on IBDs

- ◆ What is the role of hormones (including biological sex) on menstruation, pregnancy, and the perimenopausal context on the blood vessel environment as it relates to mucocutaneous bleeding?
- ◆ What is the impact of different hormonal treatments on female bleeding, including pre-menarchal (before the first period), menstruation, pregnancy, perimenopausal, and postmenopausal bleeding and during fertility treatments
- ◆ What genetic and other factors impact the phenotype of female bleeding in IBDs
- ◆ What effects do hormones, pregnancy, and age have on coagulation factor levels and reference ranges and by what mechanisms?
- ◆ What is the impact of androgenic hormone therapy on bleeding symptoms?
- ◆ What are the phenotypic differences of IBDs across the lifespan based on sex and gender?
- ◆ What is the impact of aging in IBDs for individuals assigned male at birth vs. female, particularly peri- and postmenopausal?
- ◆ What effect does female sex and hormones have on bone health in IBDs and what is the best way to study those effects?

Improve screening and diagnosis of females for risk for reproductive tract and other bleeding and determine approaches to improve implementation of treatment

- ◆ Validate general population bleeding screening tools to accurately identify females at risk for IBDs
- ◆ Identify tools to screen for clinically relevant pregnancy-associated bleeding and PPH, indicating need for an IBD work-up
- ◆ How can we link IBD screening to prepubescent screening, family planning and obstetric care in prepubescent females?
- ◆ What are the characteristics of females who are diagnosed with BDs early on vs. later?
- ◆ Identify physical factors (e.g., PCP referral), psychosocial factors (e.g., too busy being a caregiver, does not want evaluation), or other barriers impact access of care for females with hemophilia
- ◆ What evidence should be used to diagnose “hemophilia” vs. “symptomatic hemophilia carrier” vs. “asymptomatic hemophilia carrier” in females
- ◆ Improve assessments of female bleeding (e.g. quantitative, accessible, culturally appropriate)
- ◆ How often do self-reports of bleeding need to be assessed to improve care? How does frequency of reporting impact recall bias?
- ◆ What do young people with IBDs need to be prepared for puberty and menarche?
- ◆ For pregnant people with IBDs, does management in a comprehensive center such as an HTC vs. no specialized management improve maternal bleeding outcomes during pregnancy, at time of delivery, and postpartum, and does HTC care lead to differences in satisfaction with care?



- ◆ For pregnant people with IBDs, does management in a comprehensive center such as an HTC vs. no specialized management improve neonatal outcomes?
- ◆ What are the current barriers to prenatal diagnosis in IBDs?
- ◆ What is the difference in comprehensive visit care and attendance between males and females with comparable IBDs (e.g. mild hemophilia, VWD)?
- ◆ How can we ensure that female sex and pregnancy does not exclude participation in clinical trials

Determine the efficacy and safety of interventions for female reproductive tract bleeding

- ◆ What is the relative safety of intrauterine, cervical, and transvaginal procedures in the setting of IBDs (e.g., ablation, dilation & curettage, IUD placement, endometrial biopsy, LEEP, egg harvest)?
- ◆ What is the relative effectiveness and optimal dosing of gonadal steroid hormone therapies in IBDs in the acute and chronic setting?
- ◆ What is the optimal dosing of coagulation factors, antifibrinolytic agents, and desmopressin for effective management of HMB?
- ◆ What is the safety and effectiveness of combination therapies for HMB management (e.g. antifibrinolytic agents, desmopressin, gonadal steroid hormones, factor replacement)?
- ◆ What are the costs and burden associated with bleeding symptoms in females?



SPANNING TOPIC:

Joint and Bone Health

Joint and Bone Health: Scientific Areas of Interest

- ◆ Increase understanding of the pathophysiology of bone and joint disorders in inherited bleeding disorders (e.g. inflammation, iron deposition, osteopenia/osteoporosis, effects of hormones, biomechanics)
- ◆ Improve diagnosis of acute hemarthrosis, chronic hemarthropathy, and bone loss
- ◆ Identify methods to maintain joint and bone health and improve treatments of acute hemarthrosis, chronic hemarthropathy, and bone loss
- ◆ Determine approaches to effectively assess and manage the sequelae of hemarthrosis, hemarthropathy, and bone loss across the lifespan, including pain, functional limitations, and mental health conditions in hemophilia A and B
- ◆ Study the impact of non-hemophilia bleeding disorders on bone and joint health

Joint and Bone Health: Research Priorities

Increase understanding of the pathophysiology of bone and joint disorders in inherited bleeding disorders (e.g. inflammation, iron deposition, osteopenia/osteoporosis, effects of hormones, biomechanics)

- ◆ What mechanisms underlie osteopenia and osteoporosis in IBDs and what is the best way to study those effects?
- ◆ Does low endogenous expression of clotting factors (e.g. FVIII, VWF) impact bone health, and does intravenous replacement of deficient factors slow or reverse bone disease progression in IBDs?
- ◆ What role(s) do hormones play in bone and joint health and disease in IBDs?

JOINT AND BONE HEALTH

- ◆ What is the role of thrombin generation in maintaining bone and joint health?
- ◆ What processes (e.g. inflammatory, iron deposition) impact joint health in persons with IBDs?
- ◆ Does having a mucocutaneous bleeding disorder (e.g. VWD, platelet disorders) or other non-hemophilia bleeding disorder affect bone and/or joint health, and if so does pathology accelerate over time?
- ◆ How do the biomechanics of the MSK system in females change throughout the lifespan, what is the impact on bone health, joint bleeding phenotype, and which joints are affected?

Improve diagnosis of acute hemarthrosis, chronic hemarthropathy, and bone loss

- ◆ Identify measures of osteopenia and osteoporosis that can accurately identify bone loss
- ◆ Define gold standards for joint bleed diagnosis in research studies vs. the real world
- ◆ Develop and validate fast and quantitative measures (e.g. MRI sequences, MSKUS measures, biomarkers) to assess joint bleed burden and iron accumulation objectively
- ◆ Develop validated home patient self-imaging techniques for hemarthrosis and hemarthropathy and assess the value of patient self-imaging to improve management
- ◆ Determine the utility, frequency, and/or correlation of clinical and imaging joint assessment tools (e.g., HJHS, Gilbert, ROM, total arc, gait, pain, MRI, X-ray, MSKUS, POC MSKUS) on outcomes (e.g. joint damage or progression)

Identify methods to maintain joint and bone health and improve treatments of acute hemarthrosis, chronic hemarthropathy, and bone loss

- ◆ What interventions for osteopenia and osteoporosis improve outcomes in IBDs?
- ◆ What are the effects of bone strengthening agents (e.g., bisphosphonates, vitamin D, chondroitin) on bone and hemophilic joint health?
- ◆ What methods or interventions can assess and restore or regenerate osteochondral health?
- ◆ Identify medical, surgical or invasive (e.g. aspiration/injection), and/or rehabilitative measures that facilitate optimal blood/iron clearance from the joint and/or mitigate arthropathic processes
- ◆ Define optimal protocols to mitigate arthropathic processes and restore function after joint bleeding (e.g. procedures, weight bearing, POLICE)
- ◆ Determine the utility, frequency, and/or correlation of clinical and imaging joint assessment tools on rehabilitative management
- ◆ Is there a role for post-surgical interventions to reduce osteochondral and soft tissue changes?
- ◆ What mechanism-based and/or analgesic therapies can treat arthropathic pain?



Determine approaches to effectively assess and manage the sequelae of hemarthrosis, hemarthropathy, and bone loss across the lifespan, including pain, functional limitations, and mental health conditions in hemophilia A and B

- ◆ What are effective interventions to improve joint and bone health across the lifespan (e.g. bone strengthening agents, osteochondral interventions)
- ◆ What are the most important characteristics, causal factors (such as osteochondral alterations and impingement), and quantification methods of chronic hemarthropathic pain across the lifespan?
- ◆ What is the long-term impact of joint health on long term mobility, function, and pain
- ◆ Identify systems issues / inefficiencies that impact joint health, pain, and chronic hemarthropathy management across the lifespan.
- ◆ What is the prevalence of clinical and subclinical joint bleeds in people with all severities of hemophilia, including mild hemophilia and females (regardless of level)
- ◆ What is the most accurate method of assessment of subclinical joint bleeds, and how does this change with age (including assessments of joint disease and impact on daily living and function)
- ◆ What mechanism-based/analgesic therapies can treat arthropathic pain, and what is the impact of age on pain management?
- ◆ Determine if self-assessments (e.g. patient self-imaging, self-assessments, metrics of function) can improve management across the lifespan
- ◆ What medical interventions and/or rehabilitative mechanism-based measures and protocols after hemarthrosis or surgery facilitate optimal clearance of blood, reduce tissue damage, and promote healing at different ages
- ◆ Does access to PT differ across the lifespan, and are different PT interventions more effective in older vs. younger ages

Study the impact of non-hemophilia bleeding disorders on bone and joint health

- ◆ Is there an effect on bone health in non-hemophilia bleeding disorders and does it accelerate over time?
- ◆ Can we longitudinally assess joint health in people with non-hemophilia bleeding disorders and characterize prevalence, bone and joint changes, physical therapy assessment, pain symptoms, and function?
- ◆ Do people with mucocutaneous bleeding (MCB) disorders develop joint damage, what is the impact of having joint damage (e.g. affecting function, activities of daily living, QoL, mental health), and does this change with age?
- ◆ What is the prevalence of subclinical joint bleeds among females with non-hemophilia bleeding disorders, and what is the most accurate method of assessment?



- ◆ Do measures of and treatment approaches to hemarthrosis (joint bleeding) and hemarthropathy (joint damage from bleeding) in hemophilia translate to accurate diagnosis and treatment of joint bleeding in non-hemophilia bleeding disorders?
- ◆ Do acquired and immune-mediated bleeding disorders impact bone and joint health?



SPANNING TOPIC:

Lifespan

Lifespan: Scientific Areas of Interest

- ◆ What are the definitions and metrics of successful transitions at life stages (e.g. pediatric to adult, transition to older adult)?
- ◆ What are the challenges specific to sexual health in IBDs?
- ◆ What are the risks for thrombosis and special considerations for anticoagulation in individuals with IBDs occurring due to advancing age, comorbidities, or other prothrombotic risks?
- ◆ How does bleeding change over the lifespan?
- ◆ What is the impact of co-occurring conditions on persons with IBDs?

Lifespan: Research Priorities

What are the definitions and metrics of successful transitions at life stages (e.g. pediatric to adult, transition to older adult)?

- ◆ Define predictors, facilitators, and barriers to success in transition (percentage of young adults who transition, transition in HTC vs. non-HTC settings)
- ◆ Does access to a care navigator facilitate transition?
- ◆ How do changes in treatment options (e.g. change in treatment regimen, efficacy in bleeding treatment) impact transition success
- ◆ How does successful transition impact long-term outcomes?
- ◆ Do older persons with IBDs benefit from specialty geriatric care?
- ◆ What are specific needs and potential barriers for persons with IBDs palliative and end of life care?

LIFESPAN

What are the challenges specific to sexual health in IBDs?

- ◆ What specific challenges does puberty pose to young people with IBDs and how can this information help young people and families prepare for puberty (male and female)?
- ◆ How does an IBD (all sexes) affect intimacy, sexual function, and sexual relationships?
- ◆ Does IBD-oriented sex education improve sexual health, reduce bleeding risk (e.g. retroperitoneal bleeding), or reduce anxiety?
- ◆ What are the challenges and barriers reproductive planning (e.g. education, access to testing, access to GCs, access to MFM, access to HTC or specialty hematology, access to fertility treatment)?

What are the risks for thrombosis and special considerations for anticoagulation in individuals with IBDs occurring due to advancing age, comorbidities, or other prothrombotic risks?

- ◆ How can we optimize anticoagulation management in the setting of atrial fibrillation or dual antiplatelet agents, including lab monitoring?
- ◆ What is the risk for bleeding in persons with an IBD on anticoagulation or anti-platelet therapy?
- ◆ How can we optimize anticoagulation and/or anti-platelet management in IBDs the setting of atrial fibrillation or cardiovascular interventions (e.g. stents, left atrial appendage closure, venous filters, bypass, extracorporeal circuits), including bleeding assessments and lab monitoring?
- ◆ What is the role of non-factor replacement therapy (e.g. emicizumab) in the management of atrial fibrillation with DOACs or other anticoagulation (e.g. warfarin)?
- ◆ What is the role of non-factor replacement therapy (e.g. emicizumab) in the management of coronary artery, arterial or vascular stents, or after MI with antiplatelet agents?
- ◆ Do risk factors for thrombosis in non-IBD populations apply similarly to persons with IBDs?
- ◆ What is the risk of VTE in females using hormonal treatments or antifibrinolytic agents considering other risk factors (e.g. family history, immobility, post-partum, post-surgery setting)?
- ◆ What are the risk factors for thrombosis in HHT?

How does bleeding change over the lifespan?

- ◆ Does the surgical bleeding risk change with age in patients with mild mucocutaneous bleeding disorders?
- ◆ Does mucosal angiodysplasia (e.g. in VWD, HHT) worsen with advancing age?
- ◆ What is the impact of changing coagulation factor levels on bleeding phenotype with aging in females?
- ◆ What happens to VWD over the lifespan (e.g. VWF levels, the VWF level needed to prevent bleeding, how does this affect diagnosis, QoL, and can one outgrow VWD)?



- ◆ What is the impact of aging in IBDs for individuals assigned male at birth vs. female, particularly peri- and postmenopausal?
- ◆ How do the biomechanics of females change throughout the lifespan, what is the impact on joint bleeding phenotype and which joints are affected?
- ◆ What is the natural history in people with mild bleeding disorders and qualitative platelet function defects (including quality-of-life, evolution of bleeding symptoms with age)?
- ◆ Develop a lifespan cohort of patients with bleeding of unknown cause (and other rare disorders such as platelet defects) to study the natural history of bleeding

What is the impact of co-occurring conditions on persons with IBDs?

- ◆ What is the prevalence and pathophysiology of cardiovascular risk factors, especially hypertension, in different hemophilia severities and age groups?
- ◆ How does hypertension relate to hemorrhagic stroke and mortality in hemophilia and other IBDs?
- ◆ How does iron deficiency affect bleeding (all IBDs) and thrombotic risk (e.g. HHT)
- ◆ What is the effect of IBDs on bone health and does bone loss accelerate over time?
- ◆ What are the impacts of aging in IBDs on pain patterns, severity, prevalence, and impact on QoL?
- ◆ What are the symptom correlations of HMB in IBDs with dysmenorrhea/pelvic pain?
- ◆ What is the impact of acquired coagulopathy (e.g. hepatic coagulopathy, thrombocytopenia, antiphospholipid antibodies) on IBDs?
- ◆ What is the impact of comorbidities on bleeding phenotype beyond clotting factor levels (e.g. other disability, connective tissue disorder, immunotherapy, COVID-19 infection, rheumatologic disorders)
- ◆ What is the impact of prescribed medications on bleeding in IBDs (e.g. medications with platelet effects, supplements, vasoactive agents)?
- ◆ What is the impact of nutritional and other supplements on bleeding in IBDs?
- ◆ How does an IBD affect QoL and mental health and does this change over the lifespan?
- ◆ What tools are currently available to assess QoL throughout the lifespan and what is missing?
- ◆ Will implementation of a depression screening scale (e.g., PHQ-9) as standard of care during comprehensive clinic visits result in higher rates of participation of PWIBD who identify as belonging to a marginalized or minoritized population in mental health services within a 12-month period?



SPANNING TOPIC:

Mechanisms of Bleeding, Non-Immune Complications, & Treatment Response

Mechanisms: Scientific Areas of Interest

- ◆ Apply new and emerging technologies to identify the causes of IBDs and study mechanisms of bleeding
- ◆ Study the roles of tissue-specific, local, and systemic mechanisms in hemostasis and bleeding
- ◆ Understand the role of blood vessels in hemostasis and bleeding
- ◆ Investigate the mechanisms of other, non-immune complications
- ◆ Elicit mechanisms responsible for differences in response to treatment

Mechanisms: Research Priorities

Apply new and emerging technologies to identify the causes of IBDs and study mechanisms of bleeding

- ◆ Use -omics to refine diagnoses and improve understanding of mechanisms of bleeding in all IBDs (hemophilia A and B, VWD, ultra-rare coagulation disorders, platelet disorders, disorders of fibrinolysis)
- ◆ Investigate mechanisms driving novel mutations and epigenetic changes (e.g. X-chromosome inactivation, variation in modifiers of hemostasis) that cause IBDs and modulate severity
- ◆ Develop models relevant to human bleeding (e.g., animal models, organ and blood vessel on a chip, ECFC/personalized) to study mechanisms and contributors to bleeding (e.g. microenvironment, mechanical stressors, heritable factors, acquired factors)

MECHANISMS OF BLEEDING, NON-IMMUNE COMPLICATIONS, & TREATMENT RESPONSE

- ◆ Determine the impact of genomic and other variation on bleeding phenotype in people with IBDs (e.g. concomitant conditions, genetic and epigenetic modifiers, genetic ancestry, female-specific phenotypes)

Study the roles of tissue-specific, local, and systemic mechanisms in hemostasis and bleeding

- ◆ Characterize cellular (e.g. platelet, vascular, epithelial, immune cell) and tissue specific (e.g. GI, nasal, oral, endometrial) differences that impact bleeding phenotype
- ◆ Study differences in local hemostasis vs. systemic hemostasis (e.g. differences in available coagulation factors, pH, redox states, rheology, vascular supply, vascular bed phenotypes, mucins, ECM, growth factors)
- ◆ Characterize the pathways mediating the interaction of platelets and plasma proteins with the different tissue-specific vascular beds and the extravascular space
- ◆ Investigate the mechanisms of bleeding and biologic differences in the distinct microenvironments (GI tract, nasal tissue and uterus) of EDS and HHT compared to IBDs with mucocutaneous bleeding (e.g. VWD)
- ◆ Determine if defects of primary hemostasis have different effects on uterine bleeding compared to defects of secondary hemostasis
- ◆ Study how hormones, pregnancy, and age affect coagulation factor levels and bleeding risk
- ◆ Study the biology of mild bleeding disorders and mild platelet defects relative to normal function and hemostasis
- ◆ Identify the molecular basis of discrepancies between laboratory assay results (e.g. coagulation factor levels) and bleeding

Understand the role of blood vessels in hemostasis and bleeding

- ◆ Investigate the contributions of blood vessel associated pathways, the extracellular matrix, and the microenvironment to mucocutaneous bleeding
- ◆ Study why different vascular beds are more prone to bleeding, and why some vascular beds bleed disproportionately in some IBDs (e.g. joints and muscles in hemophilia, mucous membranes in VWD)
- ◆ Determine the role of vascular mural cells (e.g., pericytes), vascular integrity, and the ECM in the control of hemostasis and mucocutaneous bleeding
- ◆ Determine if VWF has any function(s) in regulating vascular integrity, and/or any other function(s) that are not currently measurable which could contribute to mucocutaneous bleeding
- ◆ Examine the role of hormones (including endogenous sex hormones) on the blood vessel environment in the context of menstrual bleeding, pregnancy-associated bleeding, and perimenopausal bleeding



Investigate the mechanisms of other, non-immune complications of IBDs

- ◆ Study the mechanisms of wound healing in IBDs (e.g. VWD, disorders of fibrinolysis)
- ◆ Investigate the pathophysiology of hypertension in hemophilia A and determine if it is present in other IBDs
- ◆ Characterize how different IBDs impact bone health and investigate the mechanisms leading to bone loss (e.g. roles of coagulation factor deficiency, biomechanical factors, hormones)
- ◆ Study the role of iron deficiency and/or anemia in bleeding phenotypes, fatigue, neurocognitive symptoms, and mental health
- ◆ Identify mechanisms responsible for differences in susceptibility to iron deficiency and/or effectiveness of iron replacement in people with IBDs experiencing significant blood loss

Elicit mechanisms responsible for differences in response to treatment

- ◆ Characterize mechanisms of response to desmopressin in VWD, hemophilia A, platelet disorders, and collagen disorders/EDS (e.g. differences in endothelial cells, genetics)
- ◆ Study the mechanisms by which exogenous hormones impact female bleeding, including impact on blood vessels, endometrial lining, ovulation, endometriosis, pregnancy
- ◆ Characterize the mechanisms responsible for inactivation and clearance of circulating clotting factors, platelets, and other drugs
- ◆ Investigate the relationship between various medication exposures, mild platelet defects, artifacts in platelet testing, and bleeding
- ◆ Identify the molecular defect(s) in HTT and study the role of iron deficiency affect bleeding and thrombosis in HHT



SPANNING TOPIC:

Immune Responses & Mechanisms

Immune Responses & Mechanisms: Scientific Areas of Interest

- ◆ Understand the risk factors for and drivers of inhibitor formation, persistence, and responsiveness to ITI in hemophilia A and B
- ◆ What is the immune basis of allergic reactions in treatments for IBDs (e.g. FIX, plasma)?
- ◆ What are the considerations around inhibitors in gene therapy for hemophilia A or hemophilia B?
- ◆ What are the mechanisms of inhibitor development and tolerance in other IBDs (e.g. VWF, platelet disorders, rare coagulation factor deficiencies)?
- ◆ What immune features impact joint and bone health?

Immune Responses & Mechanisms: Research Priorities

Understand the risk factors for and drivers of inhibitor formation, persistence, and responsiveness to ITI in hemophilia A and B

- ◆ What features of the immune architecture prior to (and after) FVIII/FIX exposure are associated with inhibitor formation?
- ◆ How are antigen-specific B and T cells quantitatively and qualitatively altered prior to and after FVIII/FIX exposure in patients who develop inhibitors compared to those who do not develop inhibitors?
- ◆ Are there multiple pathways that lead to inhibitor formation (endotypes), and can these highlight distinct mechanisms to inform precision therapies to treat/prevent inhibitor formation?
- ◆ Is altered innate immune function and/or altered adaptive immune function associated with inhibitor formation?

IMMUNE RESPONSES & MECHANISMS

- ◆ What are the risks and predictors of inhibitor development in hemophilia A?
- ◆ What are the risks and predictors of inhibitor development in hemophilia B, and are there differences from hemophilia A?
- ◆ What early life factors (e.g. placental, maternal, environmental) are associated with immune tolerance vs. inhibitor development?
- ◆ Does the inflammatory context at the time of factor exposure (e.g. routine prophylaxis, treatment of acute bleeding, tissue injury, inflammation) contribute to inhibitor development and are different immune pathways involved?
- ◆ Are there other measures of the immune response to exogenous factor (e.g. signals detectable before first clinical inhibitor, kinetics of inhibitor development, inhibitor titer) that better correlate with impact on factor treatment and responsiveness to ITI than Bethesda assays?
- ◆ Are the pathways involved in the development of inhibitors in non-severe hemophilia A or B similar or different from those in severe hemophilia?
- ◆ What are the mechanisms responsible for successful ITI and can factors be identified that predict ITI responsiveness?
- ◆ What is the optimal initial exposure and ITI strategy for hemophilia inhibitors in the non-factor replacement era?

What is the immune basis of allergic reactions in treatments for IBDs (e.g. FIX, plasma)?

- ◆ What features of the immune architecture before and after FIX exposure are associated with allergic reactions in hemophilia B?
- ◆ Is the allergic response to plasma treatment in inherited bleeding disorders different than allergic reactions to transfusion in non-IBD recipients?
- ◆ How are antigen-specific B and T cells quantitatively and qualitatively altered (e.g. specific immune cell responses, such as Th2A phenotype) before and after FIX exposure in patients who develop allergic reactions vs. not?
- ◆ Is altered innate immune function associated with allergic reactions (e.g. basophil function) and/or altered adaptive immune function associated with allergic reactions?
- ◆ Are other atopic conditions associated with allergic reactions to FIX or plasma exposures?
- ◆ Can immune tolerance or other immune modulating therapies (e.g. complement-targeting therapies, anti-IgE therapy, immune suppressing therapies, allergy treatments, desensitization) be used to safely enable factor treatment or plasma exposure after history of allergic reaction?



What are the considerations around inhibitors in gene therapy for hemophilia A or hemophilia B?

- ◆ What are the risks for PWH to develop inhibitors on gene therapy, and are they the same as risk for inhibitors with factor treatment?
- ◆ What is the safety and efficacy of gene therapy in PWH who are at high risk for or have active inhibitors?
- ◆ Is there a role for gene therapy in immune tolerance induction?

What are the mechanisms of inhibitor development and tolerance in other IBDs (e.g. VWF, platelet disorders, rare coagulation factor deficiencies)?

- ◆ What factors predict inhibitor development in non-hemophilia IBDs?
- ◆ What features of the immune architecture before and after treatment are associated with inhibitor formation in non-hemophilia bleeding disorders?
- ◆ How are antigen-specific B and T cells quantitatively and qualitatively altered before and after treatment in people with non-hemophilia IBDs who develop inhibitors vs. those with similar disease who do not?
- ◆ Is altered innate immune function and/or altered adaptive immune function associated with inhibitor formation in non-hemophilia IBDs?
- ◆ Are there multiple pathways that lead to inhibitor formation (endotypes) and do these different endotypes highlight precision therapies to treat/prevent inhibitor formation in non-hemophilia IBDs?

What immune features impact joint and bone health?

- ◆ Are there specific immune pathways or alterations that correlate with poor joint or bone health in IBDs?
- ◆ Is altered innate and/or adaptive immune function associated with joint/bone health?
- ◆ Are there correlations between local inflammatory responses and/or systemic inflammation for bone or joint health in IBDs?
- ◆ Do immune cells in the joint provide clues to key immune features that can be used to interrogate peripheral immune cells to better understand and detect joint disease?



SPANNING TOPIC:

Diagnostic Laboratory Tests, Biomarkers, & Imaging

Diagnostic Laboratory Tests, Biomarkers, & Imaging: Scientific Areas of Interest

- ◆ Develop new diagnostics to improve the diagnosis of IBDs, to identify bleeding, to detect the development of inhibitors, and to improve treatment monitoring
- ◆ Use new and emerging diagnostic technologies to better understand the mechanisms that cause (or protect from) bleeding and inhibitor development
- ◆ Define standards for existing diagnostic tests, improve implementation of bleeding disorder evaluations, and correlate current test results with bleeding phenotypes
- ◆ Improve access to testing to in order to reduce delays and improve accuracy in diagnosis and treatment, particularly for individuals in underserved areas or groups
- ◆ Advance diagnostics and approaches for rare BDs, BDUC, and non-coagulation IBDs

Diagnostic Laboratory Tests, Biomarkers, & Imaging: Research Priorities

Develop new diagnostics to improve the diagnosis of IBDs, to identify bleeding, to detect the development of inhibitors, and to improve treatment monitoring

- ◆ Create new assays to meet unmet needs in the accurate and timely diagnosis of IBDs, including development of diagnostics where current testing has limitations (e.g. VWD, platelet disorders) and for IBDs that do not have readily available clinical tests (e.g. ultra-rare BDs, disorders of fibrinolysis)

DIAGNOSTIC LABORATORY TESTS, BIOMARKERS, & IMAGING

- ◆ Develop IBD sample collection and/or diagnostic assays with form factors that enable testing outside centralized specialty laboratories (e.g. fully automated tests, rapid tests, POC tests)
- ◆ Validate existing global hemostasis assays (e.g. thrombin generation, TEG, ROTEM) and create new assays (e.g. microfluidic assays of thrombus generation and/or lysis) to screen for bleeding disorders and predict bleeding
- ◆ Develop tissue or anatomic site-specific diagnostic imaging and biomarkers to better identify and understand bleeding, bleed detection, and bleeding prediction (e.g. joint, muscle, brain, endometrium), including subclinical bleeding (e.g. joints)
- ◆ Develop methods that identify histopathological and tissue changes that correlate with bleeding (e.g. joints, endometrium)
- ◆ Use -omics tools (e.g. whole genome, methylome, transcriptome, proteome, single cell technologies, pharmacogenomics) for diagnosis and for correlation with bleeding phenotypes, treatment efficacy, and inhibitor development
- ◆ Use mechanistic understanding to drive development appropriate biomarkers in IBD diagnosis, monitoring, and treatment
- ◆ Develop specific tests for guiding the management of all kinds of hemostatic treatments (e.g. factor, non-factor, hormonal treatment) by measuring biomarkers, quantifying drug levels, and capturing other indicators of treatment efficacy (e.g. drug half-life, anti-drug antibodies, patient-reported outcomes)
- ◆ Advance pre-implantation testing methods and develop prenatal noninvasive maternal testing for IBDs
- ◆ Develop biomarkers for risk prediction, diagnosis, and management of thrombotic complications in people with IBDs

Use new and emerging diagnostic technologies to better understand the mechanisms that cause (or protect from) bleeding and inhibitor development

- ◆ Apply new digital technologies (e.g. apps, wearables) to gather rich data sets, longitudinally collect data (e.g. bleeding, treatment regimen, treatment efficacy) for clinical and translational research and to inform development of new clinical tools
- ◆ Assess and validate new techniques in imaging (e.g. MRI, CT, ultrasound, AI-assisted image processing, patient self-imaging) to identify acute bleeding and characterize hallmarks of chronic bleeding
- ◆ Use genomics, other -omics, and other technological advances (e.g. single cell technologies) to study mechanism and the impact of molecular expression patterns (e.g. genotype-specific, DNA, RNA, protein) in blood and different tissues relative to bleeding phenotype and inhibitor development



Define standards for existing diagnostic tests, improve implementation of bleeding disorder evaluations, and correlate current test results with bleeding phenotypes

- ◆ Study the correlation of test results (e.g. laboratory assays, biomarkers, imaging results, patient-reported outcomes) with bleeding and devise bleeding risk prediction tools
- ◆ Define standards for bleeding diagnostic assessments for research studies and use in the real world (e.g. patient-reported outcomes, musculoskeletal imaging tools)
- ◆ Determine the ranges of normal, abnormal, and uncertainty for tests (e.g. factor levels, platelet function, MSKUS), including ranges for non-baseline conditions (e.g. drug treatments, gene therapy, inflammation, surgery, pregnancy and postpartum, hormone therapy, age, sex-specific)
- ◆ Develop standards to minimize laboratory test variability, including common standards for assays (e.g. references, calibration, proficiency testing) and algorithms that account for different test conditions (clotting factor preparations, laboratory reagents, platelet function tests)
- ◆ Study the basis of discrepancies between different diagnostic assays (e.g. FVIII one-stage and chromogenic assays, VWF activity assays, FVII activity assays) and determine which tests correlate best with bleeding
- ◆ Identify accurate measures of iron loss and iron stores to diagnose all with or at-risk for iron deficiency, to study the impact of iron deficiency on IBDs, and to monitor and inform effective iron replacement treatments
- ◆ Develop robust tests for the detection and study of concomitant bleeding disorders and modifiers of bleeding, particularly for co-existent disorders that are challenging to diagnosis such as rare fibrinolytic defects, TFPI disorders, collagen disorders.

Improve access to testing to in order to reduce delays and improve accuracy in diagnosis and treatment, particularly for individuals in underserved areas or groups

- ◆ Determine the characteristics of people who are diagnosed with BDs early in presentation vs. those with delayed diagnoses to identify candidate interventions to improve timeliness of diagnosis
- ◆ Study the use of electronic and digital media solutions for both providers and patients shorten the time to diagnosis, aid in monitoring, and improve management
- ◆ Develop diagnostics that can be accessed outside of the specialty healthcare setting, including rapid and universally available blood testing (e.g. VWD, factor testing) and home patient self-imaging techniques to diagnose and manage bleeding.
- ◆ Study approaches to reducing variability between diagnostic laboratories while ensuring equal access to testing



Advance diagnostics and approaches for rare IBDs, BDUC, and non-coagulation IBDs

- ◆ Use -omics and other new molecular technologies to develop diagnostics for all IBDs, including ultra-rare disorders (e.g. platelet disorders, rare factor deficiencies, disorders of fibrinolysis)
- ◆ Develop diagnostics that detect and quantitatively characterize disorders of fibrinolysis
- ◆ Improve and standardize platelet function testing beyond platelet aggregation testing
- ◆ Develop methods (e.g. standardization of definitions, evaluations) to define new cohorts (e.g. BDUC, MCT bleeding) to be characterized deeply and longitudinally in order to understand the causes of bleeding, describe outcomes, devise predictive tools, and tailor effective treatments
- ◆ Develop diagnostic tests for use in undiagnosed and non-coagulation bleeding disorders (e.g. BDUC, connective tissue disorders/EDS, HHT)
- ◆ Improve regulatory frameworks to enable timely advancement of new diagnostics (e.g. LDTs, companion diagnostics, new imaging modalities) while maintaining integrity in assessments of efficacy and safety



SPANNING TOPIC:

Treatment

Treatment: Scientific Areas of Interest

- ◆ Formulate and advance novel treatments for individuals with IBDs
- ◆ Advance gene therapy and other curative therapies for hemophilia A and B
- ◆ Test the safety and efficacy of repurposing existing therapies for IBDs
- ◆ Optimize existing IBD treatment options and regimens
- ◆ Improve implementation and personalization of treatment for IBDs
- ◆ Increase our understanding of how to prevent and manage complications of therapy for bleeding

Treatment: Research Priorities

Formulate and advance novel treatments for individuals with IBDs

- ◆ Develop new bypassing hemostatic agents for use in PWH with inhibitors and rare coagulation factor deficiencies
- ◆ Advance gene therapy and other curative therapies for non-hemophilia IBDs (e.g. VWD, rare coagulation factor deficiencies, platelet disorders)
- ◆ Develop and/or advance towards approval factor replacement therapies for rare coagulation factor deficiencies without a treatment option in the U.S. (e.g. FXI, FV, longer half-life FVII)
- ◆ Develop new non-factor treatments for mucocutaneous bleeding disorders (e.g. aptamers, topical agents)
- ◆ Engineer and study mechanisms to deliver parenteral drugs (e.g. coagulation factors, VWF) locally (e.g. modified platelets, nanoparticles, intraarticular injection) and systemically (e.g. drug delivery capsules, subcutaneous injection)

TREATMENT

- ◆ Explore effectiveness of endometrial drug delivery of NSAIDs, antifibrinolytic agents, or other nonhormonal therapies via IUDs for the treatment of heavy menstrual bleeding

Advance gene therapy and other curative therapies for hemophilia A and B

- ◆ How do hemophilia and gene therapy health literacy, psychosocial and clinical wellbeing, and educational interventions, influence decision making, compliance, psychosocial changes and other clinical outcomes following gene therapy?
- ◆ What patient-related factors influence factor level outcome in gene therapy?
- ◆ What modifications of genes, vectors, dosing, and administration result in hemostatically relevant and durable increases in factor levels and reduce immunogenicity in gene therapy?
- ◆ What is the safety, efficacy, and durability of gene therapy (e.g. AAV, lentiviral-mediated) in children and in females?
- ◆ What are the risks for and mechanism of inhibitor development with gene therapy?
- ◆ What is the safety and efficacy of gene therapy in PWH with active inhibitors, and can gene therapy induce tolerance?
- ◆ Can gene therapy be done safely in PWH with other comorbidities (e.g. hypertension, diabetes, thrombophilia, pre-existing liver disease)?
- ◆ Is AAV antibody reduction feasible to allow successful AAV vector transduction?
- ◆ What is the magnitude and what are the types of vector genome integration events that occur, and how does this relate to outcomes?
- ◆ What are the safety concerns (e.g. germline integration) in offspring of individuals who received AAV-mediated or lentiviral-mediated gene therapy?
- ◆ Can gene editing provide durable factor expression and if so, can protocols be developed to provide precision treatment to individuals with varying genotypes and/or affected genes in IBDs?
- ◆ Which patients should be offered BMT/PBSCT for platelet disorders (e.g. Bernard-Soulier, Glanzmann's thrombasthenia), at what age or phenotypic severity, and (particularly if alloantibodies are present) with what conditioning?
- ◆ What are the differences in efficacy between gene therapy vs. cellular therapy vs. factor therapy for bleeding prevention and other outcomes?

Test the safety and efficacy of repurposing existing therapies for IBDs

- ◆ Are anti-angiogenesis agents effective for management of certain bleeding symptoms in people with severe mucocutaneous bleeding and/or angiodysplasia (e.g. VWD, HHT)?
- ◆ Are there other drugs with cross-over potential that could be used to treat BDUC and inherited qualitative platelet function defects?
- ◆ What is the impact of androgenic hormone therapy on bleeding symptoms?



- ◆ Can emicizumab be used effectively as subcutaneous therapy (prophylaxis) for people with severe VWD?
- ◆ What is the safety and effectiveness of combination therapies for HMB management (antifibrinolytic agents, desmopressin, gonadal steroid hormones, factor replacement)?

Optimize existing IBD treatment options and regimens

- ◆ Develop protocols to standardize personalized approaches to bleeding disorder treatment
- ◆ What are the genetic, personal, environmental, and healthcare factors that affect treatment choice and response to treatment?
- ◆ What are the characteristics of individuals with good responses to bleeding prophylaxis?
- ◆ Can desmopressin be optimized for safe and more effective management of bleeding in VWD and other desmopressin-appropriate IBDs?
- ◆ Can antifibrinolytic treatment regimens or dosing be further optimized or personalized to improve efficacy?
- ◆ What is the relative effectiveness and optimal dosing of gonadal steroid hormone therapies (and which hormonal therapies) in the acute and chronic setting?
- ◆ How can we optimize treatment for qualitative and mild platelet function defects?
- ◆ What treatment approaches can improve quality of life for fibrinolytic disorders?
- ◆ Determine the effect of the tissue distribution of various FIX products on bleeding risk in hemophilia B
- ◆ Determine whether weight-based factor replacement dosing regimens should use actual or ideal body weight in different bleeding disorders
- ◆ What factor levels are sufficient for prophylaxis to safely prevent bleeding at different levels of activity?

Improve implementation and personalization of treatment for IBDs

- ◆ What factors do providers use to consider the diagnosis of “mild hemophilia” vs. “symptomatic hemophilia carrier” vs. “asymptomatic hemophilia carrier” in females, and how does this affect treatment decisions?
- ◆ Does access to PT and/or MSKUS improve non-MSK outcomes?
- ◆ How does successful transition evolve over time with advances and changes in treatment options (e.g. with more effective treatments, less frequent dosing)?
- ◆ What care model is most effective and feasible in caring for females with inherited IBDs?
- ◆ What is the optimal prophylaxis for procedures during pregnancy?
- ◆ What are the most effective interventions to increase primary care awareness (screening, knowledge, referral) about HMB and associated IBDs?
- ◆ What interventions can improve skill acquisition?



- ◆ Does participation in a cognitive behavioral therapy social support group result in a greater improvement in adherence with prophylaxis than participation in individual therapy for PWIBD?
- ◆ For PWIBD other than hemophilia, should a hematologist, a specialized hematology nurse, a physical therapist, a social worker, or round-the-clock access to a specialized coagulation laboratory be part of the integrated care team, vs. an integrated care team with a lesser complement?
- ◆ What are the cost-benefit trade-offs and financial toxicities associated with different treatments, and how does this affect access to and adherence to prescribed treatment?
- ◆ Identify the appropriate outcomes to assess efficacy of treatment
- ◆ Develop evidence-based protocols for optimal laboratory monitoring and/or companion diagnostic testing frequency and goals for each IBD treatment
- ◆ What tools are currently available to assess QoL longitudinally and what is missing?

Increase our understanding of how to prevent and manage complications of therapy for bleeding

- ◆ What measures of bleeding, QoL, and other outcomes should be used to inform assessments of treatment efficacy and safety?
- ◆ What evidence is needed to inform expert guidance in the safe and effective prevention and treatment of bleeding for different IBDs?
- ◆ What is the incidence of anti-drug antibodies to non-factor products?
- ◆ What general thrombosis risks (e.g. underlying thrombophilia, cardiovascular risks, high blood pressure, high cholesterol, smoking, hormone exposures, vascular access devices) influence risk of thrombosis in persons with IBDs receiving factor and/or non-factor therapies
- ◆ How do HCPs manage thrombotic complications in people with bleeding disorders (determine practice patterns, risk estimation)



NRB Research Priorities Glossary of Acronyms

Acronym	Definition
AAV	Adeno-associated virus, a virus that can be engineered to make particles that cannot replicate themselves and can deliver DNA to cells, such as for gene therapy
ABR	Annualized bleeding rate, the number of bleeding episodes during a designated year
AI	Artificial intelligence, the science of making machines, usually computers, process large amounts of data to recognize patterns and make decisions and judgements
BD	Bleeding disorder
BDUC	Bleeding disorder of unknown cause
BMT	Bone marrow transplant, a treatment that gives blood-forming forming cells (stem cells) that were harvested from bone marrow
COVID-19	Coronavirus disease-2019, the infectious disease caused by the SARS-CoV-2 virus
CT	Computed tomography, a computerized x-ray imaging procedure that gives more information than regular X-rays
DNA	Deoxyribonucleic acid, the molecule that carries genetic information (inherited instructions) for the development, function, growth, and reproduction of an organism
DOAC	Direct oral anticoagulant, a class of anticoagulant drug used to prevent or treat clots
ECFC	Endothelial colony-forming cells, cells capable of becoming the specialized kind of cell that lines blood vessels
ECM	Extracellular matrix, the non-cellular component of all tissues and organs that provides support, separates tissues, and plays a role in communication between cells
ED	Emergency department, also known as the Emergency room (ER)
EDS	Ehlers-Danlos Syndrome, a group of inherited disorders affecting connective tissues, particularly in skin, joints, and blood vessels
e.g.	"such as", preceding a list of examples acknowledging that further similar items can be included in the list
ENT	Ear, nose, and throat, a specialty of medicine dedicated to disorders of the ears, nose, and throat (also known as otolaryngology)
FDA	United States Food and Drug Administration
FIX	Coagulation factor IX (factor nine)
FPG	United States Federal Poverty Guidelines used to determine financial eligibility for certain programs
FV	Coagulation factor V (factor five)
FVII	Coagulation factor VII (factor seven)
FVIII	Coagulation factor VIII (factor eight)
FXI	Coagulation factor XI (factor eleven)



GC	Genetic counselor, a health care professional with advanced training in medical genetics and genetic counseling
GI	Gastrointestinal, referring to the digestive system tract from mouth to anus, also refers the specialty of medicine dedicated to the diagnosis and care of disorders of the GI tract
GYN	Gynecology, a specialty of medicine dedicated to the care of females, particularly female reproductive healthcare
HCP	Healthcare provider
HHT	Hereditary hemorrhagic telangiectasia, an inherited disorder of blood vessels that can cause excessive bleeding
HJHS	Hemophilia Joint Health Score, a measurement of joint health
HMB	Heavy menstrual bleeding, excessive menstrual blood loss (previously known as menorrhagia)
HTC	Hemophilia Treatment Center, a designated specialized, multidisciplinary health-care center providing team-based care for people with hemophilia and other bleeding disorders
IBD	Inheritable Bleeding Disorders
IgE	A subset of antibody molecules particularly important in allergic reactions
ITI	Immune tolerance induction, a treatment to eradicate inhibitors by repeatedly and frequently exposing immune system to the target of the inhibitor (for example, ITI in hemophilia A would treat with factor VIII)
IUD	Intrauterine device
LDT	Laboratory developed test, a clinical test that is made and used within a single laboratory, can also apply to an FDA-approved test that has been modified.
LEE	Lived Experience Expert, LEEs are individuals, their caregivers, and family members directly impacted by bleeding disorders
LEEP	Loop electrosurgical excision procedure, a procedure to remove cells and tissues from the female cervix / lower genital tract
LGBTQIA+	Abbreviation of terms describing a person's sexual orientation or gender identity: Lesbian, gay, bisexual, transgender, queer or queer questioning, intersex, asexual / aromantic / agender, and more
MCB	Mucocutaneous bleeding, a pattern of bleeding that predominantly affects skin (e.g. easy bruising, prolonged bleeding from skin injuries) and mucus membranes (e.g. nose, mouth, throat, GI tract, urinary tract, reproductive tract)
MFM	Maternal Fetal Medicine, a subspecialty of OB-GYN where the physician has extra training in pregnancy and is a high-risk pregnancy expert (also known as perinatology)
MI	Myocardial injury or infarction, when the heart muscle suddenly loses blood flow (also known as a heart attack)
MSK	Musculoskeletal system, the system that includes bones, muscles, cartilage, ligaments, tendons, and connective tissues
MRI	Magnetic resonance imaging, an imaging technology that produces detailed anatomic images using powerful magnetic fields
MSKUS	Musculoskeletal ultrasound, a test that uses ultrasound to image joints, muscles, and other tissues



NBDF	National Bleeding Disorders Foundation, formerly NHF (National Hemophilia Foundation)
NRB	National Research Blueprint for bleeding disorders
NSAID	Nonsteroidal anti-inflammatory drug, a class of drug used to treat pain, fever, and other inflammatory processes
OB	Obstetrics, a specialty of medicine dedicated to the care of pregnancy, childbirth, and the postpartum period
-omics	Areas of science that study biological molecules (e.g. DNA, RNA, proteins, small molecules) at very large scale
PBSCT	Peripheral blood stem cell transplant, a treatment that gives blood-forming cells (stem cells) harvested from blood, very similar to a bone marrow transplant except the origin of the cells is different
PCOS	Polycystic ovarian syndrome, a common hormonal imbalance disorder where the ovaries do not function normally
PCP	Primary care physician, a healthcare provider who practices general medicine
PHQ-9	Patient Health Questionnaire-9, a self-administered questionnaire used to screen for depression
POC	Point-of-care test, a diagnostic test that can be performed close to or near the patient
POLICE	Protection, optimal loading, ice compression, and elevation, an acronym referring to a specific algorithm of acute care steps used after new joint or muscle bleeding
PPH	Postpartum hemorrhage, excessive bleeding after childbirth
PRO	Patient reported outcome measure, a data measure directly reported by the patient or research participant
PT	Physical therapy, a field of healthcare that uses physical treatments to preserve, restore, or improve a person's ability to move and function, reduce pain, and live better (also known as physiotherapy)
PWH	Person with hemophilia, bleeding disorders caused by deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B)
PWIBD	Person with inherited bleeding disorder
QoL	Quality of life measure, data measure of a person's wellbeing
RNA	Ribonucleic acid, a molecule that is a copy of a specific DNA instruction to make a protein, RNA can also perform other functions.
ROM	Range of motion, referring to the measurement of movement a joint or joints can achieve in a specific direction
ROTEM	Rotational thromboelastometry, a measurement of blood clot resistance to shape change and stretchiness while a clot forms and then dissolves on a rotating pin
TEG	Thromboelastography, a measurement of blood clot resistance to shape change and stretchiness while a clot forms and then dissolves in a rotating cup
TFPI	Tissue factor pathway inhibitor, an anticoagulant protein that inhibits processes in the beginning of clot formation
Th2A	A type of immune cells thought to be the most important in driving allergic immune reactions
U.S.	United States of America



VTE	Venous thromboembolism, when a blood clot forms in a vein, includes deep vein thrombosis (DVT, a clot in a deep vein) and pulmonary embolism (a clot that moves and gets stuck in blood vessels of the lung)
VWD	von Willebrand disease, a group of inherited bleeding disorders caused by defects in von Willebrand factor
VWF	von Willebrand factor, a clotting factor





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<https://www.hemophilia.org/research/national-research-blueprint>

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