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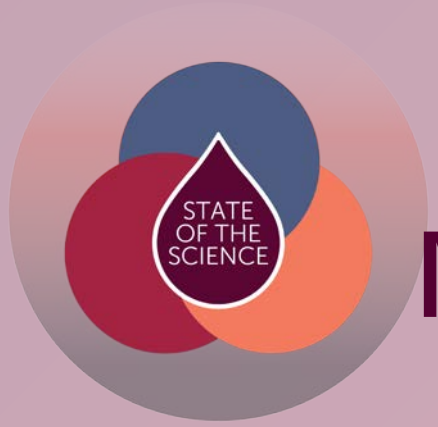

Building the Blueprint March 2022 - Workshop

Research Priorities for Hemophilia A & B

Working Group 1

Co-Chairs

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Hemophilia A & B : The Initial Scheme

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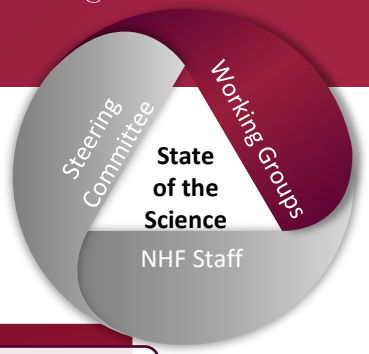

Hemophilia A & B

Multidisciplinary Basic/Translational Research

Therapeutics

Gene therapy

Novel agents

Novel administration

Tolerance

Diagnostics

Genetic testing

POC factor levels

Precision medicine/ Bioinformatics

Mechanisms of Disease

Sex/gender-based biology of joint

Multidisciplinary Clinical Studies/Trials

Clinical Studies/Trials

Post licensure therapeutic/regimen implementation /data collection

Natural history data collection across race/sex/gender/lifespan

Non-severe disease; phenotype reclassification

Comorbidities/QOL

Aging in Hemophilia

Defining clinical outcomes including gene therapy / cure

Hemophilia-related patient-centered outcomes

Many Open Questions for Aging Persons with Hemophilia

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Life Long
Bleed Control

Transition from Childhood to Adulthood

Management of Arthropathy

Cardiovascular Care

Hypertension

Bone Health

Health Literacy

Socioeconomics

Formation of 7 Working Sub-groups for Research Priorities for Hemophilia A & B

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Co-Chairs: Bobby Tran and Annette von Drygalski

Arthropathy/Pain /Bone Health **Lead: Steiner**	Inhibitors **Lead: Meeks**	Diagnostics **Lead: Drygalski**	Gene Therapy **Lead: Reiss**	Transition **Lead: Thornburg**	Disparities/ Literacy **Lead: Tran**	CV Disease **Lead: Quon**
Boice Chitlur Dunn Gupta Quon Volland von Drygalski	Chitlur Volland Martin Reding	Benson Chitlur Johnsen Martin Dunn	Martin Quon Redding Schaefer Steiner Tran	Dunn Narvaez Savage Schaefer Tran	Narvaez Savage Steiner Schaefer Thornburg	Boice Benson Reding Schaefer von Drygalski

Sub-group 1: Arthropathy/Pain/Bone Health

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Priority	Research Priority	Score
1	What medical and/or rehabilitative mechanism based measures facilitate optimal blood and or iron clearance from the joint?	20
2	What is the optimal post-hemarthrosis rehabilitation protocol (eg. joint aspiration, weight bearing, POLICE...)?	19
3	Is there a role for post-surgical interventions to reduce osteochondral and soft tissue changes ?	18
4	What is the role of thrombin generation in maintaining bone and joint health?	16
5	What are the effects of bone strengthening agents (e.g bisphosphonates, Vitamin D, chondroitin) on hemophilic joint health?	16
6	What are the characteristics, causal factors (such as osteochondral alterations and impingement), quantification methods and mechanism based/analgesic therapies to treat arthropathic pain	15
7	How do ultrasound findings and frequency of imaging sessions inform our clinical/rehabilitative management?	14
8	What is the best way to assess and restore/regenerate osteochondral health (e.g. regenerative medicine)	13
9	What are the optimal surgical or invasive (e.g. aspiration/injection) strategies to mitigate arthropathic processes	9

Sub-group 2: Inhibitors

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Priority	Research Priority	Score
1	What are the education needs for patients/families and trainees/providers in the non-factor replacement era?	19
2	What can predict inhibitor development in hemophilia A?	17
3	What are predictors of inhibitor development and allergic reactions in hemophilia B and predictors of response to tolerance?	17
4	What is the optimal initial exposure and ITI strategy in the non-factor replacement era?	16
5	What is the role for gene therapy for tolerance?	15

Haemophilia
The Official Journal of the World Federation of Hemophilia, European Association for Haemophilia and Allied Disorders and the Hemostasis & Thrombosis Research Society

ORIGINAL ARTICLE

The national blueprint for future basic and translational research to understand factor VIII immunogenicity: NHLBI State of the Science Workshop on factor VIII inhibitors

Shannon L. Meeks, Roland W. Herzog, on behalf of the Members of Working Group 3, the NHLBI State of the Science Workshop on factor VIII inhibitors: Generating a national blueprint for future research

First published: 22 July 2019 | https://doi.org/10.1111/hae.13740 | Citations: 6

Sub-group 3: Diagnostics

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Priority	Research Priority	Score
1	Develop validated home patient self-imaging techniques	22
2	Demonstrate the value of patient self-imaging to improve management	22
3	Establish a biomarker profile that can predict bleeding phenotype	19
4	Develop a site specific (e.g. joint, muscle, brain) blood test for rapid (sub)clinical bleed detection	18
5	Study genotype, genetic or other modifiers, protein expression patterns in plasma/tissue in relation to bleeding phenotype	17
6	Develop fast and quantitative MRI sequences to assess bleed burden and iron accumulation objectively	16
7	Develop and study rapid and universally available coagulation testing (factor levels, thrombin generation, global assays and drug-specific test assessments) to guide management	15
8	Determine utility and/or correlation of clinical and imaging joint assessments tools on outcomes (e.g. HJHS, Gilbert, ROM, total arc, gait, pain, MRI, X-ray, POC MSKUS)	14
9	Determine correlations between clotting factor activity levels and bleed propensity to devise a risk prediction tool	13
10	Study the incidence of anti-drug antibodies of non-factor products and provide tests	11
11	Develop companion diagnostic tests to guide management of hemostatic treatment with various factor or non-factor products	11
12	Develop algorithms to minimize test result variability taking into account variables such as different clotting factor preparations, gene therapy and laboratory reagents	8
13	Determine the effect of tissue distribution of various FIX-products on bleeding risk	6

Sub-group 7: CV Disease

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Priority	Research Priority	Score
1	How does hypertension relate to hemorrhagic stroke and mortality in hemophilia?	18
2	What is the role of nonfactor therapy (Emi and others) in the management of atrial fibrillation with DOACs?	17
3	What is the prevalence of cardiovascular risk factors, especially hypertension, in different hemophilia severities and age groups	16
4	How can we optimize anticoagulation management in the setting of atrial fibrillation or dual antiplatelet agents including lab monitoring?	16
5	What is the role of nonfactor therapy (Emi and others) in the management with stents after MI with anti- platelet agents?	16
6	What is the pathophysiology of hypertension in hemophilia	14

Sub-group 4: Gene Therapy

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Priority	Research Priority	Score
1	How does status of health literacy on hemophilia and gene therapy as well as psychosocial and clinical wellbeing, and educational interventions, influence decision making, compliance, psychosocial changes and other clinical outcomes after gene therapy?	21
2	How can knowledge and empowerment of patients be built to allow pathways of advocacy to help build health equity?	19
3	What types of methodologies can be created and will be successful to provide health equity, affordability and fairness for all stakeholders including society as a whole?	19
4	What are the most appropriate education and consenting methods for gene therapy for minors?	18
5	What types of operational methodologies can be developed and will be successful and appropriately adjustable to local or specific needs?	17
6	What patient-related factors influence factor level outcome, and how?	17
7	What modifications of vectors and dosing and administration will reliably lead to normal and durable factor levels, and can reduce immunogenicity?	16
8	What is safety and efficacy of LV-mediated gene therapy as a possibility to provide durable factor expression as well as an option for younger children?	16
9	Is AAV antibody removal feasible and effective to allow successful AAV-vector transduction?	16
10	What is the magnitude and types of integrations of vector genome and how does this relate to outcomes	15
11	What is the safety and efficacy of AAV-mediated gene therapy in children age less than 18 years and women?	15
12	What are the safety concerns in off-spring after AAV-GT or LV-GT?	15
13	Determine the risk and mechanism of inhibitor development, and safety and efficacy after gene therapy in patients with higher risk for inhibitors (risk factors, h/o inhibitor?	14
14	What is safety and efficacy of gene therapy in patients with active inhibitors?	14
15	How can gene therapy be done safely in patients with HTN, DM, or thrombophilia, or existing liver disease?	13
16	Is gene editing a possibility to provide durable factor expression?	13

Sub-group 5: Transition

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Priority	Research Priority	Score
1	What is the definition of successful transition (and key metrics)?	20
2	What are the best educational tools to facilitate medical independence?	20
3	What are the predictors/facilitators/barriers to successful transition?	19
4	What interventions can improve skill acquisition?	17
5	What percentage of patients have achieved medical independence by age 26yo?	16
6	Does access to care navigator facilitate transition?	16
7	What percentage of young adults (?18-25y) have successfully transferred from pediatrics to adult clinic?	15
8	How does successful transition evolve over time with changes in treatment options? ie change in bleeding phenotype?	13
9	How does successful transition impact long-term outcomes?	13

Sub-group 6: Disparities/Literacy

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Priority	Research Priority	Score
1	**What is the difference in comp visit care and attendance between males and females with mild hemophilia?**	**20**
2	**What factors do providers use to consider the term "girls/women with mild hemophilia" vs "hemophilia carrier"?**	**15**
3	**Do patients with hemophilia who have a PTs with more FTEs in their HTC, PT availability in their local community, or musculoskeletal ultrasound at their HTC have better functional outcomes and pain outcomes after joint bleeds?**	**15**
4	**Do patients with hemophilia who have a PTs with more FTEs in their HTC, PT availability in their local community, or musculoskeletal ultrasound at their HTC have better functional outcomes and pain outcomes after joint replacement?**	**13**
5	**Which physical (PCP referral) or psychological (too busy being a caregiver or does not want to get worked up) factors impact access of care for females with hemophilia? What are other barriers?**	**13**
	What are barriers to involvement in clinical trials for certain subsets of those with hemophilia or those with inherited bleeding disorders? Additionally, what are the driving factors that contribute to pharma choosing certain inclusion criteria?	
	How do we prevent provider bias for access to clinical trials for patients with socioeconomic barriers?	
	What are patient outcomes for those HTCs with full access to their 340B funds as compared to the HTCs which have barriers such as institutional barriers? What are the resources available at these particular HTCs vs those with barriers to the 340B fund use?	
	What unique cultural populations are associated with different bleeding disorders and is there a knowledge gap for local providers outside of the HTC?	

Other overlapping topics without formulated questions: transgender issues, health literacy

Sub-group 6: Disparities/Literacy

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Priority	Research Priority	Score
1	**What is the difference in comprehensive visit care and attendance between males and females with mild hemophilia?**	**20**
2	**What factors do providers use to consider, for girls or women, the diagnosis of "mild hemophilia" vs "hemophilia carrier"?**	**15**
3	**Do patients with hemophilia who have a PT with more FTE (full-time equivalent) hours in their HTC, PT availability in their local community, or musculoskeletal ultrasound at their HTC have better functional outcomes and pain outcomes after joint bleeds?**	**15**
4	**Do patients with hemophilia who have a PT with more FTEs in their HTC, PT availability in their local community, or musculoskeletal ultrasound at their HTC have better functional outcomes and pain outcomes after joint replacement?**	**13**
5	**Which physical (eg, PCP referral) or psychological (eg, too busy being a caregiver or does not want to get worked up) factors impact access of care for females with hemophilia? What are other barriers?**	**13**
	What are barriers to involvement in clinical trials for certain subsets of those with hemophilia or those with inherited bleeding disorders? Additionally, what are the driving factors that contribute to pharma choosing certain inclusion criteria?	
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	What unique cultural populations are associated with different bleeding disorders and is there a knowledge gap for local providers outside of the HTC?	

Other overlapping topics without formulated questions: transgender issues, health literacy

Thank you

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