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Genotyping for Progress in Hemophilia

My Life, Our Future: Research Update

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athn american thrombosis & hemostasis network
Bloodworks Northwest
National Hemophilia Foundation for all bleeding disorders
Bioverativ

the vision

Bring a national program to the hemophilia community that:

- Offers **free genotyping** to people with hemophilia and their families
- **May help improve hemophilia care** by increasing **understanding** of the disorder today
- Builds a **foundation** for the **scientific breakthroughs** of tomorrow

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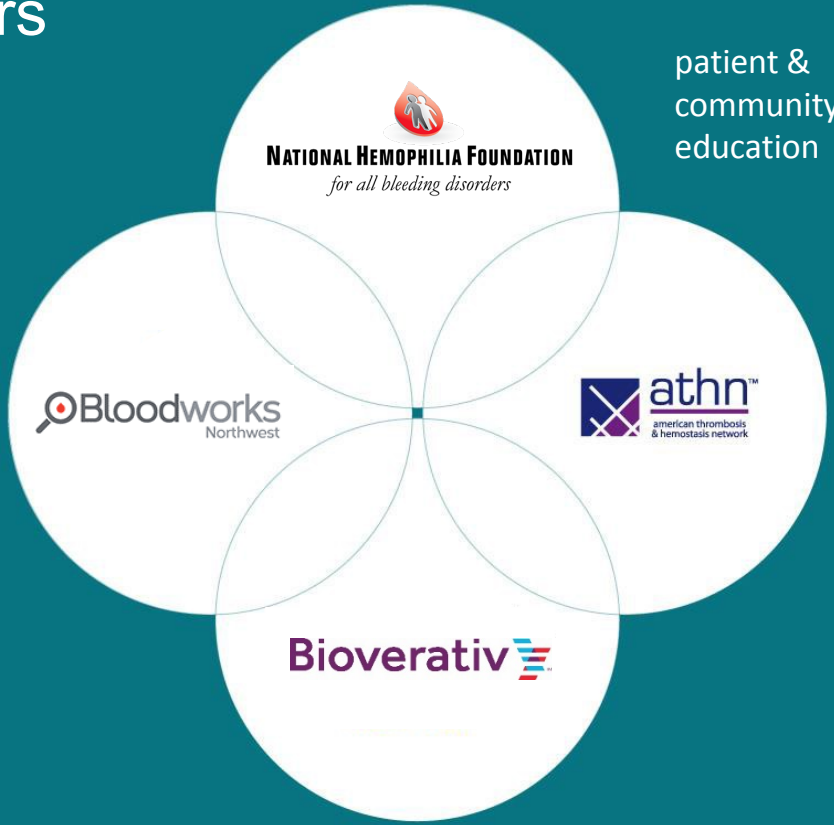
founding partners



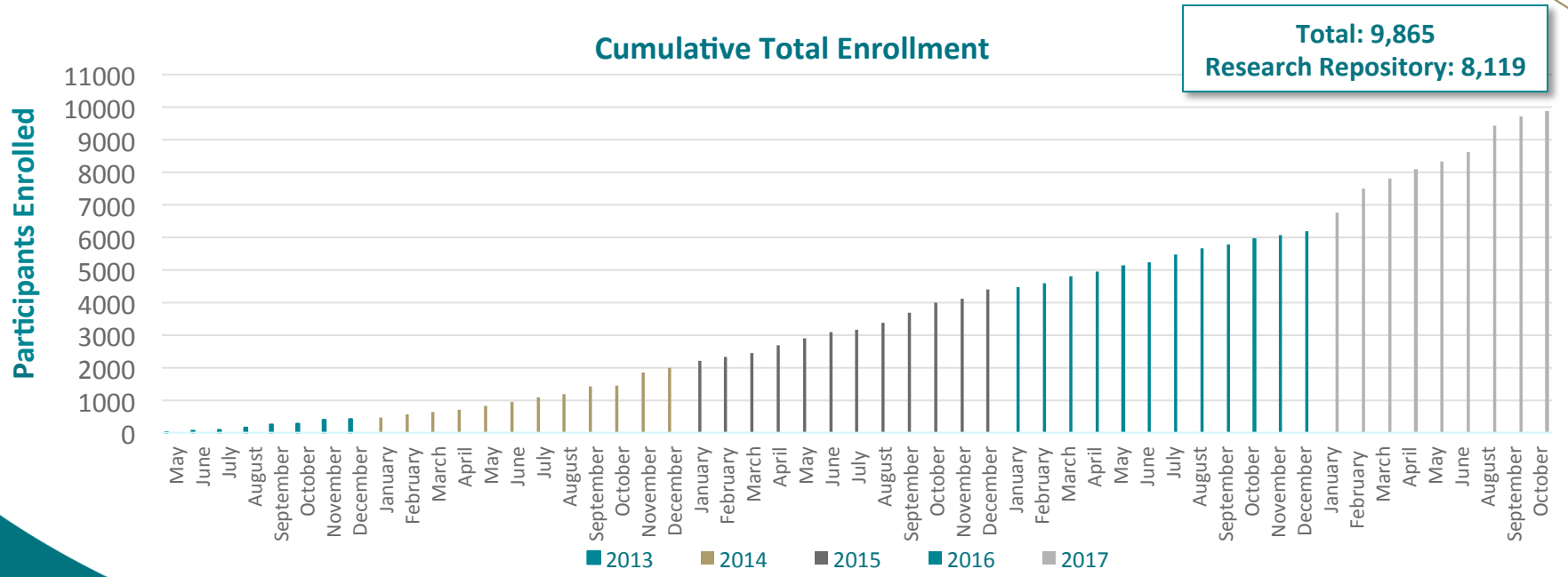
patient & community education

genetic testing & analysis; houses *My Life, Our Future* Research Repository

healthcare provider education; collects & protects genetic data; manages ATHNdataset; manages Research Review Committee

scientific collaboration & initiative support

nearly 10k have said yes to progress!



As of October 9, 2017

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carrier program research enrollment goal = 2,000

2,559 females genotyped by MLOF – **1,348** confirmed carriers, **756** pending

1,112 confirmed carriers in MLOF Research Repository; additional awaiting confirmation

78 HTCs approved to enroll carriers

As of October 9, 2017

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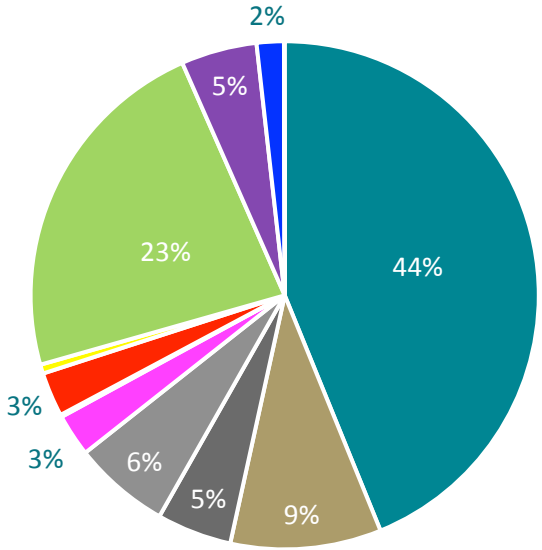
hemophilia A participant variants



- Missense
- Frameshift
- Large structural change (>50 bp)
- Nonsense
- Synonymous
- Upstream
- Splice site change
- Small structural change (in-frame, <50 bp)
- Int 22 Inversions
- Specified Variant Not Found
- No Variant Found
- Untranslated Region

As of August 22, 2017

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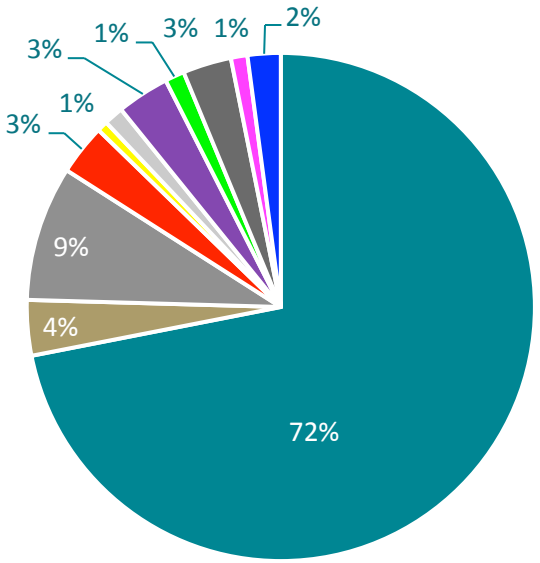
hemophilia B participant variants



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As of August 22, 2017

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…and **more than 900 novel variants** have been identified through *My Life, Our Future*!

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MLOF findings published in *Blood Advances*

REGULAR ARTICLE

blood advances

Novel approach to genetic analysis and results in 3000 hemophilia patients enrolled in the My Life, Our Future initiative

Jill M. Johnsen,[1,2] Shelley N. Fletcher,[1] Haley Huston,[1] Sarah Roberge,[1] Beth K. Martin,[3] Martin Kircher,[3] Neil C. Josephson,[4] Jay Shendure,[3,5] Sarah Reiss-Brennan,[1] Marion A. Koerper,[6] Jaime Morales,[7] Glenn F. Pierce,[8] Diane J. Aschman,[9] and Barbara A. Konkle[1,2]

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Key Points

- MLOF used an innovative approach to genotype 3000 hemophilia patients identifying likely causative variants in 98.4% of patients.
- Hemophilia genotyping should include structural variation, *F8* inversions (for hemophilia A), and consideration of gene-wide approaches.

Hemophilia A and B are rare, X-linked bleeding disorders. My Life, Our Future (MLOF) is a collaborative project established to genotype and study hemophilia. Patients were enrolled at US hemophilia treatment centers (HTCs). Genotyping was performed [illegible] generation sequencing (NGS) with an approach that detected [illegible] simultaneously with *F8* and *F9* gene sequencing followed by confir[illegible] genotyping methods. Sixty-nine HTCs enrolled the first 3000 patient[illegible] Clinically reportable DNA variants were detected in 98.1% (2357/24[illegible] 99.3% (595/599) of hemophilia B patients. Of the 924 unique variant[illegible] Predicted gene-disrupting variants were common in severe disease[illegible] predominated in mild-moderate disease. Novel DNA variants acco[illegible] variants found and were detected continuously throughout the pr[illegible] additional variation likely remains undiscovered. The NGS approac[illegible] variants in 36 patients (10 females), a finding with potential clinic[illegible] detected incidental variants unlikely to cause disease, including 11[illegible] reported in hemophilia. Although these genes are thought to be conserved, our findings support caution in interpretation of new variants. In summary, MLOF has contributed significantly toward variant annotation in the *F8* and *F9* genes. In the near future, investigators will be able to access MLOF data and repository samples for research to advance our understanding of hemophilia.

Introduction

Hemophilia A and B are X-linked recessive disorders resulting from more than 3000 different DNA variants reported to date in the genes encoding coagulation factor VIII (FVIII) and FIX, respectively.[1-4] Determination of the causative genetic variant in families affected by hemophilia is important for use in reproductive planning, for use in pregnancy and neonatal management, and also to inform risks of neutralizing antibody (inhibitor) formation and bleeding severity.[5-12] Therapies targeted to specific mutations have been studied and are likely to become more common in the future.[13]

In 2012, 2 separate surveys, 1 distributed to hemophilia providers through the American Thrombosis Hemostasis Network (ATHN) and the other distributed to the patient community through the National Hemophilia Foundation, found that only ~20% of the hemophilia patients in the United States had had their genotype determined. The most common reasons cited for not having the testing performed were the lack of medical insurance coverage and the lack of availability of testing. Furthermore, the scientific and clinical

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The full-text version of this article contains a data supplement.

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blood advances™

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MLOF Research Repository first application cycle

international and diverse expertise: the MLOF Research Review Committee

David Lillicrap, MD, PhD
molecular pathologist
committee chair

Jorge DiPaolo, MD
US hematologist

Frits Rosendaal, MD
EU hematologist

Michelle Alabeck, MS, CGC
genetic counselor

Glenn Pierce, MD, PhD
research scientist

Karl Desch, MD
molecular biologist

Craig Muir
non-physician patient representative

Alex Reiner, MD
genetic epidemiologist

Elizabeth Hauser, PhD
molecular epidemiologist
geneticist

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furthering scientific study: first application cycle

Application Process

- First application cycle opened to U.S.-based researchers in 2017
- Scientists and researchers at academic institutions or drug discovery companies submitted scientific hypothesis-driven applications

Review Process

- Completed by an independent, multidisciplinary review committee
- All applications underwent rigorous evaluation to confirm scientific integrity of project

HTCs

- Important in the translation of research findings
- Source of additional clinical data needed to execute projects

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approved research projects

- During first application cycle, **seven promising projects** were selected by the Research Review Committee

- Using genotyping data, phenotypic data, and specimens, these projects will explore questions related to:
  - **Inhibitor development** (severe hemophilia A, severe hemophilia B, both severe hemophilia A and B, and non-severe hemophilia A)
  - **Bleeding** (carriers, and hemophilia A and B without inhibitors)
  - **Factor VIII clearance**

Contact MLOF@ATHN.org to learn more

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details of approved research projects

Association Between F8 Mutation and Inhibitor Development in Patients with Non-Severe Hemophilia A

Dr. Ming Lim, Medical University of South Carolina

Genetic Burden Analysis, Including Genes Encoding Fc Receptors (FcRx) and Cell Surface Proteins Which Bind Factor VIII To Identify Genes Associated with Inhibitor Development in Hemophilia A

Dr. Tim Harris, Bioverativ Therapeutics

Genetic, Epigenetic and Antibody Signatures of Hemophilic Inhibitor Responses

Dr. Kathleen Pratt, Uniformed Services University of Health Sciences

Mathematical Immune Model for Predication of Factor VIII Inhibitor Development and Its Impact on Clinical Outcome of Treatment for Hemophilia A Patients

Dr. Zuben Suana and Dr. Hong Yang, Center for Biologics Evaluation & Research, FDA

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details of approved research projects (cont.)

Understanding the Immunologic and Bleeding Phenotypic Variation in Hemophilia	**Study of Factors Associated with Bleeding in Female Hemophilia Carriers**	**Precision Medicine to Advance Care for Persons with Hemophilia: Pharmogenomics**
Dr. Rodney Camire, Children's Hospital of Philadelphia	Dr. Jill Johnsen, Bloodworks Northwest Research Institute	Dr. Steven Pipe, University of Michigan

the future of MLOF

whole genome sequencing through TOPMed program

- Nearly 5,000 samples in the MLOF Research Repository will undergo whole genome sequencing (WGS) through TOPMed
  - ~2,000 samples sequenced; ~3,000 sent to Baylor University for sequencing
  - Obtaining WGS on remaining samples in the MLOF Research Repository depends on availability through the NHLBI TOPMed program
- Genomic data and limited phenotypic data will be accessible to qualified scientists through application to NIH for access in dbGaP
- With future application to the MLOF Research Repository, scientists will be able to link samples and data to WGS data in dbGaP

MLOF in 2017-2018, and beyond

- Primary goals have been exceeded
  - Completion of carrier enrollment goal anticipated by end of 2017
  - Ongoing program enrollment will end on December 15, 2017
    - Individuals' samples collected through December 2017 will be processed in 2018, and genotype results returned to HTCs in Q1-Q2
- Focus of program is shifting, as planned, to the utilization of the MLOF Research Repository
- MLOF is evaluating longer-term program goals and funding needs to sustain and enhance the MLOF Research Repository

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acknowledgements

HTC providers and staff
Patients and families affected by hemophilia

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Sarah Ryan
Gayle Teramura
Ann Whitney
Raquelle Williams

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questions?

thank you!