ATHN DATA SUMMIT 2016

The ATHN Database and My Life, Our Future as a Gateway to NIH Collaboration on Precision Medicine and Beyond

Keith Hoots, MD

Director, Division of Blood Diseases and Resources

National Heart, Lung and Blood Institute

NIH

athn™ american thrombosis & hemostasis network | CELEBRATING ten years

OUTLINE

1. Strategies for the use of the ATHN database to initiate studies to compete for NIH funding

1. Ongoing and projected collaborations among ATHN, *My Life, Our Future* and NHLBI

Possible Strategies that ATHN and HTCs Might Use to Increase Competitiveness for NHLBI Funding

1. Utilize the ATHN Database for hypothesis generation for possible randomized clinical trials or studies
2. ATHN and investigative team familiarizes themselves for the new two- stage clinical trial funding opportunity announcement (FOA) of NHLBI/NIH
3. Rigorously perform “in house” assessment of the potential scientific importance of the proposed questions and prioritize them accordingly
4. Ask for firm commitment from candidate HTCs to recruit for the prioritized studies *if* the proposal is funded by NHLBI: Allocate resources for recruitment, retention, GCP rigor accordingly to the sites (implies careful budgetary planning)
5. Carefully choose the Clinical Coordinating Center/Principal Investigator who will apply as the CCC to the NHLBI FOA
6. ATHN collaborates with a highly functioning data coordinating center (DCC) to compete for DCC funding

What is **Precision Medicine** and what does it have to do with Hemophilia and *My Life, Our Future*?

Precision Medicine: A new effort to account for more of the normal variation in individual human biology in the practice of medicine

e.g. In hemophilia the determination of the mutation in the Factor VIII gene (Hemophilia A) or Factor IX gene (Hemophilia B) (the aim of MLOF) may provide some indication of a participant's risk for developing an inhibitor/antibody against infused FVIII or IX.

Have Physicians not always personalized an inidividual's medical care?

Yes, *but new scientific tools such as genetic sequencing have revolutionized the potential to tailor diagnosis and management to the unique biology of every person. That is the reason the President has charged the NIH (and its Federal partners)specifically to launch the PRECISION MEDICINE INITIATIVE which includes a "million person" cohort*

How is NHLBI working with MLOF/ATHN to try to enhance the potential of Precision Medicine to improve the lives and care of people with hemophilia?

NHLBI and MLOF are collaborating to offer *whole genome sequencing** to participants in the program who already have already had their factor VIII or IX gene mutation analysis performed.

*What is *Whole Genome Sequencing* (WGS)and what scientific or medical contribution might it add to knowing the hemophilia mutation results?

1) *WGS is the new automated technology that allows one to determine every single DNA base in order of its reading (transcription) of a person's unique genetic code. It provides definitive information about every gene that individual was born with (exons) and also all the other DNA (introns) that appear to regulate expression of the approximate 300,000 exons.*

2) By knowing this scientists and physicians can begin to assess how this unique gene assortment influences the health and disease of this individual. e.g. At present knowing the mutation and other patient and family history we are still far from being able to predict inhibitors formation. Other genes and environmental exposures appear to play a role as well. WGS and other new techniques could narrow this knowledge gap.

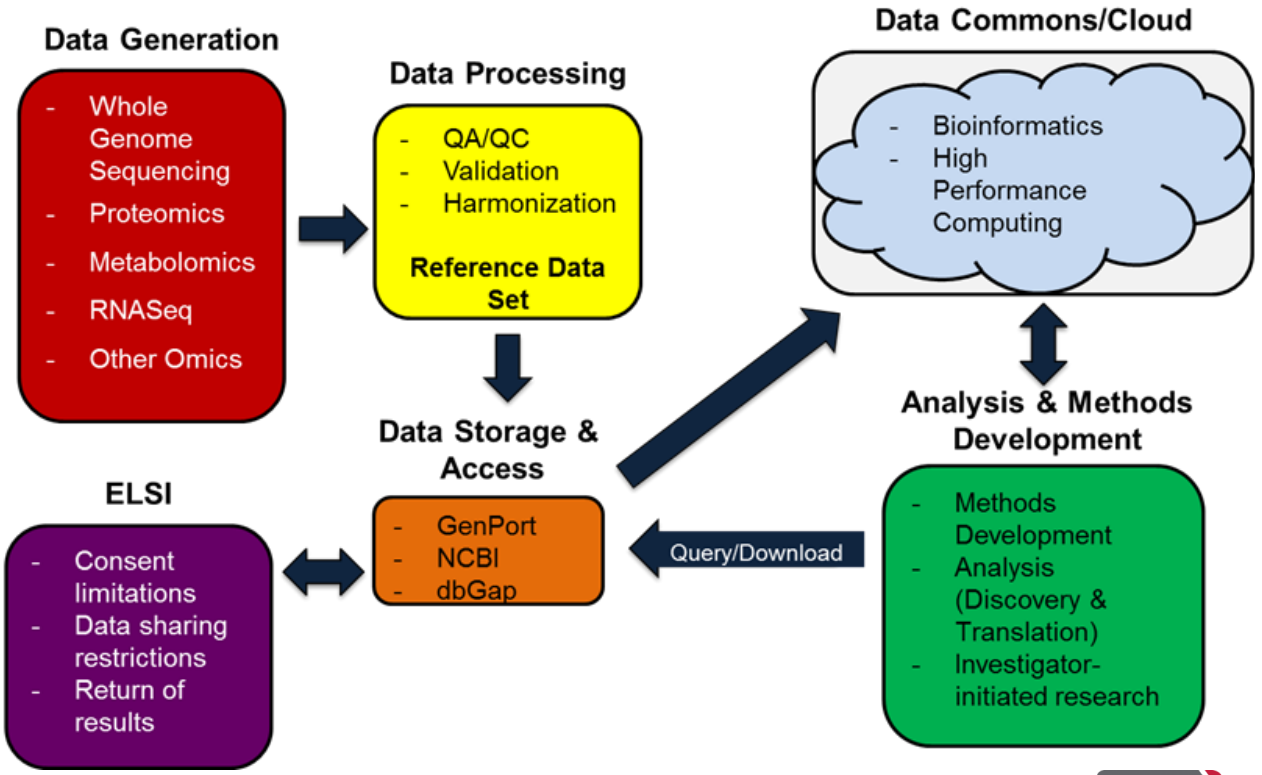
TOPMED (Transomics for Precision Medicine)

- *Genomics (as specified by Whole genome sequencing)*
- *Epigenomics* (assessment of gene regulation)
- *Transcriptomics* (assessment of the RNA message from the genes)
- *Proteomics* (assessment of the proteins that are made from translating the RNA)
- Metabolomics (assessment of markers of metabolism)
- *Glycomics* (assessment of the sugar structures that frequently add structural and functional specificity to proteins (e.g. FVIII and IX)
- *Exposome* (Measurements of environment on the above *omics*
- *Phenomics* (the personal and medical findings unique to the person

NHLBI TOPMed Goals

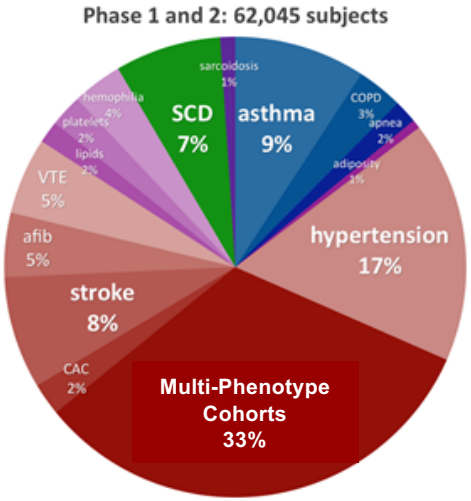
- Stimulate discovery in high impact disease areas
- Build a resource for the scientific community
- Ensure well phenotyped and genotyped participants are chosen from traditionally underrepresented populations (diversity)
- Stimulate systems medicine approaches to health and disease research
- Enable and facilitate precision medicine

TOPMed Program Components

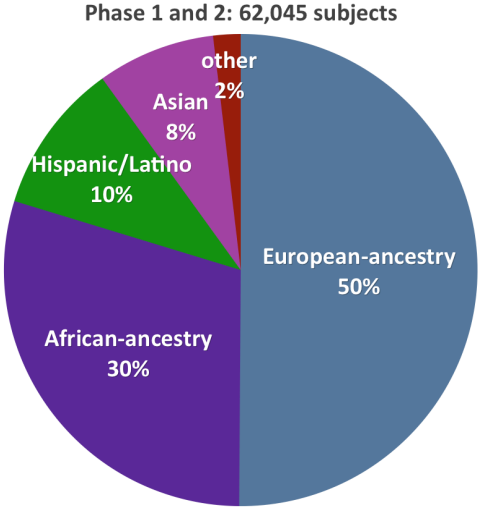


TOPMED - Where Are We Now?
Phenotype and Population Diversity

Phenotype Diversity



Population Diversity



Developing a rich data source representative of the diverse HLBS phenotypes and populations that can enable multi-omics exploration to define the mediator pathways of HLBS disorders and discovery novel therapies.

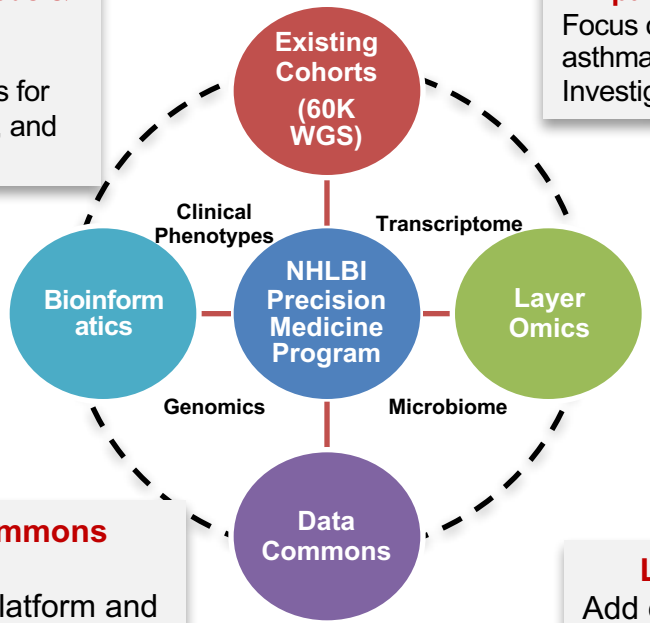
2015 Participating Studies

PI Name(s)	Title	Institution	Disease/Phenotype	Sample Size to be sequenced	Populations
Mathias, Rasika	Study of Athersclerosis Risk in Families (GeneSTAR)	Johns Hopkins Medical Institution	Coagulation, Longitudinal, iPSC, RNASeq	1,400	700 EA & **700 AA**
Arnett, Donna	Genetics of Left Ventricular Hypertrophy (HyperGen)	University of Alabama	LVH, imaging iPSC, RNASeq	3,161	**AA** Family
Arnett, Donna	Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	University of Alabama, Birmingham	Lipid Response, PGx, multi-Omics	967	EA Family
Rao, Dabeeru	Taiwan Study of Hypertension using Rare Variants (THRV)	Washington University	Hypertension, Longitudinal, multiple risk factors	2,400	1200 Taiwan Family 1200 Unrelated Controls
Montgomery, Courtney	Genetics of Sarcoidosis in African Americans	Oklahoma Medical Research Foundation	Sarcoidosis	650	**AA** **Family**
Casella, James	Silent Cerebral Infarct Trial (SIT)	Johns Hopkins University	Sickle Cell Disease	1,074	AA Pediatric
Gladwin, Mark	Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Treatment (Walk-PHASST)	University of Pittsburgh Medical Center	Sickle Cell Disease	720	AA
Custer, Brian	Recipient Epidemiology and Donor Evaluation Study (REDS III)	Blood Systems Research Institute, UCSF	Sickle Cell Disease	2,809	Brazilian
Boerwinkle, Eric	Atherosclerosis Risk in Communities Exam 5 2011-2013 (ARIC)	University of Texas	VTE, Multiple Outcomes & Risk Factors, Longitudinal, Omics	6,030	4977 EA **1053 AA**
Rotter, Jerry	Multi-Ethnic Study of Athersclerosis (MESA visit 5)	Los Angeles Biomedical Research Institute	Multiple Outcomes & Risk Factors, Imaging, Air Pollution	4,595	**1233 AA** **541 Asian** **999 Hisp** 1822 EA
He, Jiang	Genetic Epidemiology Network of Salt Sensitivity (GenSalt)	Tulane University	Hypertension, Salt Interv., Multi-Risk Factors, Longitudinal, Outcomes	1,115	**Chinese** (family can impute
Konkle, Barbara	Hemophilia Study	Blood Works Northwest	Severe Hemophilia A&B, Type, Severity, inhibitor formation, comorbidities	2,188	Majority EA
Taylor, Kent	African-American Coronary Artery Calcium Project (AA CAC)	Los Angeles Biomedical Research Institute	CAD, Controls, Multiple Longitudinal Risk Factors	787	AA (family can impute)
Kooperberg, Charles	Women's Health Initiative (WHI)	Fred Hutchinson Cancer Research Center	Stroke, Hypertension, VTE, Longitudinal, Clinical Trial, Multiple Risk Factors, Omics	11,100	Women Multiple Ethnicities
			TOTAL	**38,996**	

TOPMed and Planning for the Future: Evolving Next Steps

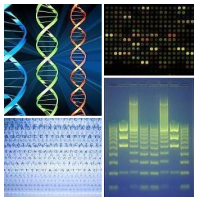
Develop analytic methods & pipelines

Incentivize new methods development and analysis for discovery and translation, and training next generation



Expanding Phenotypes and Cohorts

Focus on high impact disease (e.g., asthma, early MI, sickle cell disease)
Investigator-driven phenotypes



Develop data commons platform

Pilot data commons platform and enhance availability of data available by incorporating HLBS data from diverse sources

Layer on other "omics"

Add depth to WGS analysis and can lead to additional insights using systems approach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