ASHG Ancillary Workshop, “NHLBI TOPMed program: How to use WGS and other multi-omics data on over 140K genetically diverse and deeply phenotyped participants to advance your science”

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NHLBI's mission

Leading causes of death
World, 2016

Cardiovascular diseases: 32.3%
Cancers: 16.3%
Respiratory diseases: 6.5%
Diabetes: 5.8%
Lower respiratory infections: 4.4%
Dementia: 4.4%
Neonatal deaths: 3.2%
Diarrhoeal diseases: 3.0%
Road injuries: 2.5%
Liver disease: 2.3%

Source: IHME, Global Burden of Disease, Our World in Data
Roads toward Precision Medicine

Gary H. Gibbons, M.D., Director of the National Heart, Lung, and Blood Institute (NHLBI), joined NHLBI in 2012 with his eyes on precision medicine.

NHLBI Workshop, April 9-10, 2014: Genomic Research in Preventing and Treating Heart, Lung, and Blood Diseases

NHLBI Trans Omics Precision MEDicine (TOPMed) Program, 2014—To create a large WGS/Omics data resource supporting discovery research toward precision medicine.
Dr. Gibbons’ talk at 5:30 PM EDT, October 29, 2020, The Presidential Plenary Symposium
Impact of Genetic Research

Source: Vital Statistics of the United States, NCHS.

Age-Adjusted Death Rates for Coronary Heart Disease, U.S., 1950–2010
Actual Rate and Expected Rates if Rise Had Continued or Reached a Plateau by

- FHS 1948
- Goldstein Brown 1973
- Statins 1987
- PCSK9 Hobbs and Cohen 2006
- TOPMed 2014
- PCSK9 Inhibitors 2015
Not to comprehensively identify genetic basis of a couple of common diseases

But to build genomic databases for many heart, lung, blood diseases and sleep disorders (more than 20 diseases or conditions).

Uses existing biospecimens from existing studies.

1. Minority Populations
2. Longitudinal epidemiology studies (e.g., Framingham Heart Study (FHS, 1948-...))
3. Natural history of disease (e.g., Genetic Epidemiology of COPD (COPDGene, 2008-...))
4. Cross sectional disease studies (e.g., My Life, Our Future: Genotyping for Progress in Hemophilia (MLOF)...)
5. Family based studies, for example (e.g., Cleveland Family Study...)
TOPMed Progress – Total WGS/Omics funded in FY14-19

Total numbers of WGS and Omics

- **WGS**
  - FY14: 19,741
  - FY15: 72,409
  - FY16: 121,273
  - FY17: 145,310
  - FY18: 155,582
  - FY19: 167,894

- **Omics**
  - FY14: 13,939
  - FY15: 55,215
  - FY16: 96,295
  - FY17: 13,939
  - FY18: 55,215
  - FY19: 96,295
Type of Omics Products (FY14-19)

- RNA-seq: 31,095
- Methylome: 48,800
- Metabolome: 16,400
- Proteome: 3,000
Next, TOPMed2.0

1. Release more data to the community; 75% of WGS are released by dbGaP and NHLBI’s cloud-based platform: BioData Catalyst.

2. Build collaborations with other data sources to future empower research communities.

3. Generate more Omics data to establish molecular/cellular phenotypes between TOPMed’s clinical measurements and WGS data.

4. Support discovery studies.
TOPMed Supports Systems Biology Studies toward Precision Medicine

**Organ/tissue image**

**Single-cell Omics**

- WGS
- Metabolome
- Proteome
- Methylome
- RNA-seq

**Map risk genes to risk cells**

- mQTL + pQTL + meQTL + eQTL
- pQTL + meQTL + eQTL
- meQTL + eQTL
- Cis-/trans- regulatory elements
- Modulated by aging, race, gender, smoking, diseases

**Association Study**
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BioData Catalyst