Outline

Genetic Architecture of Health and Disease

- **Goals** $\rightarrow$ Tactics

- What are we doing?
- Why are we doing it?
- What steps can be taken in the short-medium term
- A few tactics comments
- What it means to the clinical and basic science community

Draft Overarching Goal
Health and Disease

- Define the relationships of germline, somatic and epigenetic variation to human health- and disease-related traits as a means to illuminate pathophysiology.

- Develop and deploy assays that faithfully report disease-relevant functions of mutations and genes to guide variant interpretation and therapeutic discovery.

- Create and make widely available the knowledge-base needed to interpret genome sequence variation in life science, drug discovery, prediction and clinical diagnosis

- Do so across a range of human diseases/conditions and of populations to expand discovery, define architecture, and broaden access. and do so as a matter of social justice.

Why are we doing this?

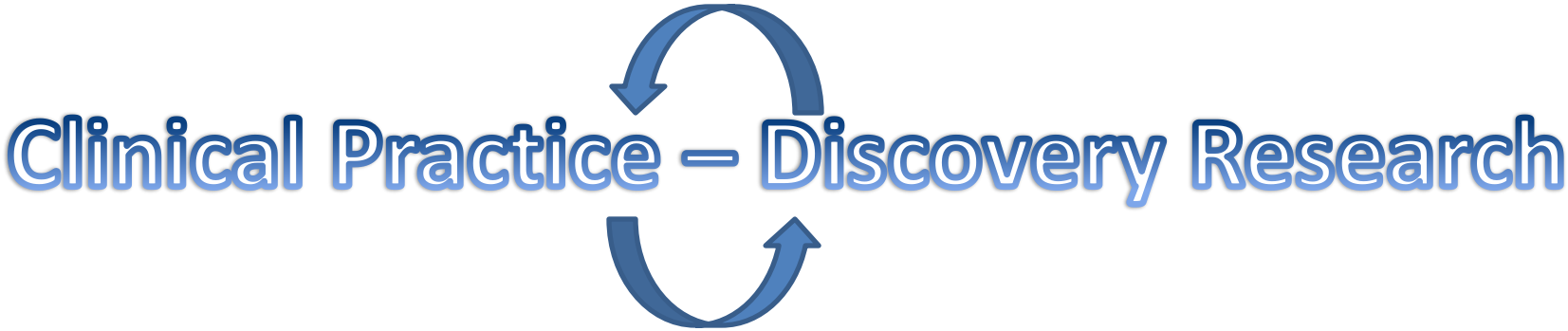
- Biology of health and disease
- Drug target discovery
- Improve the diagnosis of disease
- Enable and improve prediction

Intermediate Goals: 5-15 year plan

- Identify variants underlying exemplar conditions that represent the spectrum of health and disease-related phenotypes
  - The phenotypes should span a spectrum of Mendelian and complex disease, pediatric and adult conditions, psychiatric and metabolic and developmental and infectious conditions, molecular and clinical intermediate phenotypes, and modiers.
- Ability to test multiple research paradigms
  - Study designs
  - Role of other –omics
  - Ability to recontact individuals for further deeper phenotyping
  - Exomes and whole genomes
  - etc
- Designed from the beginning so that Mendelian and complex disease can inform each other

Clinical ↔ Research to maximize translation and discovery

- Clinical / personal sequencing will increase!
  - There is a need for research to drive discovery and create tools to increase diagnosis and translation
  - There is a need to create an infrastructure so that the clinical data can be used to drive novel discovery. Eg. Informed consent



Tactics – A biggie!

- Needs to create a database infrastructure that promotes a federated model of data and information sharing, including sequence, existing phenotype and ongoing clinical information. Consider convening a meeting to define multiple models for such a commons.

Tactics

- Selection of exemplar phenotypes.
- NHGRI should look for opportunities to partner with other ICs and private spectrum
- Large sample sizes necessary for high (not adequate) statistical power
- Multiethnic to capture a more informative allelic spectrum
- Don’t compromise at this stage. It is best to do less in a more comprehensive way than to do more with a series of compromises

Genetic Architecture as a **Translational Community Resource**

- Define the contexts in which genome-scale sequencing improves patient outcomes (i.e., assess the utility in diverse contexts)
- Improve understanding of the translational utility and validity of genomic variants by multiple approaches
- Assess “cost” and cost effectiveness of genome sequencing including the indirect costs of downstream outcomes of positive and negative
- Develop and apply in diverse populations to ensure maximal application and access to care

Genetic Architecture as a **Basic Science Community Resource**

- Define the molecular, cellular and organismal functions of genome sequences so as to inform basic biology as well as the interpretation of sequence variation.

- e.g. tools for modulating and measuring sequences at scale
- e.g. large scale functional characterization of variants and development of computational models that accurately predict molecular consequence of variation
- e.g. mechanisms of cis and trans gene regulation
- e.g. functions of non-coding genome sequences