Evidence Generation for Genomic Medicine Summary

Three Key Questions Addressed by the Panel

1. What methods can the eMERGE network develop and/or adopt to most effectively generate evidence in future phases of funding?

2. How can eMERGE leverage ongoing work in other NHGRI/NIH supported networks to facilitate and harmonize evidence generation?

3. What is the evidence that these approaches will scale given the onslaught of genomics activities/data generation in NIH supported, non-profit research, drug development and healthcare.

Current features of eMERGE evidence generation

- Consistent generation of genomic evidence across sites:
  - Early phases of eMERGE genotyping of relatively common SNPs with pharmacogenomic or disease association.
  - eMERGE 3 includes sequencing of consensus list of genes (emphasis on ACMG56 actionable genes for incidental findings)
  - Progress in generating semi-automated reporting platform to aid reporting.
- Emphasis on Mendelian disorders results in very small of proportion of subjects with “positive” findings – diminishes power.
- Although sequencing platform harmonized the reporting to subjects and re-phenotyping approach is not consistent across consortium?
  - Need to design process such that consortium can learn from the different return of result approaches.

Harmonization of NIH Efforts on Return of Results

Division of Genomic Medicine Current Research Programs

- Clinical Sequencing Exploratory Research (CSER)
- Electronic Medical Records and Genomics (eMERGE) Network
- Genotype-Tissue Expression Project (GTEx)
- Implementing Genomics in Practice (IGNITE)
- **Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)**
- PAGE Consortium
- Phenotypes and Exposures (PhenX)
- Research Programs Archive
- The Cancer Genome Atlas
- Undiagnosed Diseases Network (UDN)

NIH National Human Genome Research Institute

CCDG

Centers for Mendelian Genomics (CMG)

AGTC

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

cser
Clinical Sequencing Exploratory Research

ClinGen
Clinical Genome Resource

All of Us RESEARCH PROGRAM

Harmonization across NHGRI/NIH Efforts

- Return of results research questions included in multiple consortia (CSER, IgNIGHT, InSIGHT, AllofUS, CMG) – need to be measuring consistent variables across these diverse clinical situations.
- ClinGen consortium isn't doing any "trials" but is generating standards that can be incorporated (or improved upon) by other efforts.
  - Clinical Validity (evidence variation in gene association with disease)
  - Actionability (evidence that an action should be taken if pathogenic variant identified)
- **Standardized measures for genomic medicine of clinical utility, cost-effectiveness and actionability are essential**.

Scaling our research programs

- Costs of clinical sequencing tests (panels) in the public sector are declining rapidly.
- Allof Us is an example of increasing scale of research protocols that will include return of results.
- ClinGen is also approaching ways to include crowdsourcing to speed curation.
- Planning for next phase of eMERGE should have thoughtful approaches to scaling efforts.