Concept Clearance
Centers for Mendelian Genomics Program Renewal

National Advisory Council for Human Genome Research

September 8, 2014

National Human Genome Research Institute

Centers for Mendelian Genomics Program Renewal Purpose

- "Solve" Mendelian disorders at scale at funded centers
- Enable and coordinate with others

"Solve" all or most Mendelian disorders

Centers for Mendelian Genomics (CMGs)

Funded by NHGRI and NHLBI

Nov 2011 – Current

1. Demonstrated the power of sequencing at scale for solving Mendelian disorders
2. Discovered the genomic basis of ("solved") over 165 Mendelian disorders; over 100 publications
3. Revealed the extent of pleiotropy and genetic heterogeneity underlying Mendelian disorders
4. Developed and disseminated resources and innovative methods

Remaining Mendelian Disorders to Solve

- Mendelian disorders ~7,300
- Mendelian disorders with known molecular basis ~3,600
- Mendelian disorders with unknown molecular basis ~3,700
- Additional Mendelian disorders described every year

Much work remains to be done in order to solve all Mendelian disorders

Source: CMGs; Online Mendelian Inheritance in Man, OMIM®, including personal communications

CMG Program Renewal
Scope and Objectives - 1

1. Solving 300 or more Mendelian disorders to learn what it will take to solve all Mendelian disorders
2. Enabling others and coordination
   - Developing methods and tools
   - Disseminating resources
   - Outreach and coordination

CMG Program Renewal
Objectives and Scope - 2

1. Solving 300 or more Mendelian disorders
   - Expecting improvement of efficiency and costs, but fewer "low-hanging fruit" disorders
   - Studying disorders exhibiting a wide range of phenotypes
     - Understanding the genetic characteristics of Mendelian disorders
     - Learning what it will take to solve all Mendelian disorders
   - New features
     - Implementing whole genome sequencing
     - Performing small-scale function assays
   - Solving additional disorders with potentially available funds

CMG Program Renewal
Objectives and Scope - 3

2. Enabling and coordinating with others

- **Refining/developing methods and tools**
  - **Approaches - genotype driven, phenotype driven, or combination with non-sequencing genomic methods (through collaborations), etc.**
  - **Tools for collection and evaluation of phenotype information**
  - **Efficiency and cost improvement for sequence data production**
  - **Data analyses of difficult genomic regions, such as repeat expansions, CNVs, fusions, etc.**

CMG Program Renewal
Objectives and Scope - 4

2. Enabling and coordinating with others
   - Dissemination
     - Methods and tools
     - Data
       - dbGaP
       - “Causal” allele information at the CMG Browser and other sites
       - Allele counts

CMG Program Renewal
Objectives and Scope - 5

2. Enabling and coordinating with others

- **Outreach and coordination**
  - **Reaching out to individual researchers; training**
  - **International Rare Diseases Research Consortium (IRDiRC) activities**
  - **Coordination (sharing lists of disorders, matching samples or candidate disease genes, etc.)**

The goal of solving most/all MCs requires unprecedented cooperation & coordination among clinicians & scientists worldwide – Rod McInnes

CMG Program Renewal
Relationship to Other NIH Programs

- Proposed Common Disease Variant Discovery Centers (CDVD Centers)
- Proposed Genome Sequencing Program Coordinating Center
- NHGRI Clinical Sequencing Exploratory Research (CSER)
- NIH Undiagnosed Diseases Network (UDN)

CMG Program Renewal
Proposed Mechanism and Funds

Mechanism

- Cooperative agreement mechanism
- Advice and guidance from an external scientific panel (ESP)
- Steering committee and working groups

Funds

- $40 M NHGRI funds for Nov 2015 – Nov 2019, $10 M annually
- Seek co-funding from other NIH Institutes

RFA

- Up to three CMGs
- RFA open to all applicants

CMG Program Renewal
Summary of Concept

- Solve 300 or more Mendelian disorders using genome-wide sequencing
- Enable others with methods and resources, and coordinate projects worldwide
- Cooperative agreement mechanism
- $40 M total NHGRI funds