NHGRI Genomic Medicine IX: NHGRI's Genomic Medicine Portfolio – Bedside to Bench
April 19-20, Silver Spring, MD
Executive Summary

NHGRI's ninth Genomic Medicine Meeting focused on engaging basic scientists in genomic medicine, by convening leaders in basic and clinical genomic sciences to address a major challenge within the translational gap—characterizing and interpreting the clinical significance of variants of uncertain significance (VUS). Objectives of the meeting were to: 1) review examples of successful interactions between basic scientists and clinical genomicists and what made them successful; 2) identify ways to enhance interactions between basic scientists and clinical genomicists; and 3) determine how better to integrate basic science research efforts with clinically important questions, to enhance the exploration of clinical implications of basic discoveries. Key topics of presentations and discussions included: 1) understanding the functions of VUS and their relevance to disease mechanisms, 2) prediction and annotation of genomic variant function, 3) use of biomedical ontologies for data and knowledge integration and sharing, and 4) facilitating bedside-back-to-bench research.

Recommendations for "Bridging the Gap"

All agreed that bringing basic and clinical researchers together is critical to focusing functional studies where they can have the greatest clinical impact. Recommendations fell into broad themes related to variants, phenotypes, and people:

- Prioritizing variants and genes for functional studies
  - Convene basic and clinical scientists to identify and distribute list of "clinically impactful" genes
  - Encourage development of high-throughput assays and animal models for these genes
  - Focus on genes with known clinical relevance, such as:
    - ACMG 56 and the actionable gene/variant list in ClinGen
    - Genes widely tested for in the Genetic Testing Registry not on other actionable lists
    - Genes/variants in ClinVar with credible but widely differing pathogenicity interpretations
    - Genes of unknown function severely depleted in LoF variants in databases like ExAC
    - Genes for which high-throughput assays are available or can be developed
  - Encourage programs like UDN and CSER to submit genes of clinical interest for functional studies
- Moving variants from unknown to known function classes
  - Rely on ACMG/AMP to develop evidence guidelines but help build resources for that evidence
  - Involve basic researchers in developing evidence guidelines
  - Facilitate more innovative and systematic capture of clinical phenotype data
  - Develop infrastructure for bidirectional exchange of phenotype/genotype data on variants
  - Identify a minimal or core set of functional assays for characterizing variants
  - Develop repository for functional data and encourage deposition of data at time of publication
  - Encourage development of guidelines for frequency and depth of variant re-evaluation
  - Encourage development of high-throughput functional assays that are meaningfully scalable and closer to the disease phenotype (i.e., that minimize the "inferential distance" to disease)
- Phenotyping
  - Promote collection of deep and iterative phenotypes in those with unusual genotypes
  - Modify EMR phenotypes to yield more data-driven (vs. billing-driven) models of clinical features
  - Map electronic phenotypes to Monarch Initiative
  - Develop "next-generation phenotyping" involving patient-entered data, symptom ontologies, structured data, drug responses, comprehensive multi-scale dynamic phenotyping
  - Facilitate patient entry of phenotypic data to their EMRs, perhaps with their physician's review
  - Develop structured ways to capture family history, socioeconomic, cultural, and exposure data

    - Develop ways to push out phenotype data for given set of variants, with appropriate consent
    - Consider crowd-sourcing data for patient-entered information in disease-based groups
    - Identify for clinicians other phenotypes that might associate with a known Mendelian disease
    - Develop minimum phenotype dataset for a gene or common condition
    - Develop platforms allowing clinicians to enter phenotypic information easily
    - Provide feedback to clinicians on adequacy of phenotyping similar to PhenoTips model
    - Gather more longitudinal phenotype information
- Data sharing, using ontologies, and integrating resources
    - Encourage common vocabularies, mapping across vocabularies and databases/resources
    - Improve ontologies by standardizing traits that are routinely measured and adding clinical terms
    - Increase awareness and use of available standards across communities
    - Integrate resources on variants and standardize nomenclature for functional predictions and phenotype associations
    - Encourage analysis of existing genotype-phenotype databases with machine learning algorithms
    - Work with NSF to develop phenotype exchange standards
    - Improve regulatory guidance on data aggregation and re-use both nationally and internationally
    - Compile list of resources and brief descriptions to facilitate translational research; connect these resources with a standard API enabling queries and cross-references across multiple databases
- Improving mutual understanding of perspectives
    - Convey uncertainty and lack of determinism of genetic findings appropriately to clinicians
    - Define functional evidence clinicians consider convincing (short of randomized trials)
    - Improve dialogue between clinical lab and clinician in implicating variants and making diagnoses
    - Increase awareness across communities of standards and resources that do exist
- Enhancing interactions between bench scientists and clinicians
    - Develop funding opportunities that require basic and clinical partnerships
    - Develop Matchmaker Exchange-like platform to deposit a “clinical problem” or “research resource” for clinicians and basic scientists to exchange priorities and vexing problems
    - Expand UDN model of basic-clinical collaboration and sharing of specific clinical information to include larger numbers of labs and networks of geneticists
    - Encourage centralized approach for collecting outcomes of genetic diagnostic searches
    - Engage basic scientists in clinical forums and conferences and clinicians in basic meetings
    - Encourage basic and computer scientists to join clinical groups like ACMG and vice versa
    - Promote informal interactions to foster collaborative opportunities

Next Steps

Ideas for future Genomic Medicine meetings include having large clinical laboratories discuss and compare standards for lab reports. Involving clinicians as actual consumers of those reports would be valuable. Other ideas include an invitation to editors to determine data mining standards or to patients to promote patient-derived phenotyping and data exchange.

Next steps from this meeting will involve prioritizing recommendations and drafting a white paper for publication co-authored by all presenters and moderators who comply with International Committee of Medical Journal Editors authorship guidelines.