National Institutes of Health

National Human Genome Research Institute

Genomic Medicine 9

April 19-20, 2016
Silver Spring, MD

Organizing Committee:
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GM9 Focus

- *Characterizing and interpreting the clinical significance of variants of uncertain significance (VUS)*

Objectives

- What makes for successful interactions between basic scientists and clinical genomicists ?
- How can the virtuous cycle of “bench to bedside to bench again” be fostered and enhanced?
- How can we achieve better alignment of basic research efforts with clinically important questions?

Topics

- Understanding the function of VUS and relevance to disease mechanisms
- Prediction and annotation of genomic variant function
- Biomedical ontologies for data and knowledge integration and sharing
- Facilitating bedside-back-to-bench research
- ~~Regulatory hurdles~~
- ~~Issues with payers~~

GM9 Sessions

- Session 1 – Magnitude of the Problem
- Session 2 – Vexing Clinical Problems
- Session 3 – From Variant to Disease Mechanisms
- Session 4 –Computational Approaches to Variant Function
- Session 5 – Functionalizing VUSs
- Session 6 – Biomedical Phenotype Ontologies

GM9 in a Nutshell

- Variants
  - Align clinical and basic science priorities for variant functionalization
  - Need enhanced transparency for how algorithms arrive at a variant function prediction
  - Develop criteria/evidence standards for moving variants into clinical practice
- Phenotype
  - Phenotyping
    - Deep phenotyping for patients with rare genotypes
    - Engage patients in data collection
  - Phenotype vocabularies and standards
    - Vocabs for EHR/EMR designed for billing, not data mining
    - Vocabulary term mappings between humans and experimental models
  - Barriers to sharing phenotype/genotype data
- Bridging the gap between basic science and clinical practice
  - Data sharing and resource integration
    - Variants, function, phenotype, disease in humans and experimental models
  - Foster opportunities and conferences for workshops and speakers from different communities
    - Enhance awareness to achieve alignment
  - Significant problem clinically is legacy of portraying genetic results as definitive
    - Clinicians: embrace ambiguity!

GM9 Outcomes

- Meeting summary to be submitted to the journal, Cell
  - "Bedside Back to Bench: Building Bridges between Basic and Clinical Genomics Research"
    - Manuscript in final stages of review/revision

GM9 Manuscript in a Nutshell

"Here we highlight examples of the value of and need for greater basic-clinical integration, describe functional and informatics resources that can facilitate integration, provide recommendations for prioritizing genes for functional investigation, and suggest approaches for promoting these critical interactions."

Recommendations:

- Identify Clinically Relevant Genes as Priorities for Functional Studies
- Develop Larger Reference Variant Databases and Link to Phenotypes
- Develop and Adopt Standards for Phenotype Description and Data Sharing
- Promote Cross-Disciplinary Understanding and Opportunities for Interaction

Priority Genes and Variants

Lists for manuscript in progress…..

- Potential **sources** of clinically relevant genes for functional studies
  - 56 genes recommended for return of incidental or secondary findings in clinical genome sequencing (ACMG)
  - 33 genes with variants affecting drug response (CPIC)
  - Genes encoding proteins that are targets of cancer therapeutics
  - Genes recognized as clinically actionable (ClinGen)
  - Genes with high clinical validity
  - Genes strongly implicated in congenital or undiagnosed diseases
  - Genes depleted for LoF variants
  - Knockout genes that generate a phenotype in mice
  - Gene families targetable by drugs
- Criteria for **prioritizing** genes for functional studies
  - Number of registered tests (indicator of clinical testing volume)
  - Number of conflicting clinical significance reports (ClinVar)
  - Loss of function intolerance score (ExAC)
  - ClinGen actionability score
  - Genes with altered expression in affected cells, tissues
  - Genes with damaging *de novo* mutation, or evidence for co-segregation in affected families

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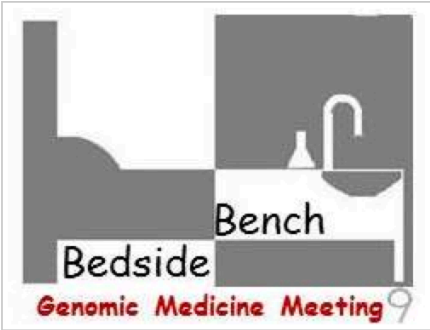
Home › Research Funding › Research Funding Divisions › Division of Genomic Medicine › Genomic Medicine Activities › Genomic Medicine IX (GM9)

Genomic Medicine Meeting IX: *Bedside to Bench - Mind the Gaps*



On April 19-20, 2016, the National Human Genome Research Institute (NHGRI) will sponsor its ninth Genomic Medicine meeting - ***Genomic Medicine IX: Bedside to Bench - Mind the Gaps*** - at the Sheraton Silver Spring Hotel in Silver Spring, Maryland.

GM9 will focus on facilitating bedside back to bench research by focusing on one of the most vexing problems in clinical sequencing: characterizing and interpreting variants of uncertain significance (VUS).

Objectives include to:

1. Review examples of successful interactions between basic scientists and clinical genomicists and explore what made them successful;
2. Identify ways to enhance interactions between basic scientists and clinical genomicists (aka, the virtuous cycle of bench to bedside and back again);
3. Determine how better to integrate basic science research efforts with clinically important questions, to enhance the exploration of clinical implications of basic discoveries.

https://www.genome.gov/27564185/nhgri-genomic-medicine-ix-meeting-bedside-to-bench--mind-the-gaps/

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