Over-Arching Topics: Variants

- Prioritizing functionalization– which genes to focus on?
  - Biological axes to organize activities for high throughput functional characterization (a la Nancy Cox presentation)
    - Many of these genes will be relevant to study in model organisms
  - Genes with known clinical relevance (ACMG 56)—those related to ongoing genomic health initiatives
  - Look to ClinVar for variants with conflicting annotations
  - GTR for those genes being tested now
  - Build on groundwork built by UDN, CSER, etc.
  - Role for ISCC?
  - ClinGen working group's gene/variant list

Variants… continued

- What evidence to move variants from unknown to known function class?
  - Domain of ACMG/AMP to develop evidence guidelines
    - Our role is to build the resources to help these groups with this process
      - Bring basic researchers to the table in developing the guidelines
      - Infrastructure for bidirectional exchange of phenotype/genotype
- Evidence criteria to demonstrate clinical utility of variants
  - Assays here should minimize inferential distance of assay to disease phenotype (Les B)

Over-Arching Topics: Phenotype

- Need for deep phenotypes in those with unusual genotypes
  - What is “deep” may change depending on patient presentation, etc. – avoid unproductive diligence!
- Work with journals on publishing guidelines for “minimal phenotyping assays for X”
- EMR phenotypes designed more for data-driven models of clinical features, methods to functionalize, not billing
- Engage pt-derived phenotyping in data collection tools
- Common vocabularies, phenotype exchange formats, mappings across vocabularies and databases/resources
  - Awareness and feedback from user communities important

Over-Arching Topics: Bridging the Gap

- Data sharing and resource integration
  - Increase awareness/use of available standards and awareness
  - Integration of resources on variants
    - variant, functional predictions, phenotype associations
- Better understanding of perspectives: clinicians
  - If clinical study is only acceptable evidence for utility of a variant, how to change this culture/mindset to accept conditional probabilities
    - Make it clear what the evidence is
    - Make reports clearer
    - Use cases

Over-Arching Topics: Bridging the Gap (2)

- Better understanding of perspectives: basic sci
  - Increased awareness across communities of standard and resources that do exist
- Expand Matchmaker approach to other domains– “need mouse model of variant X”
  - Innocentive challenge model?

  Reach out to NSF and NIGMS
- Enhanced interactions of bench and clinic
  - Major challenge is knowing what each other’s questions are
  - Can start with developing/using agreed upon lines of evidence and data standards
  - Share findings/results, not of use to a particular research question but potentially useful to someone else

Over-Arching Topics: Bridging the Gap (3)

- How to foster opportunities for informal interactions
  - Chance meetings in the hotel lobby, flight delay conversations
- Help get workshop sessions approved at specialized conferences
  - Often difficult to get approved for workshops on utility of model organism databases at meetings like ASHG, for example
  - Coursera course?

Session 1 – Magnitude of the Problem

- Evidence from animal models unlikely to convince clinicians
  - w/o clinical studies even multiple lines of evidence is a hard sell
- Getting access to full patient data critical for basic labs
- What to “put in medical record” and how to reduce risk of misuse
  - not unique to genomics
- Significant problem clinically is legacy of portraying genetic results as definitive
  - Embrace ambiguity!

Session 2 – Vexing Clinical Problems

- How to expand to all infants in ICU: what evidence needed to support it
- Develop algorithms for when pts need WES/WGS: 20K patients?
- Pressure of DTC testing overshadowing settings where have compelling case for implementation
- How to quantify “inferential distance” from experimental phenotype to clinical picture
- Identify set of functional assays and specific results that would move a variant’s classification to be more definitive

Session 3 – From Variant to Disease Mechanisms

- Difficulty defining who's unaffected as resolution of phenotyping is so low
- Next-gen phenotyping– specific to condition
- Collecting phenotype data
  - "patient derived phenotyping" – DTC already engaged in this
- Difficulties in extracting phenotyping data from EMR
  - Terminologies often designed for billing, not data mining

  Harness ongoing "phenomic efforts" supported by NIH and integrate with genomic information
- Involve clinicians to add clinical terms to existing model organism phenotype ontologies in systematic mapping effort

Session 3 – From Variant to Disease Mechanisms (cont)

- Need explanatory algorithms of why computer comes to given classification
- More intensive study of very healthy elderly individuals with genotyping, deep phenotyping
- Genome-first approaches need much better phenotyping
- Much success in diagnosis with imprecise diagnoses and imperfect clinicians of today
- Must have dialogue between clinician and lab

Session 4 – Computational Approaches to Variant Function Prediction

- Need to be able to link phenotypes to genotypes in ExAC and similar databases; regulatory support for data aggregation
- Need uniformly ascertained cases for wide variety of diseases – NIH disease studies
- Regulatory guidance on use of European samples
- How to prioritize genes for functional studies
  - Some index of clinical need over all genes?
  - Actionability?

Session 4 – Computational Approaches to Variant Function Prediction

- Honest broker model needed for phenotype data release; currently only entity with permission to store and share ExAC data is Broad

Session 5 – Functionalizing VUSs

- Lots of exciting technologies emerging for functionalizing variants..need opportunities for interaction between technology developers and clinical researchers to “direct the ship” toward scaling technologies in ways that are relevant to clinical are needed
- Prioritization of genes for characterization
  - Genes related to genomic health initiatives
- Variants used in different contexts- diagnosis, possible therapy, genetic basis of resilience
- Need for standard vocabularies for functional consequence/evidence nomenclature/variant nomenclature
  - Some efforts underway…how to raise awareness?

Session 5 – Functionalizing VUSs (cont.)

- Develop list of resources relevant to bridging the gap between basic and clinical
- Use a pathway context to assist in functional assertions
- Link Model Organism Databases more closely with Clinical Database

Session 6 – Biomedical Phenotype Ontologies

- Standards for encoding and exchanging data
  - Standards exist for genes….but what about environment, phenotypes
- Computable evidence model can aid variant interpretation
- Share the processes for data integration and resource development..as important as sharing data
- Data submission/collection