Day One Recap

Questions to Consider

- Do we have adequate data sets and accessible databases to provide the data on genetic variants and the evidence supporting clinical actionability?

Answer

- Depends on the audience
- Ensembl and ClinVar are good starting points.
- Primary care docs need something else…an EHR integration layer/Decision support
- Need much more clinical annotation associated with variants/genes, especially for VUS
- Datasets are still thin…more data needed
- Need a mechanism to capture “one-off” associations determined in clinical sequencing projects
- The database needs to carefully model classes of evidence: specificity, sensitivity, prevalence, PPV/NPV, penetrance.

Questions to Consider

- What criteria need to be met to consider a genetic variant (or pattern of genetic variants) clinically actionable?

Answer

- Need to focus on clinical validity rather than actionability.
- Use of agreed upon “bins” will facilitate “low hanging fruit”
- Do no harm
- Be willing to experiment with bins of possible validity—needs robust methodology to do this
- Avoid bins with NO validity
- Need more data
- Need to develop plans to address clinical utility

Is this the right definition of validity?

- **Clinical validity** The accuracy with which a test identifies or predicts a patient's clinical status. For genetic testing, the relevance of a particular gene to a disease can be assessed by genome-disease association studies and the accuracy of a test is evaluated in terms of its specificity, sensitivity, PPV and NPV.

From PHG foundation

Is the definition of Utility?

- **Clinical utility** An assessment of the risks and benefits resulting from using a particular test and the likelihood that the test will lead to an improved overall outcome.

- How is this different from actionability

From PHG foundation

More Questions to Consider

- What is necessary to integrate those datasets/evidence into EHR and into clinical use?

Answer

- Need to address scalability and access.
- Need to share decision support logic if not algorithms, make a publicly available library
- Need ability to draw from multiple sources and integrate, therefore need standards
- We are NOT doing a good job with better validated tests (i.e. Brca tests). We should start with those!
- Can ClinVar be the “honest broker” for variant information?

More Questions to Consider

- How do we create a dynamic “loop” that recognizes the anticipated rapid increase in available evidence and upgrades clinical actionability “validity” recommendations?

Answer

- Establish “ClinAction” curation function to build upon Ensembl, ClinVar, other relevant databases
- Need to maximize interactions between epidemiologists and informatics/genomics to facilitate obtaining needed information on clinical validity
  - Establish training program across these disciplines
- Concern about data loss and privacy threats hinders research
- Patient portals…need patients to argue for data access for research
- ClinVar should incorporate what “bin” a variant data is in?
- Collaborate with larger data warehouses (e.g., MEDCO) to conduct large scale studies to get a better evaluate outcomes.

More Questions to Consider

- What decision support and physician education will be needed in the clinics?

Answer

- Want a system to send sequences to that will guide a provider to focus on relevant variants
- Need to further explore provider education
- CDS systems need to be scalable rather than institution-specific
- Explore open models and patient controlled information

Questions to Consider

- What should NIH/Wellcome Trust do?

Answer

- Serve as a “convener” in conjunction with other NIH ICs and professional standard organizations to foster discussions on clinical validity and actionability
- Ensure that variants placed in bin 2 have identified pathway for moving out of bin 2
- Create/Support a resource for Clinical Annotation that extends Ensembl and ClinVar and captures VUS and “one-off” variant – condition association
- Ensure that discovery of gene-disease and gene-drug associations continues through funding initiatives

Answers

- Target discovery research to determine clinical validity and actionability
- Catalyze discussion with OHRP regarding IRB guidance re: clinical-research boundary issues
- Coordinate with AHRQ, ONationalCoordinator, VA, DOD and where possible commercial vendors in EHR integration
- Organize a workshop on data structures and data standards for clinical use of variant data, maximize ongoing interactions among existing databases
- Consider training programs integrating genomics, informatics
- Policy analysis to determine and develop policies needed for implementation of variants in clinical care

Next Step

- Write up recommendations
- Share with group in next few weeks with quick turnaround
- Video and slides available on genome.gov
- Develop a manuscript from the discussions