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?
• 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
• 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