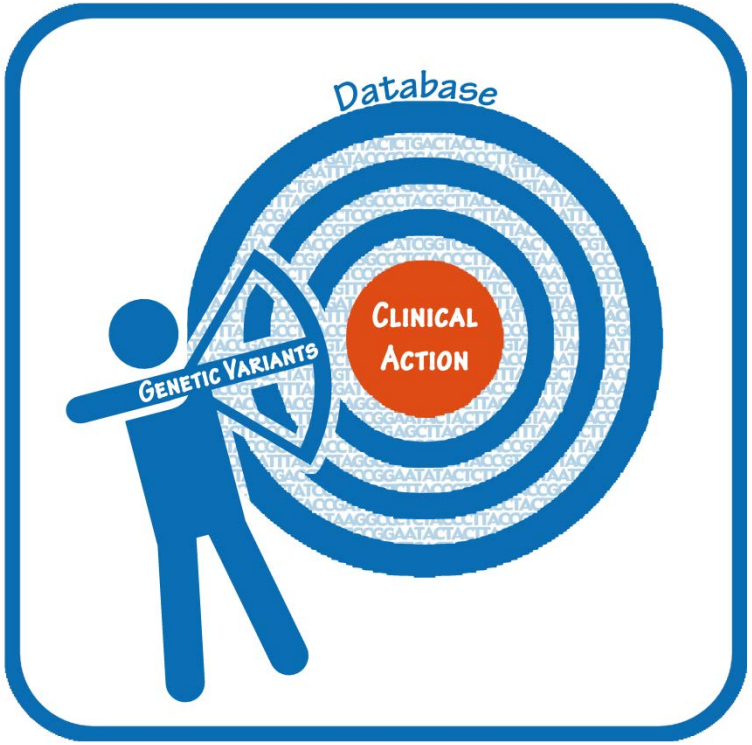
Characterizing and Displaying Genetic Variants for Clinical Action (Dec 1-2, 2011)



- Workshop is collaboration between NHGRI & Wellcome Trust
- **Goal:** **Consider processes, databases, and other resources needed** to:
  - identify clinically relevant variants,
  - decide whether they are actionable and what the action should be, and
  - provide information for clinical use.

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Background & Rationale

- GWAS & sequencing studies identifying variants of potential clinical relevance
- Systematic collection, synthesis, and evaluation of these findings are needed
- Critical to obtain the consensus on what variants are actionable and the actions to be taken
- Make this information available to clinicians and consumable by EHRs

Need for Centralized Resource

- Genomics and health information technology systems: Exploring the issues (Apr 27-28, 2011)
- Genomic Medicine Colloquium (June 29, 2011)
- IOM Workshop on Integrating Large-scale Genomic Information into Clinical Practice (Jul 19, 2011)
- NHLBI Workshop on Integration and Display of Genetic Test Results within EHRs (Aug 2-3, 2011)

Do we have adequate and accessible data for making decisions about clinical actionability?

- Depends on the audience
- Ensembl and ClinVar are good starting points
- Need more data, especially from diverse populations. When these population-based data become available, ensure they are included in databases
- Significant need for clinical annotation associated with variants/genes, especially for variants of unknown significance (VUS); just capturing VUS would be useful
- Somatic variation should be included in these databases as well

Do we have adequate and accessible data for making decisions about clinical actionability? – Cont'd

- Need a mechanism to capture "one-off" associations determined in clinical sequencing projects
- Primary care docs need user-friendly clinical support tools and/or EHR integration layer
- Database needs to carefully model classes of evidence: specificity, sensitivity, prevalence, PPV/NPV, penetrance

All are potential opportunities for genomic medicine pilot projects

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

- Some felt should focus on clinical validity rather than actionability. Others felt that a process for binning "low hanging fruit" into categories of actionability/utility could be developed now
  - **Important opportunity for genomic medicine group**
- Binning variants into categories of clinical actionability/utility will require a different approach than classifying VUS as pathogenic – need to develop processes for both
- To address scalability, ignore bins with NO validity and treat VUS as "innocent until proven guilty" rather than converse
- Do No Harm

What is needed to integrate genomic variants & evidence into EHR and clinical use?

- Disseminate decision support logic, make a publicly available library
  - **Important opportunity for genomic medicine group**
- Address scalability and access
- Need ability to draw from multiple sources and integrate, therefore need standards (including alignment with HL7)
- We are NOT doing a good job with better validated tests (i.e. BRCA1 & 2 tests) and should start with these
  - **Important opportunity for genomic medicine group**
- Can ClinVar be a central repository for variant information?

How do we create a dynamic "loop" to move actionable variants into clinical practice, evaluate outcomes, and feed outcomes data back to databases to refine variant bins?

- Establish "ClinAction" curation function to build upon Ensembl, ClinVar, other relevant databases
- Maximize interactions among epidemiologists, bioinformaticians, and genomic scientists to facilitate obtaining needed information on clinical validity and utility
  - **Possible opportunity for genomic medicine group?**
  - Establish training programs across these disciplines
- ClinVar should incorporate what "bin" a variant is in along with time stamps/versioning

Dynamic "Loop," cont'd

- Collaborate with data warehouses (e.g., Medco) on large scale studies to better evaluate outcomes of genomic medicine
- Develop approaches for long-term follow-up of patients w/ rare variants to better understand relationship of variant with disease and other phenotypes
- Concern about data loss and privacy threats hinders research
- Patient portals…need patients to argue for data access for research (see Amy Dockser Marcus' essay WSJ featuring Sharon Terry, Dec 3, 2011)
- **Genomic medicine projects incorporate pilots to explore best ways to communicate results back to researchers**

What decision support and physician education is needed in the clinic?

- Signature Project - System that enables clinicians to feed WGS data into software that produces a concise report regarding relevant genomic variants for particular patient
  - **Important opportunity for genomic medicine group**
- CDS systems need to be scalable rather than institution-specific
- Explore open CDS models and patient-controlled information
- Develop and test innovative genetic education tools for providers
- In some instances, need to improve clinicians' perception of utility of genetic information
- **All have some opportunities for this group**

Draft Recommendations for NIH & Wellcome Trust

1. Serve as a “convener” in conjunction with other NIH ICs and professional-organizations to increase the number of recommendations regarding clinical validity and actionability

2. Create and support a coordinated resource to extend Ensembl, ClinVar, and other databases by providing relevant phenotype information, other clinical annotation, and recommendations regarding clinical utility/actionability

3. Ensure that 1) ClinVar captures VUS and “one-off” variant – condition association and 2) scripts are developed to enable clinical labs to transmit data to ClinVar

4. Design studies to ensure that variants placed in bin 2 (clinically valid, but not directly actionable) have identified pathway for moving out of bin 2

Recommendations, Cont'd

5. Target discovery research to determine clinical validity and actionability
6. Ensure that discovery of gene-disease and gene-drug associations, including in diverse populations, continues through funding initiatives
7. Link basic labs studying genes with potentially relevant variants to clinicians with phenotypes
8. Support functional and other follow-up studies on specific genes with known utility (e.g., determine consequence of every BRCA1 missense mutation) to generate data to support moving variants out of Bin 2
9. Hold workshop(s) to identify technical standards for exchange of variant and clinical data, thus maximize ongoing interactions among existing databases

Recommendations, Cont'd

10. Coordinate with AHRQ, ONC, VA, commercial EHR venders, and others to address data interoperability and viable approaches for integration of genomic information and actionable variants into a variety of EHR systems

11. Consider competitions that 1) promotes development of algorithms for interpreting genomic variants and 2) compares their performance

12. Consider training programs integrating epidemiology, genomics, informatics

13. Catalyze discussion with OHRP regarding IRB guidance for clinical-research boundary issues

14. Policy analysis to determine and develop policies needed for implementation of variants in clinical care

Relevance for Genomic Medicine

- Recommendations are responsive to request from December meeting
- Genomic medicine group should provide input as database resource is developed
- Several of the recommendations lend themselves to pilot projects that could be added to implemented programs
- Genomic medicine group should provide input on some of the questions about variant classification raised by ‘ClinAction’ group
- Important to feed back successes and failures of variant classification and use to ‘ClinAction’ group to guide development of resource
- Possible topic for part of upcoming meeting?