Clinically Relevant Variants Resource

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Imperatives for Genomic Medicine

Imperatives for genomic medicine

Opportunities for genomic medicine will come from simultaneously acquiring foundational knowledge of genome function, insights into disease biology and powerful genomic tools. The following imperatives will capitalize on these opportunities in the coming decade.

Making genomics-based diagnostics routine. Genomic technology development so far has been driven by the research market. In the next decade, technology advances could enable a clinician to acquire a complete genomic diagnostic panel (including genomic, epigenomic, transcriptomic and microbiomic analyses) as routinely as a blood chemistry panel.

Defining the genetic components of disease. All diseases involve a genetic component. Genome sequencing could be used to determine the genetic variation underlying the full spectrum of diseases, from rare Mendelian to common complex disorders, through the study of upwards of a million patients; efforts should begin now to organize the necessary sample collections.

Comprehensive characterization of cancer genomes. A comprehensive genomic view of all cancers[4–7] will reveal molecular taxonomies and altered pathways for each cancer subtype. Such information should lead to more robust diagnostic and therapeutic

Practical systems for clinical genomic informatics. Thousands of genomic variants associated with disease risk and treatment response are known, and many more will be discovered. New models for capturing and displaying these variants and their phenotypic consequences should be developed and incorporated into practical systems that make information available to patients and their healthcare providers, so that they can interpret and reinterpret the data as knowledge evolves.

The role of the human microbiome in health and disease. Many diseases are influenced by the microbial communities that inhabit our bodies (the microbiome)[101]. Recent initiatives[102,103] (http://www.human-microbiome.org) are using new sequencing technologies to catalogue the resident microflora at distinct body sites, and studying correlations between specific diseases and the composition of the microbiome[104]. More extensive studies are needed to build on these first revelations and to investigate approaches for manipulating the microbiome as a new therapeutic approach.

Practical systems for clinical genomic informatics:

"…many variants associated with disease risk and treatment response are known…

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synthesis & evaluation of findings to identify clinically relevant variants

Green ED, Guyer MS. *Nature* 2011; 470:204-13.

Need for Centralized Resource

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

Characterizing and Displaying Genetic Variants for Clinical Action

December 1-2, 2011

Goal[illegible]s, and other[illegible]

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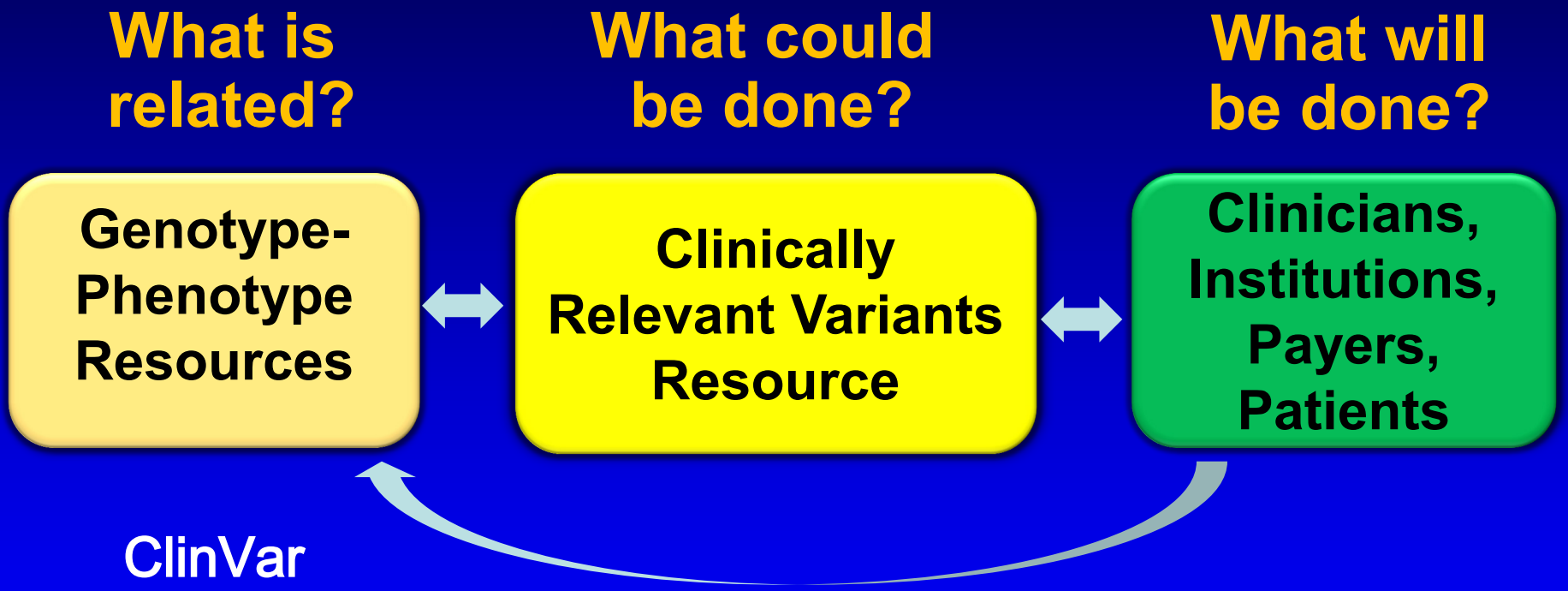
Workshop Recommendations

- Sup … use in clini… …ation & cons… …
- Serv… …ssional orga… …ons rega…
- Dev… …gorithms for i… …rmance

http://www.genome.gov/27546546

Complex Decision Making Process



Complex Decision Making Process

Clinically Relevant Variants Resource

Clinically Relevant Variants Resource: RFA-HG-12-016

Purpose: Support a process for identification and dissemination of consensus information on genetic variants relevant to clinical care

Goals:

1. Identify genetic variants with likely implications for clinical care and incorporate these variants and evidence into a resource

2. Establish a process for transferring this information to appropriate clinical organizations for guideline development

3. Build upon existing programs, unify, reduce duplicative efforts across research/clinical organizations

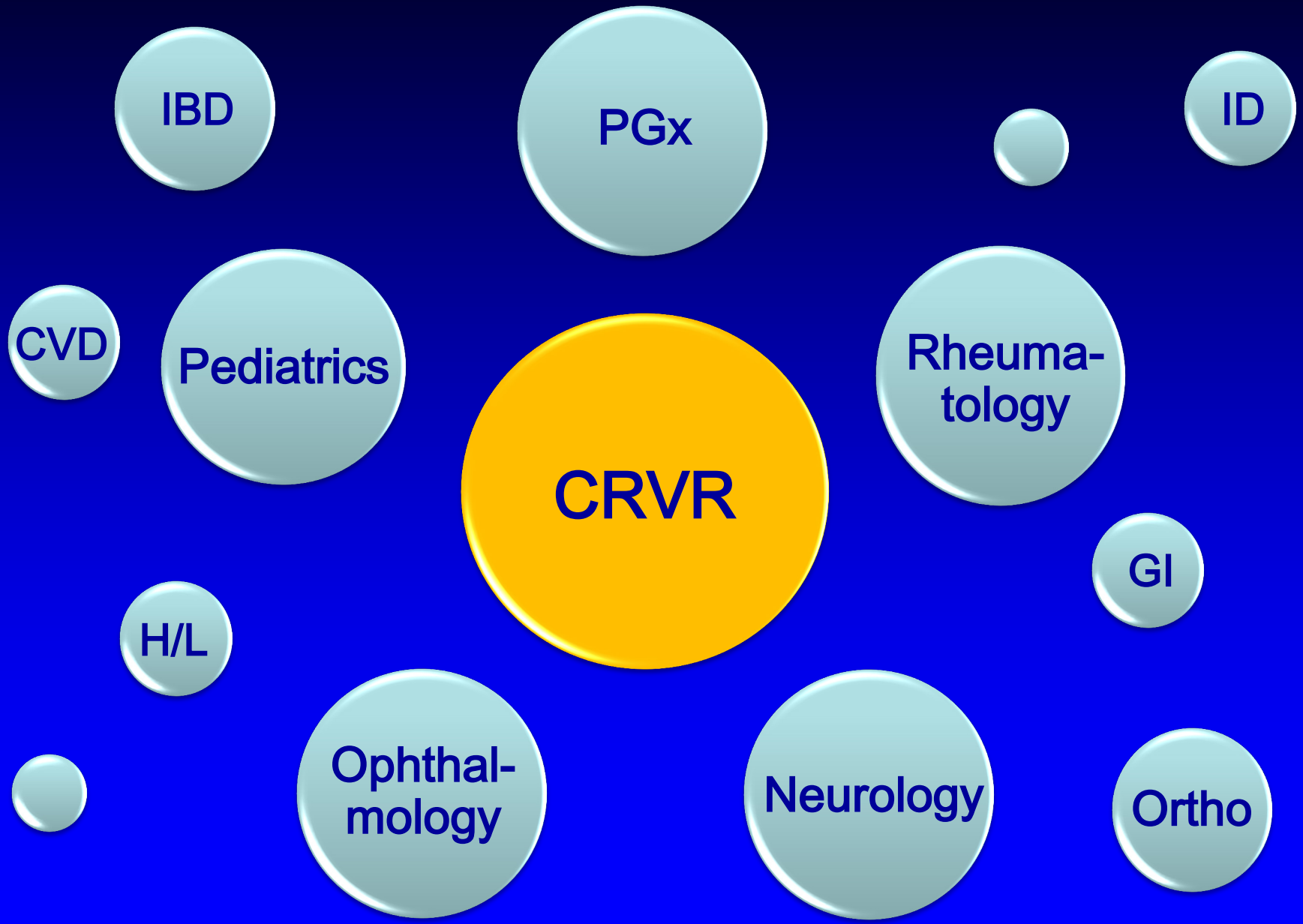
Funding

- Cooperative Agreement (U01)
- $2M in FY13, $4M/yr for FY14-FY16
- Program kick-off in Summer 2013
- Consider continuation if effectively developed and increasingly used

Synthesis/Curation

- Survey existing efforts, solicit participation
- Develop framework for evaluating available data and assessing degree of potential clinical relevance
- Generate sets of genes, variants, and supporting evidence for evaluation of clinical relevance
- Develop approaches for distributing curation & review of variants

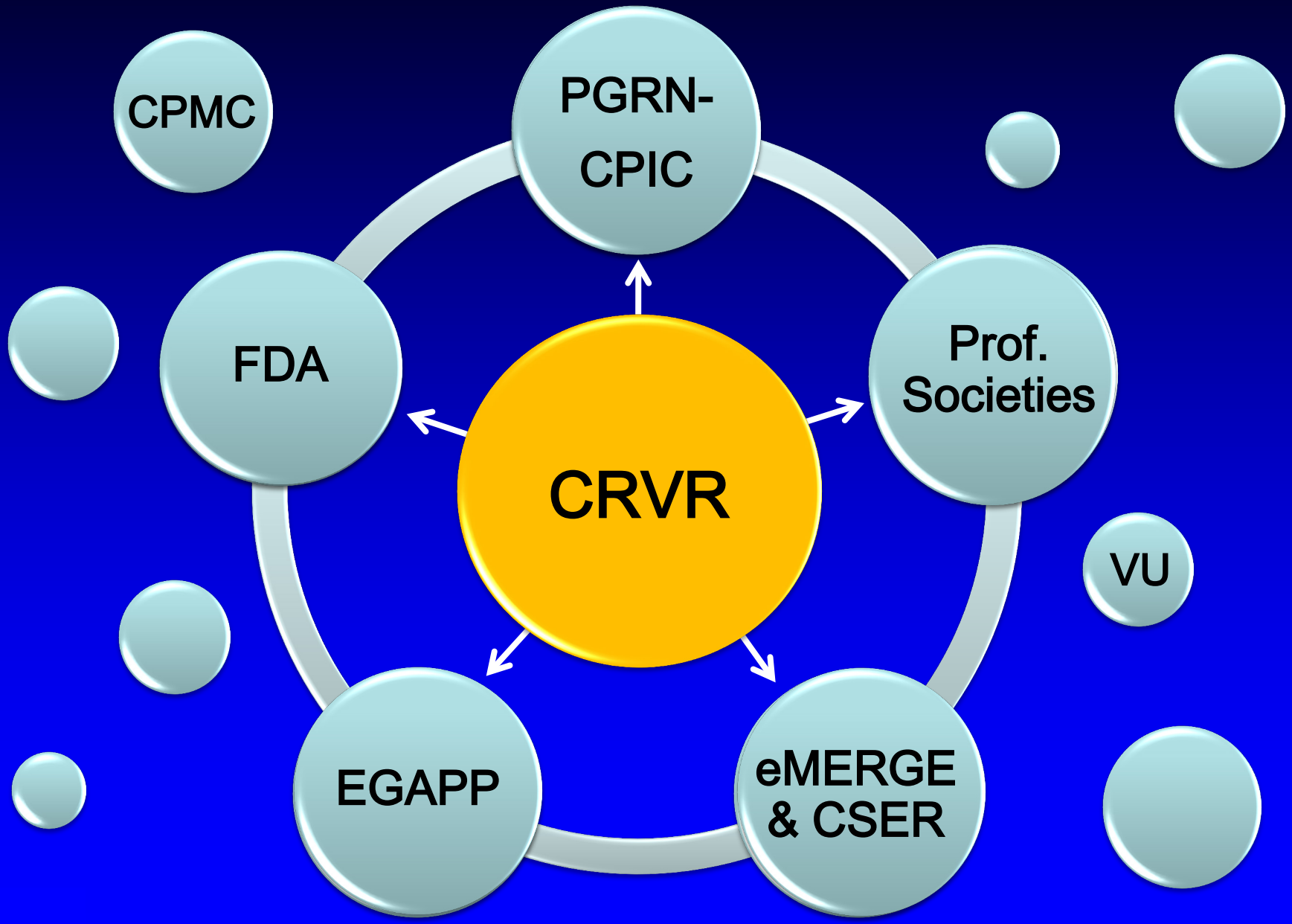
Consider Distributing Curation/Consensus Efforts



Dissemination

- Vet the specifications of the CRVR (data formats/interface) with relevant user communities
- Create user-friendly resource that includes the agreed-upon clinically relevant variants and their supporting evidence
- Ensure integration with other data resources (e.g., ClinVar)
- Disseminate consensus findings to clinical & research communities

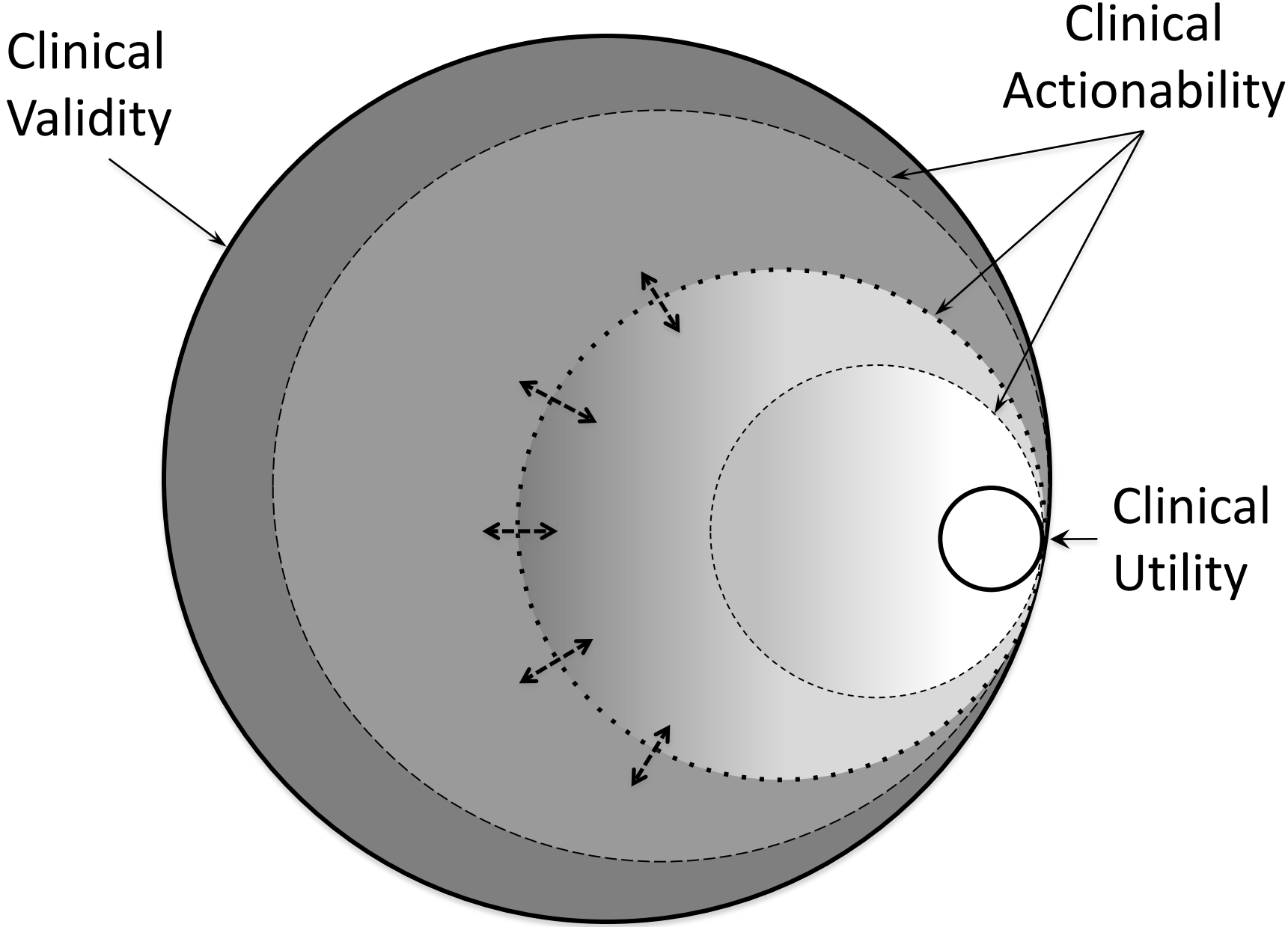
Ensuring Coordination with Related Efforts



CRVR Professional Organizations Committee

- Provide input on development and use of CRVR
- Facilitate interactions between stakeholders
- Meetings
  - 2+ teleconferences/year
  - Joint teleconference w/ Steering Committee (SC)
  - Representatives to attend SC meetings


NHGRI
genome.gov



Legend: Schematic diagram showing overlap of clinical validity (outer boundary, containing all genetic variants with a valid clinical association), clinical utility (inner white circle), and the boundaries of clinical actionability (shaded circles). Depending on the criteria used to define "actionability" (depicted by double arrows) the boundaries could be more or less inclusive (dashed circles).

Courtesy: J. Berg

Workshop Recommendations

- Encourage the dissemination of decision support logic and interpretive tools, including making a publicly available library, to enable diverse EHR systems to use the same logic and tools when developing clinical decision support tools.

- Coordinate with US and UK agencies (AHRQ, ONC, NHS), EHR vendors, and others to address data interoperability and viable approaches for integrating genomic information & actionable variants into EHR systems