Facilitating Development of a Shared Evidence Base for Healthcare Systems

- *Develop rapid learning system to capture phenotype and outcomes.*
  - *Learn from each encounter*
  - *Continue to build evidence linking genotypes to phenotypes*
  - *Encourage sharing and widespread implementation*
- *Learn from sequencing happening outside of CSER.*
- *Facilitate recommendations/guidelines in disease specific organizations.*
- *Figure out how to engage families.*
- *Develop and refine guidelines in populations and individuals, with a phenotype, in an affected family, or without a phenotype*
- *Continue work on legal/regulatory frameworks.*

Interpreting Variants / Actionability

- *Improve standards for consistency in variant classification and transparency in evidence used.*
  - *Include annotation justification*
  - *Include case-level data*
  - *Database improvement to facilitate knowledge generation through rapid learning*
- *Have phenotype/clinical context inform evaluation*
  - *Iterate a dynamic process between lab and clinician.*
  - *Bayesian perspective*
  - *What is the right thing to sequence, is it disease specific*
  - *Longitudinal studies to elucidate penetrance*
- *Clarify and improve process for re-phenotyping and guidelines for reinterpreting data*
- *Refine guidelines and address key gaps in guidelines*

Assessing Clinical Utility - I

- *Improve how we measure clinical utility, and specify what we mean by clinical utility*
  - *Clarify what individual or societal benefit we measure, for example value of diagnosis if not clinically actionable*
  - *Consider how sequencing can inform population screening*
- *Adopt multiple approaches to studying clinical utility*
  - *Encourage comparative effectiveness research, including comparison with other approaches in clinical medicine.*
  - *Deepen evaluation of outcomes including morbidity/ mortality, and aggregate measures*
  - *Acknowledge contributions that RCT's can make*

Assessing Clinical Utility - II

- *Consider protocols for re-phenotyping, what should we be measuring and how do we improve standards and common elements across studies.*
- *Develop effective and efficient methods for integrating with functional genomics studies.*
  - *Consider functional research as an important component of the virtuous cycle.*
  - *Facilitate feedback between individual patients and high throughput functional assays to elucidate deleteriousness*
- *Improve sequencing of indels, structural variants and other non SNV variation.*
  - *Identify the current holes, and how to fill them*
  - *Consider what is the clinically meaningful variation*

Patient-centered Research: From Consent to Outcomes - I

- *Consensus to incorporate patient-centered and family-centered approaches*
- *Acknowledge the value of having a diagnosis as a patient-centered outcome*
- *Acknowledge difference in meaning of "actionable" to patients/family vs. physicians*
- *Leverage resources to connect patients with researchers and foster community*
  - *Identify alternative approaches for Internet-wary patients*

Patient-centered Research: From Consent to Outcomes - II

- *Continue to study the impact of diagnosis and subsequent outcomes*
- *Pay attention to how we package results to patients, especially VUS*
- *Use flexible approaches to patient-centered approaches that can change as technology changes and the number of populations/ethnic groups increases*

Increasing Ancestral, Socioeconomic and Clinical Diversity

- *Implement targeted methodologies and approaches.*
  - *Need work to recruit, need to sustain*
  - *Focus on trust, make inroads in community-based institutions*
  - *Be sensitive to barriers (loss of work, transportation costs, etc)*
- *Design studies to achieve our scientific goals*
  - *Sufficient sample size, may be > proportional*
  - *Enhance and improve ELSI by including more diversity*
- *Ensure gains in genomic medicine are equitably distributed*
- *Integrate social determinants with sequencing enterprise*
- *Broadening all aspects of diversity*
- *Increase the diversity of our workforce*

Healthcare Utilization, Economics and Value

- *Involve payers – eg, payer advisory board*
- *Invest not only in methods for better tools, but also methods for better for health care delivery*
- *Be cognizant of regulatory issues as work in this area goes forward*
- *Study the cascade effects (secondary, diagnostic)*

Additional Questions

- *How can we clearly delineate between CSER and other DGM programs (eMERGE, UDN)?*
- *Need better Rapid Learning Systems that capture outcomes – who supports this?*
- *Relative paucity of involvement of health economists in CSER, is that an area to build going forward?*
- *Does genetics set too high of a bar for itself?*
- *How can we best engage other IC's?*