Facilitating development of a shared evidence base for healthcare systems

Moderators: Dan Roden and Ian Krantz

Challenges/Opportunities: Heidi Rehm (10 min)

Reaction: Dan Masys (10 min)

Group Discussion: 25 min

Summary: Dan Roden (5 min)

Building the Evidence Base

Challenges:

There is not yet a comprehensive resource to define the clinical relevance of all genes and variants that will be necessary to support the integration of genomics into healthcare (ClinGen work in progress but help is needed)

Even with better standards, interpretation can vary (see CSER bakeoff project, next session) and expert consensus is needed

Progress in Variant-Level Sharing

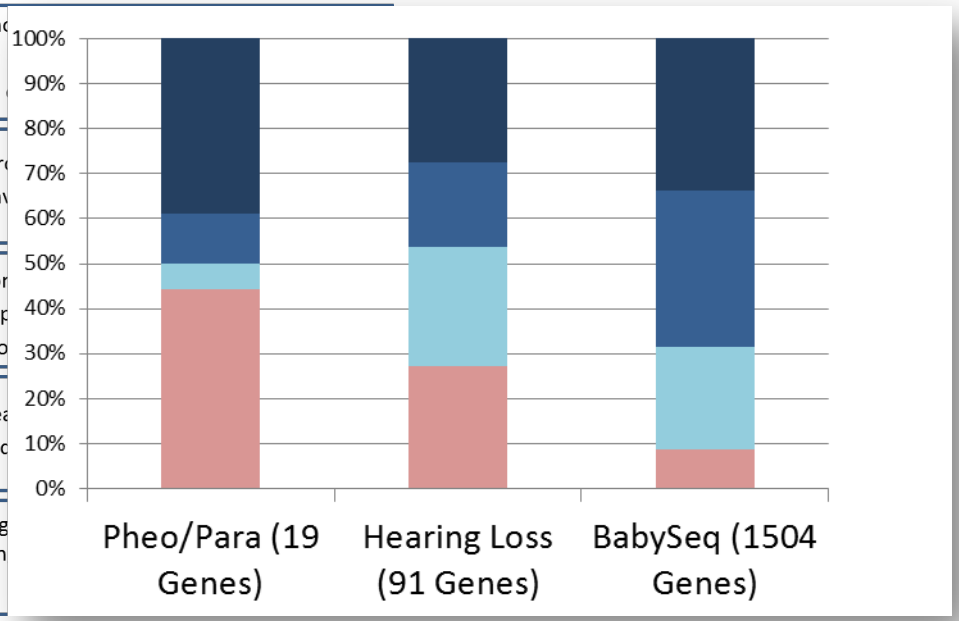
- **ClinGen**
  - >360 ClinVar submitters
  - >158,518 submissions
  - >111,104 unique interpreted variants
  - 4 groups approved as Expert Panels (CFTR2, InSiGHT, PharmGKB, ENIGMA)
  - 5 ClinGen clinical domain working groups formed, each with one or more expert panels under development

- **CSER**
  - 2617 interpreted variants submitted to ClinVar

Gene-Disease Validity and Actionability

ClinGen
Clinical Genome Resource

Definitive	Role has been repeatedly demonstrated in research & clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No convincing contradictory evidence
Strong	≥2 independent studies with: • Multiple patho • AND • Several different types of supporting pathogenic variants in cases vs. controls • No
Moderate	≥1 independent study with: • ≥3 unrelated pr Some supporting experimental data • No conv
Limited	≥1 independent study with: • <3 unrelated pr OR • Multiple variants reported in unrelated p evidence for pathogenicity • No convincing co
No Evidence Reported	No evidence reported for a causal role in disea therefore no pathogenic variants have been id
Conflicting Evidence Reported	
Disputed	Convincing evidence disputing a role for this g Disputing evidence need not outweigh existin gene:disease association
Refuted	Evidence refuting the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role • Applied at the discretion of clinical domain experts after thorough review of available evidence



Actionability Working Group Evidence-based Summaries

32 Completed

The summaries provide information on gene-condition pairs that meet a clinical actionability threshold for pathologic variants in the gene, and are prepared using a transparent, systematic, evidence-based process. A protocol guides the summary development, which includes quality rating of the evidence. An expert panel reviews the summaries and applies a semi-quantitative method to score the overall clinical actionability of gene variants discovered incidental to another diagnostic investigation.

https://www.clinicalgenome.org/knowledge-curation/

CSER Opportunities in Building the Evidence Base

- Opportunity:
  - There are limited numbers of variants and gene-disease pairs for which a clearly defined action is recommended when a patient harbors a pathogenic variant – CSER can play a critical role in defining these actions

  Steps:
  - Collaborate with ClinGen Actionability Group to document current standards
  - Engage patient and physician experiences to test and study recommended actions, and their outcomes, and define new recommendations where they are nonexistent
  - Define and test approaches to enable the collection of health data during routine clinical care
  - Work with standards bodies (HL7, GA4GH, ClinGen, DiGITIZE, etc) to inform the development of standards and interoperability for the healthcare and genomics communities (integration of health care systems, laboratories, consumer mobile technologies, etc) and test standards and tools that are developed

Identification and Return of Secondary Findings

CSER Experience: CSER sites have developed extensive experience in the identification and return of secondary genomic findings, but many subjects are without overt phenotypes

Amendola et al. *Actionable exomic incidental findings in 6503 participants: challenges of variant classification.* Genome Res. 2015 Mar;25(3):

Vassy JL, et al. *A one-page summary report of genome sequencing for the healthy adult.* Public Health Genomics. 2015;18(2):123-9.

Appelbaum et al. *Models of consent to return of incidental findings in genomic research.* Hastings Cent Rep. 2014 Jul-Aug;44(4):22-32.

Burke et al. *Return of results: ethical and legal distinctions between research and clinical care.* Am J Med Genet C Semin Med Genet. 2014 Ma

Henderson et al. *The challenge of informed consent and return of results in translational genomics: empirical analysis and recommendations.*

Jarvik et al. *Return of genomic results to research participants: the floor, the ceiling, and the choices in between.* Am J Hum Genet. 2014 Jun 5;

Lee et al. *Prioritizing disease-linked variants, genes, and pathways with an interactive whole-genome analysis pipeline.* Hum Mutat. 2014 May;35(5):537-47

McGuire et al. *Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings.* Genome Res. 2014 May;24(5):719-23.

Parsons et al. *Clinical tumor sequencing: an incidental casualty of the ACMG recommendations for reporting of incidental findings.* J Clin Oncol. 2014 Jul 20;32(21):2203-5.

Scheuner et al. *Reporting genomic secondary findings: ACMG members weigh in.* Genet Med. 2014 Nov 13.

Scollon et al. *Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients.* Genome Med. 2014;6(9):69.

Yu et al. *Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing.* Am J Hum Genet. 2014 Jul 3;95(1):77-84.

Appelbaum et al. *Informed consent for return of incidental findings in genomic research.* Genet Med. 2014 May;16(5):367-73.

Bennette et al. *Return of incidental findings in genomic medicine: measuring what patients value--development of an instrument to measure preferences for information from next-generation testing (IMPRINT).* Genet Med. 2013 Nov;15(11):873-81.

Berg et al. *Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium.* Genet Med. 2013 Nov;15(11):860-7.

Burke et al. *Recommendations for returning genomic incidental findings? We need to talk!.* Genet Med. 2013 Nov;15(11):854-9.

Challenges:

- How do we phenotype and manage these patients?
- How do we approach family members? Do we genotype and phenotype them?
- How do we improve our knowledge of disease penetrance and accurately predict disease onset?

Individual-Level Data Sharing

- Individual-level data sharing (genotypes and/or phenotypes) is critical to develop an evidence base
- Many efforts are collecting individual level data
  - dbGaP (NCBI), EGA (EBI)
  - ClinGen ILDB and GenomeConnect
  - TCGA/ICGC
  - Matchmaker Exchange: PhenomeCentral, DECIPHER, CMGs, etc
  - EHRs, Lab DBs, commercial software providers
  - Patient Registries (GenomeConnect, PEER, disease-specific)

- How can we optimize the collection and aggregation of this data?
  - Need consistent data structures for phenotype and genotype data (alignment with eMERGE, ClinGen, GA4GH)
  - Need to study the use of federated models for sharing and querying this data using common APIs (work with GA4GH)

CSER's Opportunities in the Patient Data Ecosystem

eMERGE

- Scaled phenotyping from existing data
- Enhance EHR for data storage and return

PMI

- Scaled prospective recruitment
- Capture data during clinical encounters

ClinGen

- Build an authoritative genomic knowledgebase
- *Use patient data as evidence*
- *Build connections to labs and clinics*

CSER

NSIGHT
"CSER in newborns"

- Leverage experience with robust patient interactions to study and enhance the use of genomics in clinical care
  - Continue to evolve the most effective ROR approaches
  - Develop and test better phenotyping and family history collection approaches that can be integrated into routine care
  - Improve methods for family engagement and incorporating the family unit in care models
  - Develop and test approaches to support clinical decision-making with genomic data
  - Develop seamless connection between research and clinical care

GA4GH International standards

Gene discovery **CMGs**

Facilitating development of a shared evidence base for healthcare systems:

Reaction

Daniel Masys, M.D.
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Biomedical and Health Informatics
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Wisdom from Larry Weed:

“Modern healthcare is a spectacle of fragmented intention”

“We practice healthcare as if we never wrote anything down.”

A method for ensuring that genomic medicine has little or no impact on healthcare:

Rely on
clinicians
Reading
and
Remembering
clinical reports and the published literature

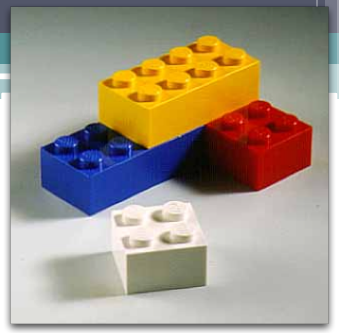
Reactions…

1. So, to paraphrase James Bond:

   "The World [of CSER, CMGs, eMERGE and ClinGen] is Not Enough."

2. The goal: a ***self-optimizing*** **healthcare system** that learns --
   - From *every decision event* that invokes an evidence rule,
   - WHETHER OR NOT the user follows best evidence guidance,
   - Contributing to both improved both local operations and the combined real world experience with the genotypes + phenotypes
   - Automatically expanding the evidence base for expert review and updating of best practice guidance *as a byproduct of care delivery*

Necessary Building Blocks for a self-optimizing Shared Evidence Base



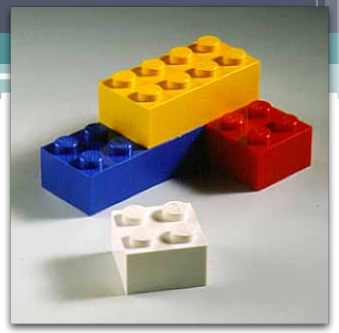
- Knowledge Representation Standards for interoperable electronic “decision support packages” containing:

1. Recognition logic for conditions of interest as represented in EHR systems (both genotype and phenotype)

2. Guidance for target users (clinician, patient, family)

3. Automated recognition logic for “closed loop decision support”: process or outcome measure to monitor, along with record of whether user accepted or rejected guidance

Computing tools for creating a self-optimizing Shared Evidence Base



- Decision support authoring systems: tools to enable local clinicians to easily import, review, and implement decision support packages received from a Public Library of Decision Support packages
- Event monitors embedded in EHR and PHR systems
- System-generated alerts at the "teachable moment" of diagnostic testing, therapy decision making, counselling
- *Automated tracking of outcomes vs. user decisions*
- *Incorporation of patient-reported outcomes (PMI engagement model)**

  **mostly missing to date*

The ‘ideal’ (Genomic) Decision Support Public Library

1. A Genomic CDS Information Commons that (spontaneously?) incentivizes bidirectional engagement by healthcare, research organizations, and individuals

2. Managed by a neutral, trusted organization (multiple possibilities)

Implementation:
Closing the Loop nationally

- *Quid pro quo* for use of public library clinical decision support packages would be automated local monitoring whether guidance was accepted or rejected, and whether subsequent clinical events (phenotypes) occurred or did not occur.

- Local uploads to the Public Library of *aggregate* local outcomes -> a national Learning Healthcare System that learns from every decision support event, whether or not recommendations were accepted by clinicians, combined with patient-reported outcomes.

Notable progress to date

1. Institute of Medicine's DIGITizE project (Displaying and Integrating Genetic Information Through the EHR) doing design and implementation plan for two pharmacogenomics use cases.
2. Electronic Medical Records and Genomics (eMERGE) and Implementing Genomics in Practice (IGNITE) networks have developed Open GCDS knowledge library; online soon.
3. PCORI-funded project at Geisinger for prospective comparative effectiveness trial to explore the role of patient facing GCDS to improve patient-provider communication; will assess which GCDS elements are required vs. optional.

Group Discussion and Moderator Summary

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Professor of Medicine , Pharmacology and Biomedical Informatics
Vanderbilt University

Discussion of CSER Opportunities

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GA4GH — International standards

Gene discovery — CMGs

Topics for Discussion

Cohorts/Data Collection

- Patient engagement
- Longitudinal data collection mechanisms
- Mechanisms to transition patients into research
- Balancing consent and open data sharing with privacy and security
- Connectivity, federation and data format standards
- Re-genotyping (CLIA confirmation) and Re-phenotyping

Knowledge Building

- Developing consistent approaches to evidence evaluation
- Building mechanisms for expert consensus
- Determining actionability and consensus on how to manage patients with “actionable” variants