Return of Genomic Results
Current Applications and Challenges

Iftikhar Kullo, MD
On Behalf of the ROR Work Group
January 22, 2014
# eMERGE ROR

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<tr>
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<th>Co-chairs</th>
<th>Workshop Panel members</th>
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<tr>
<td></td>
<td>Gail Jarvik</td>
<td>Lawrence Meyer, Susan Wolf, Lisa Parker, Iftikhar Kullo, Gail Jarvik</td>
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|     | CHOP                | John Connolly, Hakon Hakonarson, Brendan Keating                                        |
|     | CCHMC/BCH           | Armand Antommaria, John Harley, Ingrid Holm, Melanie Myers, Bahram Namjou, Cassandra Perry, Cindy Prows, Sander Vinks, Wendy Wolf |
|     | Geisinger           | Glenn Gerhard, David Ledbetter, Agnes Sundaresan, Gerard Tromp, Marc Williams            |
|     | Group Health/UW     | Gail Jarvik, David Crosslin, Kelly Ehrlich, Malia Fullerton, Carlos Gallego, Kathy Leppig |
|     | MCEIRH/PSU          | Murray Brilliant, Terrie Kitchner, Cathy McCarty, Marylyn Ritchie                         |
|     | Mayo                | Richard Sharp, Iftikhar Kullo, Jen McCormick                                           |
|     | Mount Sinai         | Erwin Bottinger                                                                          |
|     | Northwestern        | Steve Persell, Laura Rasmussen-Torvik, Maureen Smith, Cathy Wicklund                    |
|     | Vanderbilt          | Kyle Brothers, Ellen Clayton, Julie Field, Tracy McGregor, Dan Roden, Quinn Wells       |
|     | NIH/NHGRI           | Lucia Hindorff, Rongling Li, Rochelle Longbottom, Teri Manolio, Jackie Odgis, Erin Ramos |
EVOLUTION OF ROR IN EMERGE
Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network

Stephanie M. Fullerton, DPhil\textsuperscript{1}, Wendy A. Wolf, PhD\textsuperscript{2}, Kyle B. Brothers, MD\textsuperscript{3}, Ellen Wright Clayton, MD, JD\textsuperscript{3}, Dana C. Crawford, PhD\textsuperscript{3}, Joshua C. Denny, MD\textsuperscript{3}, Philip Greenland, MD\textsuperscript{4}, Barbara A. Koenig, PhD\textsuperscript{5,6}, Kathleen A. Leppig, MD\textsuperscript{7}, Noralane M. Lindor, MD\textsuperscript{5}, Catherine A. McCarty, PhD, MPH\textsuperscript{8,9}, Amy L. McGuire, JD, PhD\textsuperscript{10}, Eugenia R. McPeek Hinz, MD\textsuperscript{3}, Daniel B. Mirel, PhD\textsuperscript{11}, Erin M. Ramos, PhD, MPH\textsuperscript{12}, Marylyn D. Ritchie, PhD, MS\textsuperscript{13}, Maureen E. Smith, MS, CGC\textsuperscript{4}, Carol J. Waudby, MS\textsuperscript{8}, Wylie Burke, MD, PhD\textsuperscript{1} and Gail P. Jarvik, MD, PhD\textsuperscript{1}

- ROR in the context of the EHR
- ROR in the context of age
- Evidence of clinical validity and actionability
- Appropriate methods for ROR
- Diversity of opinion across sites
- Input from lay community, advisory bodies
Phase II- Genomic medicine pilots

- **Genetic risk scores**
  - Essentia: 7 SNPs assoc with Macular degeneration
  - Mayo: 28 SNPs assoc with heart attack

- **SNPs**
  - Mount Sinai: *ApoL1* for hypertensive renal dz in AA
  - Northwestern: *HFE* and *FV*

- **WGS**
  - Geisinger: Whole genome sequencing in trios

- **PGx**
  - *CYP2D6* results to parents and providers
  - Hypothetical return of *CYP2D6*
An EHR-based genomic medicine pilot study

MI-GENES
Myocardial Infarction Genes Study

What is Your Risk of Heart Attack?

Mayo Clinic is seeking individuals by invitation to participate in the Myocardial Infarction Genes (MI-GENES) Study. The purpose of this study is to understand how genetic information might improve assessment of heart attack risk.

You may be eligible to participate if:
- You are between the ages of 45-79
- You live in Southeast Minnesota
- You do not take statin medications
- You have participated in the Mayo Clinic Biobank or a previous research study at Mayo Clinic

The study includes 4 visits (see back for details). We will ask you to provide blood samples, complete surveys, and meet with a genetic counselor, as well as a clinician. You will be compensated for your time.

For more information, please contact the study team at (807) 269-6177.

150 patients in eMERGE-I with intermediate 10-\(\text{y}\) CHD risk

Telephone interview and information regarding trial to obtain informed consent

Blood draw and genotyping (CLIA-certified)

Genotype-informed 10-\(\text{y}\) CHD risk

Non-genotyped informed 10-\(\text{y}\) CHD risk (Framingham)

Meet with genetic counselor

Assess after meeting and at 3 and 6 months

* Comprehension of test results
* Knowledge and understanding of CHD risk
* Affect and emotions
  - Brief Profile of Mood States (POMS)
  - Impact of Event Scale (IES)
* Motivation for behavior change and self efficacy
## Phase II- Network-wide projects

- eMERGE PGx
- Copy number variation
- *HFE* variants

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<td><strong>Total</strong></td>
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<td><strong>586</strong></td>
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FUTURE DIRECTIONS
ROR: Unique potential of eMERGE

• EHR-based genomic discovery
  • ‘Longitudinal’ phenotypes
  • Pleiotropy (PheWAS)
• EHR based genomic implementation
  • Storage, visualization and integration
  • Decision support
  • Incidental findings
  • Outcomes
• The learning EHR
ROR - Discovery

• Incidental findings
• Mechanism and timing of ROR
• Consent
• Patient preferences

• CLIA confirmation
• Documentation in EHR
• Family members
• Pediatric setting

Jarvik et al, Manuscript in preparation, joint CSER and eMERGE effort
ROR - Implementation

What could be returned

- CNV?
  - recessive mutations

- Single SNVs
  - PGx
  - Disease risk

- Genetic risk scores
  - CHD, AMD, T2D

IFs from resequencing,
(whole exome, whole genome, targeted)

Prepare for return

- Jurying
- CLIA lab testing
- Statistical modeling
- EHR integration

Areas of study

- ELSI
- Storage & Re-interpretation
- Clinical Decision Support
- Outcomes

Prepare for return
- ELSI
- Storage & Re-interpretation
- Clinical Decision Support
- Outcomes
Potential projects

• **WES (n = 1000 each site):** phenotypes, penetrance, pleiotropy, pediatric considerations

• **Targeted sequencing** for the 56 ACMG genes to determine pathogenicity, penetrance, informing kin, etc.

• **Clinically indicated panels:** cardiomyopathies, pediatric syndromes

• **High-density genotyping** - common and rare variants
Consent

- Participant **privacy** and potential vulnerability to adverse social consequences
- Consent to include genomic **data in the EHR**
- **Recontact** to ascertain preferences and reconsent
- **Electronic ascertainment of preferences** over time
Stakeholders

- **Participants**, parents/guardians in pediatric projects, legally authorized representatives for adult incompetents, deceased
- **Family members**
- **Care providers**
- **Laboratorians**
- **Investigators**
- **Biorepository scientists**
eMERGE ROR interactions

- ACMG
- EGAPP
- PAYORS REG BODIES
- CLINGEN ROR CSER
- HL7 & CDSC

IMPLEMENTING GENOMICS
Summary

- eMERGE is uniquely positioned to address these knowledge gaps and challenges
  - Linkage to EHR with deep and diverse phenotypes
  - Diversity of clinical settings and EHRs
  - Diversity of genomic information
  - Best practices for implementation
  - n=50,000 including pediatric patients