Explore, within an active clinical setting, the application of genomic sequence data to the care of patients.

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CSER and eMERGE: current and potential state of the display of genetic information in the electronic health record


ABSTRACT

Objective Clinicians’ ability to use and interpret (EHRs). There is a critical need to develop systems Materials and Methods The National Institutes Records & Genomics CIR Working Groups condu to determine how genetic and genomics genetic information, and prioritize areas for EHR improvement. Results There is substantial heterogeneity in how genetic information was displayed in multiple local laboratory sources and through clinician of genetic information in the EHR. The highest priority decision support for medically actionable genetic Conclusion Heterogeneity of genetic information exammation representation are major barriers to using receive and consistently display genetic and/or recommended.

ARTICLE

Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between


As more research studies incorporate next-generation sequencing (including whole-genome or whole-exome sequencing), investigators and institutional review boards face difficult questions regarding which genomic results to return to research participants and how. An American College of Medical Genetics and Genomics 2013 policy paper suggesting that pathogenic mutations in 56 specified genes should be returned in the clinical setting has raised the question of whether comparable recommendations should be considered in research settings. The Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics Network are multisite research programs that aim to develop practical strategies for addressing questions concerning the return of results in genomic research. CSER and eMERGE committees have identified areas of consensus regarding the return of genomic results to research participants. In most circumstances, if results meet an actionability threshold for return and the research participant has consented to return, genomic results, along with referral for appropriate clinical follow-up, should be offered to participants. However, participants have a right to decline the receipt of genomic results, even when doing so might be viewed as a threat to the participants’ health. Research investigators should be prepared to return research results and incidental findings discovered in the course of their research and meeting an actionability threshold, but they have no ethical obligation to actively search for such results. These positions are consistent with the recognition that clinical research is distinct from medical care in both its aims and its guiding moral principles.
1. Expected Rate of Actionable Exomic Additional Findings

Act-ROR WG

<table>
<thead>
<tr>
<th>Participants with classification</th>
<th>European ancestry* N=4300</th>
<th>African ancestry N=2203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic variants (known)</td>
<td>30 (0.7%)</td>
<td>6 (0.3%)</td>
</tr>
<tr>
<td>Likely pathogenic variants (known)</td>
<td>52 (1.2%)</td>
<td>13 (0.6%)</td>
</tr>
<tr>
<td>Novel expected disruptive</td>
<td>6 (0.1%)</td>
<td>6 (0.3%)</td>
</tr>
<tr>
<td>Total pts with IFs</td>
<td>36 (2.0%)</td>
<td>12 (1.2%)</td>
</tr>
</tbody>
</table>

626 variant classifications deposited to ClinVar

*Caveats: No CNV included, HIGHER in Ashkenazi
Dorschner et al, AJHG, 2013 PMID: 25637381
Amendola et al., Genome Res, 2015. PMID: 25637381
2. CSER tests and clarifies ACMG/AMP guidelines for variant pathogenicity classification: Act-ROR WG “Variant bake-off”

Before consensus work the ACMG/AMP guidelines did not increase concordance across 9 CSER labs (34%). Discussion and rule clarification increased concordance from 34% to 71%.

Related publications:
- Pathogenicity calculator, Patel R et al, *Genome Med* 2017; PMID: 28081714
- Quantitative cosegregation criteria, Jarvik/Browning *AJHG* 2016; PMID: 27236918

Processes in 21 labs looking for best practices.

Recommendations:

1. Transparency and clarity regarding test methods and limitations.
   - List of genes targeted for analysis and the phenotype elements used to select them;
   - Stated threshold for minimum coverage and notation when coverage of a targeted gene falls below that threshold; and/or
   - Known pathogenic variation relevant to the indication but not detectable by the test.

2. Utilization of clinical domain expertise in case review. ...consider implementing group case review with inclusion of varied expertise including clinical domain expertise.

3. Confirmation of reported variants.

4. Data access guidelines. (patient’s right of access)

5. Data reanalysis.
3. Experiences with Obtaining Informed Consent for Genomic Sequencing

- Evaluation of all 9 CSER site consent forms
- Interviews of 29 genetic counselors and research coordinators who obtaining informed consent
- Participant questions and misperceptions
- Most important content to cover

**Common questions and concerns**
- Practical details of study
- Probability of finding an answer
- Possible results
- Privacy/ confidentiality
- Effect on other family members
- Anticipated response to results
- Insurance discrimination
- Impact of results on management

**Common misperceptions**
- Negative results mean a “clean bill of health”
- Negative result means not genetic
- Report will contain many incidental findings
- Sequencing will identify the cause of a condition
- Expect incidental results to explain diagnosis in absence of diagnostic findings
- Results will be certain
- Genome will change over time
- Results will be predictive of future health
4. Professionally Responsible Disclosure of Genomic Sequencing Results in Pediatric Practice
Pediatrics WG; McCullough *Pediatrics* 2015 PMID: 26371191

3 core concepts of pediatric ethics:
- the **best interests** of the child standard,
- **parental surrogate** decision-making,
- and **pediatric assent**.

Explain the nature of the proposed test, its scope and complexity, the categories of results, and the concept of an incidental finding. Pediatrists should obtain the informed permission of parents and the assent of mature adolescents.
5. Genome Report Toolkit
From Practitioner Education WG

**Goal:** to develop a just-in-time resource for **healthcare providers** about genomic testing reports that supports understanding of how results may impact medical care and how to discuss results with patients

**Key Elements:**
- Short, jargon-free written sections supported by visuals
- Platform/laboratory agnostic
- Links to relevant outside resources

**Implementation:** Toolkit is in pilot testing with target audience. Partnering with ASHG to host resource as a navigable webpage and downloadable document on their provider education website.
Genetics Education for Health Professionals

Mission

To develop and implement genomics education for health professionals that improves the practice of medicine and patient health outcomes.

Background

The ASHG Board of Directors has approved a strategic plan for the Society that prioritizes the education of health professionals who are not genetics specialists. These practitioners span a range from specialists (e.g., cardiology, oncology) to generalists (e.g., primary care) and constitute the vast majority of providers, yet they lack access to current genomics resources.
For a detailed review of CSER progress, please see the “Marker Paper”