Considerations for the Return of Genomic Results

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Associate Professor of Pathology, Brigham and Women’s Hospital and Harvard Medical School
Challenges to scaling genomic interpretation and ROR
Technical validity and sample identity

- Orthogonal confirmation with original sample addresses issues that happen even with CLIA NGS
  - Analytical validity of results
    - SNVs challenging in homologous regions
    - InDels often challenging
  - Sample mix-ups during testing process
- Yet, duplicate specimens and orthogonal confirmation are not scalable

Consider making some data available separately as unconfirmed research results requiring CLIA confirmation

(Courtesy: Diana Mandelker and Birgit Funke)
Quality Scores for NGS Data – When is Sanger required?

Whole Genome Variants
373 Assume True Positive
31 Require Sanger (7.4%)
13 Assume False Positive
417 Total
In non-diagnostic testing, 92% of variants reported as pathogenic in HGMD had insufficient evidence to support the claim.

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>Average Review Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant with literature</td>
<td>90 min</td>
</tr>
<tr>
<td>Variant with no literature</td>
<td>26 min</td>
</tr>
</tbody>
</table>
Interpretation Differences in ClinVar

26% (97,422/377,075) of variants have ≥2 submitters in ClinVar

17% (16,631/97,422) are interpreted differently among clinical lab submissions

11% (12,895/118,169) of variants have ≥2 submitters in ClinVar

17% (2229/12,895) are interpreted differently

3.6% medically significant (P/LP vs VUS/LB/B)

1.7% medically significant among clinical lab submissions
Ambry GeneDx Chicago LMM

87% resolution (211/242)

Pre-Discrepancy Resolution Process

Post-Discrepancy Resolution Process

Steven Harrison

Harrison et al. Genet Med, in press
Variant Knowledge Evolution

Communicating new knowledge on previously reported genetic variants

Samuel J. Aronson, ALM, MA,1,2 Eugene H. Clark, BM,1,2 Matthew Varugheese, MS1,2, Samantha Baxter, MS, CGC2, Lawrence J. Babb, BS1,2 and Heidi L. Rehm, PhD, FACMG1,4

Variant classification changes—HCM data

~4% of cases per year received medium or high alerts

MedSeq Genome Reanalysis

22% (22/100) Participants Received New or Reclassified Variants

Previously Unreported Finding(s), 9
Reclassified Finding(s), 10
Both, 3

Expert Panel interpretations sometimes change as well

Genet Med. Apr 2012 PMID: 22481129
Variant Reclassification Over 12 Years at the Laboratory for Molecular Medicine

- 88% No change (18,766 variants)
- 12% Reclassified
- 83% More certainty
- 16% Less certainty
- 1% Opposing
Variant Reclassification Over 12 Years at the Laboratory for Molecular Medicine

- Initial classification was:
  - Within 5 years: 25
  - 6-12 years ago: 209

Number of reclassifications:

<table>
<thead>
<tr>
<th>Reclassification Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>LB to B</td>
<td>1063</td>
</tr>
<tr>
<td>B to LB</td>
<td>30</td>
</tr>
<tr>
<td>LP to P</td>
<td>216</td>
</tr>
<tr>
<td>P to LP</td>
<td>81</td>
</tr>
<tr>
<td>VUS to LB/B</td>
<td>512</td>
</tr>
<tr>
<td>VUS to LP/P</td>
<td>301</td>
</tr>
<tr>
<td>LB to VUS</td>
<td>55</td>
</tr>
<tr>
<td>LP to VUS</td>
<td>228</td>
</tr>
<tr>
<td>P to VUS</td>
<td>13</td>
</tr>
<tr>
<td>B to VUS</td>
<td>2</td>
</tr>
<tr>
<td>LP to LB/B</td>
<td>11</td>
</tr>
<tr>
<td>P to LB/B</td>
<td>4</td>
</tr>
<tr>
<td>LB to P/LP</td>
<td>3</td>
</tr>
<tr>
<td>B to P/LP</td>
<td>0</td>
</tr>
</tbody>
</table>
Laboratory management of knowledge updates

1. Issue amended reports

2. Allow direct access to laboratory database (e.g. Emory)

3. Regularly deposit variants into ClinVar

4. Deliver automated knowledge updates on reported variants (e.g. GeneInsight)
Reports, Structured Variant Data and Variant Updates Returned Via EHR (GeneInsight Clinic)
Updated Variant Information

**Reported Variant Interpretation History (Variant 2 of 2)**

*Warning: This page only lists information on a single variant. This is outside of the patient report context and may be insufficient for an interpretation of the patient report.*

**Heterozygous c.484G>A (p.Gly162Arg), Exon 7, MYL2 (Germline)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Laboratory: Laboratory for Molecular Medicine</td>
</tr>
</tbody>
</table>

**Counts**

<table>
<thead>
<tr>
<th>Current Category*</th>
<th>Reported Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely pathogenic</td>
<td>Uncertain significance</td>
</tr>
</tbody>
</table>

**Alerts**

<table>
<thead>
<tr>
<th>Status</th>
<th>Date/Time</th>
<th>Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unreviewed</td>
<td>04/05/2016 02:13 PM</td>
<td>The category for the MYL2 c.484G&gt;A (p.Gly162Arg) association to Hypertrophic cardiomyopathy changed from Uncertain significance to Likely pathogenic. Reason for Update: New Evidence. Approved by: Birgit Funke</td>
</tr>
</tbody>
</table>

**Mark Alerts Reviewed**

**Current Knowledge**

*Approved 04/05/2016 02:13 PM by Birgit Funke*

<table>
<thead>
<tr>
<th>Category</th>
<th>Diseases/Drugs</th>
<th>Variant Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely pathogenic</td>
<td>Hypertrophic cardiomyopathy</td>
<td>The p.Gly162Arg variant in MYL2 has been reported in 1 individual with HCM (Olliverto 2005). It has also been identified by our laboratory in 1 individual with LVM, reduced EF and ST segment abnormalities and occurred de novo in another individual with HCM, AV block and RBBB (LMM unpublished data). This variant was absent from large population studies. In vitro functional studies provide some evidence that the p.Gly162Arg variant may impact protein function (Burghart et al., 2013). However, these types of assays sometimes do not accurately represent biological function. Glycine (Gly) at position 162 is highly conserved in evolution and the change to arginine (Arg) was predicted to be pathogenic using a computational tool clinically validated by our laboratory. This tool's pathogenic prediction is estimated to be correct 94% of the time (Jordan 2011). In summary, although additional studies are required to fully establish its clinical significance, this variant is likely pathogenic.</td>
</tr>
</tbody>
</table>

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* The current category field displays the variant significance only within the diseases/drugs that have been interpreted on each report, primarily defined by the ordered list. Additional interpretations, if present, outside these diseases/drugs are not considered.

** The Current Knowledge only includes the following Diseases/Drugs Interpreted on Report: General Genome Report Disease, Hypertrophic cardiomyopathy, Hereditary haemochromatosis
Prototype of a proposed EHR App

Will bring in 3-4 star variants from ClinVar

**ClinGen EHR App - Interpretations of patient reported variants**

**Doe, Jane**  
62yr, Female, 1/1/1954

<table>
<thead>
<tr>
<th>Variant</th>
<th>Disease</th>
<th>Source 1</th>
<th>Zygosity/Inheritance</th>
<th>Significance (reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM_007294.3(BRCA1):c.5503C&gt;T (p.Arg1835Ter)</td>
<td>FINDINGS</td>
<td>GeneDx</td>
<td>Hereditary breast and ovarian cancer syndrome</td>
<td>Heterozygous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ClinVar</td>
<td>Hereditary breast and ovarian cancer syndrome</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>NM_000179.2(MSH6):c.3632T&gt;C (p.Leu1211Pro)</td>
<td>FINDINGS</td>
<td>Ambry Genetics</td>
<td>Lynch syndrome 1</td>
<td>Heterozygous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ClinVar</td>
<td>Lynch syndrome 1</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>

**UNMATCHED VARIANTS**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Disease</th>
<th>Zygosity</th>
<th>Significance (reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM_170707.3(LMNA):c.1303C&gt;T (p.Arg435Cys)</td>
<td>Hutchinson-Gilford progeria syndrome</td>
<td>Heterozygous</td>
<td>Likely pathogenic (4/20/13)</td>
</tr>
</tbody>
</table>

**KEY**

- ✓ Match
- ! Potential discrepancy
- ▼ Discrepancy (underlined)
- 📣 Additional details
Proposal for AoU Genetic ROR

• Begin with a small set of results that reach consensus for utility and sufficient evidence
• Label “clinical” and expand scope once a successful process is achieved
  ▫ ACMG59 as starting point
  ▫ Pathogenic as starting point

• Consider approaches to share additional data – label as “research”
  ▫ Enable participants to share their raw data broadly
    • Array genotypes, BAMs, VCFs
    • List of annotated novel, rare or suspicious variants
  ▫ Allow access to data when clinical context raises the prior probability of disease
    • CLIA confirmations and interpretations can be ordered as needed
  ▫ Enable other studies that can delve deeper into the significance of these variants
Approaches to scale genomic interpretation

- For novel predicted null variants, checklist can largely be automated if gene and exon level curation is performed in advance
  - Are null variants an established mechanism of disease?
  - How frequently are predicted null variants found in the gene in large population databases? Het vs hom? What is the constraint score in ExAC?
  - Are there other known pathogenic variants in the exon? Also check ExAC for nulls in that exon.
  - Is nonsense-mediated decay predicted?
  - Are there predicted null variants reported 3' (and 5') to the variant?
  - Is the exon alternatively spliced?

- Rely on ClinVar review levels for reported variants
  - Consider reporting only 3 star or 4 star variants
  - Could add 2 star variants (all submitters agree)
Variant Curation Expert Panels (ClinGen-approved and in planning)

- Hereditary Cancer
  - ENIGMA EP
  - InSiGHT EP
  - CDH1 EP
  - PTEN EP
  - TP53 EP
- Cardiovascular Disease
  - Cardiomyopathy EP
  - KCNQ1 EP
  - FH EP
- Inborn Errors of Metabolism
  - PAH EP
  - FAO EP
  - Aminoacidopathy EP
  - Mito EP
- Neuro developmental
  - Rett/Angelman-like Disorders
- Hearing Loss
  - Hearing Loss EP
- Other
  - CFTR EP
  - PharmGKB
  - RASopathies EP
  - MODY EP
  - Somatic & Germline Cancer Curation Group

Application approved by ClinGen for 3 star submissions to ClinVar
Planning to apply to ClinGen for 3 star submission level

9318 expert reviewed variants in ClinVar (2.5%)
### Which 1-2 star variants to report?

- Not all 2 star variants are created equal
- Not all 1 star variants are created equal

- **2 star:** How many labs agree? Only 2 or many?

- **Which groups(s) reported?**
  - Single submitter criteria provided (1 star)
  - Experienced clinical lab
    - Subjective – opinion of physicians and clinical lab peers
    - Objective measures – volume of submissions in a disease area (data from ClinVar Miner)

- **Date of last evaluation (evaluated within last 1-2 years)**
## hu025CEA (Heidi Rehm) - GET-Evidence variant report– PGP Project

**http://evidence.pgp-hms.org/genomes**

### Variant 56 of 3319: MYH7-R1500W

<table>
<thead>
<tr>
<th>Variants</th>
<th>Description</th>
<th>Score</th>
<th>Zygosity</th>
<th>Polyphen</th>
<th>Prioritization Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7-R1500W</td>
<td>Heterozygous, Polyphen</td>
<td>3</td>
<td></td>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>

### Insufficiently evaluated variants (3319 variants)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Prioritization score</th>
<th>Allele freq</th>
<th>Num of articles</th>
<th>Zygo and Prioritization Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC2R-S74I</td>
<td>5</td>
<td>0.02%</td>
<td></td>
<td>Heterozygous. In OMIM, Polymorphism database, and Uniprot.</td>
</tr>
<tr>
<td>NEFL-S725STOP</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSPIA-A607STOP</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-3100G</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEP290-E2273Q</td>
<td>4</td>
<td>1.60%</td>
<td></td>
<td>Carrier (Heterozygous). Has not been evaluated.</td>
</tr>
<tr>
<td>DPDY-5534A</td>
<td>4</td>
<td>1.60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEP290-K183L</td>
<td>4</td>
<td>3.20%</td>
<td></td>
<td>Heterozygous. Has not been evaluated.</td>
</tr>
<tr>
<td>LAMC2-D247I</td>
<td>4</td>
<td>3.40%</td>
<td></td>
<td>Heterozygous. Has not been evaluated.</td>
</tr>
<tr>
<td>FS-P54E</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COL11A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3GKR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATPE81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Technical artifact

The image contains a table with variant information and a note about a technical artifact. The table includes columns for variant description, score, zygosity, Polyphen, and prioritization score. The table also includes notes about the status of variant evaluation and prioritization scores. The note about a technical artifact indicates that further investigation is needed for this variant.
Supporting Participants with a Genomic Result & Their Clinicians – Principles & Implications for All of Us

wafaucett@geisinger.edu

@andyfaucett
Relevant *All of Us* guiding principles

- “focus not just on disease, but also on ways to increase an individual’s chances of remaining healthy throughout life”
- “empower study participants with data and information to improve their own health”
Geisinger MyCode Participant Driven Principles

- Participant focus groups:
  - Wanted Geisinger to guide project
  - Comfortable receiving ALL results
  - Accepted we do not understand some results
  - Importance of placing genomic results in EHR
  - Share results with participants
  - Education, medical support to patients & clinicians

Faucett WA & Davis FD, 2016, Appl Trans Genom
Engagement to Develop Return Process

- Patient focus groups
- Ethics Advisory Council (EAC)
- Clinical Oversight Committee (COC)
- Precision Health Patient Advisory Board

Faucett WA & Davis FD, 2016, *Appl Trans Genom*
Principles of MyCode Genomic Results Program

1. Geisinger expert consensus on which genes to evaluate & return
2. Pathogenic/likely pathogenic variants in medically actionable genes
3. Minimize false positives (specificity > sensitivity)
4. Patients choose how to follow up clinically
5. Supportive infrastructure for patients & clinicians
Result return process

1. Primary care clinician notified of result via EHR
2. Patients notified in writing that result is available
3. Clinical Genomics team calls patients
   1. Disclose nature of results
   2. Schedule follow-up (detailed disclosure, clinical eval)
   3. Encourage family communication of results
4. Patients choose clinical follow-up approach
5. All patients receive educational/supportive materials on relevant genetic condition
6. Care coordination with co-managing clinicians
• Multiple service delivery models
• Genetic counselors available for phone consults 5 days/week
• Genetic counselors & physician geneticists available for in-person consults 3 days/week
• Genetic Counselor for most results
• Triage conditions with syndromic features to geneticists
## Lessons – MyCode Patient Support

<table>
<thead>
<tr>
<th>Follow-up Status</th>
<th>Positive Results</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Genomics</td>
<td>245</td>
<td>45%</td>
</tr>
<tr>
<td>PCP or specialist</td>
<td>73</td>
<td>13%</td>
</tr>
<tr>
<td>Declined immediate follow-up</td>
<td>134</td>
<td>25%</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>38</td>
<td>7%</td>
</tr>
<tr>
<td>Deceased/Withdrawn</td>
<td>9</td>
<td>2%</td>
</tr>
<tr>
<td>In Process</td>
<td>45</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>544</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
### MyCode® Results Returned

544 patient-participants have received results from the Genomic Screening and Counseling Program. For the latest results, see [go.geisinger.org/results](go.geisinger.org/results).

#### Cardiovascular Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)</td>
<td>203</td>
<td>BRCA1</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2</td>
<td>135</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (early heart attacks and strokes)</td>
<td>92</td>
<td>APOB</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDLR</td>
<td>61</td>
</tr>
<tr>
<td>Lynch syndrome (early colon, uterine and other cancers)</td>
<td>50</td>
<td>PMS2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Other Risk Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy (disease of the heart muscle with dangerous complications)</td>
<td>53</td>
<td>MYH7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYBPC3</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPM1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNNT1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNNT2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYL3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMNA</td>
<td>2</td>
</tr>
<tr>
<td>Arrhythmia (irregular heartbeat with risk for cardiac arrest)</td>
<td>38</td>
<td>SCN5A</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNQ1</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNH2</td>
<td>3</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy (disease of the heart muscle with risk for cardiac arrest)</td>
<td>27</td>
<td>DSP</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PKP2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSG2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSC2</td>
<td>1</td>
</tr>
<tr>
<td>Marfan syndrome (connective tissue disease that can cause heart, eye, and skeletal problems)</td>
<td>4</td>
<td>FBN1</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Cancer Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)</td>
<td>10</td>
<td>SDHB</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDHC</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDHD</td>
<td>3</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1 (early onset of multiple endocrine and multiple cancers)</td>
<td>5</td>
<td>MEN1</td>
<td>5</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2 (early thyroid cancer)</td>
<td>17</td>
<td>RET</td>
<td>17</td>
</tr>
<tr>
<td>PTEN hamartoma tumor syndrome (early breast, thyroid, uterine, and other cancers, with intellectual disability in some cases)</td>
<td>3</td>
<td>PTEN</td>
<td>3</td>
</tr>
<tr>
<td>Tuberous sclerosis (multiple types of benign non-cancer tumors)</td>
<td>1</td>
<td>TSC2</td>
<td>1</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome (early breast, soft tissue, brain, adrenal and other cancers)</td>
<td>8</td>
<td>TP53</td>
<td>8</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (early colon cancer)</td>
<td>2</td>
<td>APC</td>
<td>2</td>
</tr>
<tr>
<td>Von Hippel-Lindau (early kidney cancer and benign tumors of brain, eye, pancreas and adrenal gland)</td>
<td>1</td>
<td>VHL</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Other Risk Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant hyperthermia (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)</td>
<td>22</td>
<td>RYR1</td>
<td>22</td>
</tr>
<tr>
<td>Pulmonary disease (damage to lung tissue leading to decrease in lung efficiency)</td>
<td>1</td>
<td>GLA</td>
<td>1</td>
</tr>
<tr>
<td>Vascular Ehlers-Danlos (disease of the connective tissue, including arteries and muscles, that can increase the risk for health complications, such as rupture of arteries)</td>
<td>1</td>
<td>COL3A1</td>
<td>1</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (liver, nose, mouth, and skin disorders)</td>
<td>1</td>
<td>HFE</td>
<td>1</td>
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#### Totals

<table>
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<th>Condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>547</strong></td>
<td><strong>Total</strong></td>
<td><strong>547</strong></td>
</tr>
</tbody>
</table>
Support in MyCode Genomic Results Program

- **Patient support**
  - Opportunity to meet with clinical genomics team
  - Family history intake
  - Condition-specific multi-disciplinary clinics

- **Clinician support**
  - EHR tools for detailed phenotyping, documentation
  - Continuing Medical Education
  - Opportunity to consult clinical genomics team

- **Both**
  - Provider / Patient friendly genomic reports
Lessons – MyCode Patient Support

• Positive feedback from qualitative interviews
  • “[I]t’s a good thing to know for you and your family members...if you find something you can nip in the bud, it’s not nearly as expensive”
  • “Nobody’s been very upset or even my kids who have potential of having it themselves have been very laid back about it actually”
• Facilitating cascade testing is challenging
**MyCode Clinician Support**

- **CME modules**
  - Low uptake, but want to know they are there
  - PCPs prefer brief, risk management focused on support
- **PCPs prefer Genomics disclose results & guide evaluation**
  - PCP role is to support process
  - Want Genomics help with current management
- **Returning results increased clinician support of MyCode**
ClinGen Consent & Disclosure Recommendation Working Group

Pathogenic/Likely Pathogenic Variant Result

- Is patient a minor who had an adult-onset condition identified? (Yes/No)

  - Yes: Disclosure of Results by ordering clinician (via phone or in person; priority referral)
  - No: Condition associated with increased risk of adverse psychological impact? (Yes/No)
    - Yes: Targeted discussion of results by ordering clinician
    - No: Detailed discussion of results by genetics clinician

Per clinician & participant preferences

ACMG SFv2.0 gene recommendations completed

Disclosure of results via phone, patient portal, or written material
**All of Us - Thoughts On What To Return**

- ACMG 2.0 (59 genes)
  - Manageable numbers – 3.5 – 4%
  - “High Value” – medically actionable
  - GC community familiar
  - Commercial lab support – education materials
- Pharmacogenomics
  - Most participants will receive result (100%)
  - More value for older participants
  - Return with educational materials & limited GC and pharmacist support
- “Uninterpreted Data”
  - Process / Format
All of Us Results Sharing Versions

V 3.0
ACMG 2.0 & PGX
Uninterpreted Data

V 2.0
ACMG 2.0
Pharmacogenomics

V 1.0
ACMG 2.0

Confirm interest with each version
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- Precision Health Patient Advisory Board
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