Genomics: A land where clinical and research ethics must overlap

Leila Jamal ScM, PhD, CGC
Associate Director for Cancer Genomics, Johns Hopkins/NIH Genetic Counseling Training Program
Genomics Education Specialist, National Cancer Institute
Genomic testing in healthcare: a hybrid space where clinical practice and research need to co-exist

Rachel Horton and Anneke Lucassen

Clinical Ethics and Law at Southampton (CELS), Faculty of Medicine, University of Southampton, UK; Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, UK
A tale of two innovations

• #1: Advances in genetic variant interpretation – a primer
  • Ethical issues + relevant guidelines
  • Reinterpretation and variant reclassification

• #2: Paired tumor-germline sequencing in cancer
  • A new case of secondary findings

Moral of the story: Unbiased sequencing is our future – and it has consequences for how we think about ethics
Genomic sequencing 2010-present
1 – Standards for variant quality control and interpretation

Next Gen Sequencing =
• Base calling
• Read alignment
• Variant calling
• Variant annotation
• **Variant interpretation**
…because the depth of coverage for an exome is not uniform, the analytical sensitivity for exome sequencing may be lower than the sensitivity for most targeted gene panels, given that a substantial number of exons in known disease-associated genes may lack sufficient coverage…
...the ACMG strongly recommends that clinical molecular genetic testing should be performed in a Clinical Laboratory Improvement Amendments–approved laboratory, with results interpreted by a board-certified clinical molecular geneticist or molecular genetic pathologist or the equivalent.
ACMG/AMP/CAP variant interpretation guidelines (2015)

99% certain association with disease
90% certain association with disease

Everything else!

90% certain benign
99% certain benign

Richards et al. 2015, Genetics in Medicine
Types of data used

- Population data
- Segregation data
- Allelic data (phase)
- Computational data/predicted impact on protein
- "Other"
  - Specificity of gene-phenotype association
  - Extent of known benign variation in gene
  - Etc...

Application of ACMG criteria depends on what is known about a phenotype, its inheritance, penetrance, biochemistry, physiology, and epidemiology...

Strande et al. 2018, Genetics in Medicine
Since 2015

ClinGen’s Critical Questions

- Is this gene associated with a disease? (Clinical Validity)
- Is this variant causative? (Pathogenicity)
- Is this information actionable? (Clinical Utility)

Building a Genomic Knowledge Base
ClinVar & Other Resources

Improved Patient Care Through Genomic Medicine
Since 2015

<table>
<thead>
<tr>
<th>Gene</th>
<th>Expert Panel</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH VCEP</td>
<td>8</td>
<td>127</td>
</tr>
<tr>
<td>PTEN VCEP</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>CDH1 VCEP</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>RASopathy VCEP</td>
<td>127</td>
<td>51</td>
</tr>
<tr>
<td>Hearing Loss VCEP</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Myeloid Maligna...</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Cardiovascular ...</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LikelyBenign</th>
<th>LikelyPathogenic</th>
<th>Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH VCEP</td>
<td>275</td>
<td>7</td>
</tr>
<tr>
<td>PTEN VCEP</td>
<td>111</td>
<td>31</td>
</tr>
<tr>
<td>CDH1 VCEP</td>
<td>121</td>
<td>24</td>
</tr>
<tr>
<td>RASopathy VCEP</td>
<td>285</td>
<td>18</td>
</tr>
<tr>
<td>Hearing Loss VCEP</td>
<td>107</td>
<td>19</td>
</tr>
<tr>
<td>Myeloid Maligna...</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Cardiovascular ...</td>
<td>101</td>
<td>18</td>
</tr>
</tbody>
</table>
Since 2016

The Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community.

Credit: Daniel MacArthur and lab@Broad Institute
What does all this mean?

• Reanalysis of exome data after short intervals significantly increases diagnostic yield

• Estimates range from ~11% to ~200% increased diagnostic yield at reanalysis intervals as short as 12 months to six years

• Diagnostic gains vary by phenotype and our knowledge of phenotypes

Liu et al. NEJM 2019; Machini et al. AJHG 2019; Baker et al. J Mol Diag 2019; Ewans et al. GIM 2018; Wright et al. 2018....etc.
What does this have to do with ethics?

- It took a lot of work to convince research institutions that return of (high-impact, health-related) results is the ethical thing to do (and good for science)

- But what if we are returning incorrect information without realizing it?

- (Most) researchers are not clinicians

- Researchers (still) have duties to minimize harms and maximize the production of knowledge
Present day challenge
ASHG recontact guideline in a nutshell

- Recontact is difficult and resource-intensive. It is a responsibility, not a duty.

- No responsibility exists after project funding has ended.

- The responsibility to recontact is stronger if there is compelling evidence for medical benefit (or harm) of NOT re-contacting.

- The degree of relationship with a study participant is key to determining the strength of a responsibility.

- Whatever you do, leave a paper trail. Documentation/communication about the limitations of research results is key.

Bombard et al. AJHG, 2019
A new riff on a familiar theme...

Courtesy Howard Levy + Yvonne Bombard
Detecting germline genetic variants from somatic tumor sequence information

The Incidental Finding
Routine shoulder x-ray, Jan. 2, 2007

“Your shoulder will be fine ... but there's something in your lung”

The shadow was a golf-ball size tumor: kidney cancer that had spread throughout the body
## Somatic (tumor) testing

<table>
<thead>
<tr>
<th>Test Method</th>
<th>Sample Required</th>
<th>Can Germline Variants be Detected?</th>
<th>Confirmatory Testing Needed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic (tumor) only</td>
<td>Tumor specimen</td>
<td>Can be inferred</td>
<td>Yes</td>
</tr>
<tr>
<td>Somatic (tumor)-normal paired</td>
<td>Tumor and non-tumor specimens</td>
<td>Usually “masked”</td>
<td>Seldom</td>
</tr>
<tr>
<td>Somatic (tumor)-normal paired with cancer</td>
<td>Tumor and non-tumor specimens</td>
<td>Detected based on test design</td>
<td>No, as long as germline</td>
</tr>
<tr>
<td>predisposition genes DELIBERATELY analyzed</td>
<td></td>
<td></td>
<td>results are validated as a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>clinical test</td>
</tr>
</tbody>
</table>
"Incidental" germline findings in somatic sequencing

• When testing a tumor...

• Any identified variant could be
  • A somatic change
  • A germline change that has been retained in the tumor

• Germline variants may be
  • Phenotype-concordant (BRCA1 in a breast cancer)
  • Phenotype-discordant (BRCA1 in a lung cancer)
In somatic tumor testing, when might we suspect a germline result?

• Well-characterized genes associated with hereditary syndromes

• If tumor is highly specific to a syndrome, it is more likely that the patient carries a germline variant in the associated gene.
  • Eg. Adrenocortical carcinoma/TP53; uveal melanoma/BAP1

• Founder mutations
  • Eg. BRCA c.68_69delAG
  • MSH2 inversion

• Variant allele frequency (VAF) of germline variants (presumed to be heterozygous) is roughly 40%-60% but can fall outside this range.
  • NO HARD AND FAST CUTOFFS
Pay attention to clinical features

- Family history
- Age of onset
- Rare cancers
- Multiple primary cancers
- Unusual findings or comorbidities
  - Eg. dysmorphic features, congenital heart disease, skin findings
Clinical implications

- Know the test you are ordering
  - What genes are (or are not) included?
  - What are the technical limitations?
  - Does the test evaluate copy-number variation?
  - Does the lab mask germline findings?

- Informed Consent
  - Patients should be informed that tumor testing could detect germline (heritable) genetic changes
  - Germline results could influence treatment decisions and risk management in relatives
  - Guidelines suggest that patients should be allowed to opt-out of learning germline results
“Tumor testing may uncover DNA changes that increase your risk of cancer. Sometimes, these DNA changes are inherited in families. They could have health implications for you and your relatives. If found, we might refer you for some additional testing and genetic counseling. You can choose to opt-out and not learn about DNA changes that might have been inherited. However, that might mean that we can’t manage your (or your relatives’) cancer risk to the very best of our abilities"
Why do we care about germline variants?

• Your patient’s treatment + management could change

• Risk of additional cancers, cancer recurrence might higher than otherwise appreciated

• Benefits to relatives – prevention and screening

• Research: Expand our clinical knowledge of cancer syndromes in patients who don’t meet current criteria for germline testing
Unbiased genomic sequencing is our (present?) future
Flipping the script on incidental findings

2013

**COMMENTARY**

Incidental Variants Are Critical for Genomics

Leslie G. Biesecker

The topic of incidental variants detected through exome and genome sequencing is controversial, both in clinical practice and in research. The arguments for and against the deliberate analysis and return of incidental variants focus on issues of clinical validity, clinical utility, autonomy, clinical and research infrastructure and costs, and, in the research arena, therapeutic misconception. These topics are briefly reviewed and an argument is made that these variants are the future of genomic medicine. As a field, we should take full advantage of all opportunities to study these variants by searching them out, returning them to patients and research participants, and studying their utility for predictive medicine.

“In the research arena, we should study incidental variants to learn what they can tell us about the full spectrum of genotypes and phenotypes. Because this research improves our knowledge of incidental variants, they can be moved onto, or perhaps in some cases off of, the lists of genes and variants known to be medically useful.”

“In the clinical arena, we should return those variants to patients when they meet reasonable standards for proof of causality and can significantly improve the medical care of our patients.”
Reduced penetrance and variable expressivity

• Reduced penetrance
  • % of pathogenic variant carriers who develop a condition (penetrance is rarely 100%)

• Variable expressivity
  • Variable features identified in people who carry the same pathogenic variant(s) (most disorders have variable expressivity)

• Both are evidence that we don’t understand genetics as well as we would like to
Review

Living laboratory: whole-genome sequencing as a learning healthcare enterprise


M. Angrist\textsuperscript{a} and L. Jamal\textsuperscript{b}
\textsuperscript{a}Science and Society, Social Science Research Institute and Sanford School of Public Policy, Duke University, Durham
NIH Clinical Center - Overlapping Worlds

Research

Clinical Care
Bottom line

- Research findings can have impactful clinical implications; clinical tests can produce results with little or no associated evidence.

- Responsible return of results requires interdisciplinary collaboration and institutional investment.

- Policy development is crucial.

- Scientific, medical, ethical and legal experts must learn to work together in order to get the difficult cases right.
Thank you!