Returning Research Results in Oncology: Emerging Challenges and Opportunities

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Genomics Education Specialist,
Cancer for Center Research, Genetics Branch
Adjunct Faculty,
NIH Department of Bioethics
Three challenges/opportunities

1. Re-classification of research variants that have already been returned

2. Potential germline genetic findings from tumor sequencing results
   1. A “special” case of incidental/secondary findings

3. Returning results to relatives of critically ill or deceased patients
#1: Recontacting research participants when returned results are reclassified – what are researchers’ responsibilities?

ASHG POSITION STATEMENT

The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results

Yvonne Bombard,1,2,3,* Kyle B. Brothers,1,4 Sara Fitzgerald-Butt,5,6 Nanibaa’ A. Garrison,1,7,8 Leila Jamal,1,5,9 Cynthia A. James,5,10 Gall P. Jarvik,11,12 Jennifer B. McCormick,1,13 Tanya N. Nelson,14,15,16,17,18 Kelly E. Ormond,1,19 Heidi L. Rehm,20,21,22 Julie Richer,14,23,24 Emmanuelle Souzeau,25,26 Jason L. Vassy,20,27,28 Jennifer K. Wagner,1,29 and Howard P. Levy1,30,31
...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
- 90% certain benign
- 99% certain benign

Everything else!

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>Condition</th>
<th>VCEP</th>
<th>275</th>
<th>111</th>
<th>121</th>
<th>267</th>
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<td>Myeloid Malignant</td>
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<td>15</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Cardiovascular</td>
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<td>16</td>
<td>18</td>
<td>20</td>
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</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
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
Tumor sequencing is an increasingly common method in cancer research and differs from germline sequencing in fundamental ways.

Tumor Testing strategies
- Tumor-only
- Paired normal and tumor

Pros and Cons of tumor-only vs paired tumor/normal genetic testing


<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inform diagnosis and prognosis</td>
<td>• Inability to distinguish somatic vs germline variants</td>
</tr>
<tr>
<td>• Guide therapeutic decisions for targeted therapies</td>
<td>• Inadequate surrogate for direct germline testing</td>
</tr>
<tr>
<td>• Assess MSI for immunotherapies</td>
<td>• Need for further genetic testing and potential delays in care</td>
</tr>
<tr>
<td></td>
<td>• Increased costs and resources, particularly related to genetic consents and counseling</td>
</tr>
<tr>
<td></td>
<td>• Specialized curation and interpretation by molecular pathologist</td>
</tr>
</tbody>
</table>

Diagram:
- Tumor tissue
- Paired normal and tumor
- Tumor result
- Germline and somatic results

Genetic sequence:
- CGTTACCGAT
- CGGTACCGAT
- CGTTACCGAT
Tumor-normal paired testing and possible outcomes

Mandelker D, Zhang L: The emerging significance of secondary germline testing in cancer genomics. J Pathol 244:610-615, 2018
In 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

Li et al. Genetics in Medicine, 2020
# Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD1, Nazneen Aziz, PhD1,2, Sherrill Balle, PhD3, David Bick, MD4, Soma Das, PhD5, Julieth-Flanb-Foster, PhD1,3, Wayne W. Grody, MD, PhD5,6, Madhuri Hegde, PhD1,7, Elaine Lyon, PhD1, Elaine Spector, PhD1,4, Karl Voelkerding, MD8, and Heidi L. Rehm, PhD10, on behalf of the ACMG Laboratory Quality Assurance Committee

## Special Article

**A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists**

Marilyn M. Li1, Michael Datto2, Eric J. Duncavage3, Shashikant Kulkarni4, Neal I. Lindeman5, Somak Roy6, Apostolia M. Tsimeridou7, Cindy L. Vnencak-Jones8, Daynna J. Wolff9, Anas Younes10, and Marina N. Nikiforova11

## Table: Standards and Guidelines for Sequence Variants

<table>
<thead>
<tr>
<th>Population Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP is too high for disorder (0.50/0.80) or observations in controls inconsistent with variant penetrance</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Multiple lines of computational evidence support a deleterious effect on protein product</td>
<td></td>
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<tr>
<td>Novel missense change at an amino acid residue where a different pathogenic missense change has been observed before in PMD</td>
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<tr>
<td>Some amino acid change in an established pathogenic variant</td>
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<tr>
<td>Predicted null variant in a gene where LOF is a known mechanism of disease</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional Data</th>
<th>Supporting</th>
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<th>Very Strong</th>
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</thead>
<tbody>
<tr>
<td>Well-established functional studies show no deleterious effect on protein product</td>
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<tr>
<td>Missense in gene with low rate of benign variants and pathogenic common</td>
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<tr>
<td>Multifunctional hot spot or well-studied functional domain without benign variation</td>
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<tr>
<td>Well-established functional studies show a deleterious effect on protein product</td>
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</table>

<table>
<thead>
<tr>
<th>Segregation Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Very Strong</th>
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</thead>
<tbody>
<tr>
<td>Non-segregation with disease breast</td>
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<td></td>
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<tr>
<td>Co-segregation with disease in multiple affected family members</td>
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<tr>
<td>Increased segregation data</td>
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<table>
<thead>
<tr>
<th>Onco Data</th>
<th>Supporting</th>
<th>Moderate</th>
<th>Very Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed in tumors with a dominant variant</td>
<td></td>
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<tr>
<td>Observed in tumors with a pathogenic variant</td>
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<tr>
<td>For recessive disorders, detected in a tumor with a pathogenic variant</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Data</th>
<th>Supporting</th>
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</thead>
<tbody>
<tr>
<td>Reproducible source whole exome data + pathogenic</td>
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<td></td>
</tr>
<tr>
<td>Reproducible source whole exome pathogenic</td>
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<td></td>
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<tr>
<td>Patient's phenotype or other highly specific for tumor type</td>
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</tbody>
</table>

**Tier I: Variants of Strong Clinical Significance**
- Therapeutic, prognostic & diagnostic

**Tier II: Variants of Potential Clinical Significance**
- Therapeutic, prognostic & diagnostic

**Tier III: Variants of Unknown Clinical Significance**
- Not observed at a significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases

**Tier IV: Benign or Likely Benign Variants**
- Observed at significant allele frequency in the general or specific subpopulation databases for existing published evidence of cancer association

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**Notes:**
- LB: Likely Benign
- VUS: Variants of Uncertain Significance
- LP: Likely Pathogenic
Why do we care about germline variants that crop up in tumor testing?

• Your patient’s treatment + management could change
  • Eg. parp inhibitors for people with BRCA1-related ovarian cancer

• Risk of additional cancers, cancer recurrence might be much higher than previously appreciated

• Benefits to relatives – prevention and screening!

• Expand our clinical knowledge of cancer syndromes in patients who don’t meet current criteria for germline testing
Implications for Informed Consent

• Patients should be informed that tumor testing could detect germline (heritable) genetic changes

• Germline results should be disclosed because they could influence treatment decisions in patient and risk management in relatives

• Current guidelines suggest that patients should be allowed to opt-out of learning germline results
#3: Returning research results to relatives – when and how?
Questions

• To what extent do researchers have responsibilities to notify at-risk relatives of critically ill or deceased cancer patients?

• What is the most efficient way of doing this in a research setting?
Case

• 6 yo w/bilateral Wilms Tumor
  - Histology: Epithelial highly anaplastic
## Tumor results

<table>
<thead>
<tr>
<th>Alteration</th>
<th>HGVS Nomenclature</th>
<th>Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>MSH6 R1176</em></td>
<td>NM_000179: c.3526A&gt;T; p.Arg1176Ter</td>
<td>45% WGS, 52% WES, 0% RNA</td>
</tr>
<tr>
<td>TP53 R158G</td>
<td>NM_000546: c.472C&gt;G; p.Arg158Gly</td>
<td>76% WGS, 70% WES, 62% RNA</td>
</tr>
<tr>
<td>TP53 C141F</td>
<td>NM_000546: c.422G&gt;T; p.Cys141Phe</td>
<td>3% WGS, 6% WES, 5% RNA</td>
</tr>
<tr>
<td>TP53 R273S</td>
<td>NM_000546: c.817C&gt;A; p.Arg273Ser</td>
<td>10% WGS, 11% WES, 24% RNA</td>
</tr>
<tr>
<td>TP53 R342P</td>
<td>NM_000546: c.1025G&gt;C; p.Arg342Pro</td>
<td>7% WGS, 9% WES, 13% RNA</td>
</tr>
<tr>
<td>SIX1 Q177R</td>
<td>NM_005982: c.530A&gt;G; p.Gln177Arg</td>
<td>81% WGS, 87% WES, 100% RNA</td>
</tr>
</tbody>
</table>

**NOTE:** The TP53 alterations occur in a region of copy neutral LOH, see tumor ploidy.
Germline results

- **NGS Germline**
  - MSH6 R1176* ➔ Lynch Syndrome

<table>
<thead>
<tr>
<th>SINGLE NUCLEOTIDE VARIANTS AND INDELS</th>
<th>HGVS Nomenclature</th>
<th>Allele Frequency</th>
</tr>
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<tbody>
<tr>
<td>MSH6 R1176*</td>
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NOTE: The TP53 alterations occur in a region of copy neutral LOH, see tumor ploidy.
Dominant model: Proband-directed disclosure

• Risk to relatives is disclosed to the proband; who is responsible for informing at-risk relatives

• Relatives must *voluntarily* seek follow-up risk assessment

• Numerous studies show that this is not very effective (Sermijn et al. 2004; Marks et al. 2006; Montgomery et al. 2013; Hampel 2016)

• Family letters do not increase uptake of cascade risk assessment (Dheensa et al. 2017)
Barriers to communication about disease risk
Alternative model: Direct contact w/proband opt-in or out

• Research programs contact relatives directly to notify them about their increased risk and test options
  • Via letters, phone, or an invitation to join a research registry

• Probands usually opt in or out of allowing relatives to be contacted

• Cost-effective; identifies more patients at-risk; access to treatment, and helps avoid unnecessary testing

Nordestegaard et al. 2013; Kerr et al. 2017; Costland et al. 2018
ShareDNA: a smartphone app to facilitate family communication of genetic results

Chethan Jujjavarapu¹, Jeevan Anandasakaran¹, Laura M. Amendola³, Cameron Haas⁴, Elizabeth Zampino², Nora B. Henrikson⁴, Gail P. Jarvik³,⁵ and Sean D. Mooney¹*
In summary, a new riff on a familiar theme...

Courtesy Howard Levy + Yvonne Bombard
Thank you

leila.jamal@nih.gov