Secondary findings after virtual panels: A new frontier in incidental findings

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Disclosure statement

- I am an employee and stockholder of Invitae
Overview

1) Background on Incidental/Secondary findings

2) Utilization of virtual panels

3) Objectives of this study

4) Prevalence of secondary findings on a virtual panel

5) Summary
Background

- ACMG recommendations for reporting secondary findings in diagnostic whole exome or genome sequencing (WES/WGS), independent of indication

- Various studies have estimated the prevalence of secondary findings in apparently unaffected individuals using WES/WGS
  - Published estimates range between 1.0%-6%
Background

- It is now possible to perform diagnostic multigene panel testing on assay platforms that cover hundreds of genes.
  - These are used to generate “virtual panels” based on clinician indication.
Study Objectives

- Use a virtual multigene panel strategy
  - Estimate the overall prevalence of cancer gene pathogenic variants
  - In a population of patients with no known cancer history

- Determine the number of secondary findings by gene

- Assess the clinical actionability of identified gene variants
Cancer gene panel selection

Inclusive cancer gene selection strategy (benefit>risk for gene-variant clinical management)

- ACMG56 cancer-risk genes (23)
- Reviewed literature for cancer-risk genes with:
  - Strong evidence of gene-condition association
  - Clinical management recommendations
    - Surveillance
    - Family cascade testing
    - Circumstances to avoid
- 24 additional genes deemed clinically actionable by a panel of Clinical Geneticists, Genetic Counselors & PhD Scientists

### 47 gene virtual panel

<table>
<thead>
<tr>
<th>Cancer-risk genes</th>
<th>ACMG genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>RB1</td>
</tr>
<tr>
<td>BRCA1</td>
<td>RET</td>
</tr>
<tr>
<td>BRCA2</td>
<td>SDHAF2</td>
</tr>
<tr>
<td>MEN1</td>
<td>SDHB</td>
</tr>
<tr>
<td>MLH1</td>
<td>SDHC</td>
</tr>
<tr>
<td>MSH2</td>
<td>SDHD</td>
</tr>
<tr>
<td>MSH6</td>
<td>STK11</td>
</tr>
<tr>
<td>MUTYH</td>
<td>TP53</td>
</tr>
<tr>
<td>NF2</td>
<td>TSC1</td>
</tr>
<tr>
<td>PMS2</td>
<td>TSC2</td>
</tr>
<tr>
<td>PTEN</td>
<td>VHL</td>
</tr>
<tr>
<td></td>
<td>WT1</td>
</tr>
</tbody>
</table>
Methods

- 3679 patients referred for hereditary cardiovascular multigene panel testing
  - No known personal/family history of cancer

- Reviewed de-identified sequence data, under an IRB-approved protocol, for the 47-gene virtual cancer-risk panel

- Classification of variants from these 47 cancer-risk genes
  - Pathogenic if previously classified at Invitae as pathogenic
  - Novel variants predicted to be pathogenic if variant resulted in a frameshift, nonsense or splice-site disruption predicted to cause loss of function (LOF)
  - Removed known non-pathogenic LOF variants

- Predicted pathogenic variants (PPVs)
Cancer-risk gene PPV prevalence

- Prevalence of ALL cancer gene PPVs in 3769 cardiovascular patients
  - 6% of patients with PPV on virtual panel
  - 2.7% of patients with PPV when limited to ACMG cancer genes

- Positive patients after excluding lower risk variants
  - MUTYH heterozygotes (hets)
  - Low penetrance PPVs in CHEK2, MITF, FH

Cardiovascular Patients with Cancer PPVs

- 6% of patients with PPV on virtual panel
- 2.72% of patients with PPV when limited to ACMG cancer genes
- 2.96% of patients with PPV when limited to ACMG cancer genes
- 1.01% of patients with PPV when limited to ACMG cancer genes

Excluding low risk PPVs
Positive secondary findings by gene

82% of the identified PPVs were in
- ATM
- BRCA1
- BRCA2
- CHEK2
- FH
- MITF
- MUTYH
- NBN
- PALB2
- PMS2

7 patients (3% of positives) had PPVs in two cancer-risk genes.
Management guidelines for cancer genes with most PPVs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer risk</th>
<th>Management recommendations&lt;sup&gt;1,2,3,4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Breast cancer</td>
<td>Annual mammogram and consider breast MRI starting at 40 years</td>
</tr>
<tr>
<td>BRCA1/BRCA2</td>
<td>Breast, ovarian and prostate cancer</td>
<td>Breast screening, RRM, RRSO</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Breast and colon cancer</td>
<td>Annual mammogram and consider breast MRI starting at 40 years old</td>
</tr>
<tr>
<td>FH</td>
<td>Renal cell cancer</td>
<td>Annual abdominal MRI</td>
</tr>
<tr>
<td>MITF</td>
<td>Melanoma, Renal cell cancer</td>
<td>Monthly skin exams, renal ultrasound</td>
</tr>
<tr>
<td>MUTYH (het)</td>
<td>Colon cancer (moderate at most)</td>
<td>Colonoscopy at 40 years old for unaffected proband with colon cancer in 1&lt;sup&gt;st&lt;/sup&gt; degree relative</td>
</tr>
<tr>
<td>NBN</td>
<td>Breast cancer</td>
<td>Annual mammogram and consider breast MRI starting at 40 years old</td>
</tr>
<tr>
<td>PALB2</td>
<td>Breast cancer</td>
<td>Annual mammogram and consider breast MRI starting at 30 years old</td>
</tr>
<tr>
<td>PMS2</td>
<td>Colon and ovarian cancer</td>
<td>Colonoscopy every 1-2 years starting at 20-25 years of age</td>
</tr>
</tbody>
</table>

Factors impacting PPV prevalence estimate

- Secondary findings in only cancer-risk genes estimated at up to 6%
  - Possibly impacted by analyzing larger number of cancer-risk genes
  - Inclusion of variants conferring moderate risk (e.g. MUTYH heterozygotes)

- Prevalence is likely underestimated
  - We did not include novel missense or copy number variants
Summary

- Using a virtual panel strategy we estimate the prevalence of secondary findings for cancer-risk at up to 6% in individuals undergoing hereditary cardiovascular multigene testing.

- Each of the identified secondary finding PPVs is associated with published management guidelines with the potential to impact the clinical care of patients and their family members.

- This study suggests that secondary findings of potential clinical utility could be gleaned from virtual multi-gene panels, a situation not currently addressed by the ACMG 2016 recommendations.
Acknowledgements

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  - Robert Nussbaum, MD, FACMG, FACP

- Poster 2617 – Shan Yang, Cardiovascular risk PPVs in hereditary cancer patients
- Thursday 11am session – Emilie Zoltick, PeopleSeq Consortium early findings
- Friday 9am session – Eden Haverfield, Genetic screening for healthy individuals