Incidental findings in patients referred for family variant testing
COI Disclosure

I am an employee of, and shareholder in, Invitae.
Targeted cascade testing has been the standard practice

- The yield of clinically actionable information with targeted family variant testing (FVT) is high
- Genetic testing is changing quickly
- Increased accessibility of multigene panel testing has coincided with an increase in testing family members with full panels rather than FVT
- The diagnostic yield of testing individuals with family histories of pathogenic variants for additional cancer susceptibility genes is unknown
Objective: To examine the utility of comprehensive panel testing in patients with family histories of pathogenic variants

Clinician-ordered FVT test

Simulated 80 gene panel

GENES TESTED:

<table>
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<tr>
<th>ALK</th>
<th>APC</th>
<th>ATM</th>
<th>AXIN2</th>
<th>BAP1</th>
<th>BARD1</th>
<th>BLM</th>
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<tbody>
<tr>
<td>BMPR1A</td>
<td>BRCA1</td>
<td>BRCA2</td>
<td>BRIP1</td>
<td>CASR</td>
<td>CDC73</td>
<td>CDH1</td>
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<td>CDKN1B</td>
<td>CDKN1C</td>
<td>CDKN2A</td>
<td>CEBPA</td>
<td>CHEK2</td>
<td>DICER1</td>
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<td>DIS3L2</td>
<td>EGFR</td>
<td>EPCAM</td>
<td>FH</td>
<td>FLCN</td>
<td>GATA2</td>
<td>GPC3</td>
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<td>GREM1</td>
<td>HOXB13</td>
<td>HRAS</td>
<td>KIT</td>
<td>MAX</td>
<td>MEN1</td>
<td>MET</td>
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<td>MLH1</td>
<td>MSH2</td>
<td>MSH6</td>
<td>MUTYH</td>
<td>NBN</td>
<td>NF1</td>
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<td>NF2</td>
<td>PALB2</td>
<td>PDGFRA</td>
<td>PHOX2B</td>
<td>PMS2</td>
<td>POLD1</td>
<td>POLE</td>
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<td>PRKAR1A</td>
<td>PTCH1</td>
<td>PTEN</td>
<td>RAD50</td>
<td>RAD51C</td>
<td>RAD51D</td>
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<td>RB1</td>
<td>RECL1</td>
<td>RET</td>
<td>RUNX1</td>
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<td>SDHD</td>
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<td>SMARCA4</td>
<td>SMARCB1</td>
<td>SMARCE1</td>
<td>STK11</td>
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<td>TERC</td>
<td>TERT</td>
<td>TMEM127</td>
<td>TP53</td>
<td>TSC1</td>
<td>TSC2</td>
</tr>
</tbody>
</table>
2593 patients referred for family variant testing Sept ‘15-Jan ‘17

De-identified data for unrequisitioned genes unmasked

Simulated 80 gene panel for all orders

Excluded: VUSes, P/LP variants associated with AR disease only*, increased risk alleles**
* MUTYH hets, VHL c.598C>T
** APC c.3920T>A

Reported variants: Interpreted P/LP (Familial variants and incidental findings)

Clinical and family history field review
*Detailed pedigree and clinic notes not reviewed

Unrequisitioned variants: Interpreted P/LP Predicted* P/LP
* Computationally predicted LOF variants = stop gain, frameshift, indels, splice acceptor/donor site mutations in established LOF genes

Management guideline review
Family variant testing ordering patterns

- 1 gene: 86.3%
- 2 genes: 8.2%
- 3 or more genes: 5.4%
Familial variant test results matched expectations

- 1587 (61.2%) Familial variant absent
- 1006 (38.8%) Familial variant present
Additional variants identified when familial variant **present**

- 1006 orders were positive for the familial variant
- 24 orders (2.4%) were positive for an additional pathogenic/likely pathogenic variant in addition to the familial variant
- 22 of these were identified by the simulated 80 gene panel rather than the clinical order
Additional variants identified when familial variant **absent**

- 1587 orders negative for the familial variant
- 36 orders (2.3%) were negative for the familial variant but positive for an additional pathogenic/likely pathogenic variant
- 32 of these were identified by the simulated 80 gene panel rather than the clinical order
Pathogenic variants identified by simulated panel

- In total 54 cases had P/LP variants which were not requisitioned (2%)
- 89% occurring in clinically actionable genes with published management recommendations
Positive for familial variant and additional finding

CASE 1:

- Caucasian female
- Mother carries pathogenic PALB2 variant
- PALB2 only was ordered

RESULTS:

- Positive for familial PALB2 variant
- Simulated panel identified pathogenic BRCA2 variant: p.Ser2022*

Diagram:

- White/Caucasian
- PALB2 pathogenic variant
- Familial PALB2 pathogenic variant + BRCA2 pathogenic variant
Negative for familial variant positive for additional finding

CASE 2:

- Caucasian female with family history
- Mother with pathogenic CHEK2 variant
- CHEK2 only ordered

RESULTS:

- Negative for familial CHEK2 variant
- Simulated panel identified pathogenic ATM variant: c.3G>A
Limitations

- Selection limited to cases where we were aware of a known familial variant
- Family variant documentation and clinical/family history was limited to free text fields and dependent on clinician’s documentation
- Orders for familial variants of unknown significance were excluded
- Some “second hits” were already known to the clinician and thus were not requisitioned
- Presence of management guidelines was used as a proxy for estimating clinical actionability
A small proportion of cases may have benefited from larger panels

- In 98% of cases, the pathogenic and likely pathogenic variants were detected by familial variant testing.
- In 2% of cases, additional pathogenic or likely pathogenic variants were not identified by family variant testing.
- The majority of unrequisitioned additional findings were in genes with medical management guidelines.
- Most of the time, testing limited to the known familial variant is sufficient, but broader panels should be considered for patients with complex family histories.
Acknowledgments