Utilization of pathogenic mutations beyond BRCA1/2 in breast cancer patients up to 36 months post-testing

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Background

• Management for gene variants outside of \textit{BRCA1/2} have been more recently included in consensus guidelines
  – \textit{CHEK2, PALB2, ATM, RAD51C, RAD50, BARD1, BRIP1, NBN}

• Clinician actions and patient outcomes based on pathogenic variants in these genes are not yet well studied

• We report the results from a multi-site study on clinical utilization of pathogenic germline variants in cancer risk genes other than \textit{BRCA1/2}
Methods

- Retrospectively examined a cohort of 2,184 patients referred for multigene testing
- All academic medical centers
- 21 clinicians contributed de-identified data
Methods

• Ordering clinicians completed a de-identified case report form describing clinical actions recommended and patient follow-up in response to genetic test result

• Some patients were lost to follow-up and answers of “unknown” were permitted
94 (4%) patients were positive for BRCA1/2

157 (7%) were positive for other cancer risk genes
- CHEK2, PALB2, ATM, MUTYH, RAD51C, TP53, MSH6, APC, BRIP1, MSH2, NF1, NBN, PMS2, PTEN
- Variants included: pathogenic, likely pathogenic, and pathogenic low penetrance

80 (4%) had de-identified case report forms
- 79 (98%) female
- 74 (92%) white/Caucasian
- All patients had a personal history of cancer
  • 69 (86%) breast cancer
  • 12 (15%) ovarian cancer
  *one patient with both

4 (0.01%) carried double mutations in non-BRCA genes
Results

- In 85% (68/80) of cases, providers reported changes to either patient or family member medical recommendations.
Results: Proband recommendations

Type of change:

- Imaging (34)
- Surgical changes (16)
  - PALB2, ATM, CDH1, RAD51C, BRIP1, TP53, CHEK2
- Colonoscopies (2)
- Clinical trial (1)
- Pancreatic screening (1)
- Other cancer screening (1)

CHANGES TO PROBAND HEALTHCARE RECOMMENDATIONS (N = 80)

- Personal changes
- No personal changes
- "Other"

- 34% Personal changes
- 61% No personal changes
- 5% "Other"
Results: Proband recommendations

How often did recommendations change for the proband by category?

• High-risk syndromes 80% (8/10)
  - Genes included: APC, MLH1, MSH2, MSH6, PMS2, CDH1, PTEN
  - No changes: PTEN & MSH6
  *will address TP53 separately

• Moderate-risk genes 68% (25/37)
  - Genes included: ATM, CHEK2, PALB2
  - With low-penetrant CHEK2 mutation 63% (27/43)

• Other genes 63% (12/19)
  - BARD1, BRIP1, DICER1, FANCC, FH, MUTYH (het), NBN, NF1, RAD50, RAD51C
Results: Proband recommendations

• Moderate risk genes
  – *PALB2* 69% (9/13)
  – *CHEK2* 63% (12/19)
    • Typical 77% (10/13)
    • Low penetrance 33% (2/6)
  – *ATM* 55% (6/11)
Results: Family recommendations

CHANGES TO FAMILY MEMBER RECOMMENDATIONS BASED ON RESULTS (N = 80)

- Family member recommendations
- No changes for family members
- Other
- Unknown to provider

Type of change:
- Genetic counseling (50)
- Genetic testing (38)
- Imaging (16)
- Surgery (4)
Results: Family recommendations

• High-risk syndromes 80% (8/10)
  - Genes included: APC, MLH1, MSH2, MSH6, PMS2, CDH1, PTEN
  - No changes: 2 MSH6
    *will address TP53 separately

• Moderate-risk genes 76% (28/37)
  - Genes included: ATM, CHEK2, PALB2
  - With low-penetrant CHEK2 mutation 72% (31/43)

• Other genes 53% (10/19)
  - BARD1, BRIP1, DICER1, FANCC, FH, MUTYH (het), NBN, NF1, RAD50, RAD51C
RESULTS

PROVIDERS OPINION: DID TESTING CHANGE PATIENT HEALTH OUTCOMES?

- Yes: 42%
- No: 23%
- Unsure: 35%
## Results: Special considerations

<table>
<thead>
<tr>
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<th>TP53-positive patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Personal changes</td>
</tr>
<tr>
<td><strong>Patient 1</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td>Yes *provider answered other</td>
</tr>
<tr>
<td><strong>Patient 3</strong></td>
<td>No</td>
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<tr>
<td><strong>Patient 4</strong></td>
<td>No</td>
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</tbody>
</table>
This study provides evidence that mutations in cancer genes beyond BRCA1/2 changed clinical management recommendation for a majority of patients (61%) or their family members (66%)

Changes to clinical management varied by the level of cancer risk
• This study provides evidence that pathogenic or likely pathogenic variants in cancer genes beyond BRCA1/2 changed clinical management recommendations for a majority of patients and have already impacted patients’ health outcome.

• Pathogenic or likely pathogenic findings in genes beyond BRCA1/2 have clinical utility in patient care consistent with established management guidelines; however, insurance does not always cover testing for these genes.

• More research is needed to understand barriers to patients following up on medical management recommendations.
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