Assessing the Clinical Validity of Genes Implicated in Hereditary Breast and Ovarian Cancer Susceptibility Using the ClinGen Framework

Bryce A. Seifert¹, Kristy Lee¹, Hermela Shimelis², Rajarshi Ghosh³, Emily Lauer², Natasha T. Strande¹, Ozge Ceyhan-Birsoy⁴, Jonathan S. Berg¹, Sharon E. Plon³, Fergus J. Couch²

Affiliations:
¹University of North Carolina, Chapel Hill, NC
²Mayo Clinic, Rochester, MN
³Pediatrics-Oncology, Baylor College of Medicine, Houston, TX
⁴Partners Laboratory for Molecular Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA
Clinical Validity: What do we do with the information?

When to Consider Multigene Panel Testing

By Andrea Peirce on Thursday, April 23, 2015

Multigene panel testing enables people to learn about not just one but many inherited mutations at once.
The Clinical Genome Resource

ClinGen’s Critical Questions

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

Curated Genomic Knowledge Base
*ClinVar & Other Resources*

Improved Patient Care
ClinGen Hereditary Cancer Working Group

- Paraganglioma/Pheochromocytoma
  - 21 genes

- Pancreatic Cancer
  - 20 genes

- Breast/Ovarian Cancer
  - 34 genes

- Polyposis/Colorectal Cancer
  - 37 genes
Clinical Validity Framework

Five Key Evidence Types

1. Genetic Evidence (probands)
2. Experimental Evidence (functional studies)
3. Publications
4. Time (first clinical publication)
5. Strength of conflicting evidence (contradictory evidence)
### Clinical Validity Summary Matrix

<table>
<thead>
<tr>
<th>Assertion Criteria</th>
<th>Description</th>
<th>Score</th>
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<tbody>
<tr>
<td>Genetic Evidence</td>
<td>Probands from case reports and case-control studies</td>
<td>0-7 points</td>
</tr>
<tr>
<td>Experimental Evidence</td>
<td>Gene-level experimental evidence</td>
<td>0-6 points</td>
</tr>
<tr>
<td>Publications</td>
<td>Quantity of clinical literature</td>
<td>0-5 points</td>
</tr>
<tr>
<td>Time</td>
<td>Years since first clinical publication</td>
<td>0-2 points</td>
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<tr>
<td><strong>Is there valid contradictory evidence?</strong></td>
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<td>6</td>
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Counting all genetic evidence from case-control studies and case reports

- **Genetic Evidence**
- **Publications**
- **Experimental**
- **Time**

### Score Categories:
- **Definitive**
- **Strong**
- **Moderate**
- **Limited**

### Gene Scores:
- **PALB2**
- **BARD1**
- **RECQL**
- **RAD51C**
- **SLX4**
- **RAD51D**
- **RINT1**
- **XRCC2**
- **GEN1**
- **RAD51C**
- **PALB2**
- **BARD1**

### Cancer Types:
- **Breast Cancer**
- **Ovarian Cancer**
Challenges in evaluating Assertion Criteria

• Scoring individual probands may inflate the scores if stringent criteria for pathogenicity (e.g. segregation) are not applied.

• Using only case-control studies establishes a more “conservative” threshold for genetic evidence.
Correcting the Genetic Evidence score for case-control studies reduces the evidence of a gene-disease association.
Conclusions

• Assessing the Mendelian contributions to common diseases requires a hybrid approach to evaluate evidence from probands/kindreds and case-control studies.

• Many genes that are included on hereditary breast cancer panels may have limited clinical validity.

• A systematic method is needed to evaluate the strength of gene-disease associations and provide transparent assessments of clinical validity.
## Acknowledgments

### ClinGen Hereditary Cancer Working Group

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<tr>
<th>Sharon Plon</th>
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<th>Fergus Couch</th>
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<tr>
<td>Matthew Ferber</td>
<td>Rajarshi Ghosh</td>
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<td>Kenneth Offit</td>
<td>Kristy Lee</td>
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<tr>
<td>Katherine Nathanson</td>
<td>Hermela Shimelis</td>
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### ClinGen Gene Curation Working Group

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<tr>
<th>Natasha Strande</th>
<th>Rajarshi Ghosh</th>
<th>Michael Murray</th>
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<tr>
<td>Erin Riggs</td>
<td>Ozge Ceyhan-Birsoy</td>
<td>Julianne O’Daniel</td>
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<tr>
<td>Adam Buchanan</td>
<td>Laura Milko</td>
<td>Erin Ramos</td>
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<tr>
<td>Selina Dwight</td>
<td>Heidi Rehm</td>
<td>Avni Santani</td>
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<tr>
<td>Christa Martin</td>
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