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

Bryce A. Seifert[1], Kristy Lee[1], Hermela Shimelis[2], Rajarshi Ghosh[3], Emily Lauer[2], Natasha T. Strande[1], Ozge Ceyhan-Birsoy[4], Jonathan S. Berg[1], Sharon E. Plon[3], Fergus J. Couch[2]

Affiliations:

[1]University of North Carolina, Chapel Hill, NC

[2]Mayo Clinic, Rochester, MN

[3]Pediatrics-Oncology, Baylor College of Medicine, Houston, TX

[4]Partners Laboratory for Molecular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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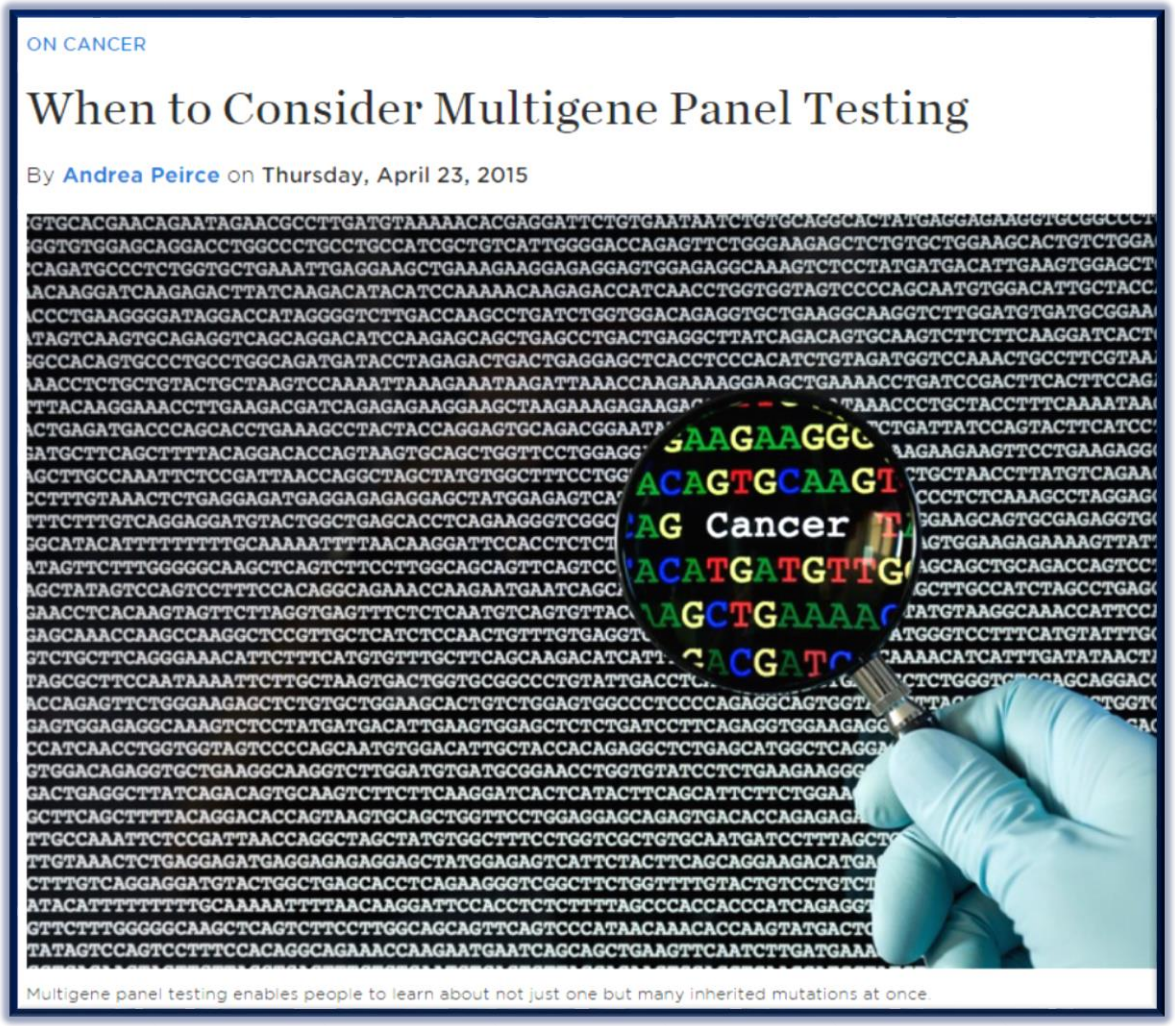
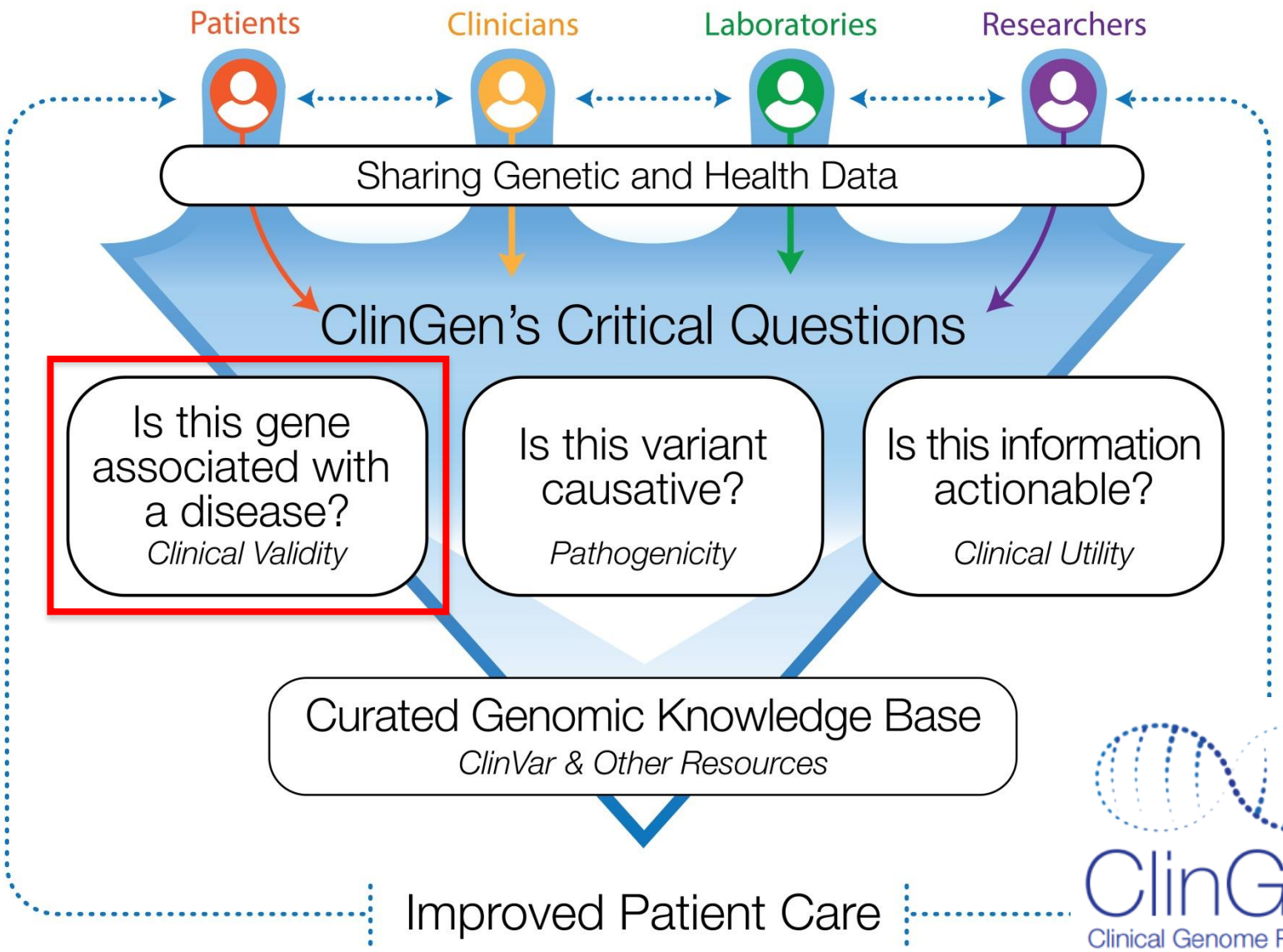
Clinical Validity: What do we do with the information?



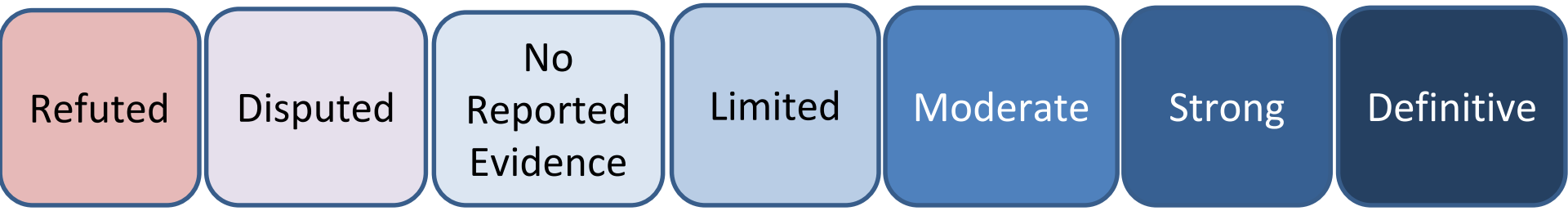
The Clinical Genome Resource



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



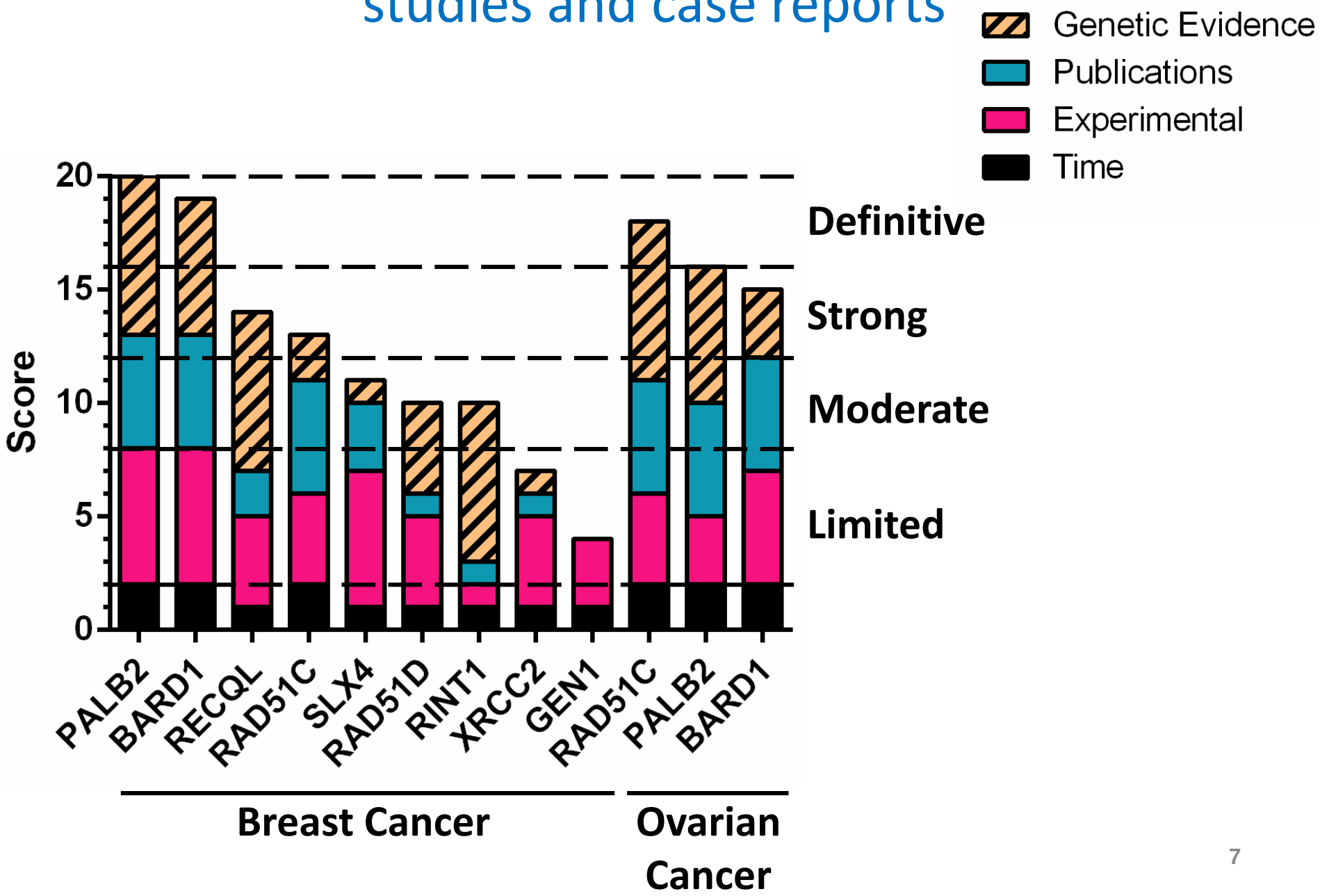
Five Key Evidence Types

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

Assertion Criteria	Description	Score
Genetic Evidence	Probands from case reports and case-control studies	0-7 points
Experimental Evidence	Gene-level experimental evidence	0-6 points
Publications	Quantity of clinical literature	0-5 points
Time	Years since first clinical publication	0-2 points
Is there valid contradictory evidence?		

Counting all genetic evidence from case-control studies and case reports

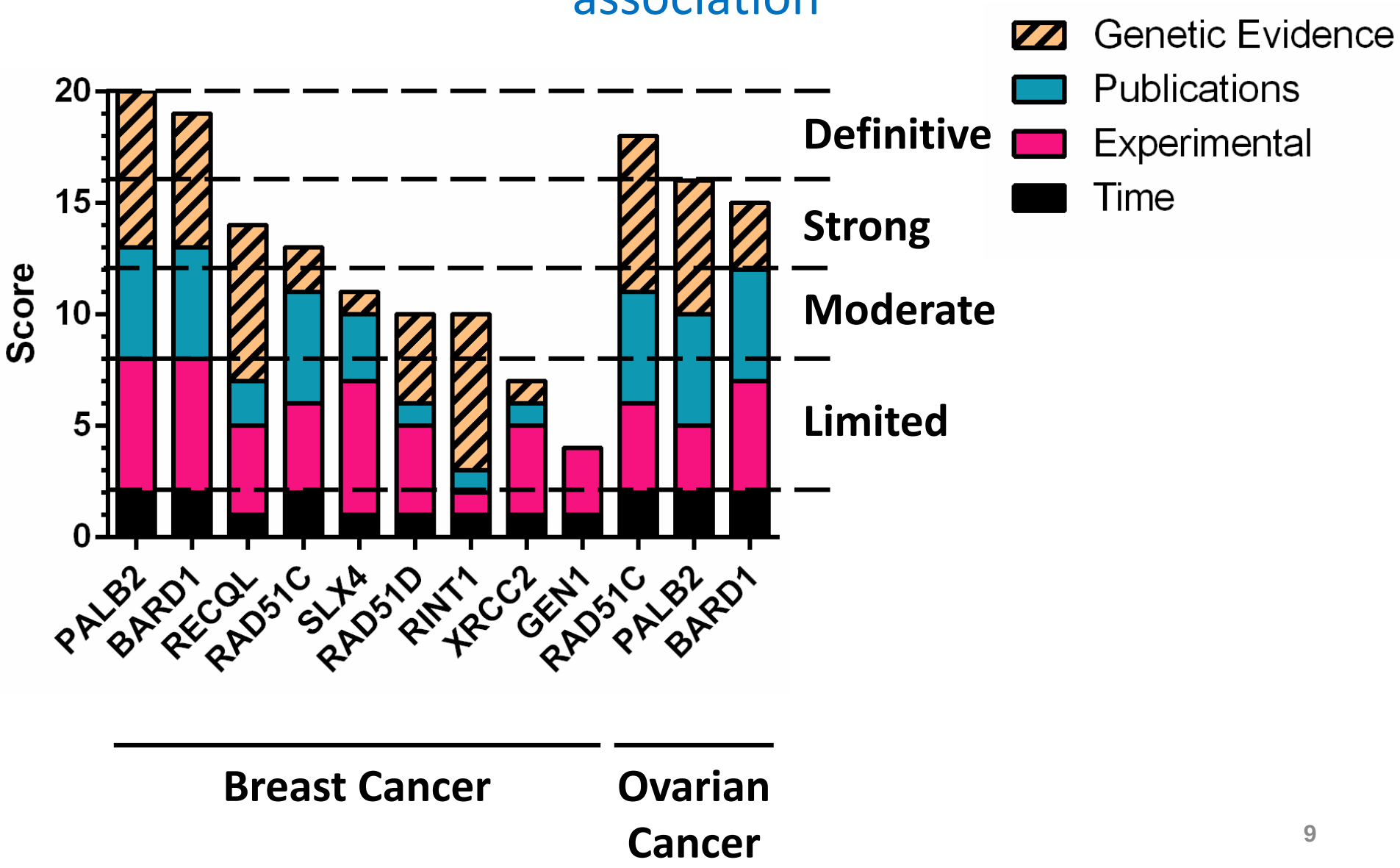


Challenges in evaluating Assertion Criteria

- 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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Hermela Shimelis
Fergus Couch

Booth 421

ClinGen Gene Curation Working Group

Natasha Strande
Erin Riggs
Adam Buchanan
Selina Dwight
Christa Martin
Jonathan Berg
Rajarshi Ghosh
Ozge Ceyhan-Birsoy
Laura Milko
Heidi Rehm
Monica Giovanni
Michael Murray
Julianne O'Daniel
Erin Ramos
Avni Santani
Alan Scott

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL