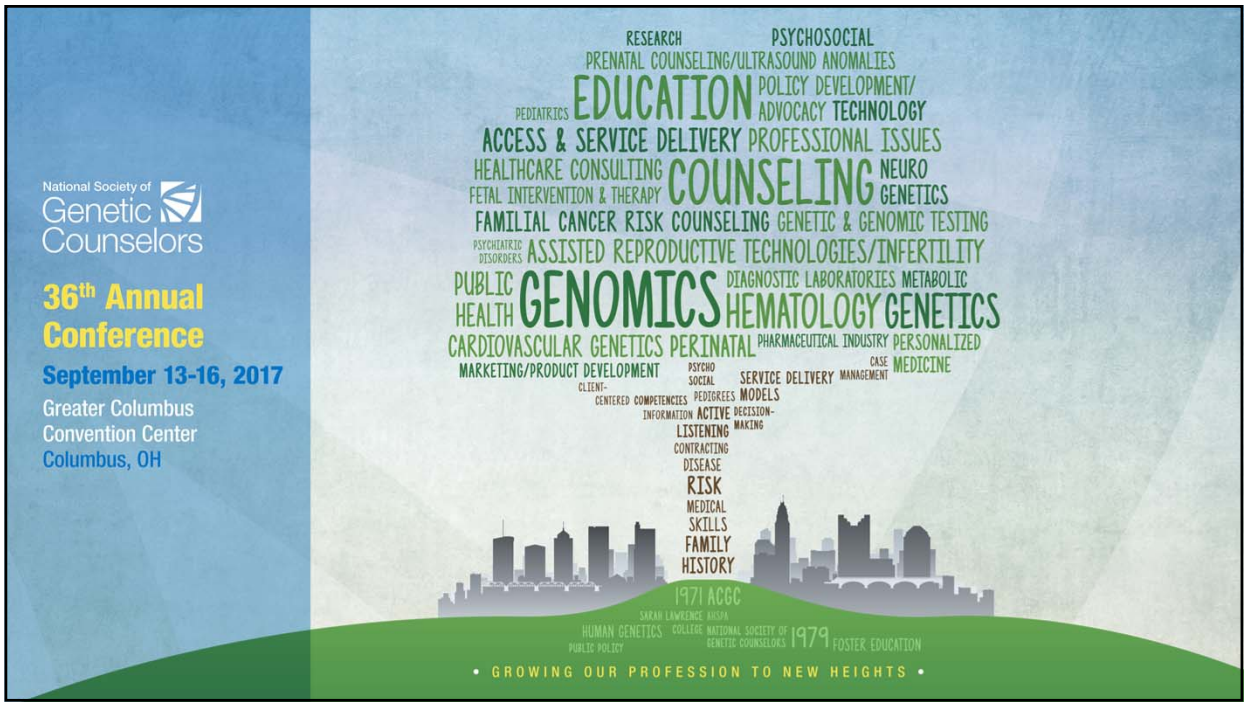

National Society of Genetic Counselors

36th Annual Conference
September 13-16, 2017
Greater Columbus Convention Center
Columbus, OH

Development and Validation of a Residual Risk Score to Predict Breast Cancer Risk in Unaffected Women Negative for Mutations on a Multi-Gene Hereditary Cancer Panel

Elisha Hughes, PhD, Thaddeus Judkins, MS,
Susanne Wagner, PhD, Eric Rosenthal, PhD, Richard Wenstrup, MD,
Jerry S Lanchbury, PhD, Alexander Gutin, PhD

Myriad Genetics, Inc.

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COI Disclosure

I am employed by Myriad Genetics, Inc. and receive salary and stock options as compensation.

Hereditary Breast Cancer Risk

- Unaffected women who have a significant family history of breast cancer are frequently referred for hereditary cancer testing with multi-gene panels.
- Despite being at high familial risk for development of breast cancer, < 10% of such patients carry a clinically actionable variant in a breast cancer-risk gene.
- More than 14% of missing breast cancer heritability is explained by well-established common variants – mainly single-nucleotide polymorphisms (SNPs).[1]
  - Individually, SNPs confer modest breast cancer risk, but together may be associated with genetic susceptibility for breast cancer.

1. Michailidou K et al. *Nat Genet*. 2013;45(4):353-361.

Objective

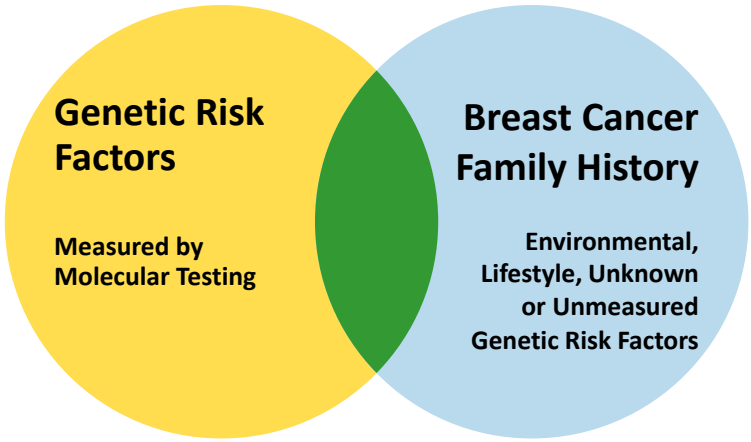
- To expand upon the large body of published evidence for SNPs as breast cancer risk factors through the development and validation of a polygenic residual risk score in large, consecutive cohorts of women of European ancestry who tested negative for mutations in known breast cancer susceptibility genes.

Acknowledgements

- *We are indebted to the authors and researchers who paved the way for our current understanding of polygenic breast cancer susceptibility. Without their contributions, this work would not have been possible.*
  - Easton DF et al., *Nature*. 2007 Jun 28;447(7148):1087-93.
  - Michailidou K et al., *Nat Genet*. 2013 Apr;45(4):353-61.
  - French et al., *Am J Hum Genet*. 2013 Apr 4;92(4):489-503.
  - Mavaddat et al., *J Natl Cancer Inst*. 2015 107(5).
  - Fergus Couch and Celine Vachon (Mayo Clinic)
  - Many Others!

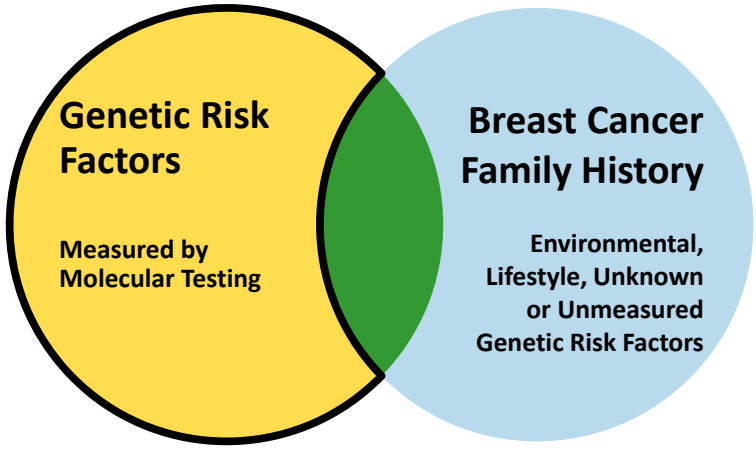
Statistical Methodology

- There are multiple sources of breast cancer risk.
- Some breast cancer risk information is common to molecular genetic factors and family history.



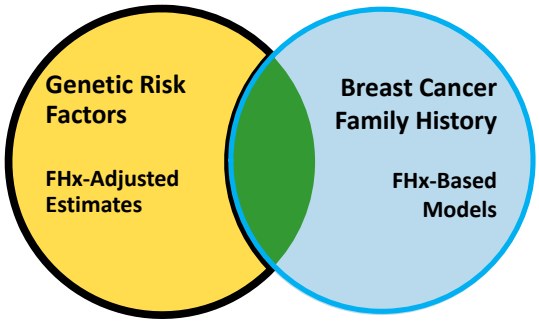
Statistical Methodology

- Multivariate analyses *adjusted* for family history tell us how much breast cancer risk conferred by genetic markers is independent of the risk captured by family history.



Statistical Methodology

- With proper multivariate methodology, unbiased estimates of genetically conferred risk independent of family history (FHx-adjusted estimates) may be obtained from clinically ascertained populations.[1]
- FHx-adjusted estimates are the appropriate values to use in combination with a FHx-based model.



1. Kurian AW, et al. *JCO Precision Oncology*. 2017; DOI: 10.1200/PO.16.00066.

Training Cohort

- Consecutive series of women who had pan-cancer panel genetic testing (Myriad Genetic Laboratories).
  - European descent
  - Negative for mutations in breast cancer-risk genes (*BRCA1, BRCA2, ATM, CDH1, CHEK2, TP53, PTEN, STK11, PALB2, NBN, BARD1*)
  - July 2016 to November 2016
- Clinical information from provider-completed test request forms.

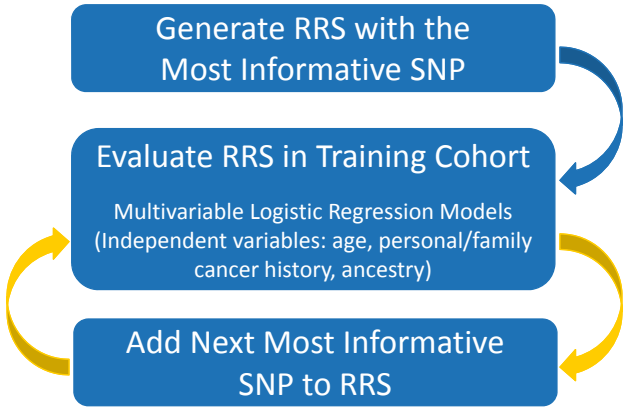
	All Patients	BC Cases
Total Patients	11,771 (100%)	2,089 (18%)
Age at Hereditary Cancer Testing		
Median (Range)	46 (18–84)	54 (22–84)
Tested ≤ 50	61%	7%
Ancestry		
West/North European	8,744 (74%)	1,661 (80%)
Central/East European	2,728 (23%)	385 (18%)
Ashkenazi	299 (3%)	43 (2%)
Cancer History in First Degree Relatives		
No BC or OC	6,367 (54%)	1,349 (65%)
≥1 Breast Cancer (BC)	4,262 (36%)	642 (31%)
≥1 Ovarian Cancer (OC)	1,491 (13%)	132 (6%)

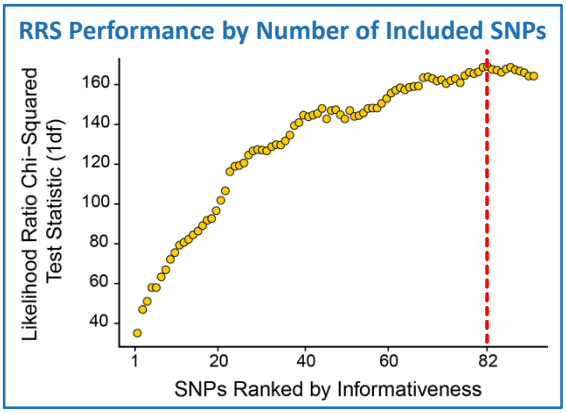
Residual Risk Score (RRS) Development

- Genotypes were determined with next generation sequencing and validated with Sanger sequencing or the IonTorrent Ampliseq platform.
  - 100% concordance
- SNP genotypes were coded as the number of effect alleles (0, 1, or 2).
- SNP coefficients (β_i) were estimated using weighted averaging of log odds ratios from the training cohort, and published studies.[1,2] Weights were inversely proportional to squares of confidence intervals.
- SNP "informativeness" was defines as $2f_i(1-f_i)\beta_i^2$, where f_i is the effect allele frequency for SNP_i.

1. Mavaddat et al. *J Natl Cancer Inst.* 2015;107:djv036. 2. Michailidou et al. *Nat Genet*. 2015;47:373.

Residual Risk Score (RRS) Development





- It was determined that the 82 most informative SNPs provided the optimal RRS.

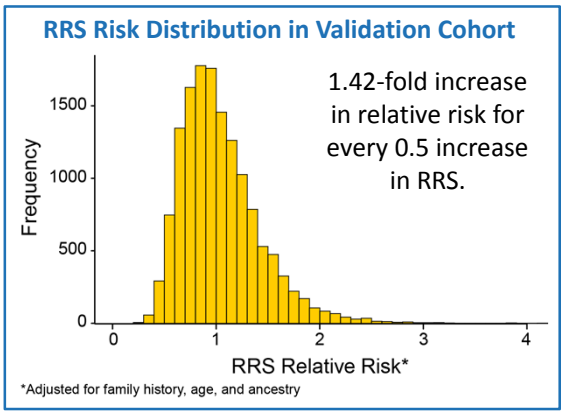
Validation Cohort

- The 82 SNP residual risk score was validated in a consecutive series of women who were negative for mutations in breast cancer risk genes.
  - November 2016 to March 2016
- No substantial differences from the Training Cohort.
- Analysis of the validation cohort was conducted according to a pre-specified Statistical Analysis Plan.

	All Patients	BC Cases
Total Patients	17,205 (100%)	2,917 (17%)
Age at Hereditary Cancer Testing		
Median (Range)	47 (18–84)	54 (22–84)
Tested ≤ 50	61%	7%
Ancestry		
West/North European	1,661 (80%)	2,349 (81%)
Central/East European	4,008 (23%)	509 (17%)
Ashkenazi	475 (3%)	59 (2%)
Cancer History in First Degree Relatives		
No BC or OC	9,507 (55%)	1,919 (66%)
≥1 Breast Cancer (BC)	6,111 (36%)	892 (31%)
≥1 Ovarian Cancer (OC)	2,042 (12%)	160 (5%)

Residual Risk Score (RRS) Validation

- The 82 SNP RRS was strongly associated with personal history of breast cancer in the validation cohort ($p<10^{-50}$).
  - Odds ratio per unit standard deviation of the RRS is 1.42 (95% CI = 1.36-1.49).
- This is lower than a published polygenic risk score (77 SNPs; odds ratio 1.55) that was not adjusted for family history.[1]
- In a model including both scores, only the RRS was significantly associated with breast cancer ($p=3x10^{-5}$ vs $p=0.2$).



1. Mavaddat et al. *J Natl Cancer Inst.* 2015;107:djv036.

Conclusions

- The 82 SNP residual risk score was highly predictive of breast cancer risk in unaffected women of European ancestry with a significant family cancer history who tested negative for germline mutations in known breast cancer risk genes.
- In the validation cohort, the residual risk score significantly outperformed the published polygenic risk score. This may have been due to inclusion of more SNPs, inclusion of the most informative SNPs, and/or refined odds ratio estimates for individual SNPs.
- The validation and clinical implementation of a residual risk score for women at risk for hereditary breast cancer may offer significant potential for the management of high-risk, unaffected women who test negative for monogenic mutations in breast cancer-risk genes.