THE PREDICTIVE POWER OF BREAST CANCER FAMILY HISTORY IN THE CLINIC

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BACKGROUND

- Women with an estimated >20% lifetime risk of breast cancer are candidates for more aggressive clinical management including screening at younger ages, at more frequent intervals, and with more sensitive technologies, i.e. breast MRI.
- Family history is a key component of most models for estimating breast cancer risk, but family history analysis may be insufficient to identify at-risk individuals carrying moderately penetrant pathogenic mutations due to small sibship sizes in contemporary families.
- We utilized pedigree simulation to estimate the probability that a female proband, who is a carrier of a pathogenic mutation conveying a moderate increase in breast cancer risk, will be identified as having at least a 20% lifetime breast cancer risk as determined by the Claus model.[1]

TABLE 1. GENE-SPECIFIC BREAST CANCER RISKS

Age Range	Gene*	Breast Cancer Risk for Mutation Carriers
To age 70	*BRCA1*	Up to 87%
	BRCA2	Up to 84%
	STK11	45 - 50%
To age 80	*TP53*	Greatly increased
	PTEN	77-85%
	CDH1	39 - 52%
	PALB2	20 - 40%
	CHEK2	23 - 48%
	ATM	17 - 52%
	NBN	Up to 30%
	BARD1	Elevated Risk
	BRIP1	10 - 20%, or higher
	RAD51C	Possibly elevated

*Genes may also be associated with other cancer risks. Additional information regarding risks can be found at www.myriadpro.com/myrisk/why-myriad-myrisk/gene-selection/

METHODS

PEDIGREE SIMULATION

- The SIMLA[2] and SLINK[3] pedigree programs were used to simulate 1000 three-generation pedigrees each for 2, 3, 4, or 5-member sibships (Figure 1).
- Two alleles were present at the disease locus (wild-type and mutant) and were simulated according to Mendel's laws for subjects whose parents were in the pedigree, ignoring the possibility of *de novo* mutation and assuming an allele frequency of 0.001.
- The proband was assumed to be a 40-year old female carrying one copy of an autosomal dominant pathogenic mutation.
- Simulated pedigrees were one-sided and limited to either the maternal or paternal side segregating the disease allele (Figure 1).
- Phenotypes were simulated according to age-dependent liability classes modeled from the SEER breast cancer incidence data.[4]

RISK ASSESSMENT OF SIMULATED PEDIGREES

- Resulting pedigrees were assessed by the Claus model to determine the proband's eligibility for modified medical management irrespective of the proband's phenotype (Figure 2).
  - Liability Class I = Generation 3 females 40-49 years of age (although cancer Dx may be younger)
  - Liability Class II = Generation 1 and 2 females > 70 years of age (although cancer Dx may be younger)
  - Liability Class III = All males
- Claus model estimates were not adjusted for the proband's current age, most likely resulting in over-estimation of proband eligibility.

FIGURE 1. SIMLA PEDIGREE MODELS

Three-generational pedigrees were simulated with 2, 3, 4 and 5 offspring per reference couple.

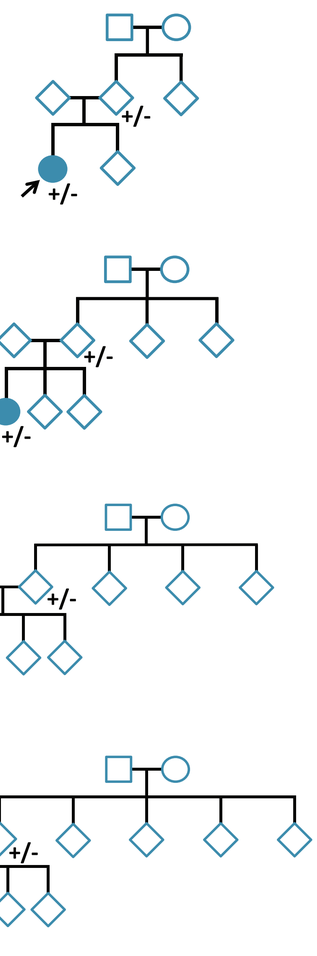
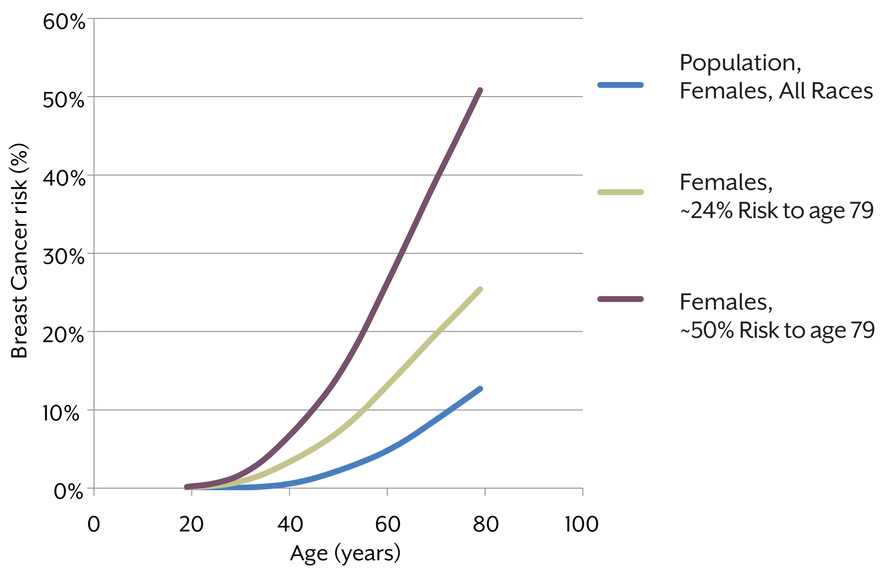


FIGURE 2. TRAIT AND GENOTYPE MODEL PARAMETERS FOR THE SIMULATED PEDIGREE SETS



RESULTS

- The phenotype distributions for Liability Class I and II followed a predicted female breast cancer risk of ~24% and ~50% to age 79.
- Analyses of simulated pedigrees indicate that <9% of female probands, carrying a pathogenic mutation conveying a ~24% risk of breast cancer, would receive modified clinical risk management based only on Claus model risk assessment (Figure 3A).
- Analyses of simulated pedigrees indicate that <25% of female probands, carrying a pathogenic mutation conveying a ~50% risk of breast cancer, would receive modified clinical risk management based only on Claus model risk assessment (Figure 3B).

FIGURE 3A. CLAUS RISK MODEL ELIGIBILITY: RESULTS OF 1000 SIMULATIONS FOR ~24% LIFETIME RISK

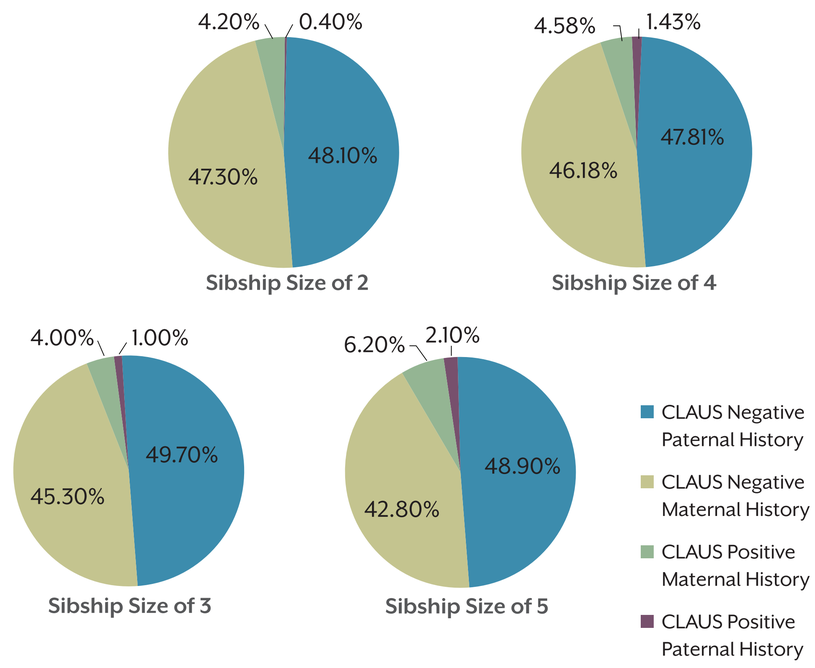
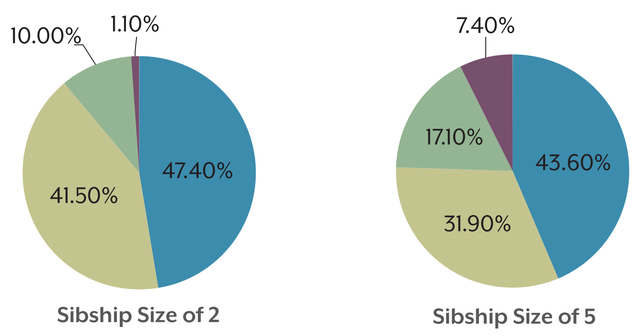


FIGURE 3B. CLAUS RISK MODEL ELIGIBILITY: RESULTS OF 1000 SIMULATIONS FOR ~50% LIFETIME RISK



CONCLUSIONS

- Family analysis alone fails to identify the majority of patients who should receive modified medical management due to the presence of a gene conveying a moderate to high increase in breast cancer risk.
- Simulated analysis of pathogenic mutations of high or moderate penetrance failed to identify >75% and >91% of appropriate patients, respectively.
- Genetic testing is critical for identifying individuals carrying pathogenic mutations in moderate penetrance breast cancer susceptibility genes who would benefit from increased surveillance, as outlined in current professional society guidelines.
- Clinicians should consider broader pan-cancer panel testing when screening the patient as family analysis is insufficient to identify carriers of moderate and high risk cancer genes.
- Clinical diagnostic testing of actual patient samples confirms the results of this pedigree simulation approach.
  - For more information, visit Poster 2441S (Rosenthal et al. Detection of Pathogenic Mutations in Moderate Penetrance Breast Cancer Genes Significantly Increases the Number of Patients Identified as Candidates for Increased Screening).

REFERENCES

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4. Surveillance, Epidemiology and End Results Program, National Cancer Institute (seer.cancer.gov) Dec 10, 2013.

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