



Does *ATM* gene positivity change breast cancer screening recommendations?



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BACKGROUND

- Next generation sequencing technologies have led to plummeting costs and enables the simultaneous analysis of multiple genes (commonly referred to as “multi-gene tests”)
- Multi-gene tests can include high and moderate penetrance genes
- ATM* is a moderate penetrance gene that confers a >20% lifetime risk of breast cancer¹⁻⁶
- Individuals with a ≥20% lifetime risk of breast cancer should consider high risk breast surveillance (annual mammogram and annual breast MRI)⁷
- Carrier frequency for *ATM* mutations in the Caucasian population is 1/100

PURPOSE

- Determine breast cancer risks among unaffected first and second degree relatives of *ATM* mutation carriers
- Determine proportion of *ATM* carriers' relatives for whom surveillance recommendations would be impacted if they were to test positive compared to the proportion who have a ≥20% lifetime risk of breast cancer based solely on their family history.

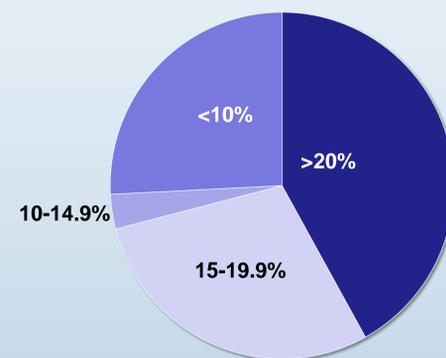
METHODS

- A registry based sample of 18 *ATM* mutation carriers was used to abstract data for female first degree relatives (FDR) and second degree relatives (SDR) who met the following criteria:
 - Age ≤ 80
 - Without a diagnosis of breast cancer
 - Current age recorded
- Breast cancer risk was assessed for each individual through the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)
- Summary statistics were generated based on level of breast cancer risk which is determined by family breast cancer history for relatives of *ATM* mutation carriers

RESULTS

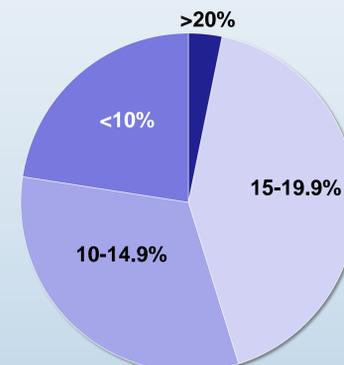
FDR LIFETIME BREAST CANCER RISK ESTIMATES

- 41.9% of FDR had a lifetime breast cancer risk ≥ 20% based on family history alone



SDR LIFETIME BREAST CANCER RISK ESTIMATES

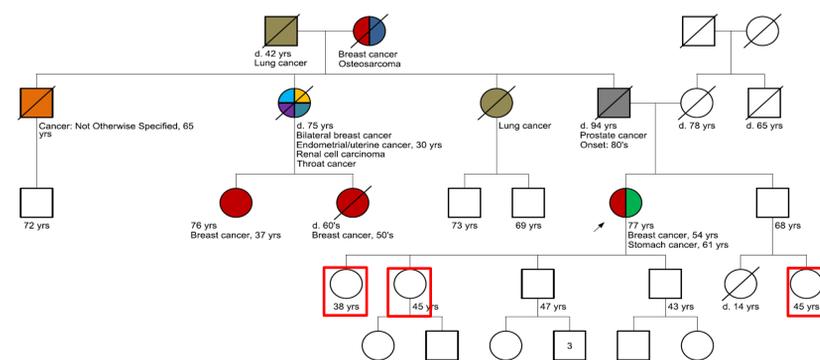
- 3.2% of SDR had a lifetime breast cancer risk ≥ 20% based on family history alone



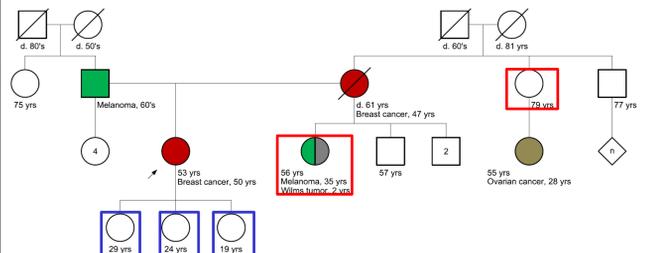
PEDIGREE EXAMPLES

□ = ≥ 20% lifetime breast cancer risk based on family history □ = < 20% lifetime breast cancer risk based on family history

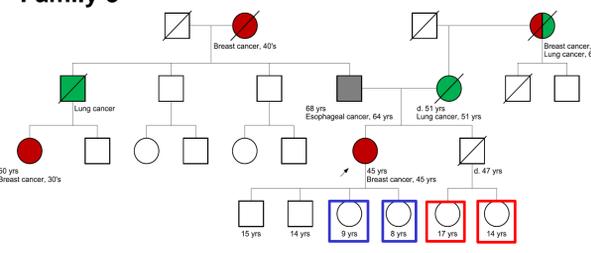
Family 1



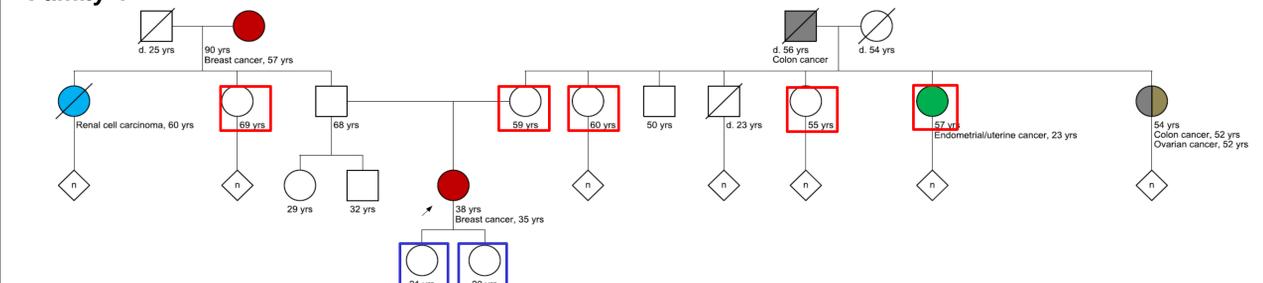
Family 2



Family 3



Family 4



CONCLUSIONS

- A positive result in what is currently defined as a moderate penetrance gene may not impact cancer risk above what would be recommended based on family history alone
- Some relatives who have not undergone genetic testing for a known familial *ATM* mutation may already have a lifetime risk of breast cancer that exceeds 20%, thus results may not alter breast cancer surveillance
- Negative genetic test results for individuals within *ATM* carrier families may not be reassuring for breast cancer risk as there could be additional genetic risk factors influencing cancer risk
- Data suggests cancer risk management based on *ATM* positivity more frequently impacts SDR than FDR
- When testing for moderate penetrance breast cancer genes, family history is an important tool to provide indication for testing and high-risk breast cancer surveillance recommendations

CONSIDERATIONS

- Small sample size (n=18)
- BOADICEA calculates risk to age 80 so some individuals likely had an underestimate of their risk based on their age. Additionally, risk estimation is based only on family history and does not include personal risk factors
- Other considerations, such as reproductive implications, may impact an individual's decision about genetic testing for a familial *ATM* mutation
- Individuals with the high risk *ATM* allele (c.7271T>G) have similar lifetime breast cancer risk to carriers of *BRCA2* mutations, thus predictive testing among at-risk family members would be counseled similar to *BRCA2* carriers

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