The Clinical Impact of Mutations Beyond BRCA1/2 in Breast Cancer Patients

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BACKGROUND

- The clinical impact of germline genetic testing for *BRCA1* and *BRCA2* has been long established.
- Increasingly hereditary cancer testing is expanding to multiple gene panels and consensus guidelines have begun to incorporate recommendations for expanded testing.
- However the impact of findings in genes other than *BRCA 1/2* has yet to be explored.
- We performed a multi-center survey of clinical actions taken in patients presenting for Hereditary Breast and Ovarian Cancer (HBOC) testing and carrying a Pathogenic or Likely Pathogenic (P/LP) germline variant in cancer risk genes other than *BRCA1* or *BRCA2*.

METHODS

- A retrospective review identified 2,184 patients with a personal history consistent with HBOC who had been referred for multigene testing from three major academic medical centers.
- Clinicians completed a short case report form (CRF) describing the clinical actions taken in response to a P/LP finding in a non-*BRCA1/2* cancer risk gene for each positive patient. Some patients were lost to follow-up and answers of unknown were permitted.
- CRFs were available for 90 patients as of our cut off date and these data were de-identified and analyzed.

RESULTS

- In the total series, 157 (7%) of patients were positive for a pathogenic variant in a gene other than *BRCA1/2*
  - 96 (4%) of patients had a *BRCA1/2* pathogenic variant identified
- Surveys were completed for patients with positive germline findings in: *APC, ATM, BARD1, BRIP1, CHEK2, CDH1, DICER1, FANCC, FH, MSH2, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C* and *TP53*

RESULTS

In 81% (73/90) of cases with findings in genes other than *BRCA1/2*, clinicians reported that counseling and/or clinical management recommendations were changed for patients or their family members in response to the genetic test findings.

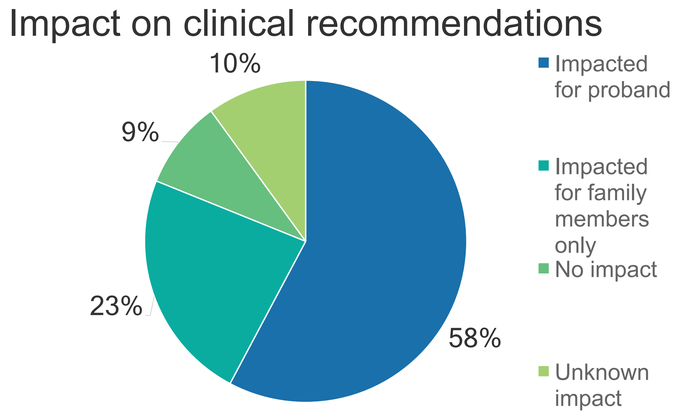

Figure 1.

Specific clinician recommendations

Recommendation	% cases (n=90)
Family member undergo genetic counseling	57
Family member undergo genetic testing	43
Modified of proband's imaging plan	38
Family member modify imaging plan	20
Proband consider (or recommended) surgical prophylaxis	16
Modified proband's oncologic surgical plan	4
Family member consider surgical prophylaxis	4
Modified proband's oncologic medical management	2

RESULTS

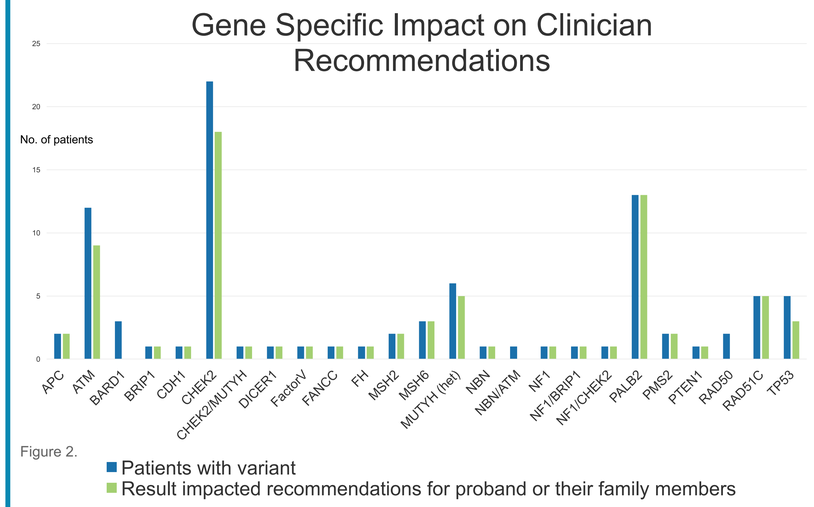

Figure 2.

Variants in ATM, CHEK2, MUTYH, PALB2, RAD51C and TP53 accounted for 70% of the findings in this series and impacted clinical recommendations 84% of the time.

Reasons for results not impacting clinician recommendations included: patient already having bilateral mastectomy prior to genetic testing, variant being classified as Pathogenic Low Penetrance, being adopted or having small family size and patients dying before results counseling

PROVIDER COMMENTS

- "Results lead to enrollment in a clinical trial for PARP inhibitors"
- "We discussed screening for pancreatic cancer"
- "Screening for cancers other than existing malignancy was recommended"
- "We encouraged the patient to see a hematologist"
- "Results may have altered chemotherapy choice"
- "Genetic testing extended this patient's life"

CONCLUSIONS

- Pathogenic variants in genes other than *BRCA*1/2 were identified in 3-11% of patients undergoing germline genetic testing for HBOC.
- This study suggests results from multigene panel testing change management of patients, lead to identification of new carriers, and directly impact treatment decisions.
- An impact on health outcome was reported in almost half of patients including being disease free after undergoing interventional or prophylactic surgery informed by the genetic test result.
- Additional efforts are need to improve implementation of genetic-testing-based management, better understand how results are utilized by family members and explore emerging implications such as impact on chemotherapy choice.

Disclosures: S.M., S.Y., S.L., R.N., and E.E. are stockholders and employees of Invitae.