Comprehensive germline multigene panel testing changes clinical care for patients with breast cancer: Untapped clinical utility and PARP inhibitor trial eligibility.

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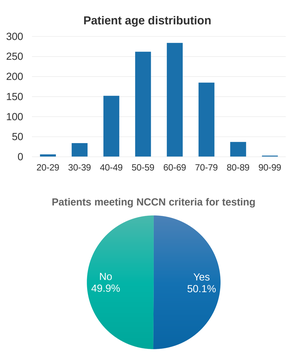
BACKGROUND

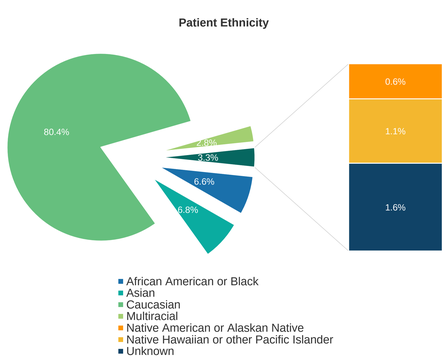
- Guidelines for testing hereditary breast and ovarian cancer (HBOC) patients for BRCA1/2 were established years ago to identify patients with clinically actionable variants and limit the economic burden.
- The cost of genetic testing has plummeted, and the number of breast cancer-risk genes with management guidelines has expanded.
- A community-based registry was established to test all breast cancer patients on a comprehensive multigene panel.
- We report the potential impact of germline results on health outcomes based on clinical decision making and treatment interventions.

METHODS

- An IRB-approved multicenter prospective registry was initiated with 20 community-based and academic breast sites.
- Patients with current or prior breast cancer were tested with an 80-gene panel.
- Clinical information was collected, including pretesting risk assessment and physician management recommendations after test results were received.

PATIENTS





Physician management changes upon receiving genetic testing results

- Pathogenic/likely pathogenic (P/LP) germline mutations were found in 8.7% of patients.
- There was no significant difference in P/LP rate between patients who meet the NCCN testing guidelines and who do not meet the guidelines (p = 0.44).

	Patient with P/LP variants	Patient without P/LP variants
Patients meeting NCCN testing guideline	46 (9.5%)	438 (90.5%)
Patients NOT meeting NCCN testing guidelines	39 (8.1%)	443 (91.9%)

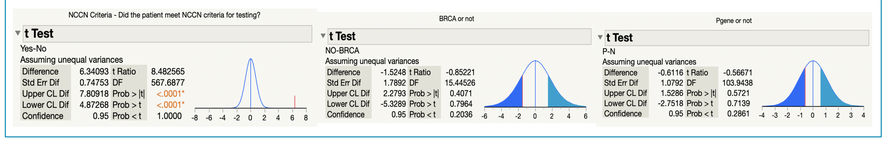
- For 62.4% of patients with a P/LP germline mutations, clinicians reported germline results impacted patients' health outcome, and 69.4% of patients' P/LP results impacted the health outcome of patients' relatives.
- Physician reported impact on patient outcome associated significantly with the presence of P/LP germline findings (p<0.00001).
- There was no significant difference in the clinician reported clinical utility of variants of uncertain significance (VUS) compared to negative results (p=0.49).

Comprehensive Panel Clinical Management & Treatment Implications

- Of all patients with P/LP findings, 88% had variants in cancer-risk genes with established management recommendations and 65% had germline variants conferring eligibility for clinical trials and precision medicine-based cancer treatments, such as PARP inhibitors (e.g. NCT02401347).

	Patients	Variants
With breast cancer management guidelines (ATM*, BRCA1*, BRCA2*, CHEK2*, NBN*, NF1, PALB2*, TP53*)	48 (56.5%)	51 (56.7%)
With cancer management implications (BARD1*, FH, MITF, MSH6*, MUTYH*, PTCH1, RAD50*, RAD51C*, RAD51D*, RB1, RET, VHL)	32 (37.6%)	34 (37.8%)
Evidence of actionability accruing (BLM, DIS3L2, RECQL4)	5 (5.9%)	5 (5.6%)
Total	85	90

- BRCAPRO score is significantly associated with patients meeting NCCN testing guidelines.
- However, there was no significant association between BRCAPRO scores and patients with P/LP findings, whether in BRCA1/2 alone (p=0.41) or for any cancer gene (p=0.57).



CONCLUSIONS

- This study shows that comprehensive panel testing of breast cancer patients impacts physician assessed patient outcomes, and informs changes in surgical treatment strategy, medical therapies and proactive screening.
- The data suggest that BRCAPRO calculators are poor predictors of germline presence of P/LP findings.
- Physicians in this study also demonstrate the ability to discern the clinically actionable value of P/LP mutations from non-actionable VUS, and act accordingly.
- This study suggests multigene panels impact breast cancer patient care by informing implementation of precision medicine treatment interventions, and guiding long-term medical management and preventive surveillance for patients and their family members.