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ASO AUTHOR REFLECTIONS

# ASO Author Reflections: Germline Testing for All Patients With Breast Cancer: Has the Time Finally Come?

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**ABSTRACT** For the young breast cancer population in India, the burden of hereditary breast cancer is not well defined. Moreover, genetic testing criteria (National Comprehensive Cancer Network and Mainstreaming Cancer Genetics (MCG) plus) have never been validated for the Indian population. Therefore, this study tested 236 consecutive breast cancer patients for germline pathogenic mutations using next-generation sequencing and reflex Multiplex Ligation Probe Amplification (MLPA). The findings showed a high prevalence of pathogenic/likely pathogenic (P/LP) mutations (18.64%), with 34% mutations in non BRCA genes. The sensitivity of the testing criteria was inadequate (88.6% for NCCN and 86.36% for MCG plus criteria), reiterating the need to expand the criteria. The uptake of cascade testing was low (10% of eligible previvors), highlighting this as an area of unmet need. Multicentric studies to validate these data and provide further insight into the hereditary cancer burden in India are the need of the hour.

## PAST

India harbors a young breast cancer population versus the West, with a high prevalence of triple-negative breast cancer.[1] Therefore, it is expected that the burden of hereditary breast cancer would be high in India. However, due to a lack of well-conducted population- and hospital-based studies, this burden remains largely undefined. Moreover, with the decline in cost and an easier access to germline genetic testing, the question remains as to which patients would benefit the most from testing. The NCCN criteria are almost universally followed, and the practice at the majority of Indian centers is based on these criteria. However, the criteria have never been formally validated in the Indian setting. Recent Western studies have highlighted the deficiencies of the NCCN criteria when applied to a white Hispanic population and have stressed the need to test all women with breast cancer to better define risk and inform management for the patient as well as her family.[2,3] This study aimed to assess the prevalence of hereditary breast cancer among Indian patients by testing all new consecutive patients and to determine the applicability of the NCCN and Mainstreaming Cancer Genetics (MCG) plus criteria for the Indian population.

## PRESENT

This study recruited 236 women with breast cancer during a 1-year period. Unsurprisingly, most of the women were young (median age, 47 years; 62.9% <50 years of age), and 35% had triple-negative disease. Multigene panel testing by next-generation sequencing followed by reflex Multiplex Ligation Probe Amplification (MLPA) was performed for all the patients. The findings showed an alarmingly high rate of pathogenic/likely pathogenic (P/LP) mutations in this cohort, with 44 (18.64%) of 236 women having a mutation, compared with an average of 5% in the West.

Although BRCA1 and BRCA2 were the two most commonly implicated genes, 34% of the mutations were observed in non-BRCA genes, highlighting the significance



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of multigene panel testing. Testing only by NCCN criteria or MCG plus criteria would have missed five and six patients respectively (sensitivity of 88.6% and 86.36%, respectively). Expanding the criteria to include all patients up to the age of 60 years could potentially increase sensitivity to 97.7%. Practically, by testing 22 additional women, five more mutations could have been detected. Additionally, 10 patients underwent risk-reducing mastectomy, and 7 patients underwent risk-reducing bilateral salpingoophorectomy. Delays related to COVID-19 led to the postponement of many surgeries, which hopefully will be performed in the future.

The study also was able to perform cascade-testing for 16 families and could identify 23 unaffected previvors with mutations. However, acceptance of cascade testing was low (10% of all eligible previvors underwent testing). The results suggest that criteria-based testing is inadequate even in the Indian context and needs expanding.[4] Although testing of more women is likely to increase variant of uncertain significance (VUS) and may put further strain on health care, it needs to be integrated into routine oncologic care for all breast cancer patients.[5] Enough evidence exists to suggest the cost effectiveness of this approach, and with the evidence for poly ADP ribose polymerase (PARP) inhibitors in the adjuvant setting, mutation testing results have a definite potential to impact patient management from the outset.[6]

## FUTURE

This study recruited patients at a tertiary care referral center in North India. Although we found a high prevalence of P/LP mutations in breast cancer patients, a multicentric collaborative study including patients from all parts of India to define the hereditary cancer burden among Indian breast cancer patients and influence policy decisions is the need of the hour. Validation of these data in a larger cohort will provide confidence for clinicians to discuss genetic testing with patients early and integrate it into their treatment plan. More data on the prevalence of P/LP mutations in patients from India older than 65 years are needed to define a testing strategy for this population. Unaffected previvors need special attention, and pretest counseling for family members of affected patients needs to be prioritized.

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