The usefulness of CanAssist breast in the assessment of recurrence risk in patients of ethnic Indian origin

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A B S T R A C T

Accurate recurrence risk assessment in hormone receptor positive, HER2/neu negative breast cancer is critical to plan precise therapy. CanAssist Breast (CAB) assesses recurrence risk based on tumor biology using artificial intelligence-based approach. We report CAB risk assessment correlating with disease outcomes in multiple clinically high- and low-risk subgroups. In this retrospective cohort of 925 patients [median age-54 (22–86)] CAB had hazard ratio (HR) of 3 (1.83–5.21) and 2.5 (1.45–4.29), P = 0.0009) in univariate and multivariate analysis. CAB’s HR in sub-groups with the other determinants of outcome, T2 (HR: 2.79 (1.49–5.25), P = 0.0001); age < 50 (HR: 3.14 (1.39–7), P = 0.0008). Besides application in node-negative patients, CAB’s HR was 2.45 (1.34–4.47), P = 0.0023) in node-positive patients. In clinically low-risk patients (N0 tumors up to 5 cms) (HR: 2.48 (0.79–7.8), P = 0.03) and with luminal-A characteristics (HR: 4.54 (1–19.75), P = 0.004), CAB identified >16% as high-risk with recurrence rates of up to 12%. In clinically high-risk patients (T2N1 tumors (HR: 2.65 (1.31–5.36), P = 0.003; low-risk DMFS: 92.66 ± 1.88) and in women with luminal-B characteristics (HR: 3.24; (1.69–6.22), P < 0.0001; low-risk DMFS: 93.34 ± 1.34)), CAB identified >64% as low-risk. Thus, CAB prognostication was significant in women with clinically low- and high-risk disease. The data imply the use of CAB for providing helpful information to stratify tumors based on biology incorporated with clinical features for Indian patients, which can be extrapolated to regions with similarly characterized patients, South-East Asia.

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1. Introduction

Endocrine therapy after surgical resection of tumor with or without radiotherapy is the standard of care in ER+/HER2-breast cancer disease; unfortunately, if the patient is risk stratified based on clinical risk factors, then almost 60% of them would receive some form of chemotherapy with the benefit of 7–11% in patients aged below 50 and 2–3% in women aged above 50 years over a period of 10 years [1]. To improve up on the chemotherapy benefit breast cancer has been characterised and defined based on genomic expressions by multigene tests with a caveat of not having data for non-Caucasian population and the vast difference of the genomic understanding and interrelationship between tests; besides expertise and costs [2–7]. The need is for a test which is cost-effective, is based on commonly performed platform of IHC, uses few biomarkers from pathways which give information on cancer progression, drug resistance and relapse. When this platform is integrated with a dynamic algorithm based on machine learning for clinical characters of tumor size, node status and grade give a more
holistic scoring system with a wider range of application globally. A test which incorporates this principle is CanAssist Breast (CAB) [8]. A test developed on patients of Indian origin and ethnicity and validated in the same population along with a wider exposure in Caucasian patients. The test has followed the principles of analytical validity and clinical validity in Indian as well as in Caucasian subjects [9,10].

CAB predicts risk of distant recurrence in 5 years from diagnosis by segregating the patients into low- and high-risk groups for distant recurrence; based on this recurrence risk prediction an informed decision can be made on use of systemic anti-cancer therapy for the patient [8,11,12].

The usefulness of the prognostic test lies in its validation in the ‘application population’ delegated within geographical and ethnic limits which can be used in making informed decision. In this real-world analysis of retrospective cohort (median follow-up 67 months, range: 4–132), we assessed the prognostic value of CAB based risk stratification in clinically high-risk patients which included younger patients (≤50), node-positive patients and patients with luminal B characteristics, more commonly seen in Indian and neighbouring South-East Asian countries. In short, CAB has been studied in the re-stratification of ‘clinically high- and low-risk’ ethnic Indian patients with applicability extrapolated to South-East Asian regions.

2. Methods

2.1. Ethics approval

This is the real-world analysis of a non-interventional, anonymized retrospective cohort using archived patient tumor FFPE samples. It was conducted with the approval of the institutional review board (IRB) and/or Ethical and Scientific Committees of all the participating hospitals (both from urbanised and semi-urbanised settings) and with the approval from Bangalore Ethics Committee (ECR/87/Indt/KA/2013).

2.2. Patient selection

Primary surgical FFPE blocks of women diagnosed with stage I-IIIA hormone receptor-positive and HER2/neu disease who had a minimum of 5-year clinical follow-up post-diagnosis or an event at a distant site within 5 years were used. All the patient information and treatment follow-up details such as age, year of diagnosis, type of surgery, clinical parameters, hormone receptor status, treatment regimen, date of recurrence or death were obtained from the hospital. Tumor samples of patients diagnosed between 1997 and 2016 were used. Patients had undergone either mastectomy or breast conserving surgery or lumpectomy. Samples of patients who underwent neoadjuvant chemotherapy were not included.

2.3. Immunohistochemistry

Tumor content of every block was assessed by Haematoxylin and Eosin staining and blocks with ≥30% tumor were used for the study. IHC stainings for ER/PR/HER2 & Ki67 were performed at the ISO/CAP accredited reference laboratory of OncoStem.

2.4. CAB test

CAB uses 5 biomarkers (CD44-a stemness marker; N-Cadherin, pan-Cadherin-cell adhesion and invasion markers; ABCC4 and ABCC11-drug exporter) which are reflective on biology of the tumor beyond proliferation with a focus at on pathways involved in the tumor cell migration from a primary site to a distant site, drug resistance and dormancy in tumor cells which causes metastasis. CAB test predicts risk of recurrence using an artificial intelligence algorithm by incorporation of IHC staining information of these 5 biomarkers along with 3 clinical parameters-tumor size, grade and node-status. IHC staining for 5 CAB biomarkers and grading were carried out as described earlier [8]. Further details are provided as appendix.

Luminal subtype characterization: Luminal A and B subtypes classification was based on Ki-67 IHC levels as described by Tang et al. with cut-off of 14% [13].

2.5. Statistical analyses

Kaplan-Meier (KM) curves (GraphPad 8), univariate hazard ratios (HR) and P-values (log-rank test), multivariate Cox proportional model (MedCalc software) were used to assess the association between CAB risk score and clinical outcomes. Distant Metastasis Free Survival (DMFS) for the risk groups was estimated from KM survival curves.

3. Results

3.1. Cohort description

A cohort of 925 early-stage hormone receptor positive, HER2/neu negative breast cancer patients of Indian ethnic origin was analysed for this current report. Of this cohort, 730 patients were part of the earlier work that showcased a different analysis [10]. The current cohort has 38% of patients aged ≤50 years and 12% ≤ 40 years. The median age at diagnosis in the node-positive and node-negative sub-cohort is similar with 54 (range: 22 to 86) and 55 years (range: 26–85) respectively. Seventy percent of the cohort had stage II diagnosis. Half of the cohort had either node-negative tumors or moderately differentiated tumors (G2). Eighty-three percent of the cohort was positive for both ER and PR. Only 2% of patients had ER-/PR+ tumors. All patients were treated with endocrine therapy for at least five years post-surgery and local therapy. Seventy-nine percent of them had undergone chemo endocrine therapy (Table 1). The median follow-up was for 67 months (range: 4–132).

4. Prognostication by CanAssist Breast

4.1. Unaffected by chemotherapy

Based on KM curves and HR analysis shown in Fig. 1a and Table 2 CanAssist Breast (CAB) provided significant prognostic information (HR: 3 (95% CI, 1.83–5.2), P < 0.0001) in the total cohort (chemo endocrine + endocrine therapy alone) (n = 925) with distinct low-(72%) and high-risk (28%) groups. The DMFS estimate in the low-risk patients from the KM curves at five years from the time of diagnosis was 95 ± 0.84 (Table 2). This was further improved in endocrine therapy alone cohort (n = 196) (HR: 6.5 (95% CI, 1.5–27), P = 0.0008) (Fig. 1b) with DMFS of 97.37 ± 12.9 (Table 2). In the multivariate analysis, CAB risk score had a higher and significant HR of 2.5 (95% CI, 1.45–4.29, P = 0.0009) compared to age and clinical parameters alone (Table 3).

4.2. Independent of tumor anatomical features

Prognostic information provided by CAB was superior to tumor anatomical features, node status and tumor size with higher HR (Fig. 2). Based on node status, HR was 2.32 (1.45–3.72), P = 0.0005 while CAB had a HR of 3 (1.83–5.2), P < 0.0001 (Fig. 2). In the node-negative (HR: 2.56 (0.9–6.7), P = 0.01) and node-positive (HR: 2.45
(1.34–4.47), \( P = 0.0023 \) sub-groups, CAB provided similar prognostic information with similar HRs (Fig. 1c and d, Table 2). Eighty-one percent of the node-negative sub-cohort was stratified as low-risk with a DMFS of 95.8 ± 0.88 (Table 2), while 61% in the node-positive sub-cohort were stratified as low-risk with a DMFS of 92.82 ± 1.62 (Table 2). In node-negative sub-cohort, CAB high-risk patients (19%) were significantly lower (\( P < 0.0001 \)) compared to that of node-positive patients (39%).

Based on tumor size, HR was 1.95 (0.83–4.5, \( P = 0.08 \)) (Fig. 2). In T1 and T2 tumors, CAB had higher HR of 3.34 (0.86–12), \( P < 0.0001 \) and 2.79 (1.49–5.24), \( P = 0.0001 \) (Table 2) respectively.

### 4.3. In young patients (≤50 years)

CAB risk stratification was unaffected by age of the patient at diagnosis. CAB provided significant prognostic value in patient groups aged above (HR: 2.75 (95% CI, 1.3–5.76), \( P = 0.0018 \), low-risk DMFS: 95.77 ± 1) and below 50 years (HR: 3.14 (95% CI, 1.39–7), \( P = 0.0008 \), low-risk DMFS: 94.3 ± 1.4) (Fig. 1e and f) with similar low-risk proportions (above 50, 72%; under 50, 74%) (Table 2).

Additionally, we assessed the prognostic performance of CAB in patients under 50 years with T2/G3 tumors. It was interesting to see out of 69% of patients under 50 who had T2 tumors, CAB segregated 76% of these patients as low risk with DMFS of 94.11 ± 1.7 and HR of

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**Table 1**

| Tumor Size | n (%) | P-value |
|------------|-------|---------|
| T1         | 223 (23) | <0.0001 |
| T2         | 642 (70) | <0.0001 |
| T3         | 60 (7) | <0.0001 |

**Histological grade**

| Grade | n (%) | P-value |
|-------|-------|---------|
| Highly differentiated, G1 | 83 (9) | <0.0001 |
| Moderately differentiated, G2 | 472 (51) | <0.0001 |
| Poorly differentiated, G3 | 370 (40) | <0.0001 |

**ER/PR status**

| Status | n (%) | P-value |
|--------|-------|---------|
| ER+/PR+ | 766 (83) | <0.0001 |
| ER+/PR- | 136 (15) | <0.0001 |
| ER-/PR- | 23 (2) | <0.0001 |

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* Age at diagnosis for 8 patients was unknown.
* For one patient node-status was unknown.
4.4. In clinically low-risk sub-groups

In node-negative patients with tumors up to 5 cms (n = 496), CAB stratified 16% patients as high-risk for recurrence with a low risk DMFS of 96.3 ± 0.9 (Table 2). Finally, we had 41% of patients with grade 3 tumors. In this sub-group CAB had a HR of 2.79 (0.76–10.2, P = 0.09), with 64% identified as low risk (DMFS of 95.45 ± 2.08) (Table 2).

4.4. In clinically low-risk sub-groups

In node-negative patients with tumors up to 5 cms (n = 486), CAB stratified 16% patients as high-risk for recurrence with a low risk DMFS of 96.3 ± 0.9 (Table 2, Fig. 1g). In endocrine therapy alone sub-cohort of these patients with T ≤ 5 cm, N0 tumors (n = 152), 14% were at high risk for recurrence with an event rate of 23% and with an excellent DMFS of 97.66 ± 1.33 in the low-risk group (Figure A1 and Table 2). In the TN1 sub-group (n = 143) CAB identified (P = 0.04, Fig. 1i) 11% of the sub-group as high risk with about 5 times higher recurrence rate compared to the low-risk group (12.5% vs 2.4%) which had a DMFS of 97.62% ± 1.36 (Table 2, Figure A2).

Patients with luminal A characteristics (with low Ki67 expression) are perceived to have a low risk for recurrence. In a sub-cohort of 732 patients, based on Ki67 (14% cut off) and PR IHC, 263 patients (36%) were with Luminal A while 469 (64%) patients were with Luminal B characteristics (Fig. 1h). In a HR of 2.31 (95% CI, 1.37–3.9), P = 0.0072 (Table 2 and Fig. 2). We observed 19% of patients with luminal A characteristics were at high risk by CAB (DMFS = 87.75 ± 4.68), P = 0.004 (Table 2 and Fig. 1i). The study cohort had 76 and 79 patients with luminal A and luminal B characteristics respectively, treated with endocrine therapy alone.

CAB provided weak prognostic value with non-significant segregation in KM analysis (Figure A3) with a DMFS of 95% in patients with luminal A and 92% in patients with luminal B characteristics (P = 0.5) (Figure A3). While in the patients treated with endocrine therapy alone, CAB provided superior and significant prognostic value (P = 0.0004) (Figure A4). CAB identified 14% of this endocrine therapy alone treated patients with luminal A characteristics as high-risk with 27% event rates (P < 0.0001) (Figure A5).

4.5. Prognostication in clinically high-risk patients

Using CAB based stratification we identified 74% (P < 0.0001) (Fig. 1) of patients with luminal B characteristics as low risk for distant recurrence (DMFS = 93.34 ± 1.34) (Table 2) and 26% as high-risk with DMFS of 79.65 ± 3.63 (Table 2) and HR of 3.24 (1.69–6.22) (Fig. 2).

In patients with T2N1 tumors CAB had a HR of 2.65 (1.31–5.36) (P = 0.003) (Figs. 2 and 1k) with 64% as low-risk with a DMFS of 92.66 ± 1.88 (Table 2).

5. Discussion

The basic concept of medical care today has undergone a change which is now based on the principles of personalised, predictable, preventive and participatory (P4) [14]; these principles are more applicable in cancer medicine more so in breast cancer and well summarised by multigene and multiparametric testing widely adapted in North America and Europe for prognostication of patients as well as in predictability of use of type of drugs. However, these tests have not been well adopted in a low- and middle-income countries more so, coming in from Asia. There are multiple reasons for this, including that these tests have not been validated clinically and analytically in ethnic subjects. The Indian council of Medical Research does not recommend the use of ‘multigene’ tests for prognostication in breast cancer due to lack of validation on Indian patients [15]. CanAssist Breast (CAB) was developed for bridging this gap for Asian ethnic women as a well validated and cost-effective test. Moreover, the test had 83% concordance with Oncotype DX in selecting patients at low risk of recurrence who can avoid systemic therapy despite the fact that CAB uses biomarkers which are different to that of Oncotype DX [12]. Thus, the molecular markers of CAB enable disease prognostication beyond the standard clinical parameters and markers of
proliferation, hormonal indices. The cost effectiveness analysis showed that with CanAssist Breast there is a savings of 41% on expenditure incurred due to chemotherapy compared to expenses in the absence of a prognostic test. This test has been used in good number of breast cancer patients over a period of last 5 years [10,11].

The most important use of prognostic tests is aiding in treatment decision of ‘clinically high-and low-risk’ patients since emerging evidence suggests that while clinical parameters are valuable to predict prognosis, are limited by the lack of informative correlation with tumor biology [8,10,16]. In this manuscript, we specifically showcase the usefulness of CAB in segregating the ‘clinically’ high- and low-risk patients seen frequently in South Asia in an extended dataset. Studies have shown that the disease strikes Asian women in premenopausal age with a median age at 50 [17–19]. Disease at young age is often aggressive and considered to be high risk with high grade tumors leading to treatment with chemotherapy [20–23]. However, we believe that ‘tumor biology’ plays a paramount role in cancer recurrence and hence assessed the performance of CAB in young patients (<50 years). Thirty eight percent of patients in this cohort was under and equal to 50 years. CAB stratified about a third of them as low risk for cancer recurrence and hence assessed the performance of CAB in young patients (<50 years). CAB stratified a third of them as low risk for cancer recurrence with 94% DMFS (P < 0.0008). Additionally, young age coupled with further high-risk features like T2/G3/N1 tumors makes ‘prescribing or not prescribing’ chemotherapy decision even more difficult. It was encouraging to note 76% of young patients with T2 tumors (69% of ≤ 50 sub-cohort) were low risk by CAB with 3 times lower recurrence rates (5.9% versus 16.9%) than high-risk patients. Of these young patients with N1 disease (34%), 66% patients were stratified as low risk with half the recurrence rates (8.7% versus 17.5%) (Appendix Table 1), compared to high-risk patients. Finally, of the 41% of this under 50 years sub-cohort with grade 3 tumors, 64% of them were low risk for cancer recurrence with recurrence rates of 4.5% as against 11.5% in high-risk patients by CAB. This data showed CAB was indeed able to find the ‘low-risk’ patients with lower recurrence rates amongst the ‘clinically high-risk’ patients. It is notable here, that many of these young patients had been treated with chemo endocrine therapy. We agree that this data would have been even more robust with the same patients treated with endocrine therapy alone. Since this an ambidirectional study and due to unavailability of prognostic tests, the number of patients treated without chemotherapy was less (~10%) in the current cohort. Nevertheless, this data implies that risk stratification by CAB in these ‘clinically high-risk’ patients could help to avoid chemotherapy in young patients who do not wish to take it for various reasons like fertility preservation or co-morbidities. We hope to do a prospective randomized trial in future to further substantiate the usefulness of CAB in this group. We also have shown similar performance of CAB in an ethnically different patients from Europe (under review).

Another important issue in managing cancer treatment is preventing under treatment of ‘clinically low-risk’ patients ie patients with small, node-negative tumors who are typically spared of chemotherapy based on clinical parameters alone. We analysed performance of CAB in these clinically low-risk patients to assess if CAB can identify a subset of patients with high-risk of recurrence based on ‘tumor biology’. Of the 52% patients who belong to T1/T2 N0 category, CAB stratified 16% as ‘high risk’ with a HR of 2.48 (95% CI, 0.79–7.8, P = 0.03) showing CAB was able to find the high-risk patients with aggressive tumor biology who otherwise could be

Fig. 2. Hazard ratios by Univariate log-rank test for distant recurrence. Hazard ratios (HR) for age, across clinical parameters-tumor size, node status; luminal sub-types are shown. HRs for CanAssist Breast risk score across various clinically high-risk sub-groups is also shown. HR above 2 is considered significant. The horizontal lines represent the 95% confidence interval.
missed. Based on the limited data on 31% of endocrine therapy alone treated patients in this category, we see that 14% of the high-risk patients had increased recurrence rates of 23% within five years of diagnosis. This data from endocrine therapy alone patients substantiates CAB is indeed assessing tumor biology beyond clinical parameters and is thus helpful in finding the correct set of patients who would benefit from taking chemotherapy.

Treatment planning based on luminal A/B characteristics is a widely adopted approach. Comparison of CAB based risk stratification with that based on luminal A and B features showed CAB is more accurate in assessing the risk of recurrence. Luminal B patients categorised based on inputs from ER, PR, HER2 and Ki 67, are perceived to have a high risk of recurrence [24]. In these high-risk patients with luminal B characteristics CAB found significant number (74%) of patients as low-risk and 19% of patients with luminal-A characteristics with a high risk of recurrence. CAB uses 5 biomarkers reflective of aggressiveness of the tumor regarding spread of tumor cells from primary to the secondary site and does not use ER, PR, HER2 and Ki 67 in its algorithm. This data in luminal subtypes showcases the added benefit of CAB biomarkers in assessing tumor biology beyond proliferation markers.

Finally, how is the risk stratification beneficial to clinician or patient especially in clinically high-risk patients? Recently concluded monarchE trial showed ‘clinically high-risk’ patients benefit from CDK4/6 inhibitors in their treatment beyond chemotherapy [25]. While this data is relatively new and extended follow up will substantiate the benefit further. The clinical high-risk category used in the monarchE study was based on tumor size, node, Ki67 and grade. CAB segregated (HR-2.44 (1.2–4.94) (Fig. 2) only 47% of these ‘clinically high-risk patients’ as high-risk with the remaining 53% as low-risk (P = 0.016) (Fig. 1) with a DMFS of 92.87 ± 2.17 (Table 2) which is equivalent to the DMFS of the arm of high-risk patients who received CDK4/6 inhibitors of this trial. In this context, CAB seems to help identify a subset of these ‘clinically high-risk’ patients as ‘prognostically high-risk’ based on tumor biology who will benefit from CDK inhibitor therapy. Patient selection for any drug is an important factor to balance the benefit to toxicity aspects. Keeping this in mind, we, therefore, think that CAB based risk stratification is certainly useful in patient selection for additional targeted drugs in first line adjuvant settings.

6. Conclusion

The strength of the study is the well-balanced cohort representing the real-world ethnic Indian patient demographics and tumor characteristics, with a good representation of young (≤50 years) and women with node-positive tumors which is extrapolatable to South-East Asia. The limitations of the study are the mixed cohort of patients treated with chemoendocrine and endocrine alone, lack of higher proportion of chemotherapy untreated patients, lack of data on 10-year follow-up and lack of chemotherapy benefit predictive ability. Another limitation of the study is the lack of validation of CAB in a prospective setting. We recognize the importance of prospective data and have initiated validation of CAB in samples from a prospective randomized clinical trial to overcome this.

CAB thus provided sufficient and significant molecular prognostic information based on tumor biology for choosing the HR+/HER2 negative early-stage breast cancer patients who do not require chemotherapy. CAB’s prognostic information was clinically meaningful and superior in clinically low-risk and high-risk patients, young patients, and patients with node-positive tumors.

Author contributions

MB conceived the idea. AG analysed the data and performed statistical analyses. MB and AG interpreted the data, drafted the manuscript. MB, AG and GS reviewed the manuscript. CP was involved in data acquisition. MA and NK performed all the histopathological analysis. DC, AM, SP, GS, AB, SK, DG, RA were involved in patient sample and clinical data acquisition. All authors read and approved the final manuscript.

Declaration of competing interest

S.P. Somashekhar, MD and G.S. Bhattacharyya, MD report of receiving fees for the advisory role from OncoStem Diagnostics. All other authors have no other competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.007.

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References

[1] Early breast cancer trialists’ collaborative group polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930–42.
[2] PaiK S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351(27): 2817–26.
[3] Chia S, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype test for prognosis and prediction of benefit from adjuvant tamoxifen. Clin Canc Res 2012;18: 4465–72.
[4] Veer LJ, Dai H, Vijver MJ, et al. Gene expression profiling predicts clinical outcomes of breast cancer. Nature 2002;415:530–6.
[5] Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Canc Res 2011;17: 6012–20.
[6] Varga Z, Sinn P, Seidman AD. Summary of head-to-head comparisons of patient risk classifications by the 21-gene Recurrence Score® (RS) assay and other genomic assays for early breast cancer. Int J Canc 2019;145:882–93.
[7] Bartlett J, Bayani J, Marshall A, Dunn JA, et al. Comparing breast cancer multi-parameter tests in the OPTIMA prelim trial: no test is more equal than the others. J Natl Cancer Inst: J Natl Cancer Inst 2016;108(9).
[8] RamKumar C, Buturovic L, Malpani S, et al. Development of a novel proteomic risk-classifier for prognostication of patients with early-stage hormone receptor-positive breast cancer. Biomark Insights 2018;13:1–9.
[9] Atteluri AK, Prakash C, Aparna G, et al. Analytical validation of CanAssist-Breast: an immunohistochemistry based prognostic test for hormone receptor positive breast cancer patients. BMC Canc 2019;19:249–58.
[10] Bakre MM, Ramkumar C, Atteluri AK, et al. Clinical validation of an immunohistochemistry-based CanAssist-Breast test for distant recurrence prediction in hormone receptor positive breast cancer patients. Cancer Med 2019;8:1755–64.
Sankaran S, Dixit JB, Prakash SVC, et al. CanAssist breast impacting clinical treatment decisions in early-stage HR+ breast cancer patients: Indian scenario. Indian J of Sur Oncology 2019. https://doi.org/10.1007/s13193-019-01014-4.

Sengupta AK, Gunda A, Malpani S, et al. Comparison of breast cancer prognostic tests CanAssist Breast and Oncotype DX. Cancer Med 2020:1–9. https://doi.org/10.1002/cam4.1395.

Tang P, Tse GM. Immunohistochemical surrogates for molecular classification of breast carcinoma luminal subtyping. Arch Pathol Lab Med 2016;140(8):806–14.

Tang P, Tse GM. Immunohistochemical surrogates for molecular classification of breast carcinoma luminal subtyping. Arch Pathol Lab Med 2016;140(8):806–14.

Leroy Hood, Stephen H. Friend Predictive, personalized, preventive, participatory (P4) cancer medicine. Nat Rev Clin Oncol 2011;8(3):184–7.

Hudis AC biology before anatomy in early breast cancer—precisely the point. N Engl J Med 2015;373(21):2079–208.

Kim Y, Yoo Keun-Young, Marc T, et al. Goodman differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. Asian Pac J Cancer Prev APJCP 2015;16(7):2857–70.

Malvia S, Appalaraju R, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia-Pacific. J Clin Oncol 2017;13(14):289–95.

Agarwal G, Pradeep PV, Agarwal A, Yip CH, Cheung PSY. Spectrum of breast cancer in Asian women. World J Surg 2007;31(5):1031–104.

Leong Stanley PL, Shen Zhen-Zhou, Liu Tse-Jia, et al. Is breast cancer the same disease in asian and western countries? World J Surg 2010;34(10):2308–24.

Dubsky PC, Gnant MF, Taucher S, et al. Young age as an independent adverse prognostic factor in premenopausal patients with breast cancer. Clin Breast Canc 2002;3(1):65–72.

Chung M, Chang HR, Bland KI, Wanebo HJ. Younger women with breast carcinoma have a poorer prognosis than older women. Cancer 1996;77:97–103.

Fan L, Goiss PE. Wegplk KS current status and future projections of breast cancer in Asia. Breast Care 2015;10(6):372–8.

Felipe A, Dimitrios Z, Ivana BS, et al. Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. J Clin Oncol 2014;32(25):2794–803.

Johnston SRD, Heerbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 2020;38(34):3987–98.