Should we perform gene expression profiling in all patients with early luminal breast cancers?

Dr Geeta Kadayaprath MS FRCS
Director, Breast Surgical Oncology
Max Institute of Cancer Care
Max Hospitals Patparganj, Vaishali, Noida

PREREQUISITES OF A ROBUST GENOMIC TEST

Clinical Validation

- The test should be validated in a cohort independent of the training set and should not be used in a patient population in which the test was not validated unless re-validation is performed
- Determining the target population

Clinical Validation

- Assessing the effect on clinical outcome between the different test outcome groups.
- Since the utility of genomic testing is aimed at guiding decisions regarding chemotherapy, a predictive test able to predict which patients will benefit from chemotherapy is more useful than a solely prognostic test

Clinical Utility

- Applying the test should shift the indication of chemotherapy compared to indications based on traditional parameters.
- The assay should add value

Economic Value

The cost of the test should be justified by its clinical and health benefits, and the reduction in costs by reducing adjuvant therapy use

Clinicians’ Dilemma

- How to use these tests appropriately
- The utility of these tests in different patient populations
- How to best incorporate these tests into daily use.
- Which test is most appropriate to use
- Whether one test has any advantages over another.

What is the basis for choosing a test?

information that is provided (or not provided) with each specific test.

- Prognostic Tests-tests providing information that is ***prognostic***—that is, provide information about the natural history of disease (eg, risk of recurrence within 5 years)

- Predictive Tests- tests providing information that is ***predictive***—that is, providing information on the likely outcome for a specific treatment or intervention (eg,chemotherapy or

Oncotype Dx

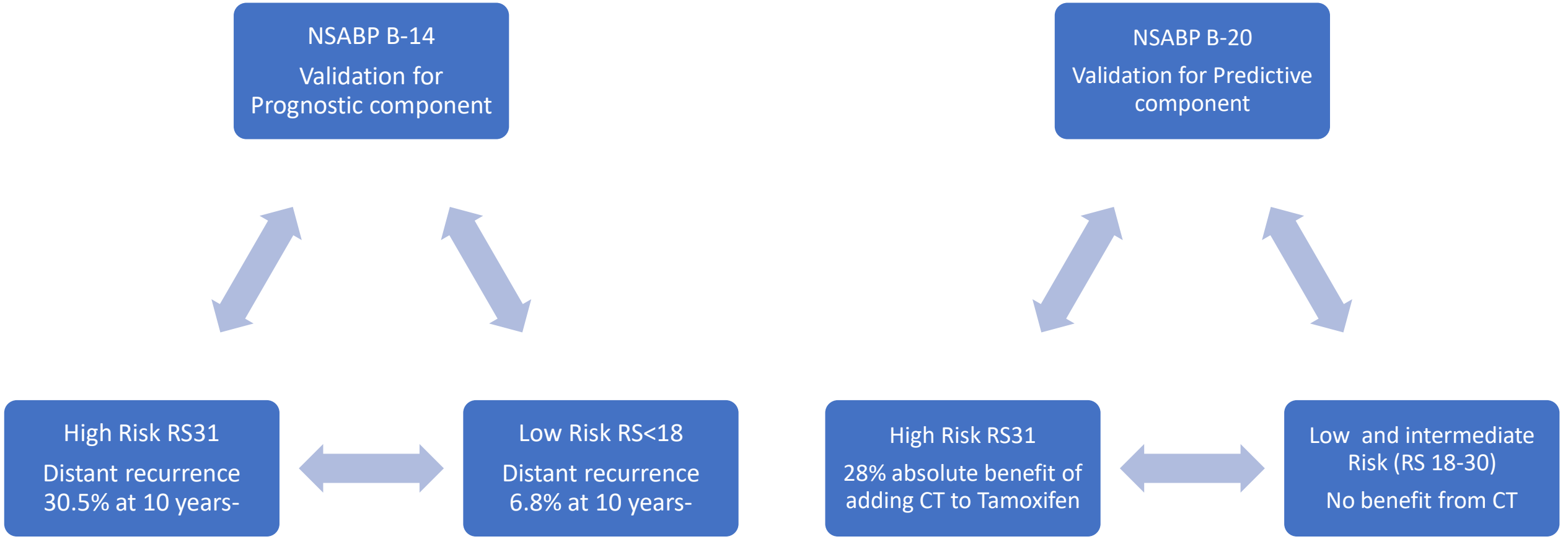
- 16 breast cancer related genes (including those involved in estrogen signaling and proliferation) as well as 5 reference genes.
- The assay reports a recurrence score (RS), which ranges from 0 to 1[illegible] pla[illegible]f 3

Low Risk (RS 0-17)

Intermediate risk (RS 18-30)

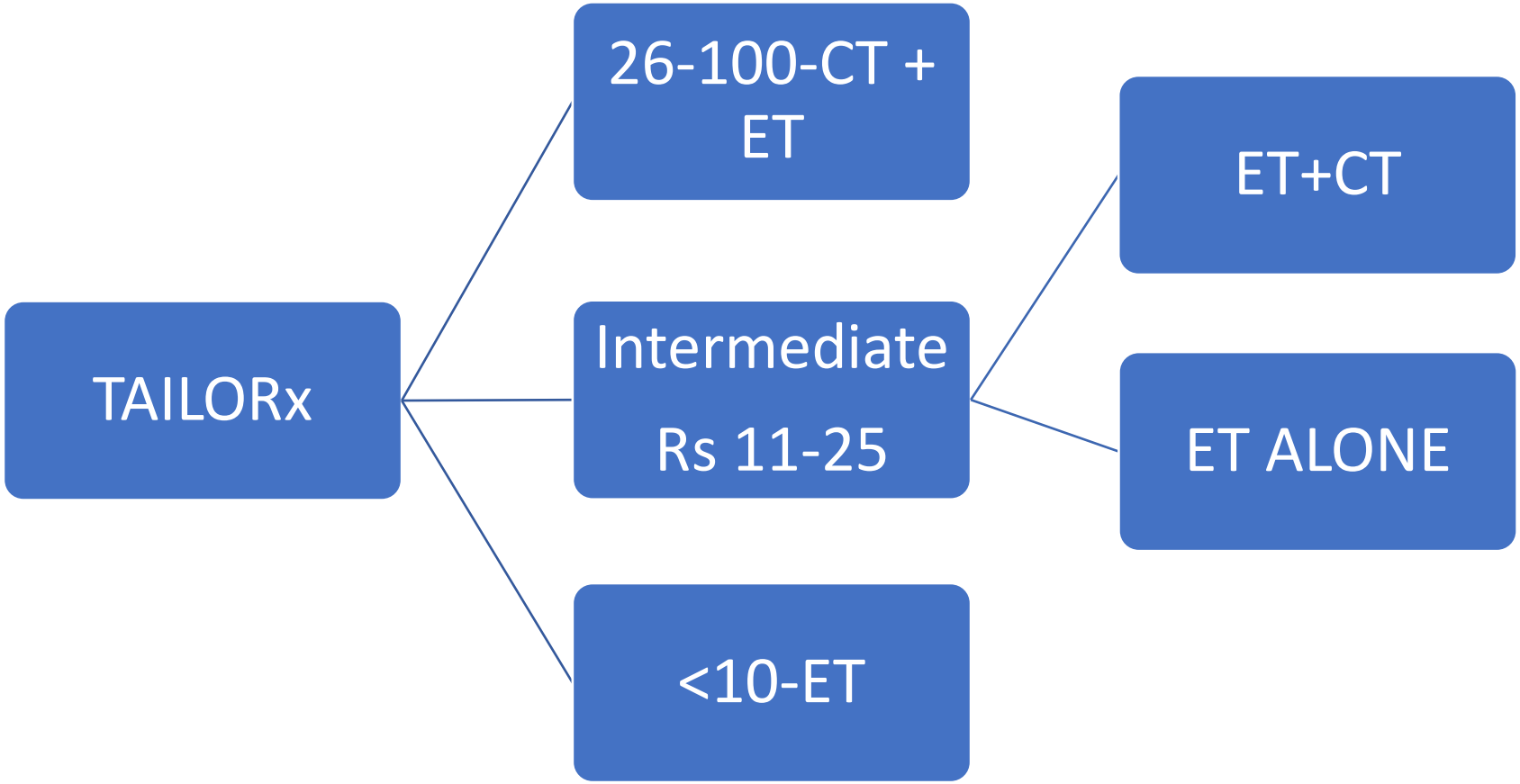
High risk (RS 31-100)

The resultant score is both prognostic for distant recurrence at 10 years and predictive for chemotherapy benefit.



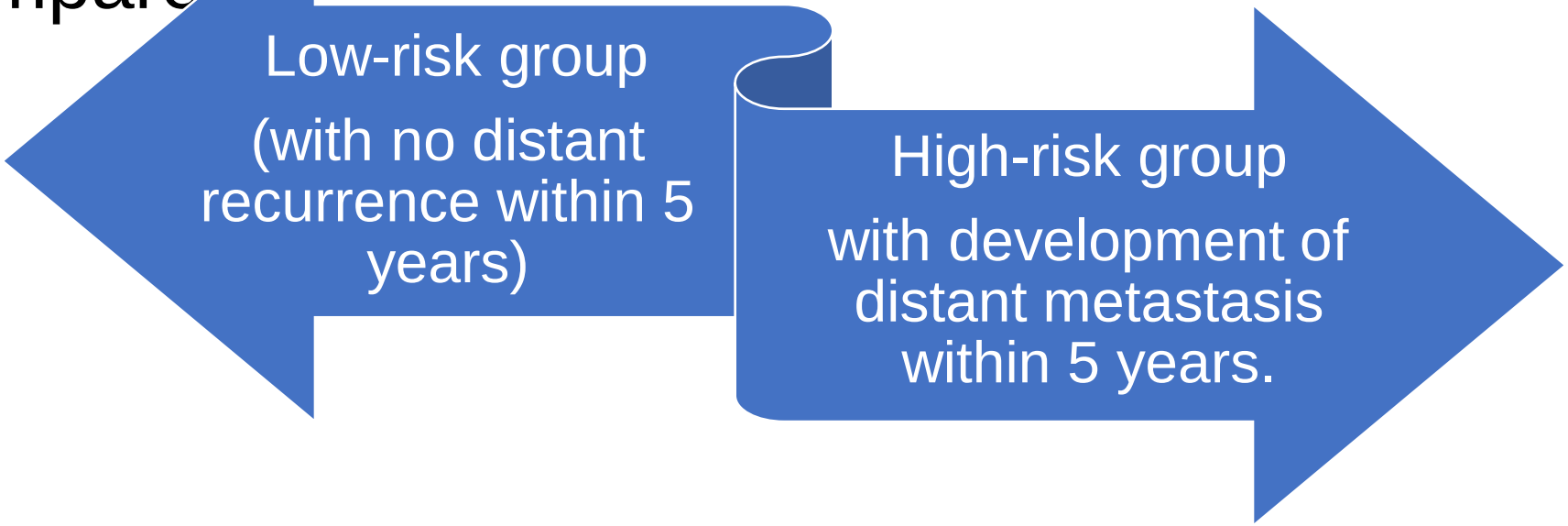
- The first to distinguish which node-negative, ER + patients would benefit from CT based on the biology of their tumor (RS31) versus those who

What about the intermediate risk (RS 18-30)?



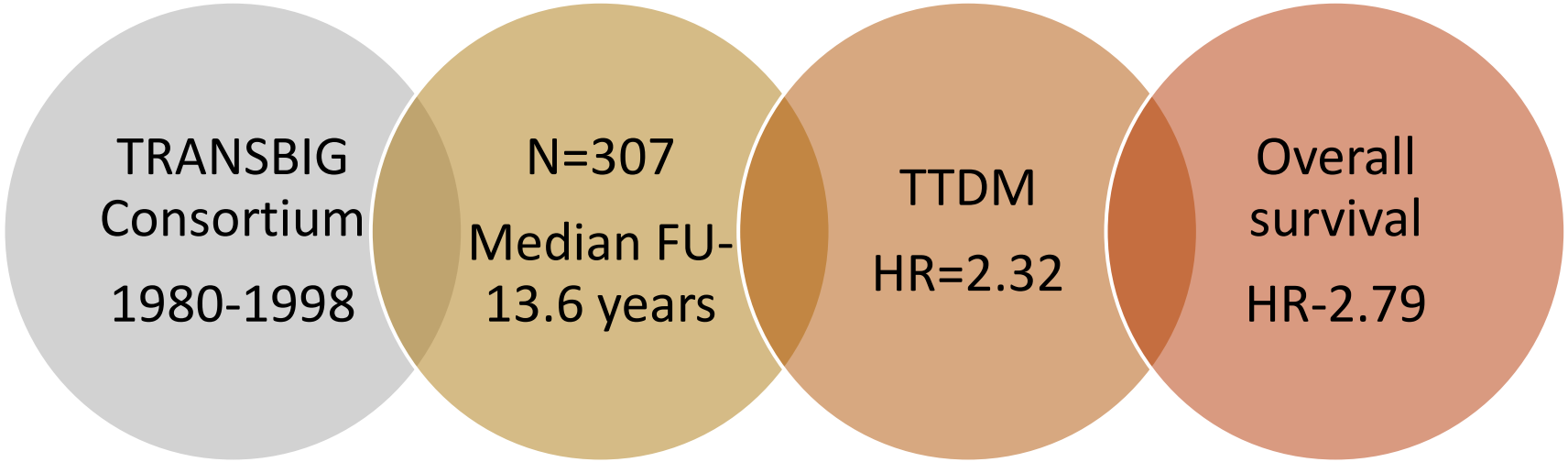
Mammaprint

- This assay was developed from an analysis of untreated breast cancer patients with 20-year follow-up in which 2 risk groups were compared



- From these studies, a 70-gene assay was developed that was prognostic for early recurrence.

Mammaprint- 70 gene Validation study



- The results of the MINDACT trial provided the current evidence for the use of MammaPrint in both node-negative (N0) and node positive EBC

Breast Cancer Index (BCI)

Prognostic 5 gene molecular grade index

1300 ER+/LN+ patients

Tamoxifen or AI

BCI Score- Risk of late recurrence

(5-10years)

Low risk-0-5

High Risk-5.1-10

2 gene predictive biomarker Ratio HoxB13/ IL-17b-H/I

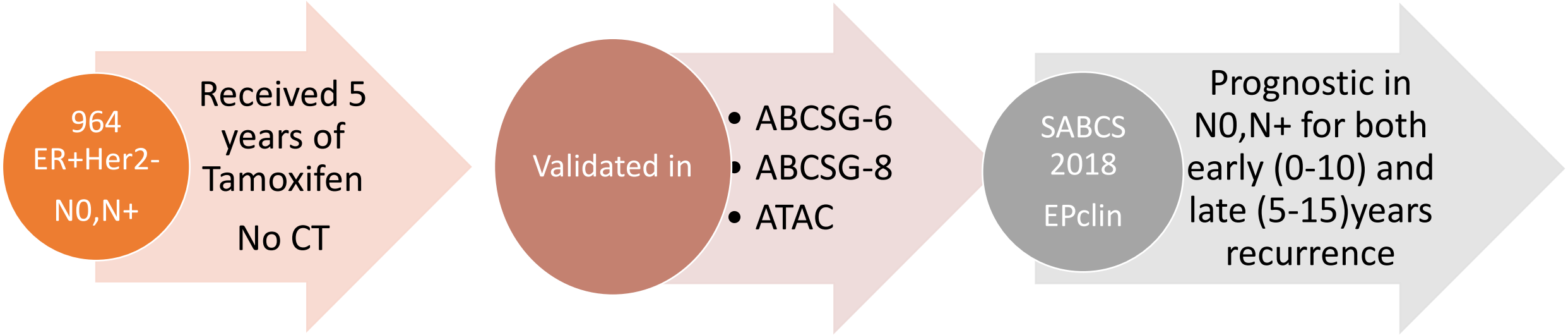
TransATAC study-

Low risk BCI score -3.5% risk of late distant recurrences(5-10 years)

ENDOPREDICT

- Prognostic information on 10-year risk for recurrence for patients with ER+/HER2-EBC.
- It is a 12-gene molecular score that combines established prognostic factors such as tumor size (T) and node status (N) to generate an individualized score (EPclin) with a binary (low or high risk) result.
- The test can be used for patients with either node-negative (N0) or node-positive(N+) disease.

ENDOPREDICT VALIDATION



- ***So, the test may be useful to determine which patients maybe less likely to obtain benefit from EA ET***

Prosigna PAM-50

50 Classifier Genes

5 control genes

Luminal A

Luminal B

Her-2 enriched

Basal like

Quantitative data

Proliferation

Luminal gene expression

ESR1,PGR, ERBB2

Risk of recurrence score (ROR)

Postmenopausal women with ER+ breast cancer

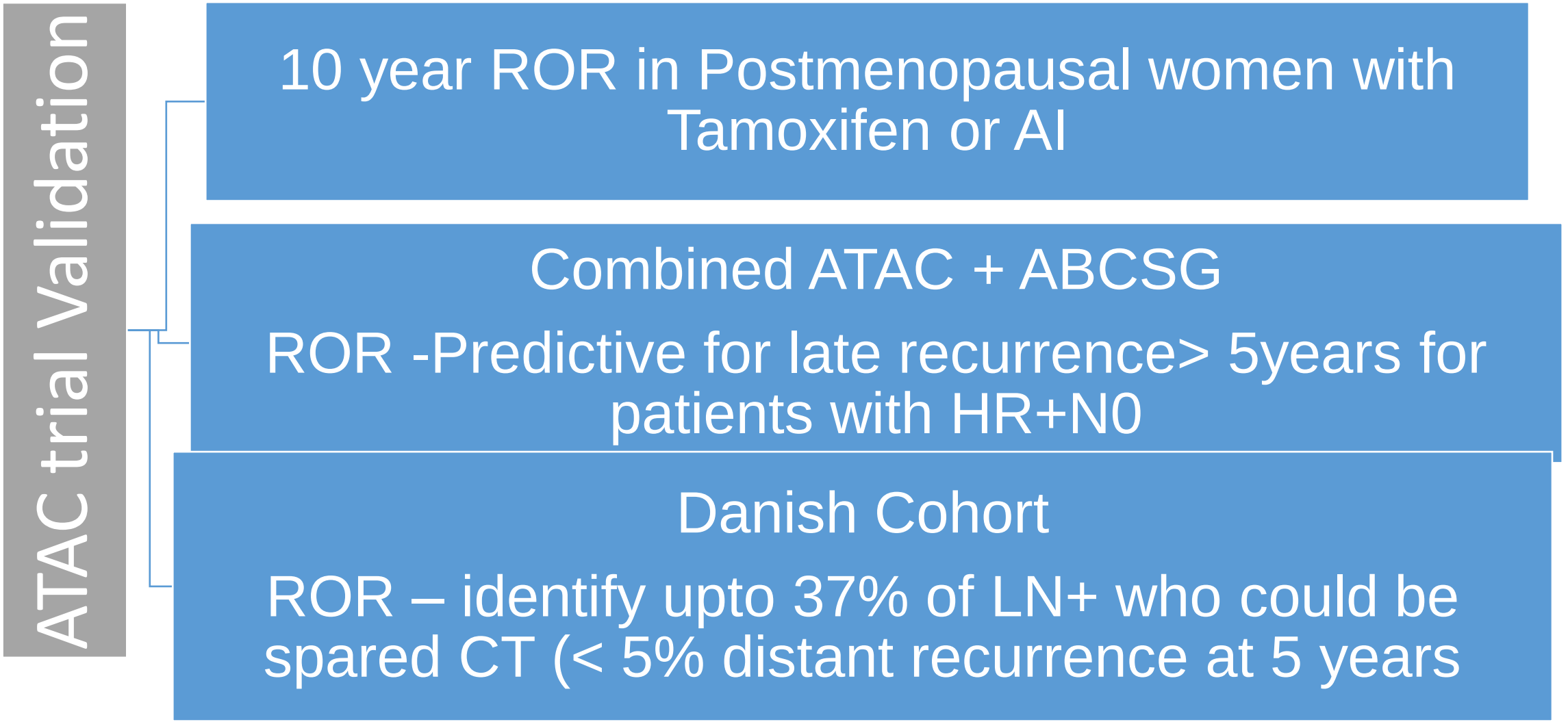
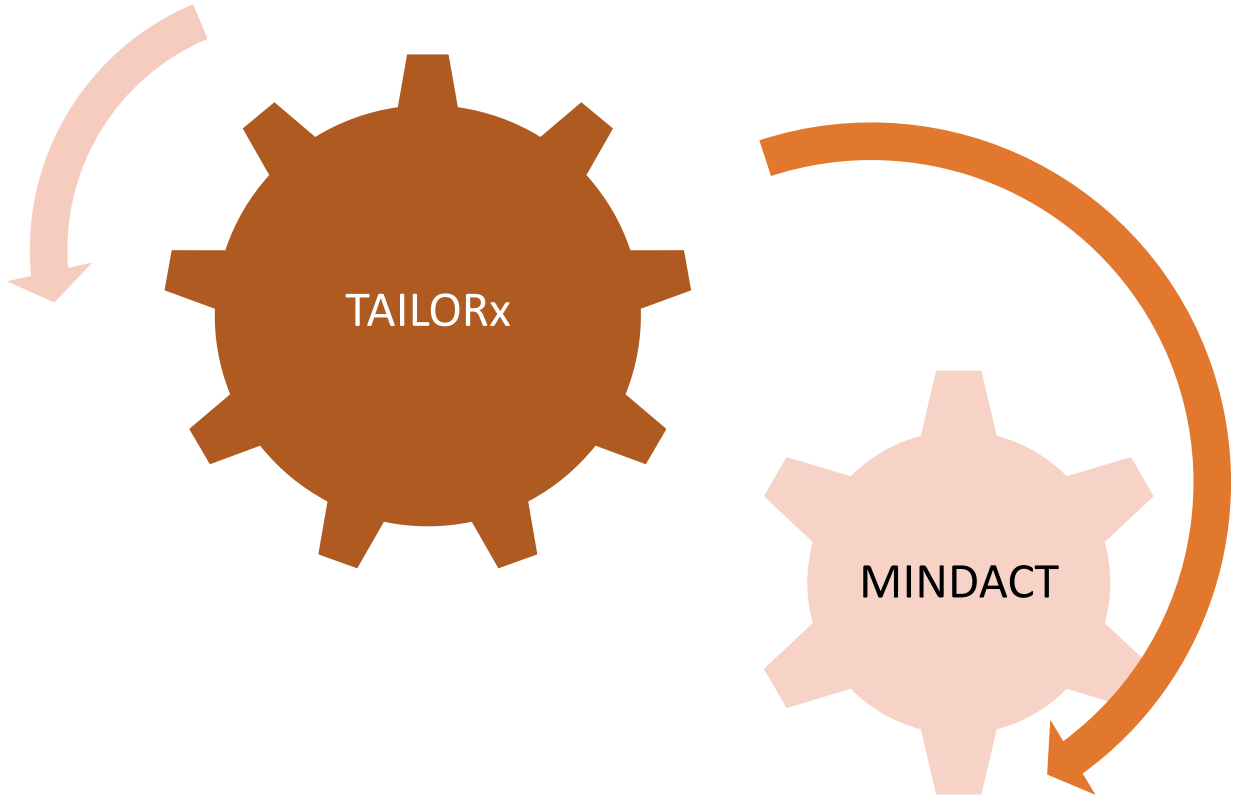

ATAC trial Validation
10 year ROR in Postmenopausal women with Tamoxifen or AI
Combined ATAC + ABCSG
ROR -Predictive for late recurrence> 5years for patients with HR+N0
Danish Cohort
ROR – identify upto 37% of LN+ who could be spared CT (< 5% distant recurrence at 5 years

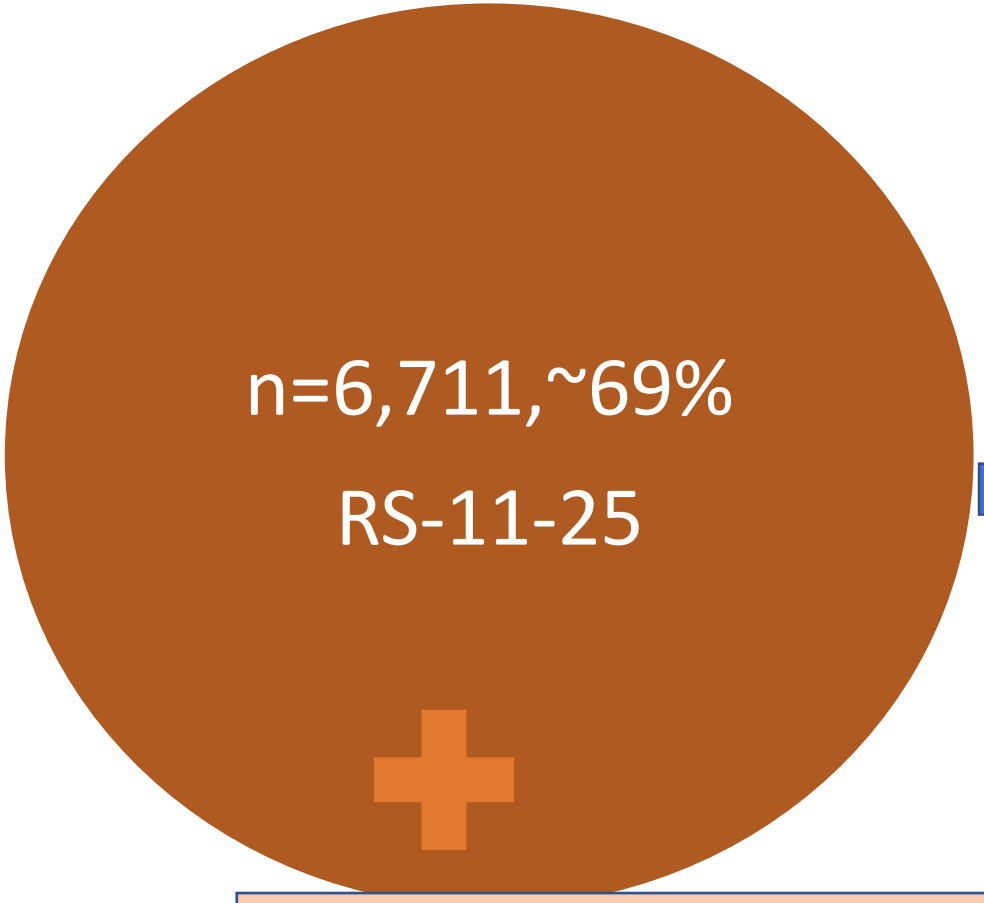
Table 1 Commercially Available Genomic Tests in Breast Cancer and Current Guidance

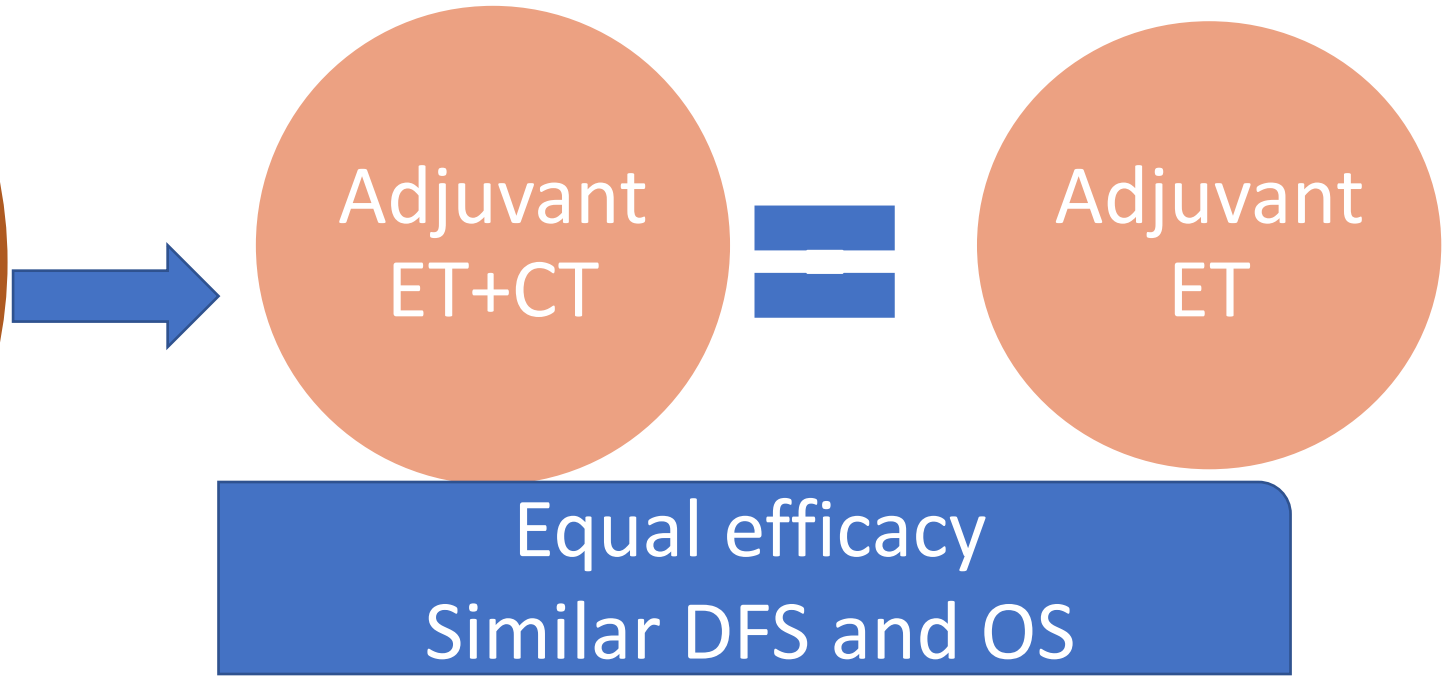
Test	Type of Information Provided	Indication and Current Guidance	Key Prospective Trials (If Available)
Oncotype DX (21-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant chemotherapy.[a]	TAILORx
	• Predictive—Adjuvant chemotherapy benefit.	• NCCN: Best validated for its value as a prognostic test and in predicting disease most likely to respond to systemic chemotherapy.[a]	
MammaPrint (70-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease and HIGH clinical risk (as per MINDACT criteria)[a] OR $ER^+/PgR^+/HER2^-$ node-positive disease 1-3 positive nodes and HIGH clinical risk (as per MINDACT criteria) to guide decisions on withholding systemic adjuvant chemotherapy.[b]	MINDACT
		• NCCN: No recommendation.	
Breast Cancer Index (BCI)	• Prognostic—10-year recurrence risk; late recurrence risk (5-10 years).	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant therapy.[b]	NA
	• Predictive—Extended adjuvant endocrine therapy benefit.	• NCCN: No recommendation.	
EndoPredict (12-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant chemotherapy.[b]	NA
		• NCCN: No recommendation.	
Prosigna (50-gene assay)	• Prognostic—10-year recurrence risk.	• ASCO: $ER^+/PgR^+/HER2^-$ node-negative disease to guide decisions on systemic adjuvant therapy in conjunction with other clinicopathologic variables[a]	NA
		• NCCN: No recommendation.	

PROSPECTIVE TRIALS- VALUE OF GENOMIC TESTING IN EBC



TAILORx Trial- 21 Gene Score





Overall, however, theTAILORx trial provides level 1 data that a sizable proportion of EBC patients can be identified using the 21-gene assay who can bespared adjuvant chemotherapy

The Exception

- Exploratory Analyses-Benefit of chemotherapy According to Age
- For patients<50 years of age, the addition of chemotherapy improved invasive DFS by 2.7% in the RS 16 to 20 group, and by 5.8% in the RS 21 to 25 group.
- The latter finding could be related to the off-target effects of chemotherapy resulting in premature menopause, a notable adverse effect associated with improved DFS.
- To further refine the 16-20 group, TAILORx population was subdivided based on clinical risk (as defined by a modification of Adjuvant! Online).

- The majority of patients (74%) randomized in TAILORx were clinically low risk, and that even patients who were clinically high risk (26%) and who had a low RS, a benefit to chemotherapy could not be identified
- Another caveat of the TAILORx trial was that ovarian suppression was only received by approximately 13% ofpatients, with 87% of the patients receiving only tamoxifen monotherapy; in this regard, the panelists thought that
- The benefit of chemotherapy in the under-50 group may be related to the effects of chemotherapy on ovarian suppression. Such an effect has been demonstrated to be of importance in the longer follow-up of the SOFT/TEXT trials

RxPonder- Oncotype Dx in Node Positive-awaited

- SWOG 8814- This subset analysis showed, for patients with 1 to 3 positive LNs, no benefit of chemotherapy in those with low RS, whereas a benefit was shown for those with high RS>31
- Results from West German Study Group (WSG) Plan B, a prospective trial showed excellent 3- and 5-year DFS (98% and 94%, respectively) for patients with high clinical risk (~62% grade 2;~35% N1) and RS<11

Table 4 Genomic Testing in $HR^+/HER2^-$ Node-Positive Breast Cancer in RxPONDER and OPTIMA Trials

Study	Study Population	Study Description and Primary Endpoint	Timeline
RxPONDER [NCTNCT01272037]	• $HR^+/HER2^-$ disease.	• Phase 3 study of standard adjuvant ET (tamoxifen or AIs) with or without chemotherapy.	Forthcoming; primary completion estimated for 2022.
	• 1 to 3 positive nodes.	• Cox regression will be used to examine the interaction of linear RS with chemotherapy benefit; goal will be to define a cut point for recommending chemotherapy for patients with RS 0 to 25.	
	• Oncotype DX (21-gene assay) RS of 25 or less.		
OPTIMA [research.uk]	• $HR^+/HER2^-$ disease.	• Phase 3 study examining the impact of chemotherapy with 5 to 10 years' ET in patients with $HR^+/HER2^-$ node-positive disease.	Forthcoming; trial is currently recruiting until 2021.
	• Age $\geq$ 40 years.	• Group 1 will receive chemo-ET without testing	
	• Chemotherapy eligible.	• In group 2, Prosigna (50-gene assay) will be used to stratify patients to chemo-ET or ET alone.	
	• Up to 9 LNs positive[a]; or LN0 with $\geq$ 30 mm tumor.		

MINDACT-70 gene signature- Clinical and Genomic Discordance

RESULTS- C-High, G-Low

- Patients who were C-high and G-low who did not receive adjuvant chemotherapy(primary-test population) had a rate of survival without distant metastasis of 94.7% (95% confidence interval, 92.5-96.2).
- In secondary analyses for chemotherapy benefit (not adequately powered to detect small differences), the 5-year rate of survival without distant metastasis was 1.5 percentage points higher for patients in the C-high/G-low group who received adjuvant chemotherapy versus those who did not (not statistically significant).
- The results thus imply that a sizable proportion of patients

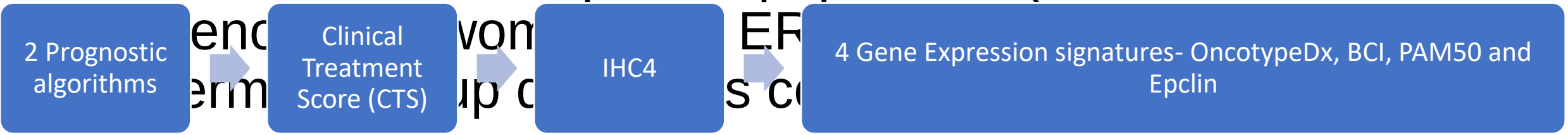
RESULTS- C-Low, G-High

- There was no difference in 5-year distant metastasis-free survival when assigning treatment based on clinical risk (ie, no chemo-therapy, 95.0%) or when assigning treatment based on genomic risk(ie, with chemotherapy, 95.8%). The results thus imply no advantage of assigning treatment based on genomic risk in clinically low-risk patients. Despite this 10 year follow up planned
- Results from EBCTCG on 20-year recurrence risk show that most of the chemotherapy benefit occurs early in the course of disease. So , probably 5 year follow up is good
- Sparano's Rule of 4-(>3cm+grade 1:>2cm + grade 2:>1cm+

Table 2 Summary of Available Prospective Data in Genomic Testing for TAILORx and MINDACT Trials[10,13]

Trial	Population Studied	Main Objective	Key Findings	Implications for Practice
TAILORx	• N = 10,273 women (18-75 years) with hormone receptor — positive/HER2⁻/axillary N0 breast cancer meeting NCCN criteria for consideration of CT.	To determine whether, among patients with an intermediate score by 21-gene assay (Oncotype DX), ET alone is noninferior to ET + CT.	• ET was noninferior to ET + CT for invasive disease-free survival at 9 years (83.3% vs. 84.3%; HR = 1.08; 95% CI = 0.94-1.24; *P* = .26).	• Adjuvant CT was not beneficial for patients with an intermediate RS of 11-25 on the 21-gene assay (Oncotype DX).
	• N = 6711 with intermediate RS 11-25.		• Similar results seen for freedom from disease recurrence at a distant site (94.5% and 95.0%) and overall survival (93.9% and 93.8%).	• Use of the assay could identify up to 85% of early breast cancer patients who can be safely spared CT (RS = 25 or less).
			• Varying degrees of CT benefit demonstrated in women ≤ 50 years with RS of 16 to 25.	• For patients < 50, consideration should be given to offering CT.
MINDACT	• N = 6693 women (18-70 years) with primary invasive early breast cancer (stage T1/T2/operable T3); 79% had N0 disease.	To determine whether women with high risk clinical (C) features and low genomic (G) risk (C-high/G-low) who did not receive CT had noninferior outcomes to those who did receive CT.	• Total of 1550 patients (23.2%) had C-high/G-low status; 5-year DMFS was 94.7% among patients in this group who did not receive CT, meeting the criteria for noninferiority.	• The 70-gene signature (MammaPrint) can be useful to identify a subset of high-clinical-risk patients with a low genomic risk (C-high/G-low) who can safely forgo CT without impairing outcomes.
	• Clinical and genomic risk determined by modified Adjuvant! Online and 70-gene assay (MammaPrint).		• Prespecified secondary analysis showed that for patients with C-high/G-low status, the rate of distant metastasis-free survival was 1.5 percentage points lower than those who did receive CT (95.9% vs. 94.4%). The result was not statistically significant. The findings were consistent in node-positive and node-negative patients. Trial was not sufficiently powered to identify a benefit to CT in this group.	• The findings represent the only prospective data set supporting a decision to safely forgo CT in a node-positive population.
				• For C-low/G-high, patients, a benefit to CT could not be demonstrated.
				• Long-term results are pending; 10-year follow-up analysis planned.

- The remaining tests—BCI, Prosigna, and EndoPredict—have thus far not been evaluated prospectively, treatment decisions are limited to retrospective evaluations across different clinical trial populations.
- In 2018, Sestak et al published a comparison of 6 prognostic tests across the same patient population (n=774 enc von ER erm up c s c



- The results showed that all of the signatures provided prognostic

- BCI,PAM50, and EPclin provided independent prognostic information for both N0 patients and those with 1 to 3 positive nodes- more prognostic in years 5-10. Could be used to provide information on the need for EA ET to reduce recurrence risk
- Combination of molecular features with clinical factors (eg,EPclin) was more informative, particularly for patients with N+disease.
- Likelihood Ratios comparing prognostic information to CTS- this comparison favored all three esp EPclin

Extended Adjuvant Endocrine therapy-BCI

- The predictive ability of this biomarker was demonstrated in the MA.17 trial, which evaluated the use of letrozole, an AI, in the EA setting.
- For those with a high H/I ratio, there was a significant reduction in recurrence with EA letrozole, from 27.0% to 10.7% (P<.007),whereas for those with a low H/I ratio, there was no statistically significant reduction in recurrence with EA letrozole therapy
- In a further analysis of N1patients (1-3 positive nodes), a BCI model incorporating tumor size and grade could identify 20% of N1 patients with a low risk of distant recurrence over 15 years (1.3%) who might be safely spared EA ET

CANASSIST

- CAB uses IHC based evaluation of expression levels of 5 key biomarkers (CD44, N-cadherin, pan-cadherin, ABCC4 and ABCC11) and three clinicopathological prognostic parameters tumor size, tumor grade and node status (as obtained from the medical records from hospitals where these patients were treated) to arrive at a “CAB-Risk Score”.
- Analytical validation has been established by demonstrating reproducibility and repeatability of the test
- Retrospective validation on Indian patients has been done but more needs to be done prospectively in the

Three Questions for the Clinicians

Is there a need? → Which assay? → How to interpret results?

Table 3 Genomic Testing in Breast Cancer: Clinical Practice Points

• Genomic testing is generally only indicated in patients with hormone receptor–positive (ER^+/PgR^+) and $HER2^-$ tumors, and those with up to 3 positive nodes.
• Genomic testing should generally not be performed for patients with hormone receptor–negative disease, > 3 positive nodes, HER2 positivity, or TNBC outside the context of a clinical trial.
• Genomic testing should generally not be performed in patients for whom the results of the testing will not affect the course of treatment.
• Importantly, neither ASCO nor NCCN guidelines currently imply the superiority of any one genomic test over another.
• Discordance between available genomic tests is expected because the different tests were developed and validated across a range of patient populations and treatment backgrounds; performing more than one genomic test on a patient should be avoided, as uncertainties in risk assignment may result.

Alternative Scoring systems-Algorithms such as the CTS, 4-marker immunohistochemical score (IHC4), and the McGee equation have shown high concordance

Chemotherapy Decisions- The Clinical High Risk

- The first case scenario- consider a young patient (40 years old) with N+ disease; the patient's tumor is grade 2 (T2/N1), ER+, and HER 2 negative

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
MammaPrint	Most applicable	Prospective	MINDACT
Oncotype DX	Applicable	Prospective	WSG PlanB
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Chemotherapy Decisions- The Clinical High Risk

- The second case, an older patient (65 years old) having no comorbid conditions, with node-negative disease. The patient's tumor is 1.9 cm and grade 3, ER+, HER2-, and N0.

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
Oncotype DX	Most applicable	Prospective	TAILORx
MammaPrint	Applicable	Prospective	MINDACT
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Chemotherapy Decisions- Clinical Low Risk

- Patients in the clinical low-risk category, a 65-year-old postmenopausal woman with a pT1c (1.0 cm), N0, grade e ductal

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
Oncotype DX	Applicable	Prospective	TAILORx
MammaPrint	Less applicable	Prospective	MINDACT
Prosigna PAM50	Less applicable	Retrospective	NA
EndoPredict	Less applicable	Retrospective	NA

Extended Endocrine Therapy Decision

- A post-menopausal woman (48 years old) who was perimenopausal at the time of diagnosis; her tumor was 2 cm and grade 3 with 1 positive node. She subsequently received adjuvant chemotherapy and has just completed 5 years of adjuvant tamoxifen-

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
BCI	Most applicable	Retrospective	NA
MammaPrint	Applicable	Retrospective	MINDACT
Oncotype DX	Applicable	Retrospective	TAILORx
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA

Decisions regarding EA ET in low-risk patients

A 64-year-old patient with a grade 2 tumor that is node negative (T2/N0) ER+(80%), PgR+(70%), and HER2-.

The patient received adjuvant tamoxifen for 5 years but is concerned about extending adjuvant therapy with an AI for fear of adverse events and concern about having a late r

Test	Applicability	Type of Evidence	Relevant Prospective Randomized Study
BCI	Most applicable	Retrospective	MA.17
MammaPrint	Applicable	Retrospective	NA
Oncotype DX	Applicable	Retrospective	NA
Prosigna PAM50	Applicable	Retrospective	NA
EndoPredict	Applicable	Retrospective	NA


THANK YOU


THANK
YOU