What Genomic Test to Choose for Your Patient with Early Stage Cancer

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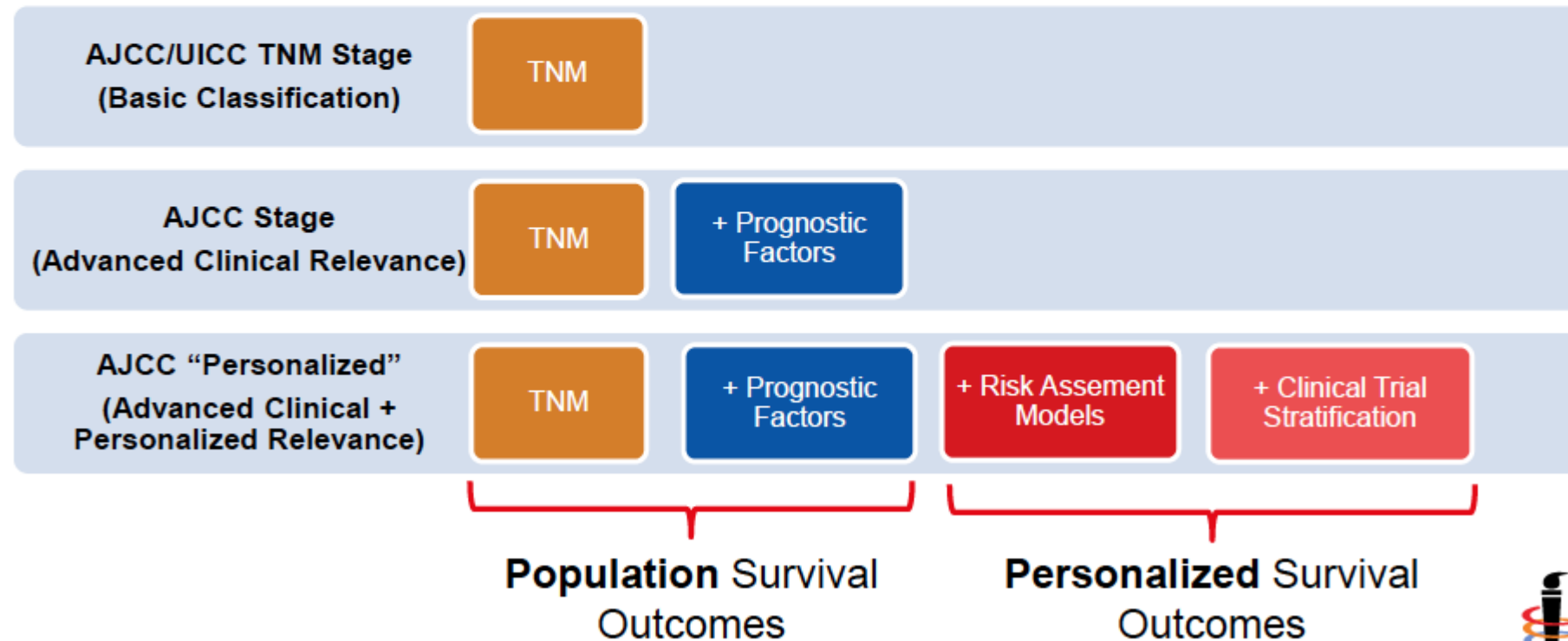
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What is the unmet need?

- Early breast cancer in general has good prognosis
- Within the realms of traditional clinical pathological features we can separate early breast cancer into different groups according to their risk of relapse and offer appropriate adjuvant recommendations.
- Adjuvant treatment recommendations for HR+ HER2 –ve patients which make up of the majority of our case load consists of mainly anti-hormone therapy and chemotherapy
- With the introduction of the AJCC v8, features beyond clinical pathological features are in cooperated into the staging to give maximal prognostic information for patients

AJCC Vision

The Transition from Population Based to a more "Personalized" Approach

AJCC/UICC TNM Stage (Basic Classification)	TNM			
AJCC Stage (Advanced Clinical Relevance)	TNM	+ Prognostic Factors		
AJCC "Personalized" (Advanced Clinical + Personalized Relevance)	TNM	+ Prognostic Factors	+ Risk Assement Models	+ Clinical Trial Stratification

Population Survival Outcomes

Personalized Survival Outcomes

The emergence of multigene assay

- The use of chemotherapy is not without its short and long term side-effects

- For HR+ HER2-ve patients extra predictive and prognostic information beyond clinical pathological criteria can help us in formulating the best adjuvant treatment decision for our patients

- The availability of genomic assays which gives us another dimension of the biology of the tumor is a welcome addition to our information base for adjuvant discussion

Addition of Multigene Assays

- Test for levels of expression of a large number of genes in the tumor at the RNA level

- Oncotype Dx, Mammaprint, Endo- Predict, PAM50, and Breast Cancer Index.

CHANGE	DETAILS OF CHANGE	LEVEL OF EVIDENCE
Inclusion of multigene panels (when available) as stage modifiers—21-gene recurrence score (Oncotype Dx)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0, and the tumor is staged using the AJCC prognostic stage group table as stage I.	I
Inclusion of multigene panels (when available) as stage modifiers—Mammaprint	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—EndoPredict	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 12-gene (EndoPredict) low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—PAM50 (Prosigna)	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a PAM50 risk–of-recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II
Inclusion of multigene panels (when available) as stage modifiers—Breast Cancer Index	For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Breast Cancer Index in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.	II

Major change

- For the first time in history, the integration of genomic test results into clinical staging

- The molecular information gained from these test is used to down stage the tumor, irrespective of Grade and Size

Genomic test available

Table 2 Summary of multi-gene/molecular scores for the prediction of recurrence

Score	Abbreviation	Details	Reference
MammaPrint	MammaPrint	70 gene-based expression profile using DNA microarray. Fresh frozen material is used to perform analysis.	[20,21]
Genomic Grade Index	GGI	97 gene-based assay using DNA micro array. Fresh frozen material is used to perform the analysis.	[23,24]
Oncotype Dx Recurrence Score	RS	21 gene-based expression profile score using qRT-PCR (16 cancer genes, 5 housekeeping genes). FFPE blocks used to extract RNA.	[25]
Immunohistochemical Score 4	IHC4	Includes information on estrogen receptor (ER), progesterone receptor (PgR), Ki67, and HER2. Score developed on transATAC data. FFPE blocks used to extract RNA to perform IHC for ER, PgR, Ki67, and HER2.	[31]
Prosina Risk of Recurrence Score	ROR	50 gene-based expression profile score using qRT-PCR. FFPE blocks used to extract RNA to perform analysis on nCounter system.	[34]
Breast Cancer Index	BCI	Multi-gene assay using qRT-PCR. Combination of two biomarkers HOXB13/IL17BR (H/I) and molecular grade index (MGI). FFPE blocks used to extract RNA to perform analysis.	[38,53]
EndoPredict	EPclin	12 gene-based expression profile score using qRT-PCR (8 cancer genes, 4 housekeeping genes). FFPE blocks used to extract RNA to perform analysis.	[41]

ATAC, Arimidex, Tamoxifen, Alone or in Combination; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor; qRT-PCR, quantitative real-time polymerase chain reaction.

Sestak and Cuzick Breast Cancer Research (2015) 17:10

Quick review of the tests

TABLE I Currently available genomic assays in estrogen receptor–positive early-stage breast cancer

Assay	Classifiers (n genes)	Platform	Binary (high vs. low)	Decentralized testing	Recommended by ASCO clinical practice guideline[25] (node-negative)	Validated in N0 and N1	Utility in late recurrence
Oncotype DX[a]	16	qPCR	No	No	Evidence quality: high Strength recommendation: strong	Yes	Possibly
Prosigna[b]	50	nCounter	No	Yes	Evidence quality: high Strength recommendation: strong	Yes	Yes
Mammaprint[c]	70	Microarray or qPCR	Yes	No	Evidence quality: intermediate Strength recommendation: moderate	Yes	No
EndoPredict[d]	8	qPCR	Yes	Yes	Evidence quality: intermediate Strength recommendation: moderate	Yes	Possibly
Breast Cancer Index[e]	7	qPCR	Yes	No	Evidence quality: intermediate Strength recommendation: moderate	No	Yes
Genomic Grade Index[f]	97	Microarray	Yes	No	Not discussed	No	No

Chia S Curr Oncol. 2018 Jun;25(Suppl 1):S125-S130

TABLE II Pivotal studies in which genomic assays have been evaluated for clinical utility

Assay	Pivotal study or studies	Study design	Sample size (*n*)	Intervention	Clinical utility
Oncotype DX[a]	NSABP B20[4]	Prospective-retrospective	651	Tamoxifen ± CMF	■ Significant benefit to chemotherapy when recurrence score is high; limited benefit when recurrence score is low
	TAILORx[5]	Prospective	1626	Endocrine for 5 years	■ Very favourable prognosis with endocrine therapy alone when recurrence score is 10 or less
Prosigna[b] (PAM50 ROR)	ABCSG-8 and TransATAC[6]	Prospective-retrospective	2137	Endocrine for 5 years	■ Very favourable prognosis with endocrine therapy alone when risk-of-recurrence score is low or subtype is luminal A
	DBCG[7]	Retrospective	2749	Endocrine for 5 years	
MammaPrint[c]	MINDACT[8]	Prospective randomized controlled trial	6693 (entire study) 2142 (randomized component)		■ Discordance in clinical and genomic results randomized to chemotherapy or not ■ Favourable prognosis with or without adjuvant chemotherapy when 70-gene signature is low-risk
EndoPredict[d]	ABCSG-6 and ABCSG-8[9]	Prospective-retrospective	1702	Endocrine for 5 years	■ Very favourable prognosis with endocrine therapy alone when EPclin score is low
Breast Cancer Index[e]	CCTG MA.17[10]	Nested case–control study	249	Letrozole vs. placebo after 5 years of tamoxifen	■ Greater benefit to extended hormonal therapy when the Breast Cancer Index is high

CMF = cyclophosphamide, methotrexate, 5-fluorouracil; ROR = risk of recurrence; ABCSG = Austrian Breast and Colorectal Cancer Study Group; DBCG = Danish Breast Cancer Group; CCTG = Canadian Cancer Trials Group.

a   Genomic Health, Redwood City, CA, U.S.A.

The Optima trial

Table 1. Characteristics of the 302 patients

Characteristic	Total
Age, median (range), y	58 (40–78)
Menopausal status of participant, No. (%)	
Pre/perimenopausal	97 (32.1)
Postmenopausal	205 (67.9)
Number of involved nodes, No. (%)	
None	57 (18.9)
1-3	192 (63.6)
4-9	42 (13.9)
Positive sentinel node biopsy without clearance surgery	11 (3.6)
Histological grade, No. (%)	
1	19 (6.3)
2	201 (66.6)
3	82 (27.1)
Largest tumor size, median (range), mm	28 (2–170)
≤30 No. (%)	172 (57.0)
>30 No. (%)	130 (43.0)
Lymphovascular invasion reported, No. (%)	
No	169 (56.0)
Yes	122 (40.4)
Not known	11 (3.6)
Tumor type, No. (%)	
Ductal	214 (70.9)
Lobular	65 (21.5)
Tubular/cribriform	2 (0.7)
Mucinous	4 (1.3)
Micropapillary	1 (0.3)
Mixed	16 (5.3)

Table 3. Risk categorization by each test

Risk group	Oncotype DX* No. (%)	MammaPrint† No. (%)	Prosigna No. (%)	IHC4 No. (%)
No. of patients (%)	301 (99.7)	298 (98.9)	299 (99.0)	257 (85.1)
Low risk	163 (54.2)	183 (61.4)	108 (36.1)	62 (24.1)
Intermediate risk	84 (27.9)	–	88 (29.4)	123 (47.9)
Mid risk	–	–	–	–
High risk	54 (17.9)	115 (38.6)	103 (34.5)	72 (28.0)

Table 4. Kappa statistics for tests providing risk predictions*

| Test	MammaPrint (low), Kappa statistic (95% CI)	Prosigna (low/intermediate), Kappa statistic (95% CI)	IHC4 (low/intermediate), Kappa statistic (95% CI)	IHC4-AQUA† (low/low-mid), Kappa statistic (95% CI)
Oncotype DX (recurrence score ≤25)	0.40 (0.30 to 0.49)	0.44 (0.33 to 0.54)	0.53 (0.41 to 0.65)	0.40 (0.30 to 0.51)
MammaPrint	–	0.53 (0.43 to 0.63)	0.33 (0.21 to 0.44)	0.42 (0.30 to 0.53)
Prosigna (low/intermediate)	–	–	0.39 (0.27 to 0.50)	0.43 (0.31 to 0.54)
IHC4 (low/intermediate)	–	–	–	0.60 (0.50 to 0.70)

*Kappa statistics are for agreement between categorization into combined low and intermediate risk vs high risk. CI = confidence interval.
†IHC4-AQUA mid risk and high risk are combined for this analysis.

Table 6. Relationship between Prosigna subtyping and the continuous risk of recurrence score*

	Subtype			
Prosigna test result	Luminal A No. (%)	Luminal B No. (%)	Basal like No. (%)	HER2 enriched No. (%)
No. of patients (%)	178 (59.5)	113 (37.8)	2 (0.7)	6 (2.0)
ROR, Median (IQR)	37 (28–44)	70 (63–78)	53 (47–58)	76 (72–78)
Range	5–59	43–96	47–58	64–84
Risk groups, No. (%)				
Low risk	108 (60.7)	0	0	0
Intermediate risk	70 (39.3)	16 (14.2)	2 (100)	0
High risk	0	97 (85.8)	0	6 (100)

*HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; ROR = risk of recurrence.
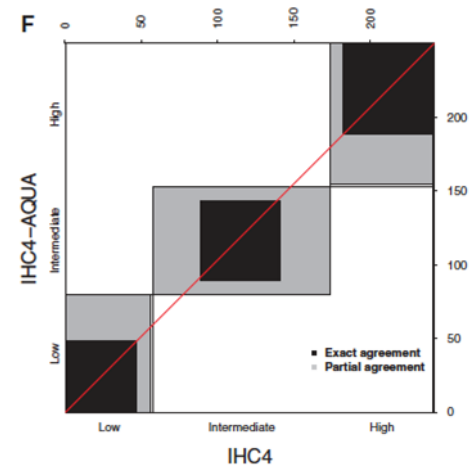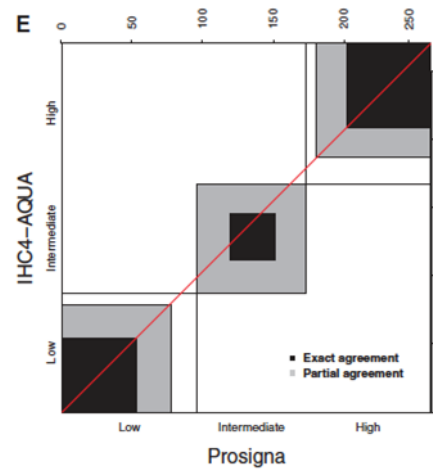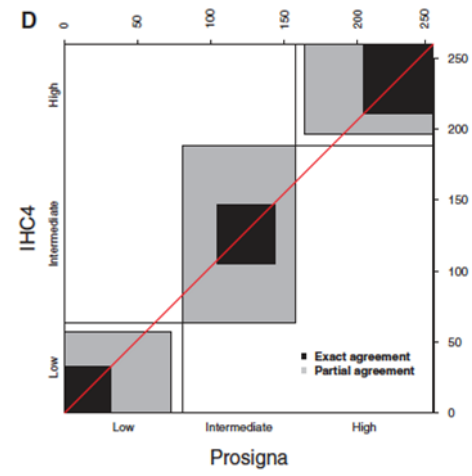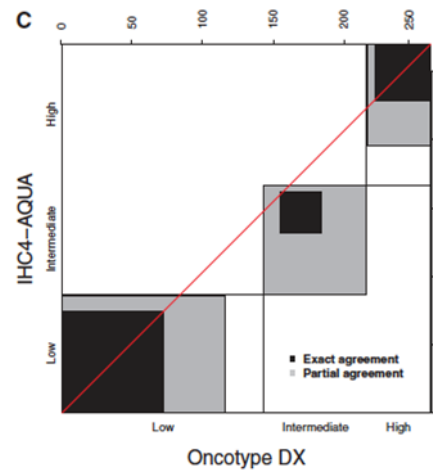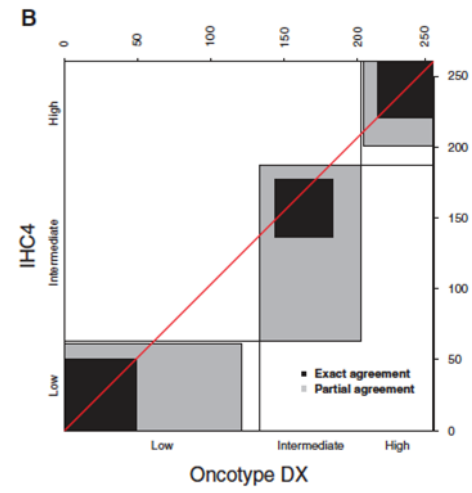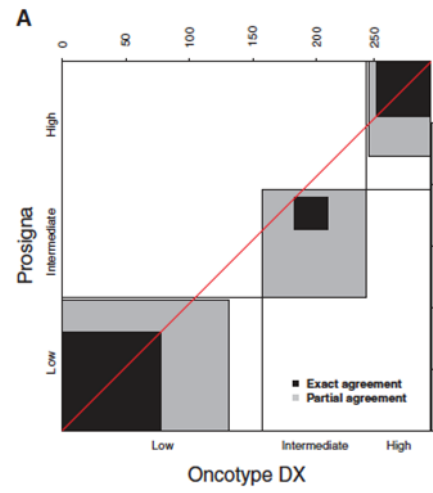
- TransATAC study

- Post M HR+ HER2-ve

- No chemotherapy allowed

- N0 or up to 3 + LN

- Tam or Anastrazole

- Up to 10 years follow up for relapse

- These individual samples were subjected to Oncotype, MMP, EPClin, BCI, CTS and IHC4 analysis

- All the test loose some power of prediction for N+ disease

Sestak et al JAMA Oncol. 2018 Apr 1;4(4):545-553

Figure 2. Kaplan-Meier Curves for Recurrence During Years 5 to 10
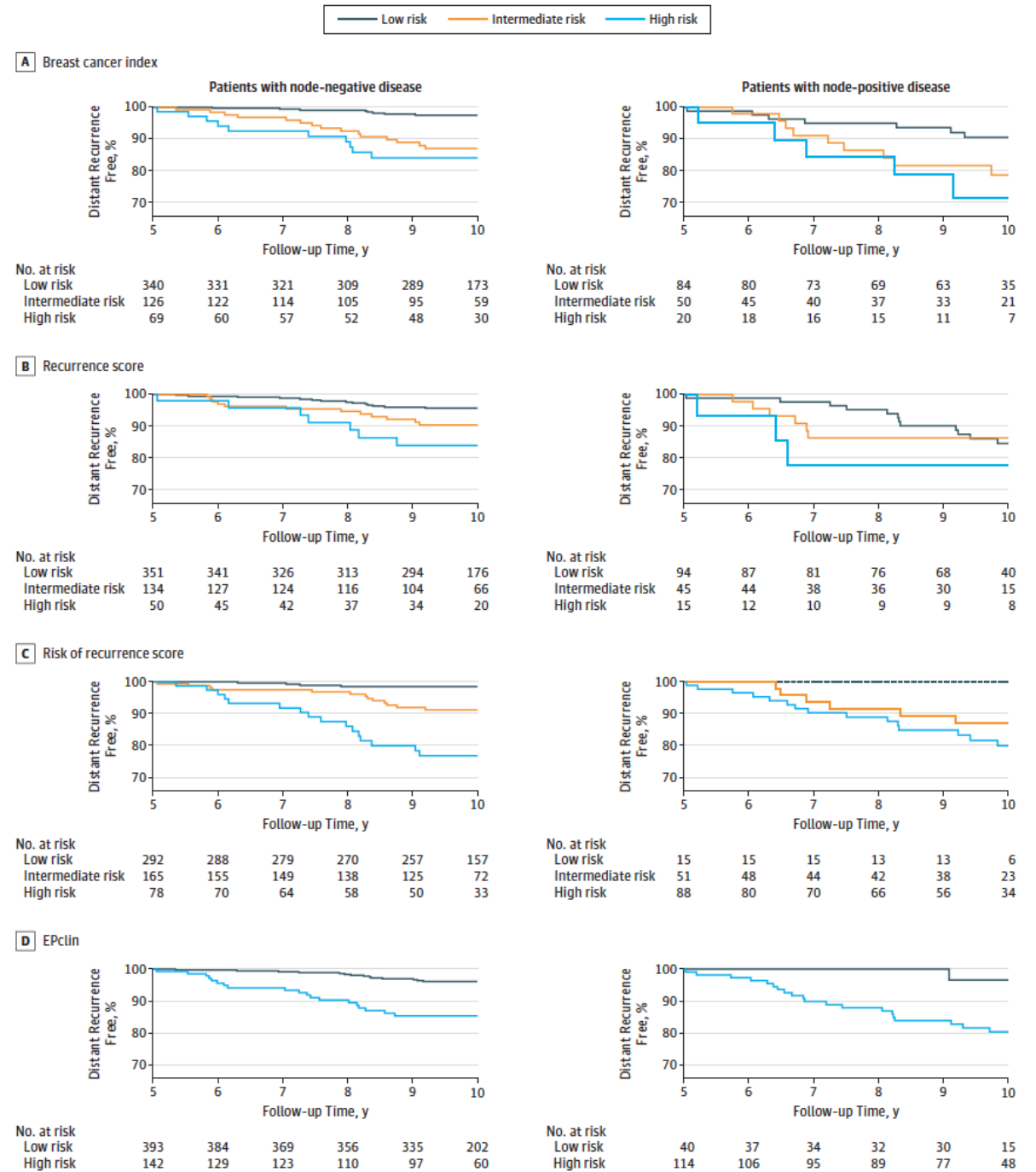
Are young women different?

- In the TAILORx study NEMJ 2018 publication RX score <11 conferred excellent outcome and can be safely spared for adjuvant chemotherapy

- RX 11-25 who were randomised to endocrine vs chemo-endocrine therapy also showed no clear benefit of adding chemotherapy to endocrine therapy

- In an exploratory analysis, women age less than 50 and a RX score 15-25 seemed to have a minor benefit of adding chemotherapy

ORIGINAL ARTICLE

Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer

J.A. Sparano, R.J. Gray, P.M. Ravdin, D.F. Makower, K.I. Pritchard, K.S. Albain,
D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively,
S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood,
M.M. Keane, H.L.G. Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky,
D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.
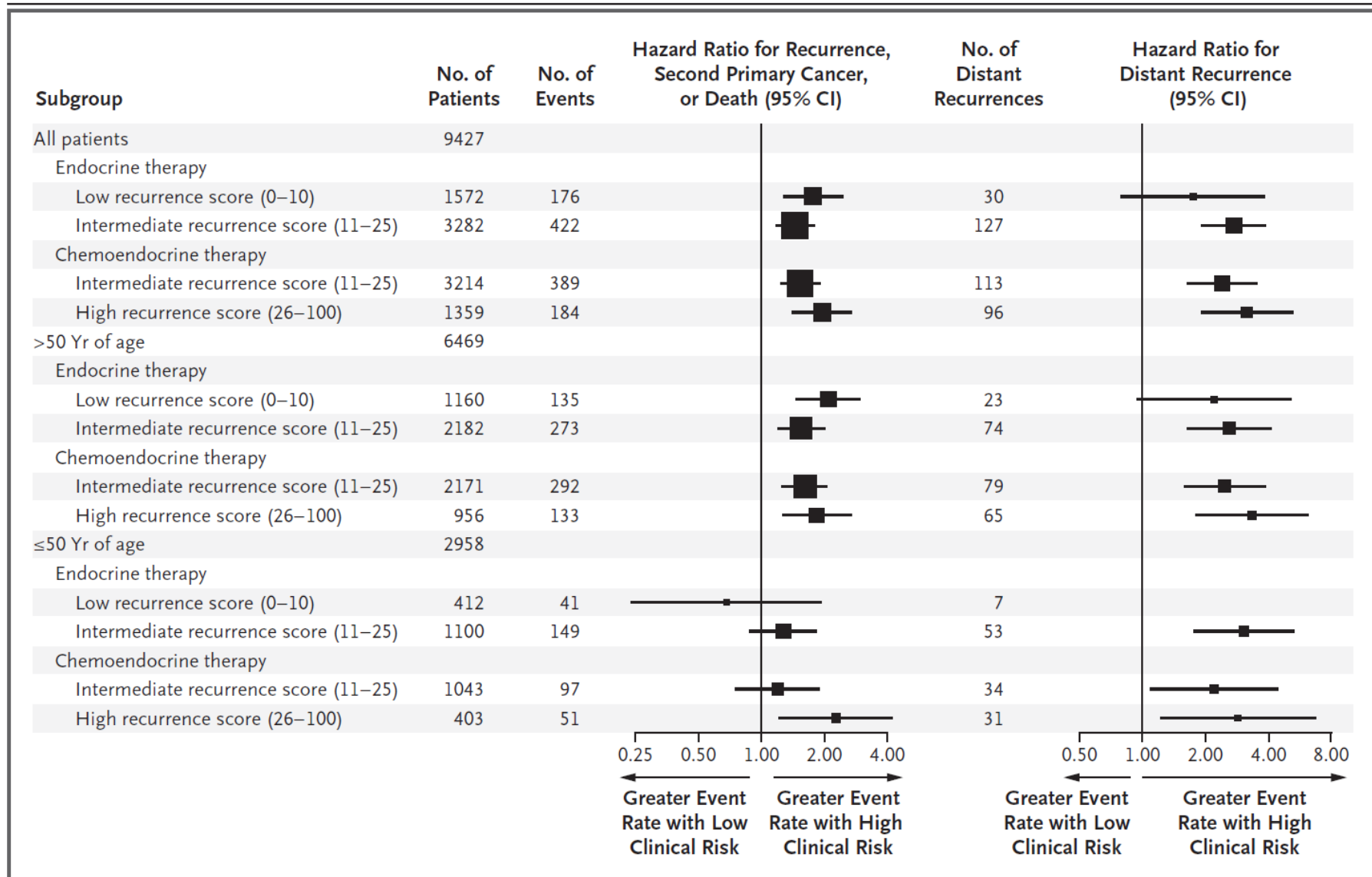
ABSTRACT

Subgroup	No. of Patients	No. of Events	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)	No. of Distant Recurrences	Hazard Ratio for Distant Recurrence (95% CI)
All patients	9427				
Endocrine therapy					
Low recurrence score (0–10)	1572	176		30	
Intermediate recurrence score (11–25)	3282	422		127	
Chemoendocrine therapy					
Intermediate recurrence score (11–25)	3214	389		113	
High recurrence score (26–100)	1359	184		96	
>50 Yr of age	6469				
Endocrine therapy					
Low recurrence score (0–10)	1160	135		23	
Intermediate recurrence score (11–25)	2182	273		74	
Chemoendocrine therapy					
Intermediate recurrence score (11–25)	2171	292		79	
High recurrence score (26–100)	956	133		65	
≤50 Yr of age	2958				
Endocrine therapy					
Low recurrence score (0–10)	412	41		7	
Intermediate recurrence score (11–25)	1100	149		53	
Chemoendocrine therapy					
Intermediate recurrence score (11–25)	1043	97		34	
High recurrence score (26–100)	403	51		31	

Hazard Ratio for Recurrence, Second Primary Cancer, or Death axis: 0.25 0.50 1.00 2.00 4.00

Greater Event Rate with Low Clinical Risk — Greater Event Rate with High Clinical Risk

Hazard Ratio for Distant Recurrence axis: 0.50 1.00 2.00 4.00 8.00

Greater Event Rate with Low Clinical Risk — Greater Event Rate with High Clinical Risk

Figure 1. Effect of Clinical Risk on Prognosis in the Entire Population and Stratified According to Age.

Hazard ratios and 95% confidence intervals (CIs) for a high versus low clinical risk of invasive disease recurrence, second primary cancer, or death and for distant recurrence (a hazard ratio of >1 indicates a higher event rate with high clinical risk) are shown. There were no distant recurrences among 64 patients in the subgroup who had a high clinical risk and a low recurrence score. CIs have not been adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. The size of each square corresponds to the size of the subgroup; the horizontal lines represent the 95% CI.
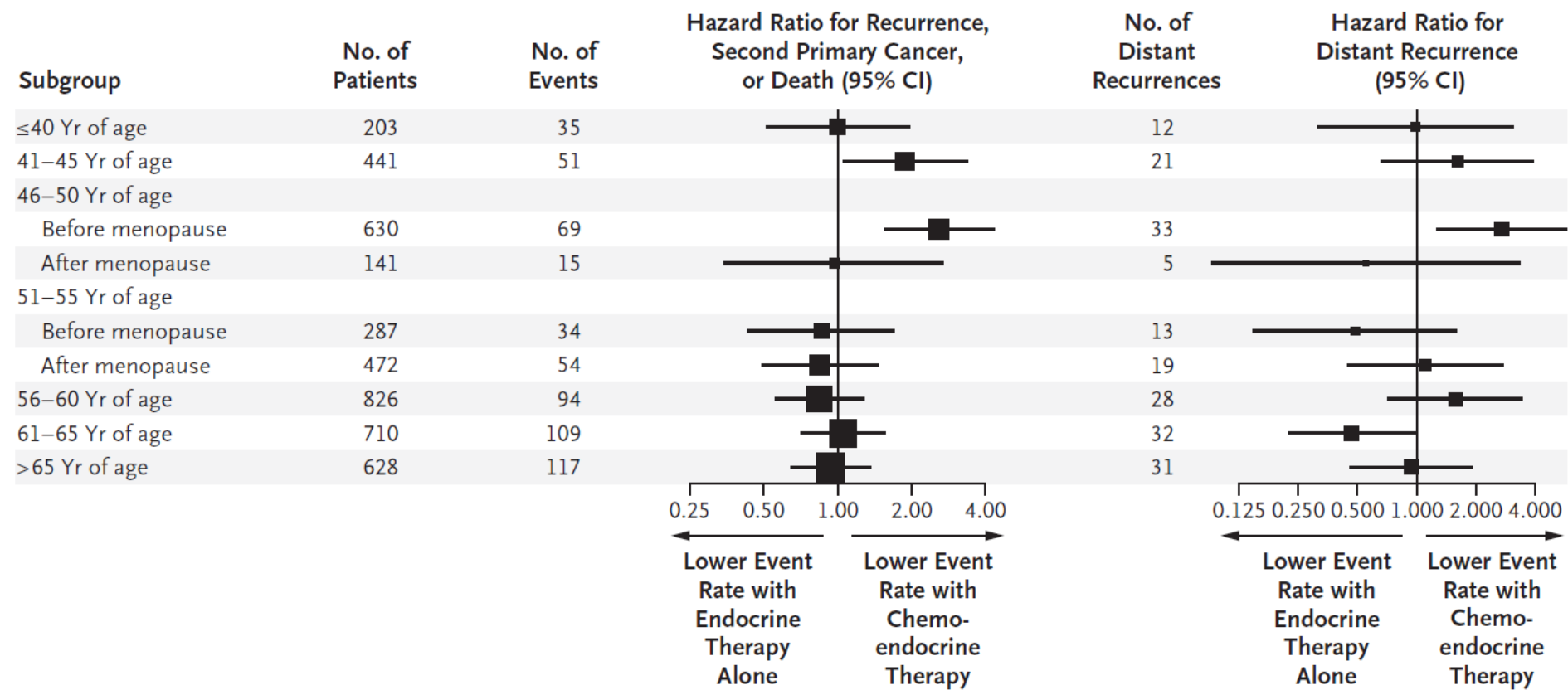
Subgroup	No. of Patients	No. of Events	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)	No. of Distant Recurrences	Hazard Ratio for Distant Recurrence (95% CI)
≤40 Yr of age	203	35		12	
41–45 Yr of age	441	51		21	
46–50 Yr of age					
Before menopause	630	69		33	
After menopause	141	15		5	
51–55 Yr of age					
Before menopause	287	34		13	
After menopause	472	54		19	
56–60 Yr of age	826	94		28	
61–65 Yr of age	710	109		32	
>65 Yr of age	628	117		31	

Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI) axis: 0.25 0.50 1.00 2.00 4.00
Lower Event Rate with Endocrine Therapy Alone ← → Lower Event Rate with Chemo-endocrine Therapy

Hazard Ratio for Distant Recurrence (95% CI) axis: 0.125 0.250 0.500 1.000 2.000 4.000
Lower Event Rate with Endocrine Therapy Alone ← → Lower Event Rate with Chemo-endocrine Therapy

Figure 3. Effect of Age and Menopausal Status on Chemotherapy Benefit.

Shown is the effect of age and menopausal status on chemotherapy benefit in 4338 women who had a recurrence score of 16 to 25 and were randomly assigned to endocrine therapy or chemoendocrine therapy. Estimated treatment hazard ratios (endocrine vs. chemoendocrine therapy) and 95% CIs for rates of distant recurrence at 9 years are shown (a hazard ratio >1 indicates that chemoendocrine therapy is better). Menopause was defined as an age of 60 years or older; an age of 45 to 59 years with spontaneous cessation of menses for at least 12 months before registration; an age of 45 to 59 years with cessation of menses for less than 12 months before registration and a follicle-stimulating hormone (FSH) level in the postmenopausal range (or >34.4 IU per liter if the institutional range was not available); prior bilateral oophorectomy; or age younger than 60 years with prior hysterectomy without bilateral oophorectomy and an FSH level in the postmenopausal range (or >34.4 IU per liter if the institutional range was not available). CIs have not been adjusted for multiple comparisons, and inferences drawn from the intervals may not be reproducible. The size of each square corresponds to the size of the subgroup; the horizontal lines represent the 95% CI.

Table 2. Recurrence, Second Primary Cancer, or Death, and Distant Recurrence at 9 Years, According to Use or Nonuse of Adjuvant Chemotherapy in Women Younger than 50 Years of Age, Stratified According to Recurrence Score and Clinical Risk (Intention-to-Treat Population).*

Variable	Clinical Risk	No. of Patients	Estimated Probability of Recurrence, Second Primary Cancer, or Death	Hazard Ratio for Recurrence, Second Primary Cancer, or Death (95% CI)†	Estimated Probability of Distant Recurrence	Estimated Absolute Chemotherapy Benefit	Hazard Ratio for Distant Recurrence (95% CI)†
			percent		*percent*	*percentage points*	
Recurrence score of 16–20							
No chemotherapy	Low	328	19.6±3.1	1.89 (1.18–3.04)	4.6±1.5	−0.2±2.1	1.00 (0.44–2.28)
Chemotherapy	Low	343	9.5±1.8		4.8±1.5		
No chemotherapy	High	107	19.0±4.5	1.68 (0.76–3.72)	11.9±3.9	6.5±4.9	2.26 (0.70–7.34)
Chemotherapy	High	108	16.3±5.8		5.5±3.0		
Recurrence score of 21–25							
No chemotherapy	Low	158	19.7±4.5	1.38 (0.74–2.57)	11.4±3.9	6.4±4.9	3.16 (1.01–9.94)
Chemotherapy	Low	161	15.8±4.0		5.0±3.0		
No chemotherapy	High	75	26.4±5.4	2.63 (1.14–6.05)	18.8±5.0	8.7±6.2	1.86 (0.73–4.74)
Chemotherapy	High	82	11.4±3.8		10.1±3.7		

Sparano et al June 20, 2019N Engl J Med 2019; 380:2395-2405

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Sparano et al June 20, 2019N Engl J Med 2019; 380:2395-2405

In Practice

- To predict who benefits from extended endocrine therapy beyond 5 yrs BCI is the preferred test

- To identify HR+ low risk patients who can be safely treated with ET alone and spare chemo :- Oncotype, MMP, Prosigna, Endopredict

- Node positive disease- all need some caution

- These test do not agree with each other so do not order more than one test for the patient unless you want trouble

- There are new refinements being added to these test as we are gathering more and more data with prospective trials

- There is emerging data about biological difference with younger patients and the complex interaction of chemotherapy and premature menopause with risk reduction for recurrence