Use of Genomic Assays and Biomarkers to Assist in Management of ER-positive Early Breast Cancer

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Disclosures

Advisory Committee	Pfizer Inc
Data and Safety Monitoring Board	Genentech BioOncology, Merck, Novartis
Steering Committee	Genentech BioOncology

Potential Clinical Utility of Genomic Assays and Biomarkers in Early Stage Breast Cancer

- Prognosis
  - Risk of recurrence, death
- Selection of therapy
  - Indication for adjuvant chemotherapy
  - Late relapse - extended endocrine therapy?
  - Locoregional recurrence – indication for radiation therapy?

Multiparameter Genomic Assays for Early Stage Breast Cancer

Prognosis and Indication for Chemotherapy

	ASCO[1]	NCCN[2]	ESMO[3]	ETMG[4]
21-gene Recurrence Score - Onco*type* Dx	X N0 only (+/- N1mic)	X 0-3+ LN	X	X 0-3+ LN
70-gene MammaPrint		Other multigene assays may be considered to help assess recurrence risk but are not validated to predict chemo response	X	X 0-3+ LN
EndoPredict	X N0 only		X	X 0-3+ LN
Prosigna PAM50 ROR Score	X N0 only		X	X 0-3+ LN
Breast Cancer Index	X N0 only			X N0 only

[1] Harris LN et al, J Clin Oncol 2016; [2] NCCN clinical practice guidelines in oncology. Breast cancer — version 2 2017; [3] Senzus E et al, Ann Oncol 2015; [4] Duffy MJ et al, Eur J Cancer 2017

St Gallen International Expert Consensus on the Primary Therapy of Breast Cancer 2015

Coates AS et al, Ann Oncol 26:1533-1546, 2015

	% Yes	% No	% Abstain
21-gene RS – Onco*type* Dx			
Prognosis: Years 1-5?	82.9	14.6	2.5
Indication for chemo?	80.5	14.6	5.0
70-gene MammaPrint			
Prognosis: Years 1-5?	81.0	9.5	10.0
Indication for chemo?	35.0	47.5	17.5
EndoPredict			
Prognosis: Years 1-5?	70.3	10.8	18.0
Indication for chemo?	23.5	53.9	23.5
Prosigna PAM50 ROR score			
Prognosis: Years 1-5?	92.9	0	7.1
Indication for chemo?	38.2	47.1	14.7
Breast Cancer Index			
Prognosis: Years 1-5?	58.3	8.0	33.0
Indication for chemo?	10.0	50.0	40.0

Use of 21-gene RS in LN+?

Prospective German PlanB Trial: High Risk ER+, HER2- pN0 or pN1-3

Gluz O et al, J Clin Oncol 34: 2341-2349, 2016

- 3,198 patients

3-year DFS

	No Chemo if RS < 12	Chemo if RS ≥ 12	
Nodal Subset	**RS<12**	**RS 12-25**	**RS > 25**
pN0 (high risk)	98.6%	98.5%	97.0%
pN+	97.9%	97.2%	89.4%

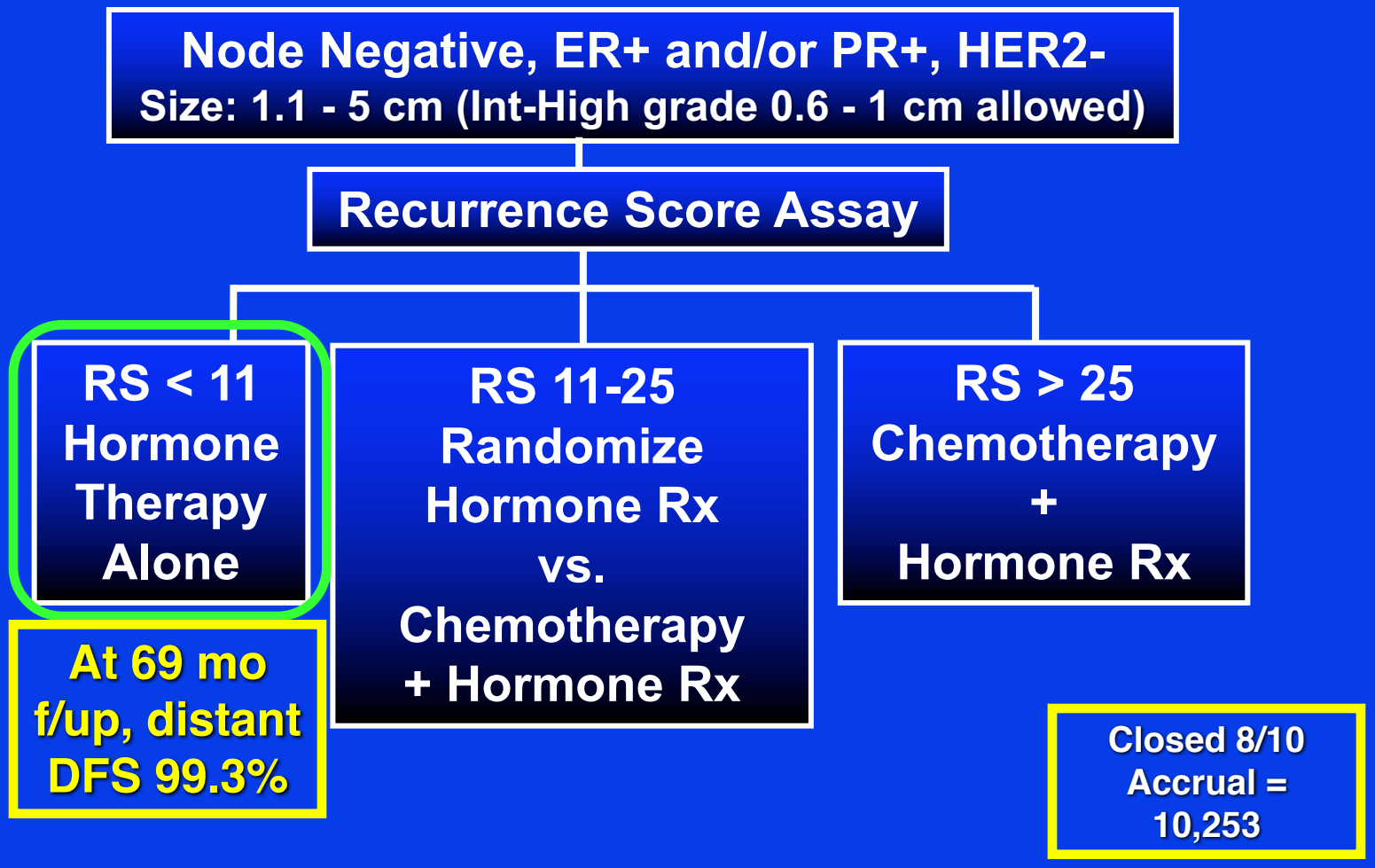
Data published post-ASCO guideline publication

Multiparameter Genomic Assays for Early Stage Breast Cancer
Prospective Validation Studies

	Prospective Studies
21-gene Recurrence Score - Onco*type* Dx	TAILORx/PACCT-1: LN negative Low risk group (RS< 11) reported RS 11-25 randomized +/- chemo Ongoing RxPONDER/SWOG S1007: 1-3+ LN- RS< 25 randomized +/- chemo Ongoing
70-gene MammaPrint	MINDACT/EORTC 10041: 0-3+ LN Discordant Genomic/Clinical Risk group data reported

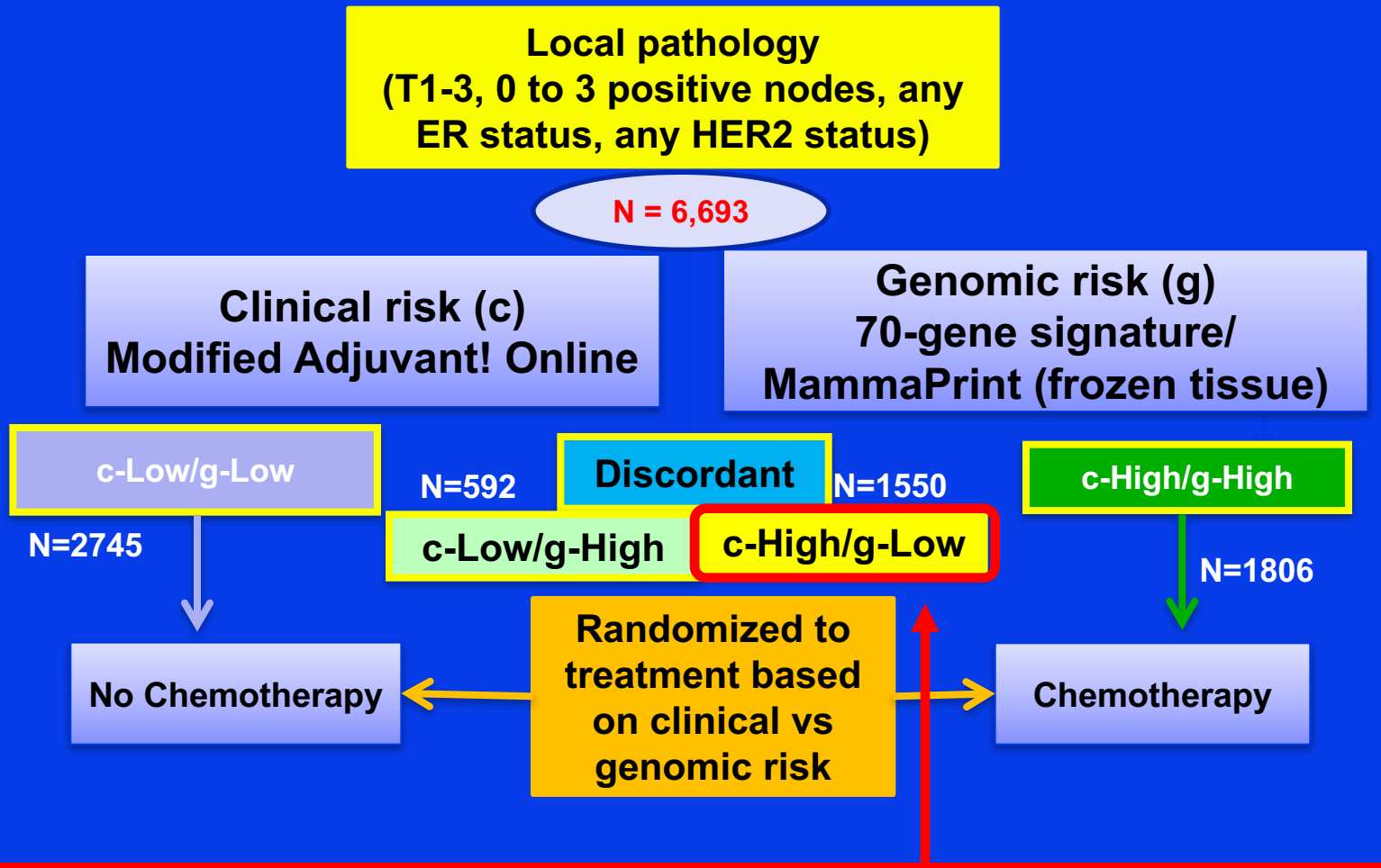
PACCT-1/TAILORx: Prospective Validation Trial for 21-Gene Recurrence Score (LN-)

Sparano J et al, *N Engl J Med* 373:2005-2014, 2015



MINDACT: Prospective Validation Trial for 70-gene Signature

Cardoso F et al, *N Engl J Med* 375:717-29, 2016

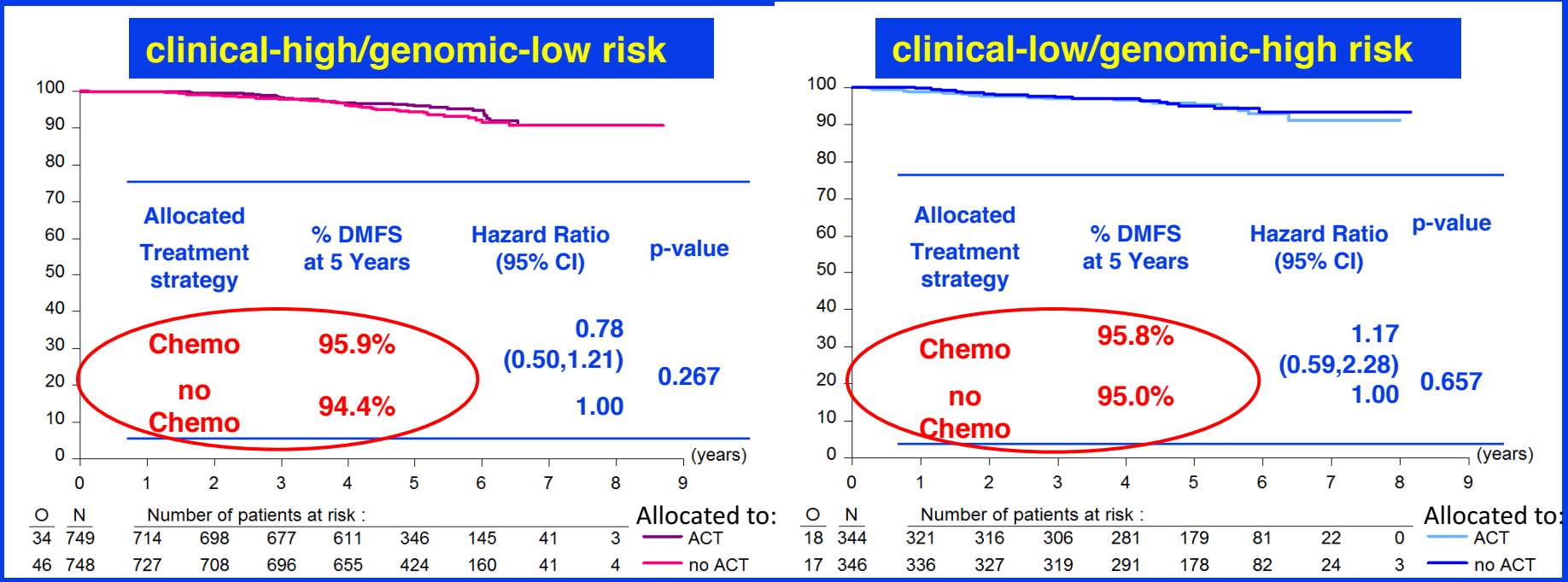


Endpoint: Achieve 5-year metastasis-free survival > 92% in clinical-high/genomic-low risk group randomized to no chemotherapy

MINDACT: Prospective Validation Trial for 70-gene Signature

Cardoso F et al, N Engl J Med 375:717-29, 2016

Discordant groups - 5-year distant metastasis-free survival



c-high/g-low risk group randomized to no chemo achieved 5-year DMFS > 92%
No benefit from chemotherapy

c-low/g-high risk group also received no benefit from chemotherapy

Chemo given: optional randomization to anthracycline regimen (w/ taxane only if LN+) or docetaxel/capecitabine

MINDACT Editorial

C Hudis et al, NEJM 375:790-791, 2016

- Achieved primary study goal of > 92% DMFS in c-high/g-low risk group at 5 years without chemo
  - Results met study criterion for non-inferiority
  - Secondary endpoint comparing chemo vs not in c-high/g-low risk group showed non-significant 1.5% survival advantage for chemo (underpowered)
  - No advantage of chemo in c-low/g-high risk group (also underpowered)
- *Adequately powered randomization or higher threshold for 5-year met-free survival might have provided a more convincing result*
- Clinicians may consider using 70-gene signature for patients in line for chemo who hope to forgo it with low risk genomic result

Using 21-gene Recurrence Score (RS) Assay to Choose Neoadjuvant Therapy

Bear HD et al, SABCS 2016 abstract P2-10-04

- HR+, HER2- invasive breast cancer not suitable for breast conserving therapy (BCS) (≥ 2 cm; median size 3.5-4 cm)
- 21-gene RS tested on core needle biopsy
  - RS< 11: Neoadjuvant hormonal therapy (NHT)
  - RS 11-25: Randomized to NHT vs neoadjuvant chemotherapy (NCT)
  - RS > 25: NCT

64 patients	RS< 11	RS 11-25 NHT	RS 11-25 NCT	RS > 25
Clinical Response	83.3%	50%	72.7%	92.9%
pCR (breast, LN)	0	0	0	14.3%
Successful BCS	75%	72.2%	63.6%	57.1%

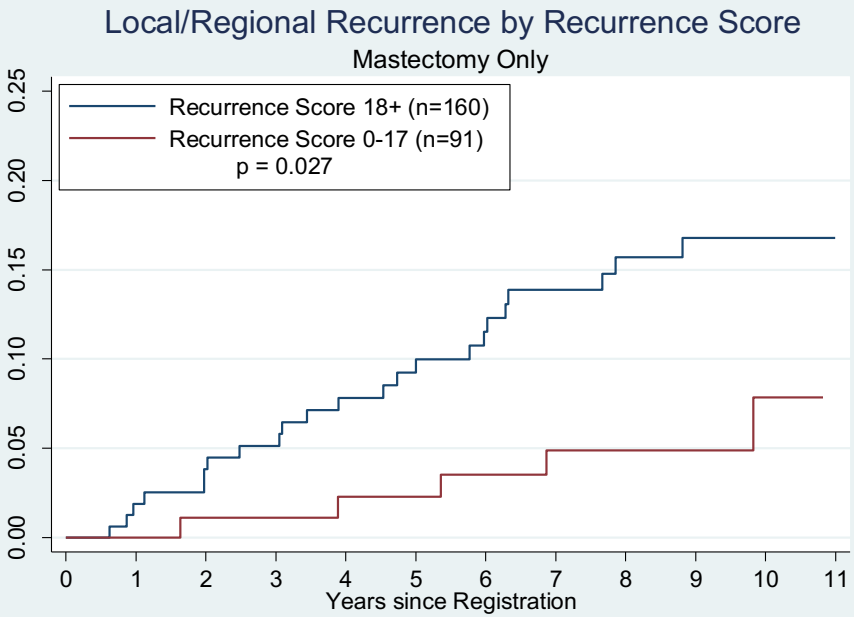
- Conclusion: Pilot showed feasibility of using 21-gene RS to guide neoadjuvant systemic therapy

21-gene RS and Locoregional Recurrence (LRR) in ER+, LN+ Breast Cancer Post-Mastectomy without Radiation: SWOG S8814

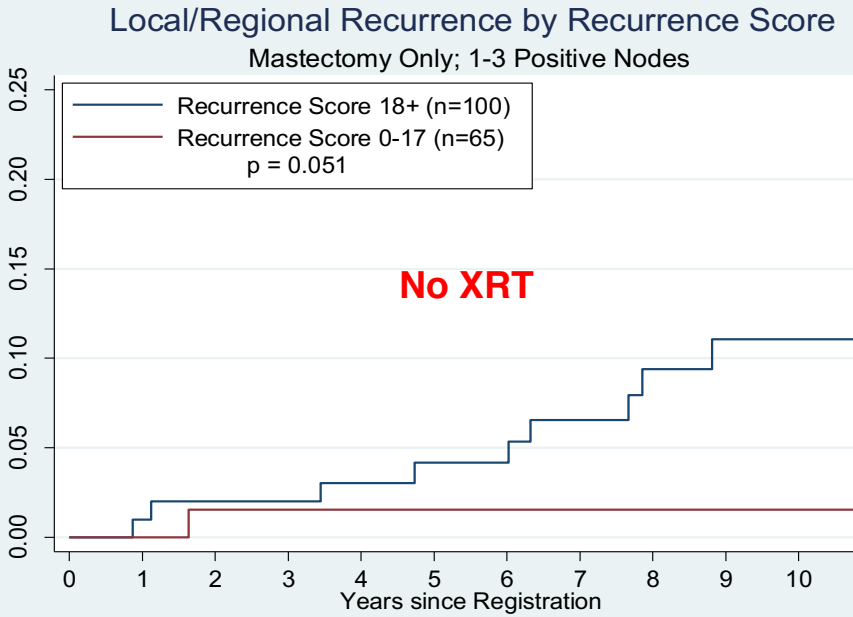
Woodward WA et al, ASTRO 2016, abstract 329

Background: 21-gene RS correlated with LRR in LN- pts in NSABP B-14/B-20 (Mamounas 2010), LN+ in B-28 (Mamounas 2017)

All Mastectomy



Mastectomy 1-3 LN+



- **Low RS ER+, 1-3+ LN, may avoid XRT after a mastectomy with low risk if validated on further study**

Multiparameter Genomic Assays for Early Stage Breast Cancer

Late Recurrences and Extended Endocrine Therapy

	Late Recurrences
21-gene RS - Onco*type* Dx	Not predictive of late distant recurrence in transATAC (Sgroi 2013) Predictive of late distant recurrence in NSABP B-14/B-28 when combined with ESR1 expression (Wolmark 2016)
EndoPredict	Prognostically significant beyond 5 years in ABCSG 6 and 8 (Dubsky 2013)
Prosigna PAM50 ROR	Prognostically significant beyond 5 years in ATAC/ABCSG 8 (Sestak 2015)
Breast Cancer Index	Prognostic for early and late recurrences in 2 series (Zhang 2013) Superior to 21-gene RS and IHC4 in transATAC (Sgroi 2013)

- No group endorses use in extending endocrine therapy or not
- ASCO Guideline: Should not use gene expression or protein assays to guide decisions on extended endocrine therapy

American Joint Committee on Cancer (AJCC) 8th edition: Breast Cancer Changes
Released 10/16 – in effect Jan 2018

- "Next Generation" AJCC Staging – "More Personalized Approach"
- Two stage group options for breast cancer:

  Anatomic – biomarkers (ER, PR, HER2) not available
  - Classic T, N, M

  Prognostic – for use on all US patients
  - Groups pts with similar prognosis +/- treatment approach
  - Inclusion of ER, PR, HER2, grade
  - Inclusion of multigene panels in specific situations
    - » Currently 21-gene RS (Onco*type*) only assay included
  - Prognostic stage IA - includes T1-2, N0 ER+ with low RS
  - Prognostic stage IIA – includes T1, N0 TNBC

AJCC edition 8 webinar on breast cancer by G Hortobagyi:
https://cancerstaging.org/CSE/Physician/Pages/8th-Edition-Webinars.aspx

Genomic Assays and Biomarkers in Determining Adjuvant Therapy for ER+ Breast Cancer

- Both classic "disease burden" (anatomic stage) and "tumor biology" are important in selecting adjuvant systemic therapy
  - Node positivity not absolute requirement for chemo
  - AJCC edition 8 changes attempting to combinein "prognostic stage"
- Multiple genomic assays provide prognostic and predictive info
  - 21-gene RS (and now 70-gene signature?) appear predictive for chemotherapy benefit/lack of benefit
  - Many assays predict late recurrences but none yet validated for decisions on extended endocrine therapy
  - Trials in design for selection of XRT postmastectomy in LN+
- Ongoing trials will further inform
  - Direct comparisons will be important
- Cost (and availability) may ultimately drive utilization
- Personalized therapy includes taking patient's preferences into account