Webinar: **Genomic Profiling and the Future of Early Breast Cancer Care.**

Comparison of performance and components of genomic assays

Mitch Dowsett, September 2020

- Ralph Lauren Centre for Breast Cancer Research, Royal Marsden Hospital
- Breast Cancer Now Research Centre, Institute of Cancer Research

prosigna® Breast cancer gene signature assay

veracyte.

Comparison of performance and components of genomic assays

- Oncotype DX, Prosigna, EndoPredict
- Information the tests draw upon to calculate risk
- Comparative performance in TransATAC
- The correlation of the scores with key molecular features

All calculate the residual risk of distant recurrence over 10 years for ER+ patients on the assumption that they receive 5 years of endocrine therapy *(not MammaPrint: purely prognostic)*

Summary comparison: some key features

	Oncotype	Endopredict	Prosigna
Prognosis 0-10 yrs	✓	✓✓	✓✓✓
Prognosis 5-10 yrs	✓	✓✓	✓✓✓
Includes T-size	✗	✓	✓
Risk groups	L, I, H* <11, 11-20, >20%	L, H <10, >10%	L, I, H <7, 7-15, >15%
Predictive of chemo benefit (adjuvant)	?	✗	✗
Subtyping	✗	✗	✓
Testing	central	local	local or central
Endocrine treatment	Tamoxifen	Tamoxifen	Tam/AI

* pre-TAILORx

Kwa M, Makris A, Esteva FJ.Nat Rev Clin Oncol. 2017 Oct;14(10):595-610

prosigna® Breast cancer gene signature assay

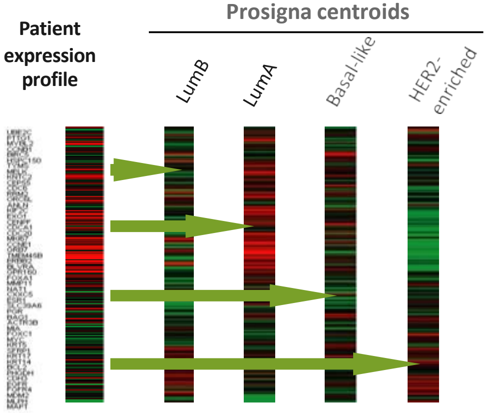
veracyte.

Prosigna Algorithm Generates An Individualized Risk Assessment

- **Gene expression data weighted with clinical variables**
- **Scale of 1-100 related to probability of distant recurrence**

- **Calculated correlation to PAM50 intrinsic subtypes**
- **Add proliferation score and tumor size**

Determine intrinsic (molecular) subtype through Pearson's correlation to centroids

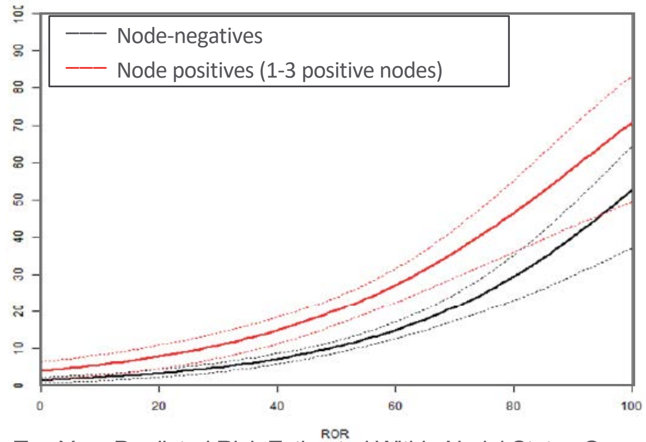


Calculate Prosigna Score

$$\text{Prosigna Score} = \left.\begin{matrix} aR_{LumA} + \\ bR_{LumB} + \\ cR_{Her2e} + \\ dR_{Basal} + \end{matrix}\right\} \text{Pearson's correlation to centroids}$$

$$\left.\begin{matrix} eP + \\ fT \end{matrix}\right\} \begin{matrix} \text{Proliferation score} \\ \text{Tumor size} \end{matrix}$$

Estimate 10-Year Risk of Distant Recurrence on Endocrine Therapy Alone: node –ve and node +ve



Ten Year Predicted Risk Estimated Within Nodal Status Group

Adapted from Wallden et al. BMC Medical Genomics (2015) 8:54

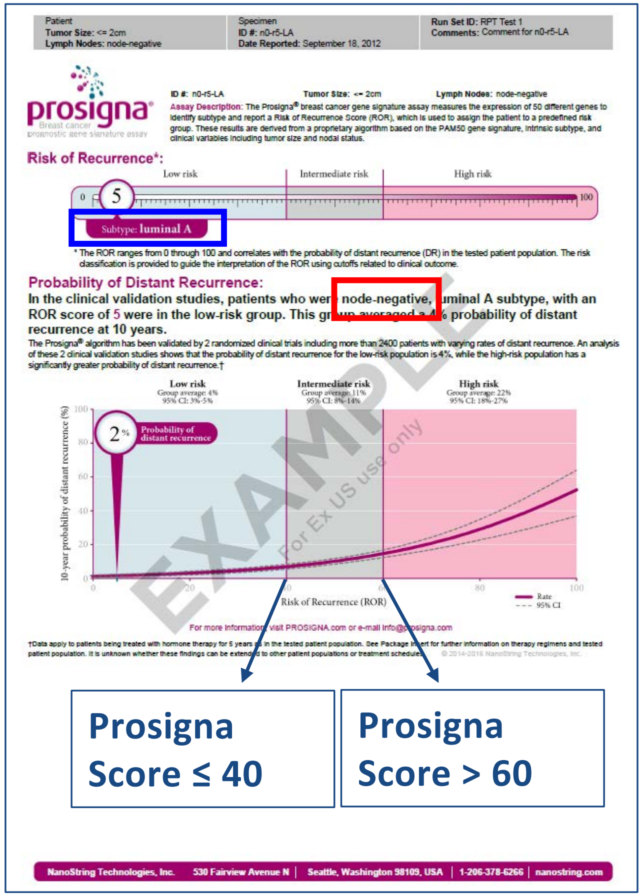
prosigna® Breast cancer gene signature assay

veracyte.

Prosigna Report: Node-Negative

Prespecified Risk Group	Avg. 10yr Prob. Distant Recurrence	Range of 10 yr Prob. DR
Low	4%	0 - 7%
Intermediate	11%	7% - 15%
High	22%	15% - 55%

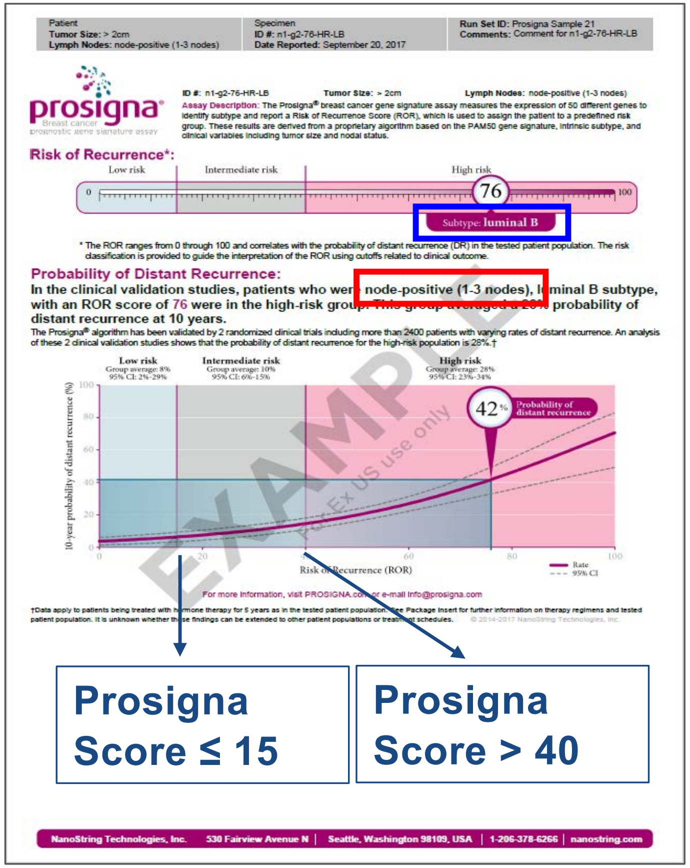
Risk is average 10yr DR if 5yr tam or AI



Prosigna Report: Node-Positive

Prespecified Risk Group	Avg. 10yr Prob. Distant Recurrence	Range of 10 yr Prob. DR
Low	8%	5% – 7%
Intermediate	10%	7% - 15%
High	28%	15% - 70%

Risk is average 10yr DR if 5yr tam or AI



Oncotype DX Genes

PROLIFERATION	HER2	ESTROGEN
Ki-67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	ER PGR Bcl2 SCUBE2

INVASION		REFERENCE
Stromelysin 3 Cathepsin L2	GSTM1 CD68 BAG1	Beta-actin GAPDH RPLPO GUS TFRC

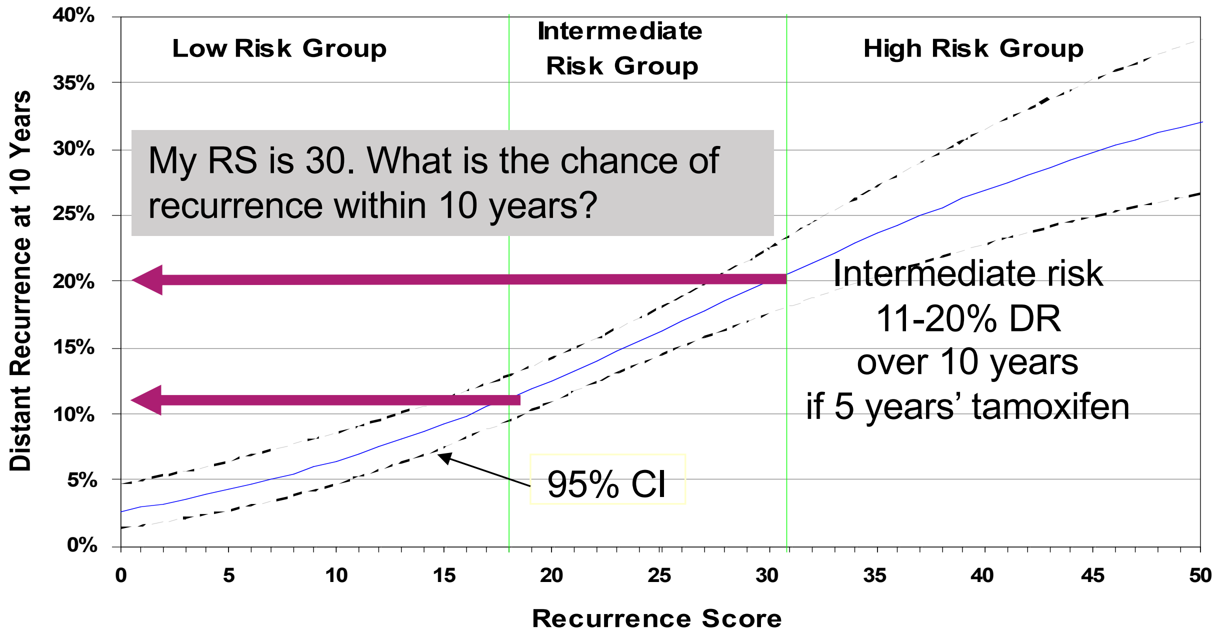
RS_U =
+ 0.47×*GRB7* group
– 0.34×*ER* group
+ 1.04×prolif group*
+ 0.10 invasion group
+ 0.05 × *CD68* – 0.08 × *GSTM1* – 0.07 × *BAG1*.

*proliferation group score = (*Survivin*+*KI67*+*MYBL2*+*CCNB1*+*STK15*)÷5

(if the result is less than 6.5, then the proliferation group score is considered 6.5)

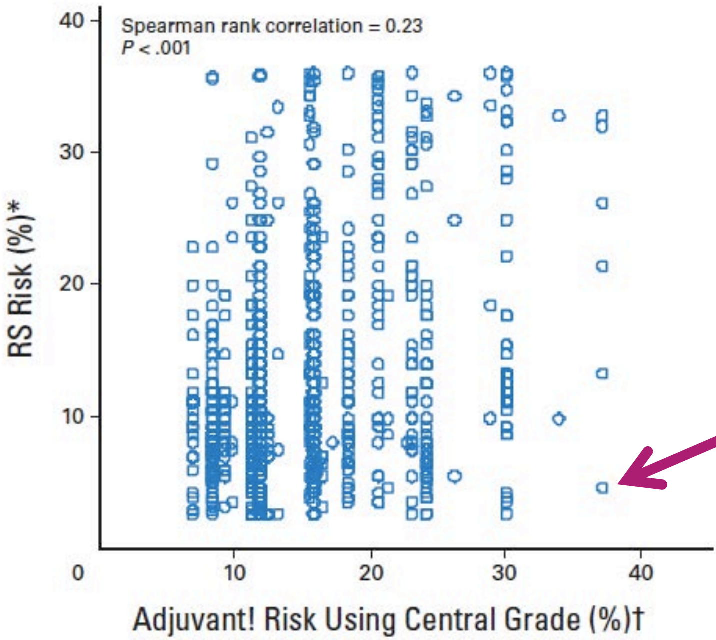
Onco*type* DX Node Neg until TAILORx

Recurrence Score as a Continuous Predictor



Also gives single gene scores for ER, PgR and HER2

Lack of correlation between estimates of DR risk with Oncotype RS and Adjuvant Online: Node negative



LRΔX^2 = 21.9, p<0.001
for each
AND <5% overlap

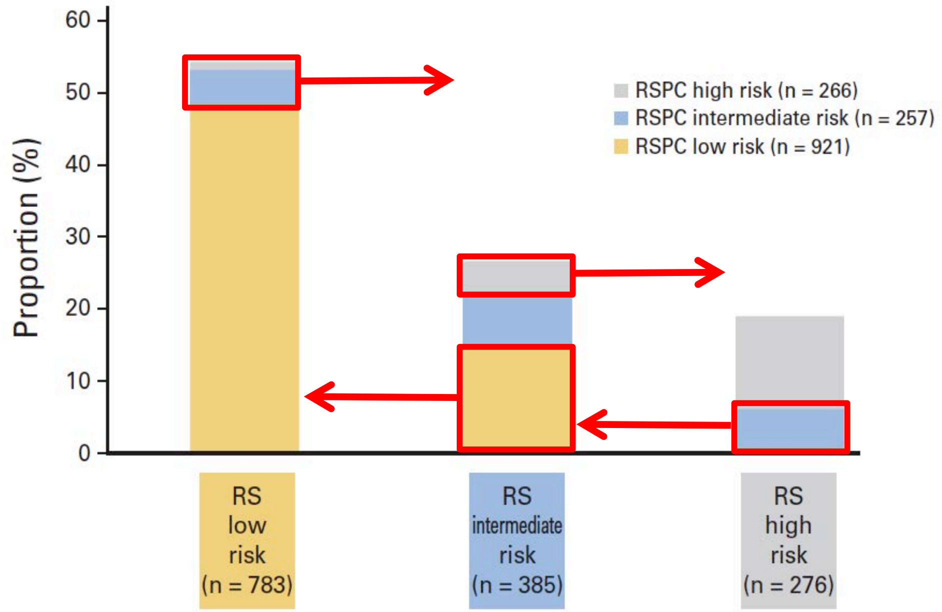
Adjuvant! 37%
RS 4%
Integrate

Predicted risk of recurrence by recurrence score (RS) and Adjuvant! N0 patients (n=872). (*) Predicted risk of distant recurrence at 10 years from RS. (†) Predicted risk of recurrence at 10 years from Adjuvant!

Dowsett et al, JCO, 2010, 28, 1829-34

RS vs RSPC (for N-ve: RS+age/grade/T/Rx)

“The RSPC model had significantly improved prognostic value compared with a model using RS alone (P<.001)”



Tang et al, JCO, 2011: 29, 4365: NSABP-B14 and TransATAC metanalysis

JAMA Oncology | Original Investigation

Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer
A Secondary Analysis of a Randomized Clinical Trial

Ivana Sestak, PhD; Richard Buus, PhD; Jack Cuzick, PhD; Peter Dubsky, MD; Ralf Kronenwett, MD; Carsten Denkert, MD; Sean Ferree, PhD; Dennis Sgroi, MD; Catherine Schnabel, PhD; Frederick L. Baehner, MD; Elizabeth Mallon, PhD; Mitch Dowsett, PhD

2018, 4, 545-553

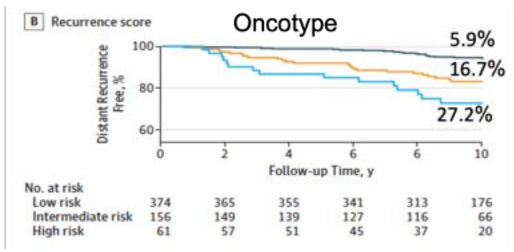
Oncotype DX
vs
Prosigna
vs
EndoPredict

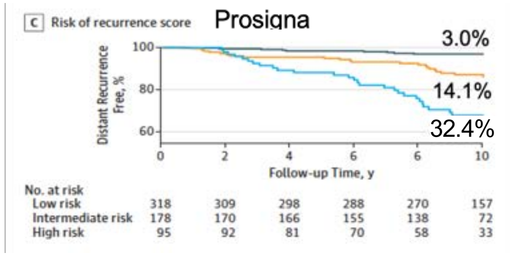
Conducted using commercial assays

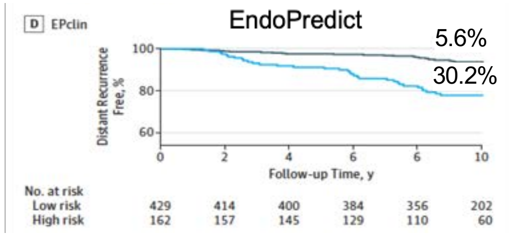
	Node-negative (N=591)	Node-positive (N=227)
Mean age, years (SD)	63.4 (7.9)	67.2 (8.2)
Mean BMI, kg/m^2 (SD)	27.3 (4.9)	27.1 (5.0)
Grade		
1	23.2%	18.9%
2	59.7%	61.2%
3	17.1%	19.8%
Mean tumour size, mm (SD)	17.6 (8.5)	25.7 (13.6)
Distant recurrence		
0-10 years	60 (10.2%)	66 (29.1%)
5-10 years	34 (5.7%)	31 (13.7%)

Direct comparison of tests in TransATAC node negative: risk years 0-10 & risk years 5-10

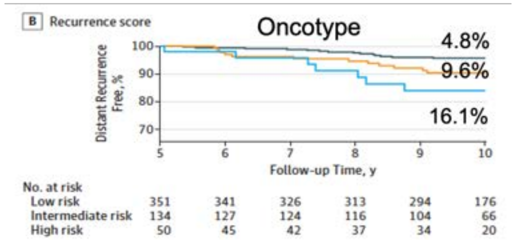
Test-specified categories; years 0-10

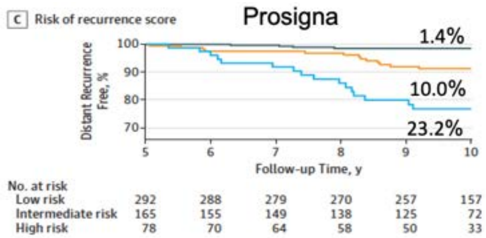


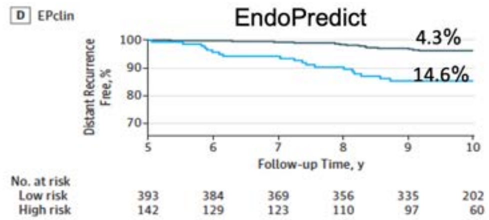




Test-specified categories; years 5-10







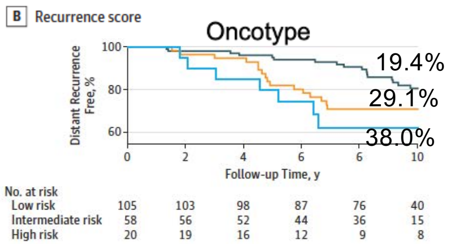
(Sestak et al, JAMA Oncol, 2018, 4, 545-553)

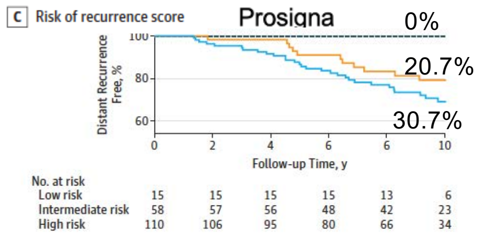
prosigna® Breast cancer gene signature assay

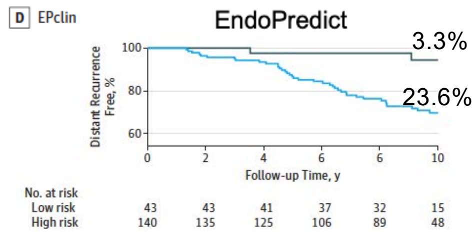
veracyte.

Direct comparison of tests in TransATAC node positive: risk years 0-10 & risk years 5-10

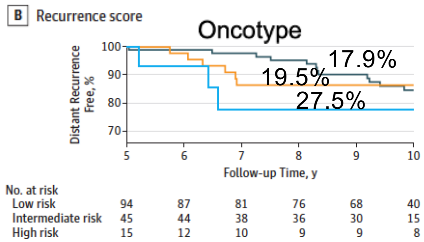
Test-specified categories; years 0-10

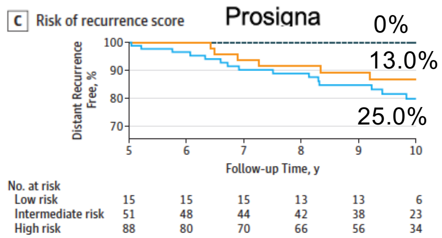


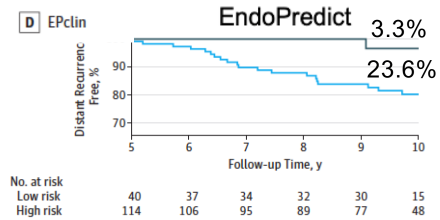




Test-specified categories; years 5-10





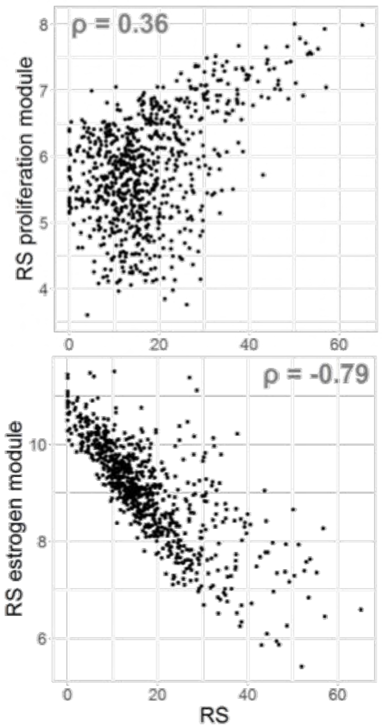


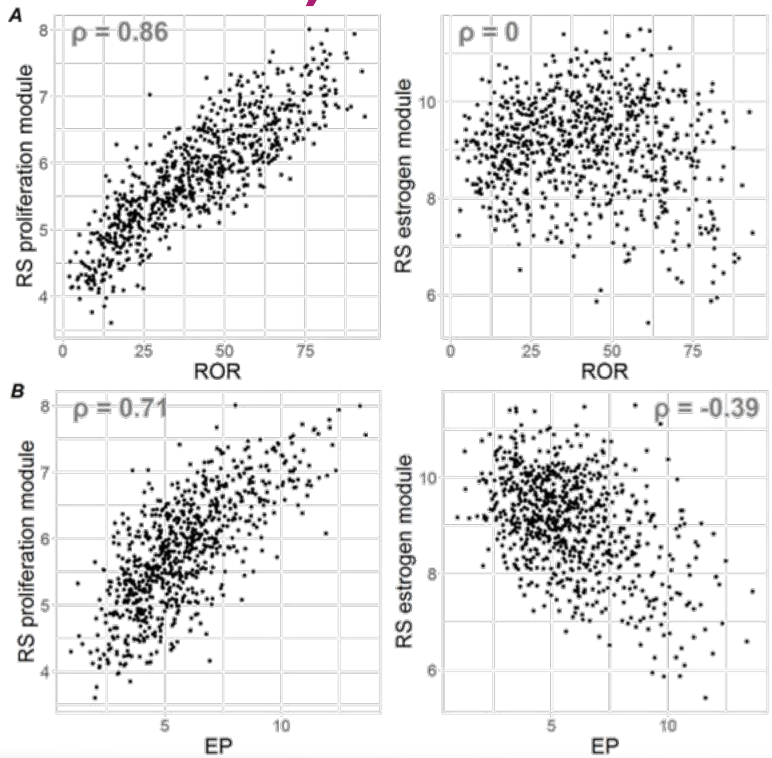
(Sestak et al, JAMA Oncol, 2018, 4, 545-553)

prosigna® Breast cancer gene signature assay

veracyte.

Relationship of scores with proliferation and estrogen pathways (RS modules)



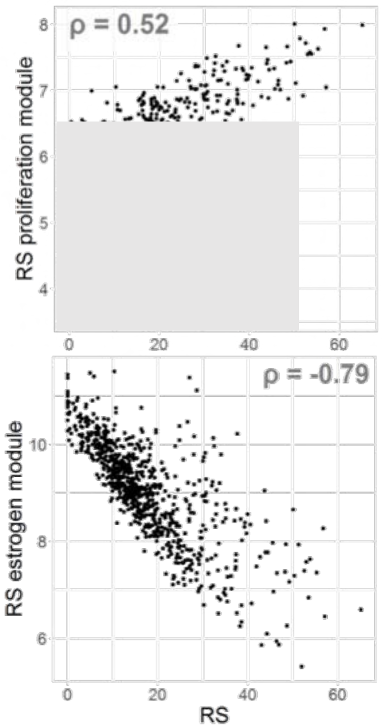


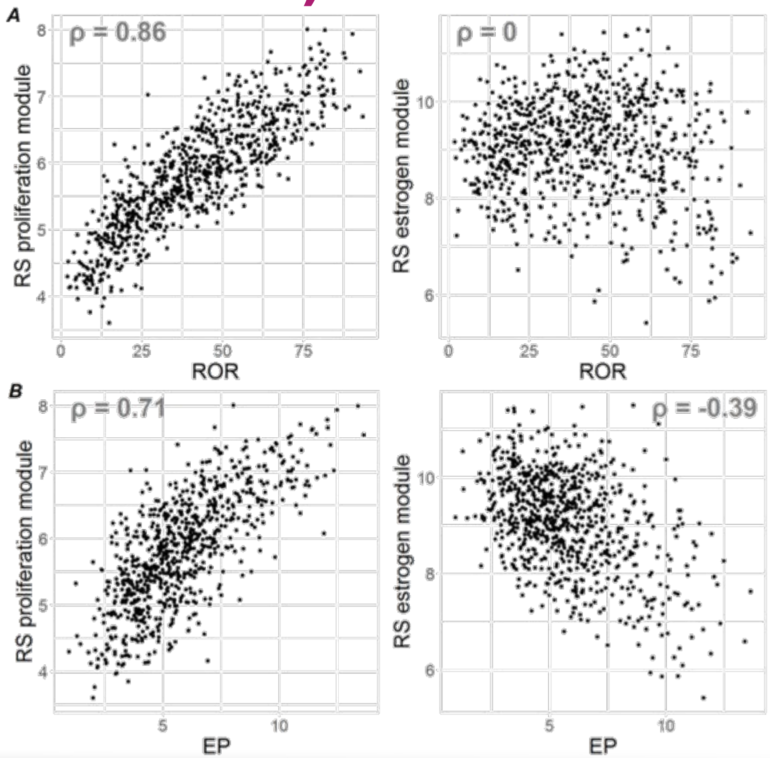
Buus et al, 2019

prosigna® Breast cancer gene signature assay

veracyte.

Relationship of scores with proliferation and estrogen pathways (RS modules)





Buus et al, 2019

How much notice to take of the chemotherapy benefit prediction in node-negative patients?

prosigna® Breast cancer gene signature assay

veracyte

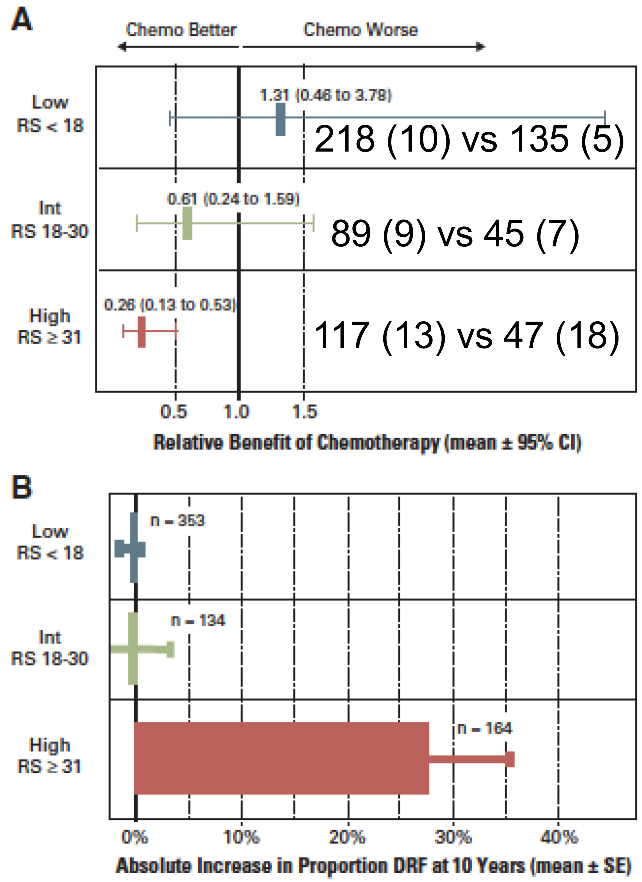
Oncotype DX and benefit from chemotherapy

NICE (2013 guidance)

"In the absence of robust data the Committee concluded that equal benefit of chemotherapy should be assumed across all Oncotype DX risk groups."

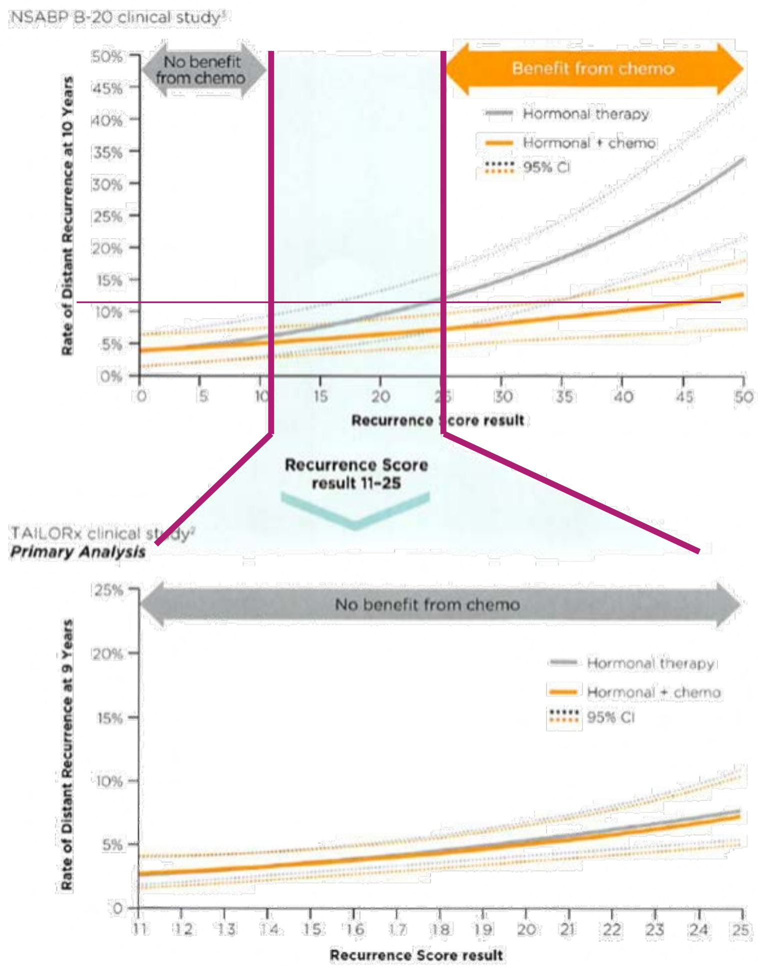
NICE (2018 guidance: post-TAILORx)

"The only evidence available to show a relative treatment effect for chemotherapy across different risk groups was for Oncotype DX, and the evidence included in the diagnostics assessment report was weak because it was at high risk of bias from potential confounding."



Paik et al JCO, 2006, 24, 3726

Absolute chemotherapy benefit shows the extent to which chemotherapy reduces the risk of your breast cancer coming back



The NSABP B-20 study shows that patients with **Recurrence Score* results 0–10 will not receive a benefit from chemotherapy...**

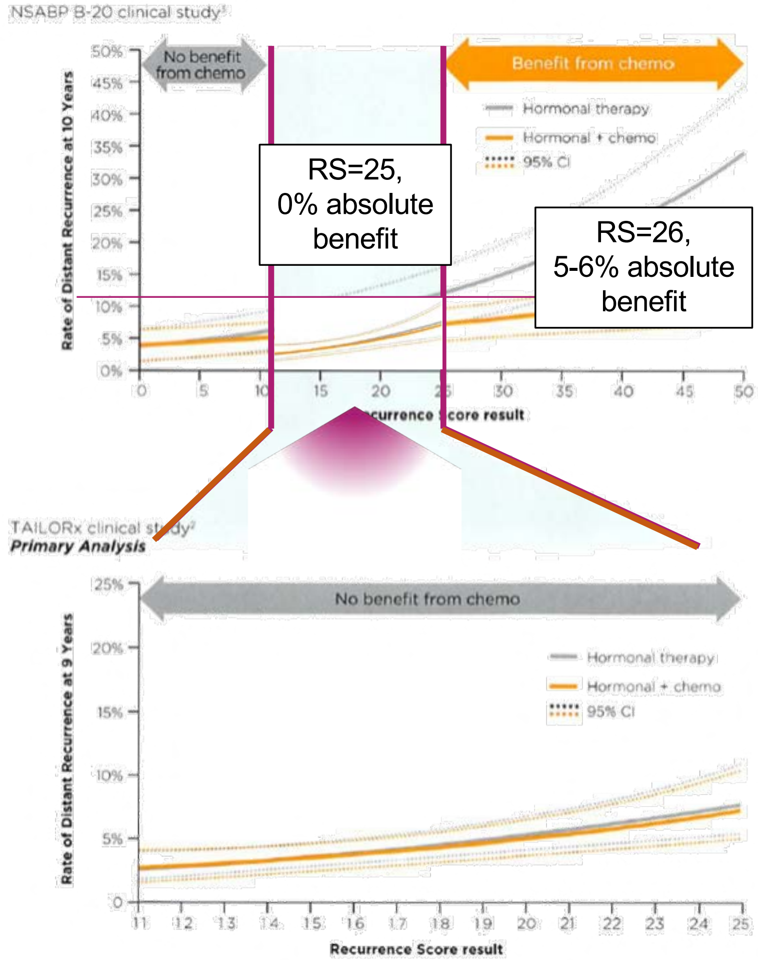
...while those with **Recurrence Score results 26–100 will receive a benefit from chemotherapy.**[3,4,7]

The TAILORx study shows that patients with **Recurrence Score results 11-25 will not receive an additional benefit from chemotherapy (over hormonal therapy alone).***[2]

prosigna® Breast cancer gene signature assay

veracyte.

Absolute chemotherapy benefit shows the extent to which chemotherapy reduces the risk of your breast cancer coming back



The NSABP B-20 study shows that patients with **Recurrence Score* results 0–10 will not receive a benefit from chemotherapy...**

...while those with **Recurrence Score results 26–100 will receive a benefit from chemotherapy.**[3,4,7]

The TAILORx study shows that patients with **Recurrence Score results 11-25 will not receive an additional benefit from chemotherapy (over hormonal therapy alone).***[2]

prosigna® Breast cancer gene signature assay

veracyte.

Acknowledgements

- Iva Sestak
- Jack Cuzick
- Richard Buus
- Elena Lopez-Knowles
- ATAC Trialists and TransATAC committee
- Colleagues at GHI, Nanostring, Myriad