

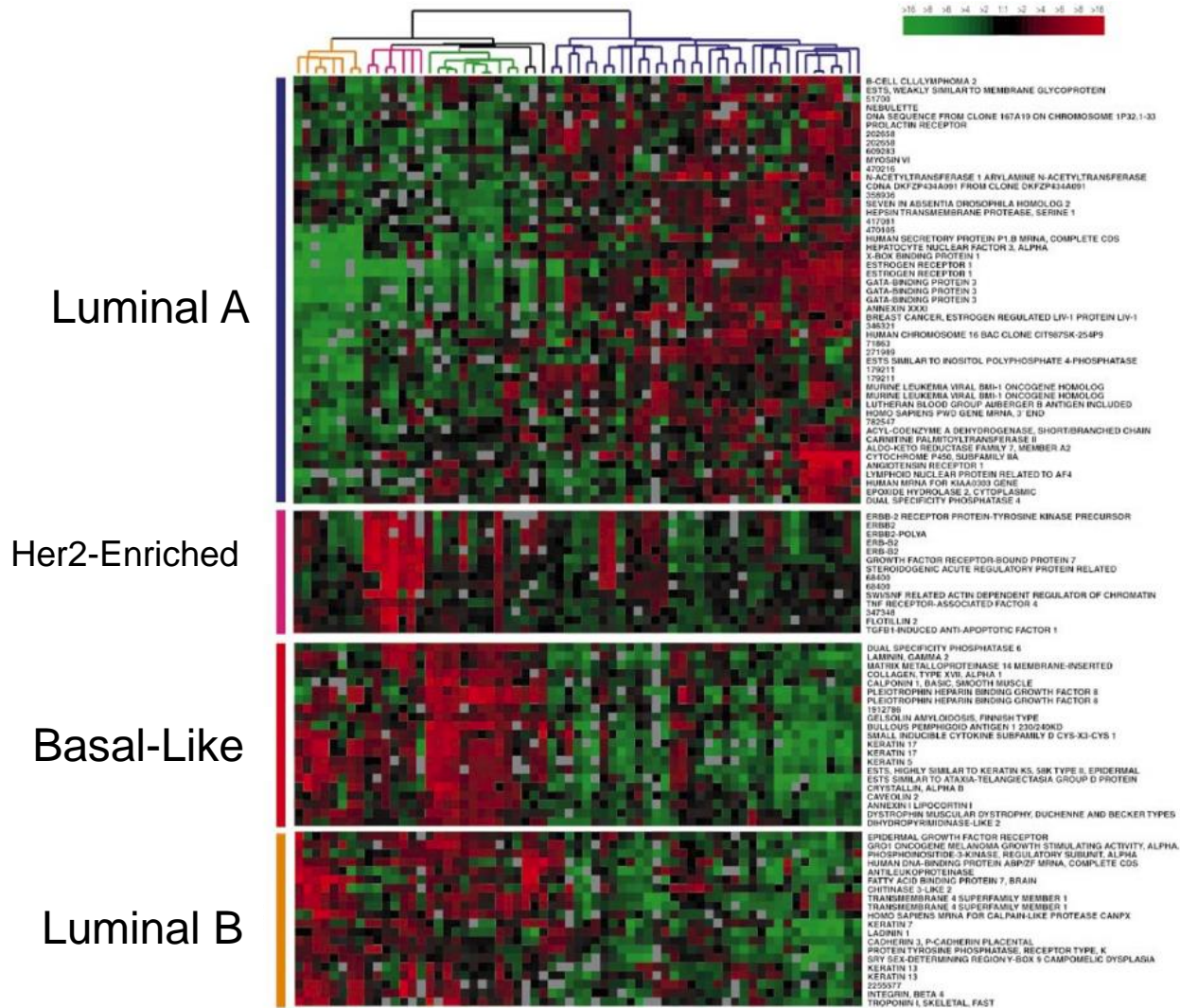


# Gene Expression Profiling in Breast Cancer

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**Tehran-Iran**  
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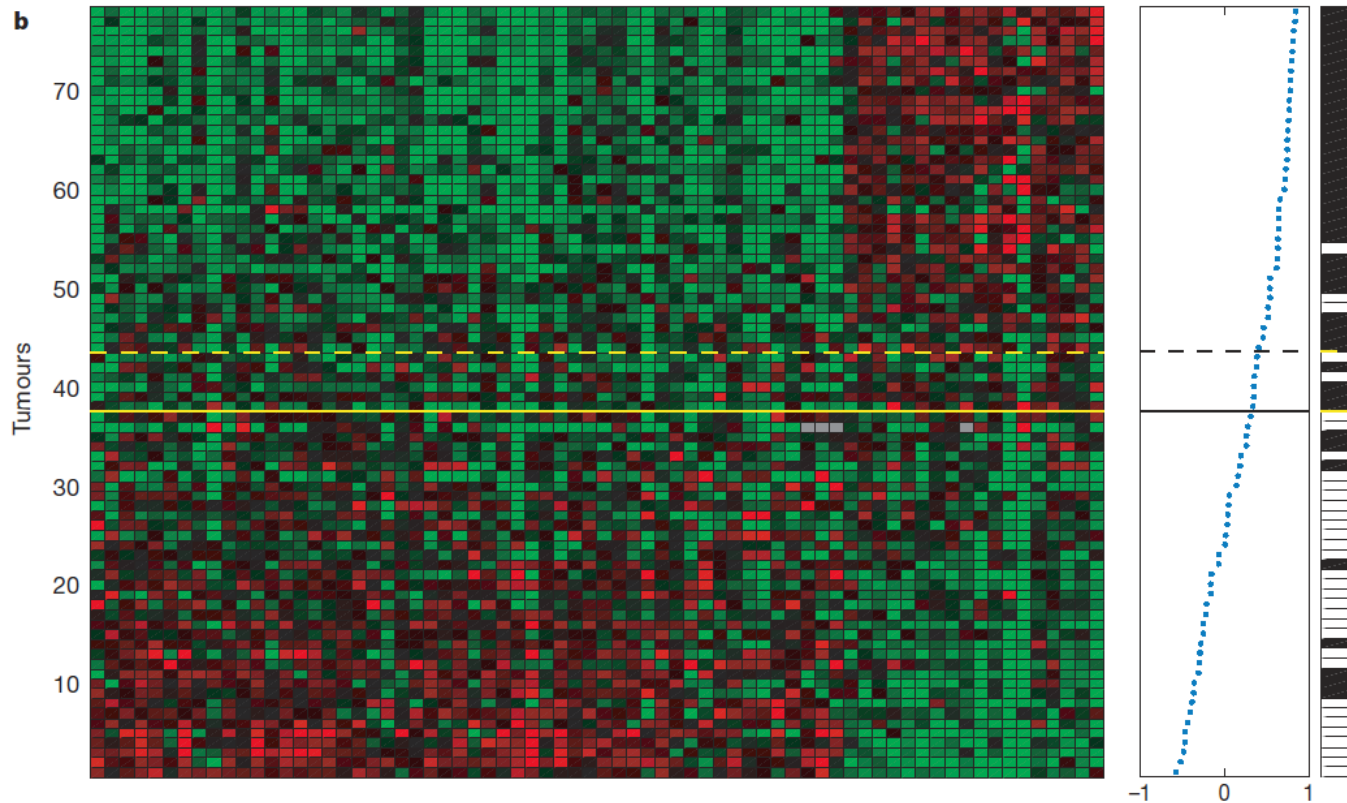
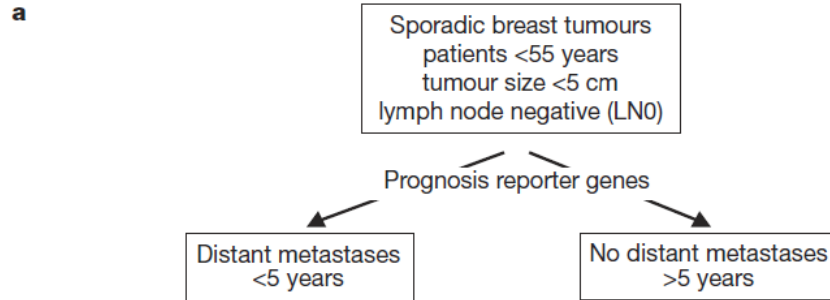
# Intrinsic Subtypes of BC:



# Intrinsic Subtypes vs IHC:

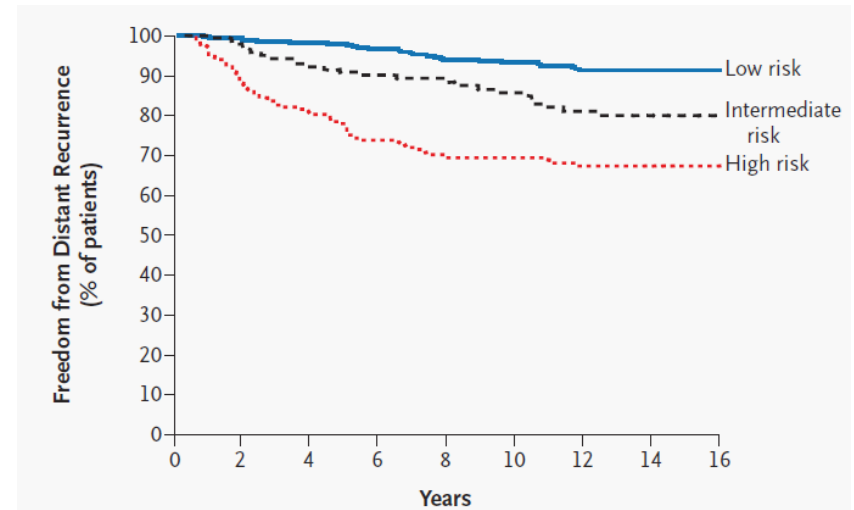
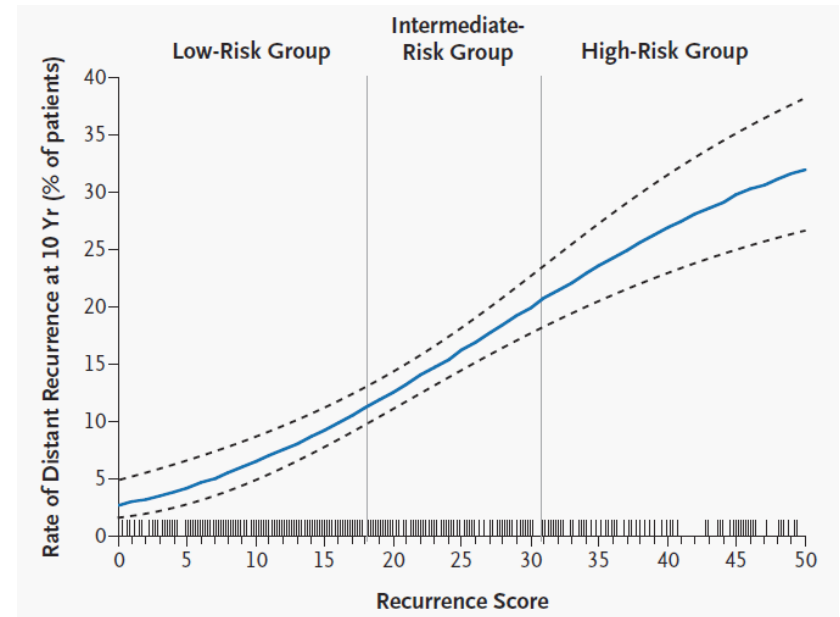
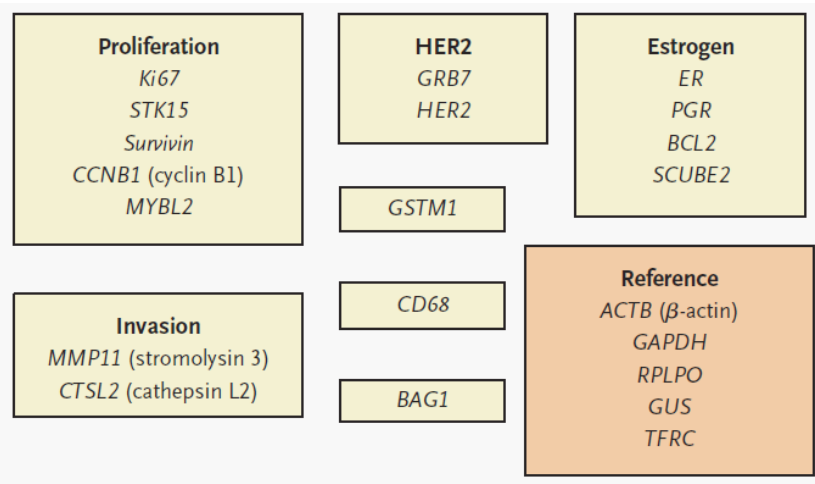
Intrinsic subtypes (GEP)	IHC classification (St Gallen)	Agreement IHC/GEP
Luminal A	'Luminal A' ER and/or PR positive HER2 negative Ki-67 <14%	73%–100%
Luminal B	'Luminal B (HER2 negative)' ER and/or PR positive HER2 negative Ki-67 ≥14% 'Luminal B (HER2 positive)' ER and/or PR positive Any Ki-67 HER2 over-expressed or amplified	73%–100%
HER2-enriched	'HER2 positive (non-luminal)' HER2 over-expressed or amplified ER and PR absent	41%–69%
Basal-like	'Triple negative' ER and PR absent HER2 negative	80%

# Mammaprint:



Veer et al., 2002

# Oncotype:

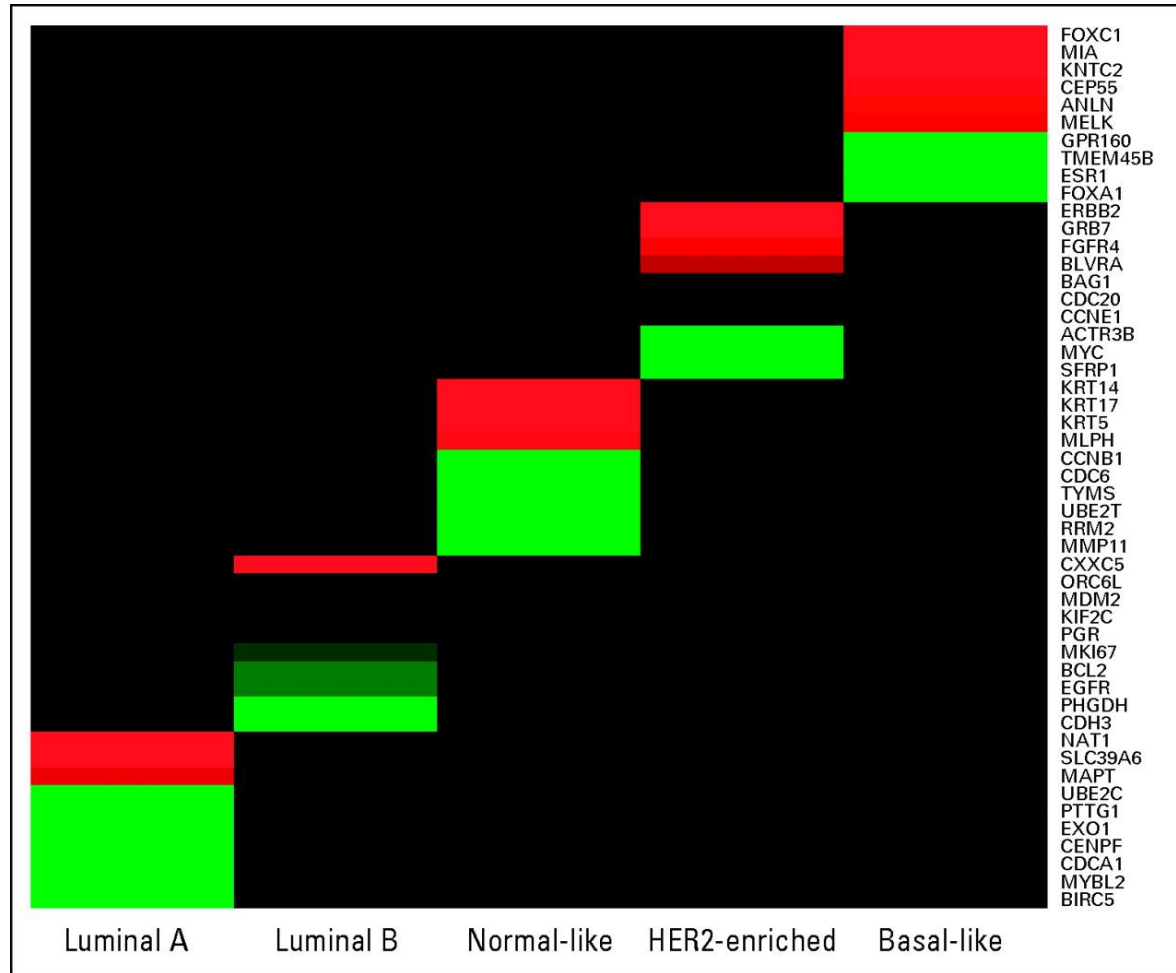


No. at Risk	0	2	4	6	8	10	12	14	16
Low risk	338	328	313	298	276	258	231	170	38
Intermediate risk	149	139	128	116	104	96	80	66	16
High risk	181	154	137	119	105	91	83	63	13



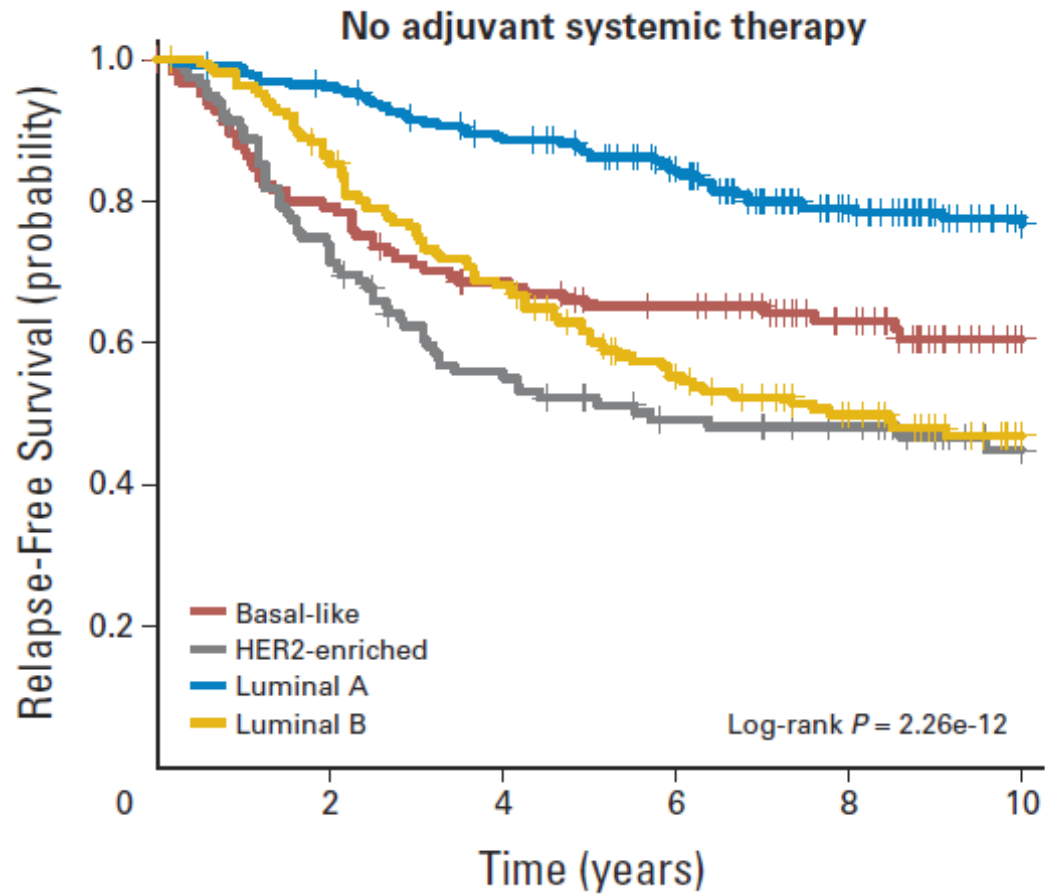
Paik et al., 2004

# PAM50:

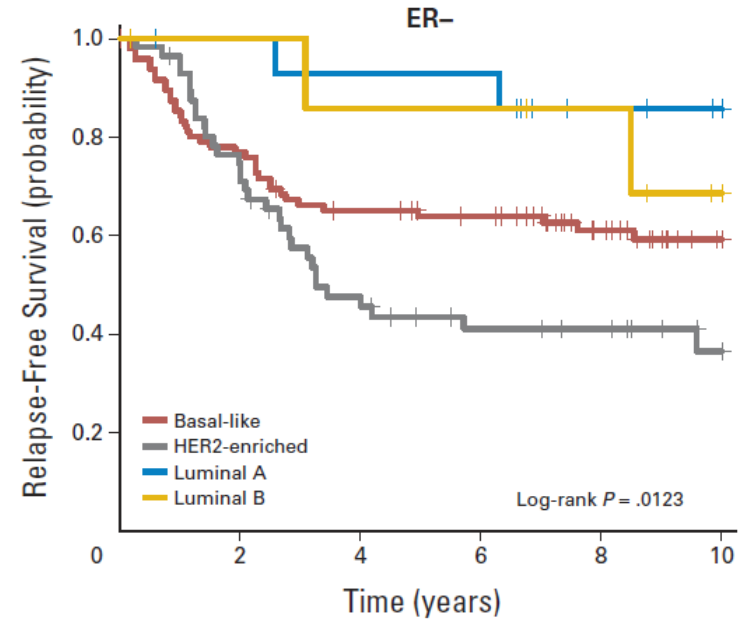
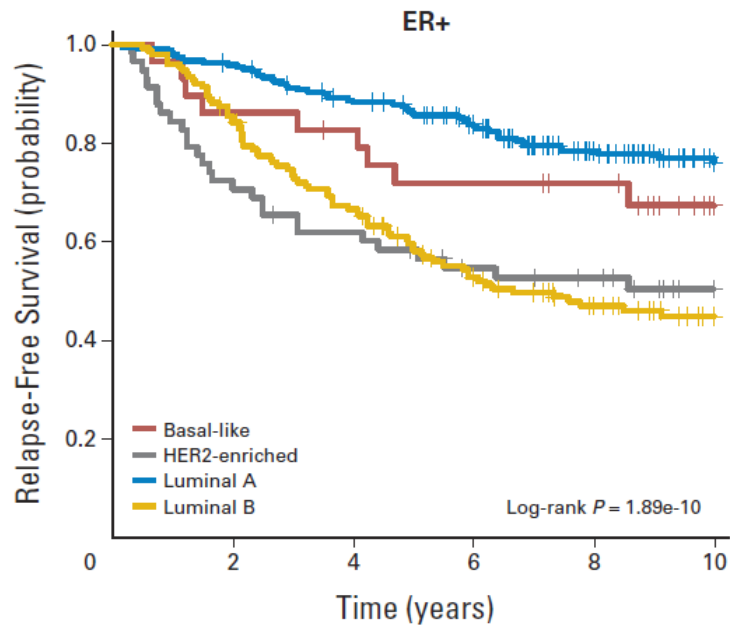




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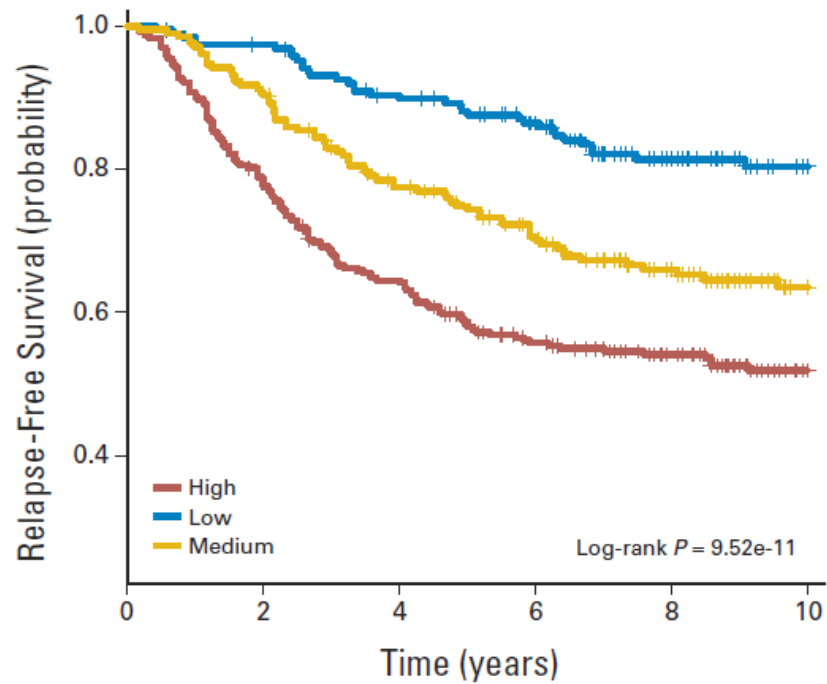
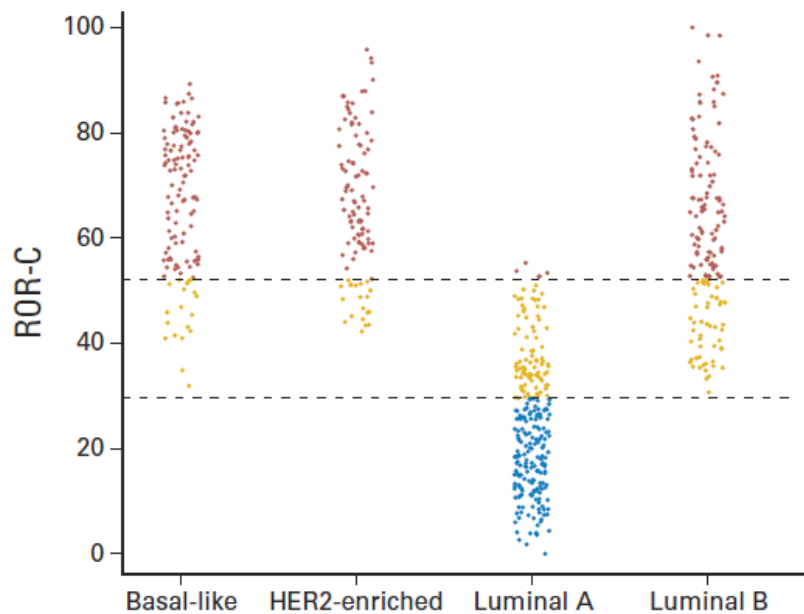


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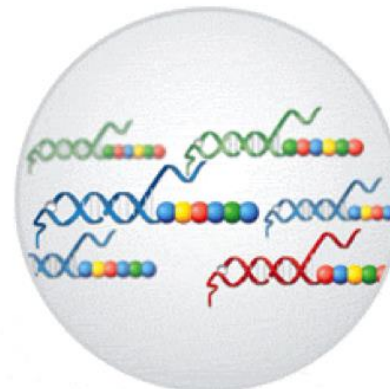
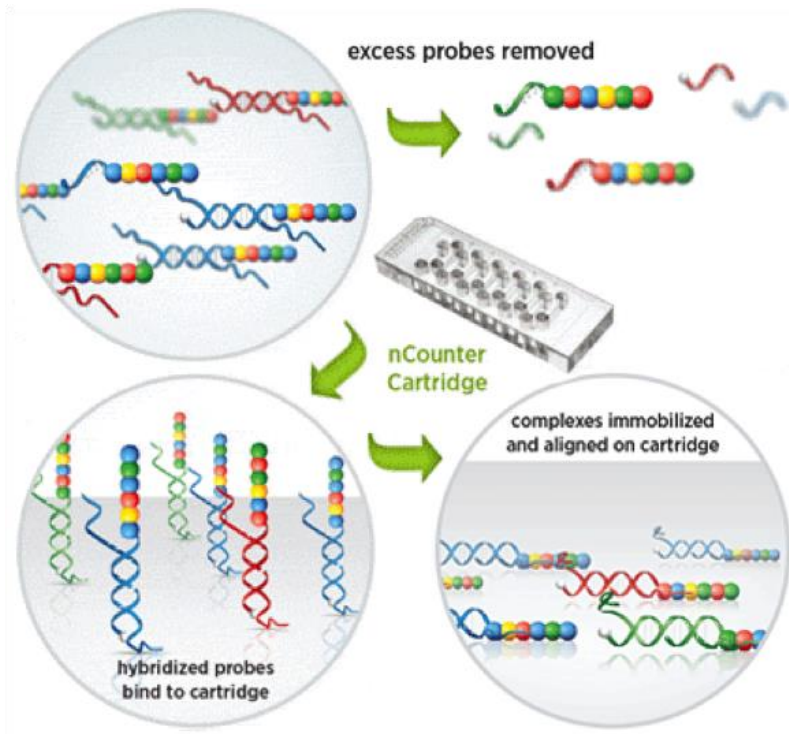




# PAM50 (ROR):

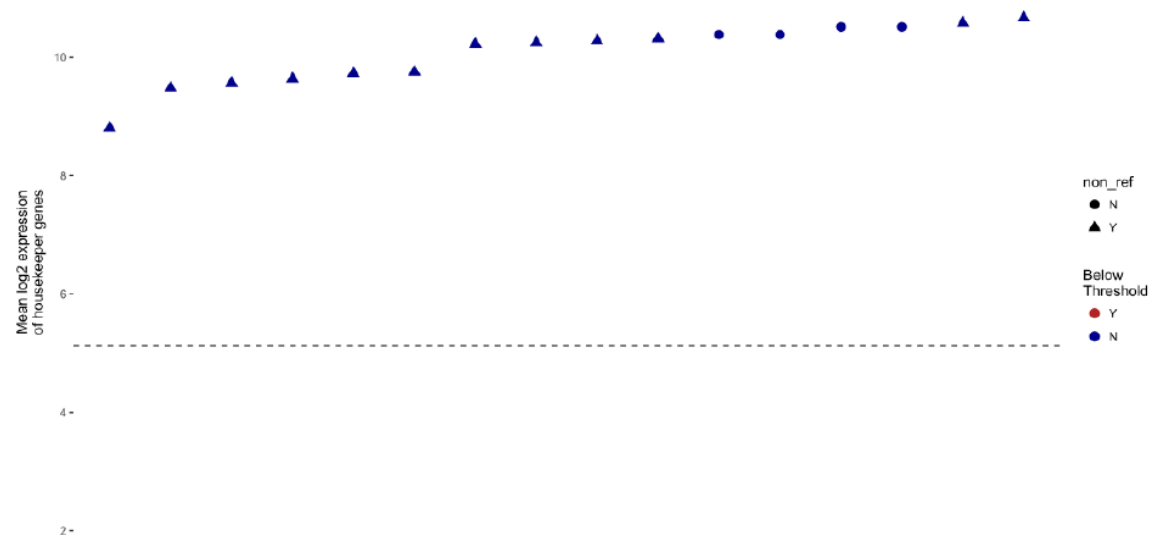
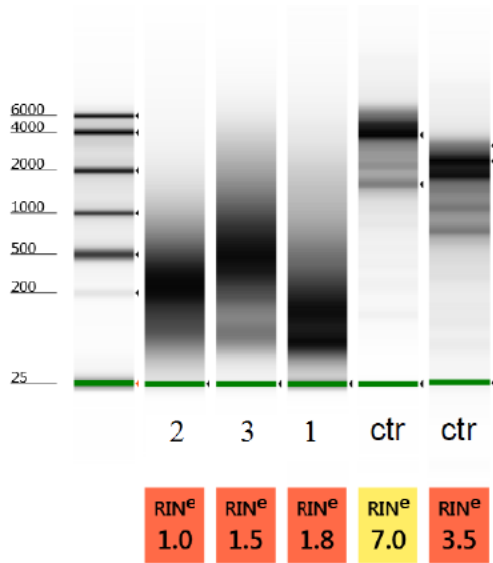


# Nanostring (Prosigna):



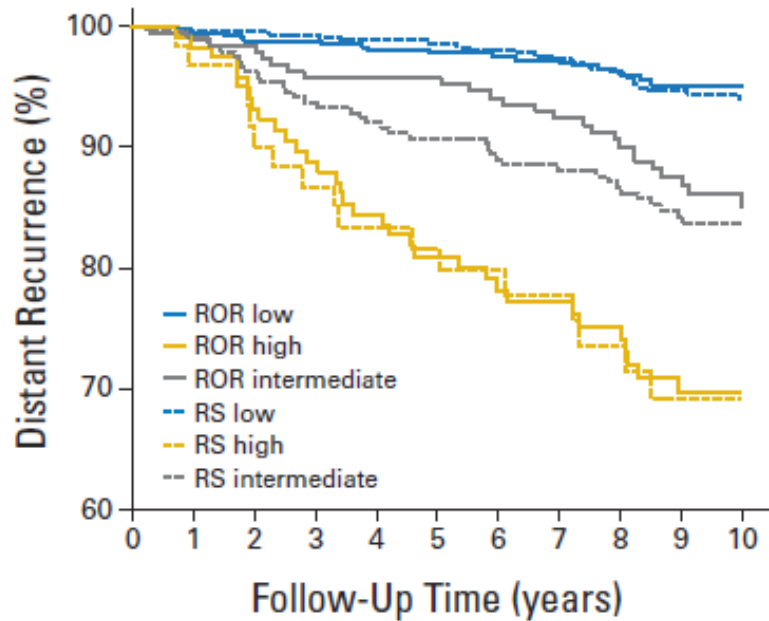
Barcode	Counts	Identity
	3	XLSA
	2	FOX5
	1	INSULIN

# Nanostring (Prosigna):

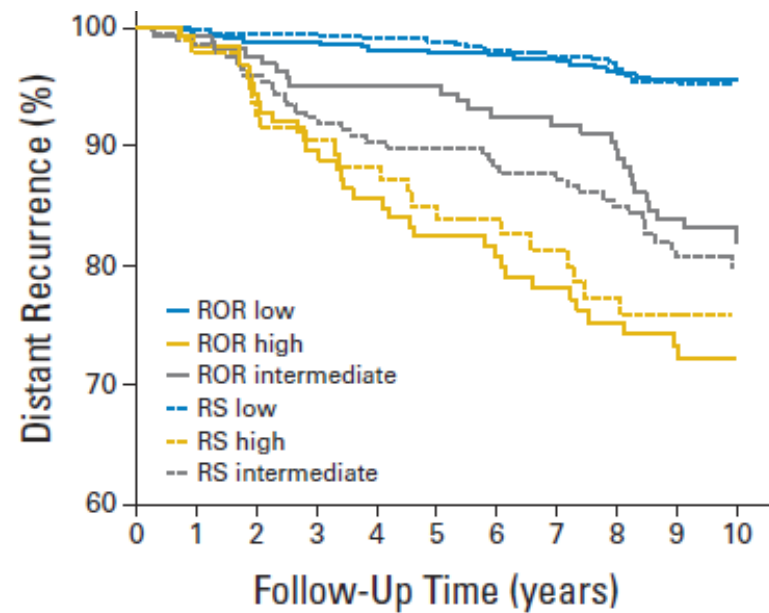


Sample ID	Molecular Subtype	Proliferation Score	Tumour Size (mm)	ROR (Prosigna) Score
1	HER2-enriched	6.67	2.5	65
2	Luminal B	6.64	20	82
3	Luminal A	4.67	15	21
4	HER2-enriched	6.37	23	83
5	Basal-like	6.65	21	55
6	HER2-enriched	6.25	40	56
7	Luminal A	4.15	7	13
8	Luminal A	3.81	33	43
9	Basal-like	9.19	23	53
10	Luminal A	4.23	14	36

# ROR vs RS: ATAC Trial

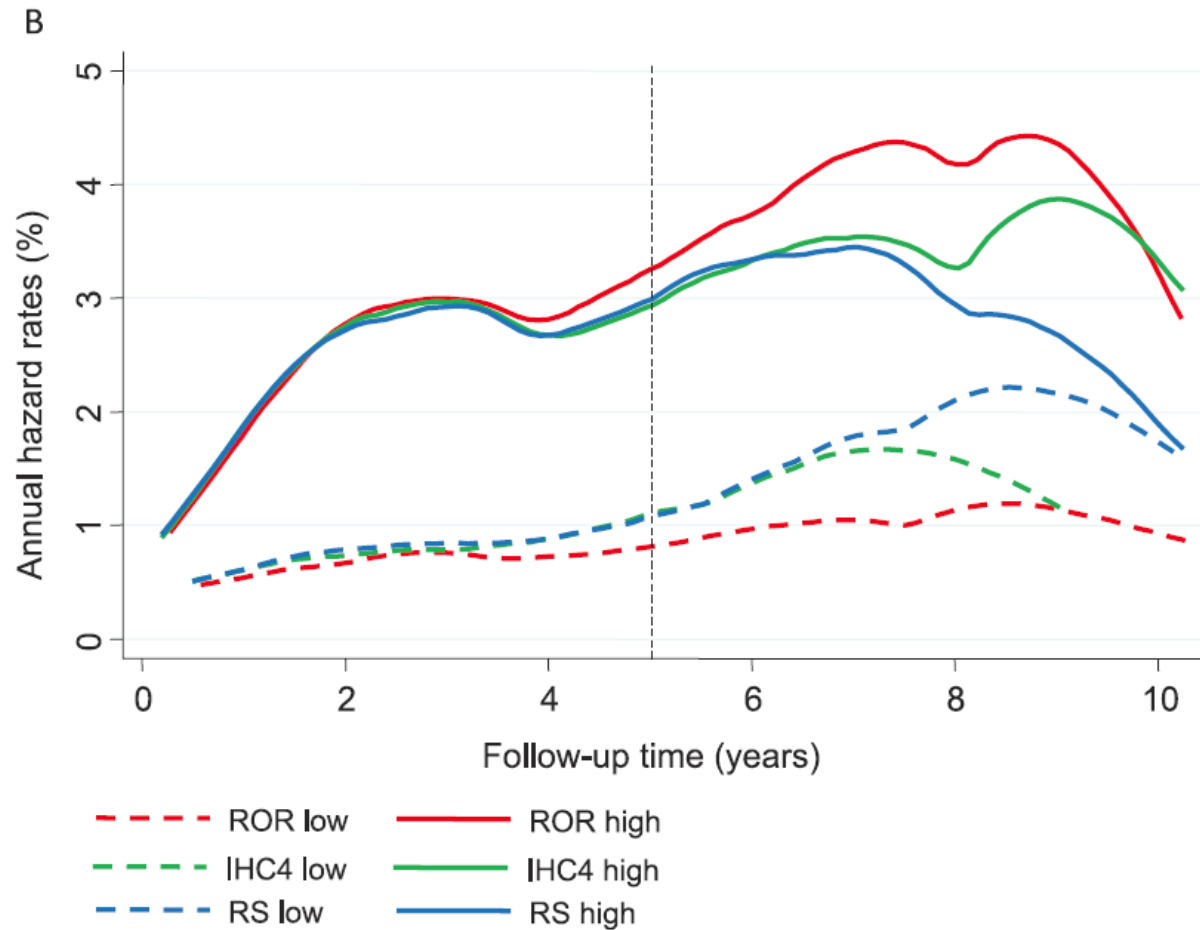


Without Tumour Size

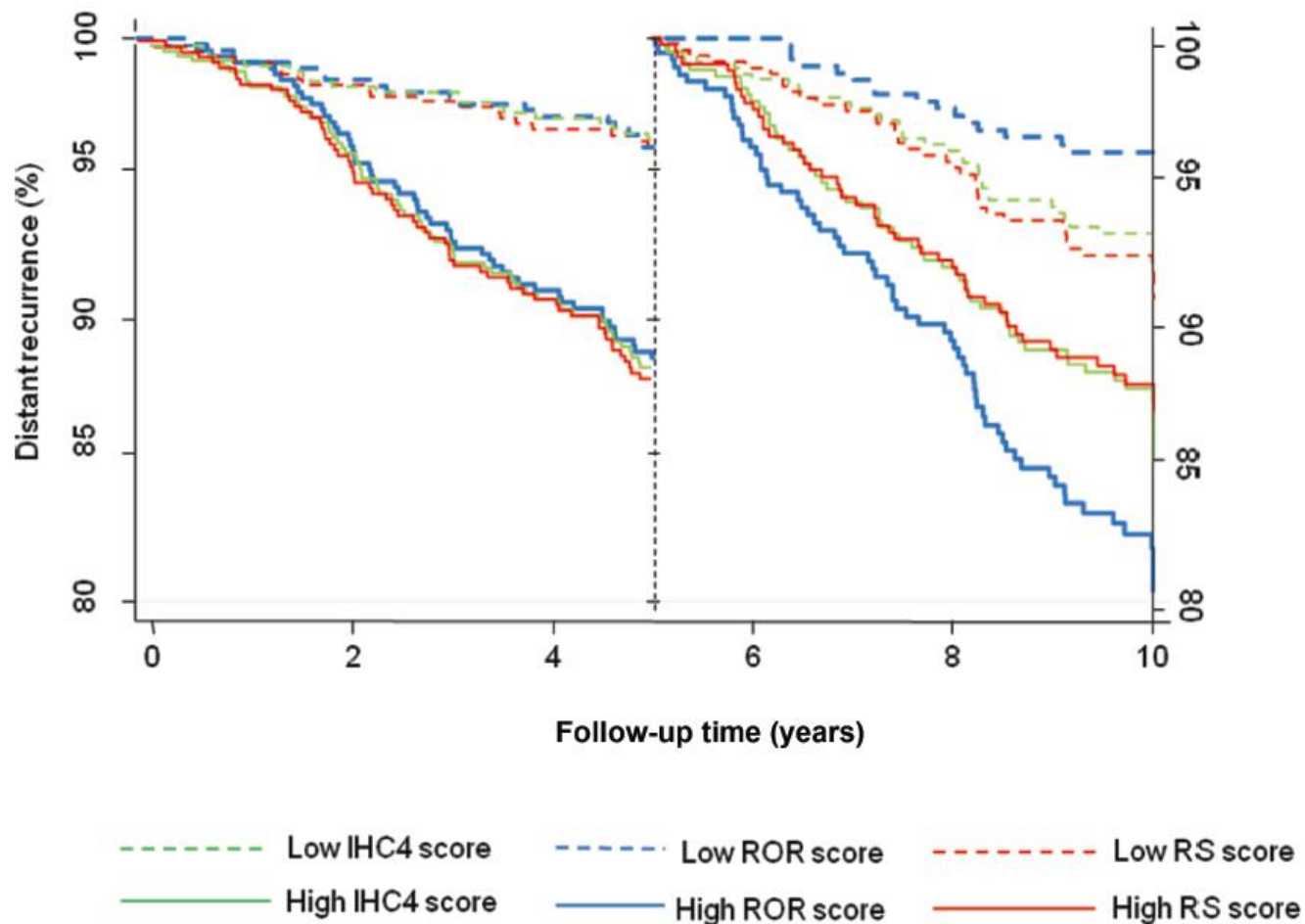


With Tumour Size

# ROR vs RS: ATAC Trial



# ROR vs RS: ATAC Trial



# ROR vs RS:

Prosigna	Oncotype Dx		
	Low (20)	Intermed (16)	High (4)
Low (21)	15	6	0
Intermed (9)	4	5	0
High (10)	1	5	4

Annotations: Red arrows point from Prosigna Low to Oncotype Dx Low (15) and from Prosigna Intermed to Oncotype Dx Low (4). A blue arrow points from Prosigna Intermed to Oncotype Dx Intermed (5). A green arrow points from Prosigna High to Oncotype Dx High (4). A note states: "All Odx High are ProS High".

How the tests compared with Oncologists decisions around patient treatment...

How the two tests differed in their calls

Prosigna	Oncotype Dx		
	Low (20)	Intermed (16)	High (4)
Low (21)	15	1 / 6	0
Intermed (9)	4	1 / 5	0
High (10)	1 / 1	3 / 5	4 / 4

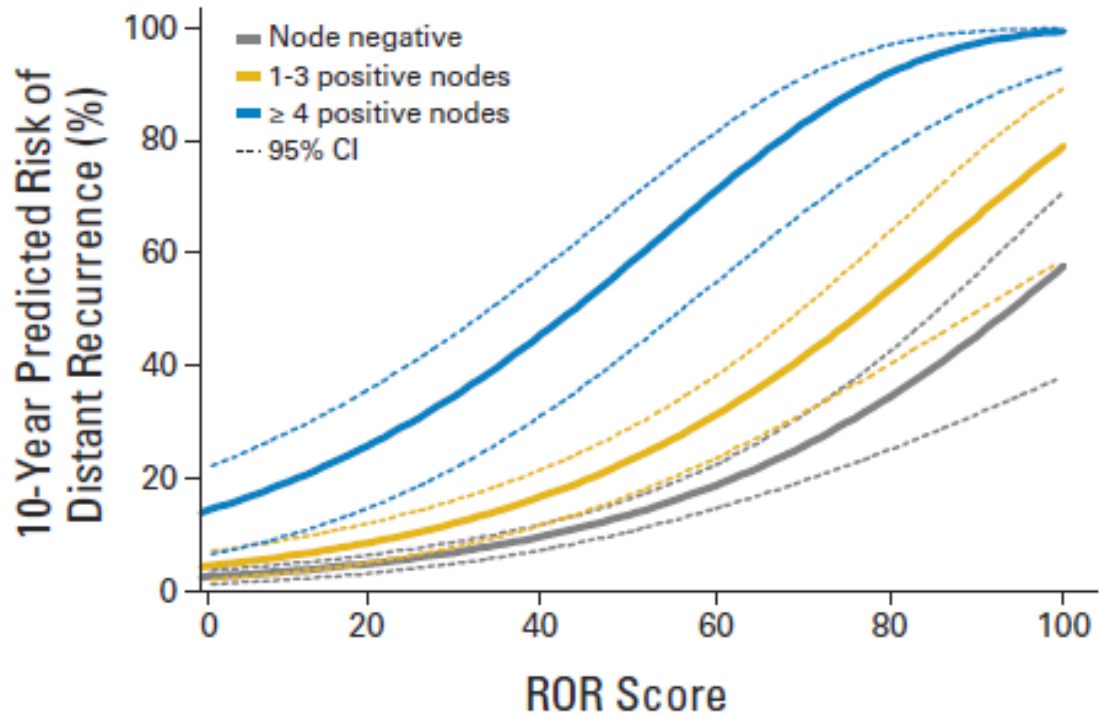
31%

11%

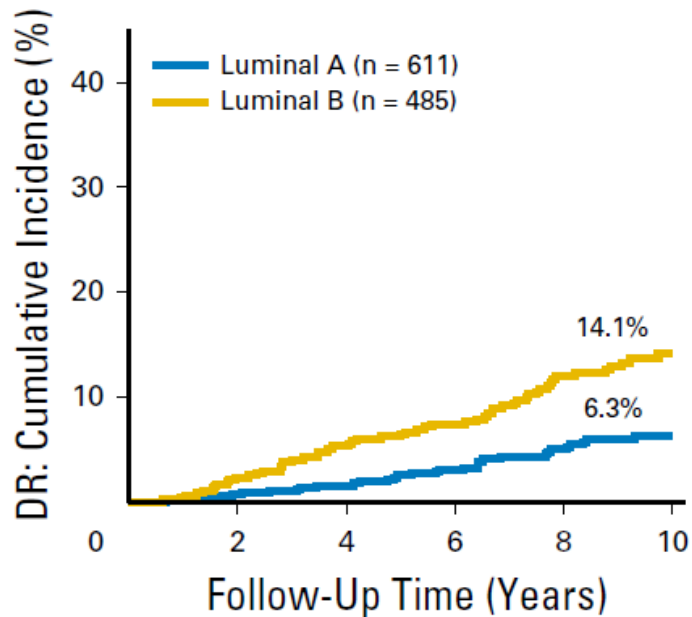
80%



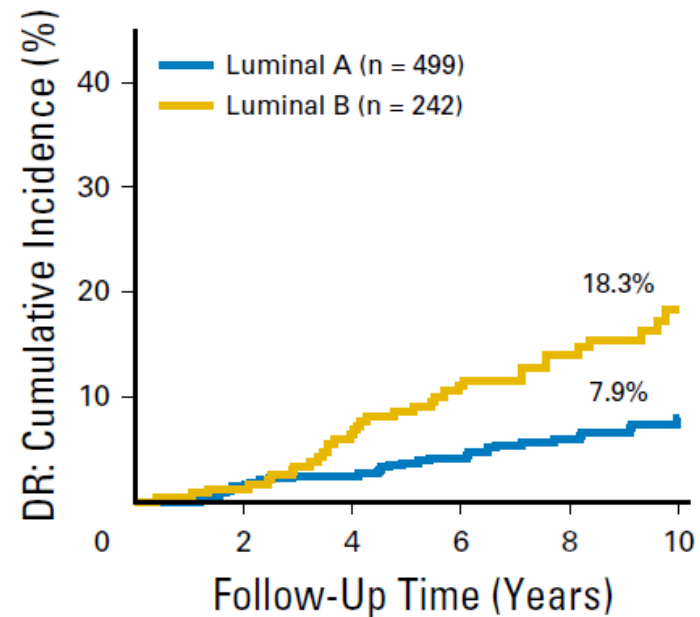
# Prosigna (ROR): ATAC Trial



# Prosigna (ROR): Danish Cohort

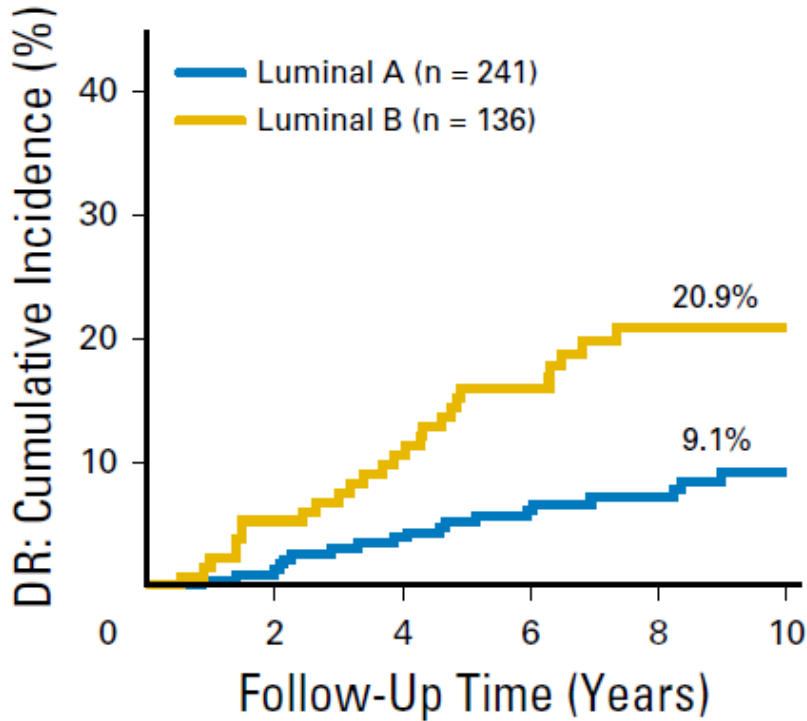


Zero Node

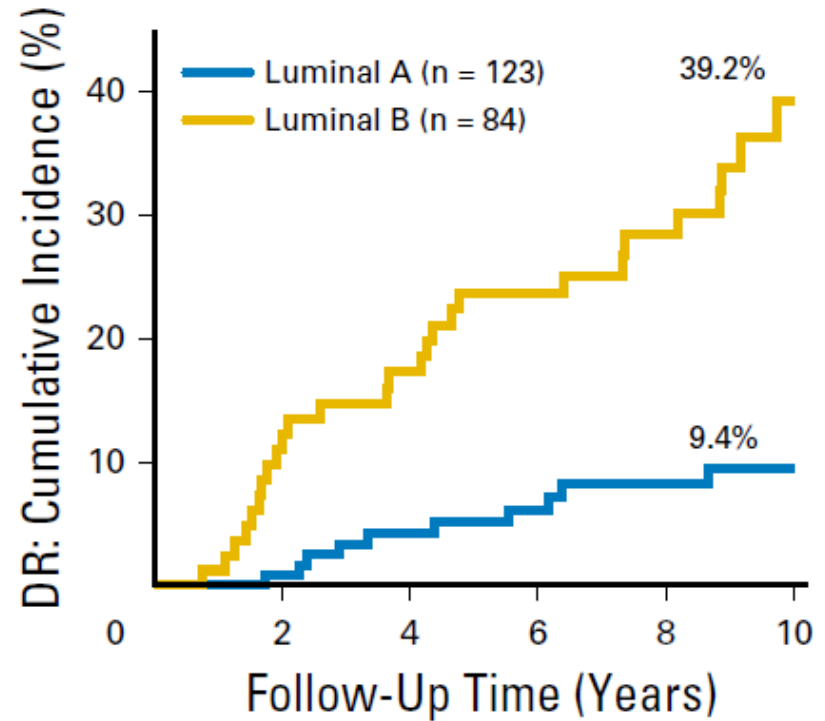


One Node

# Prosigna (ROR): Danish Cohort

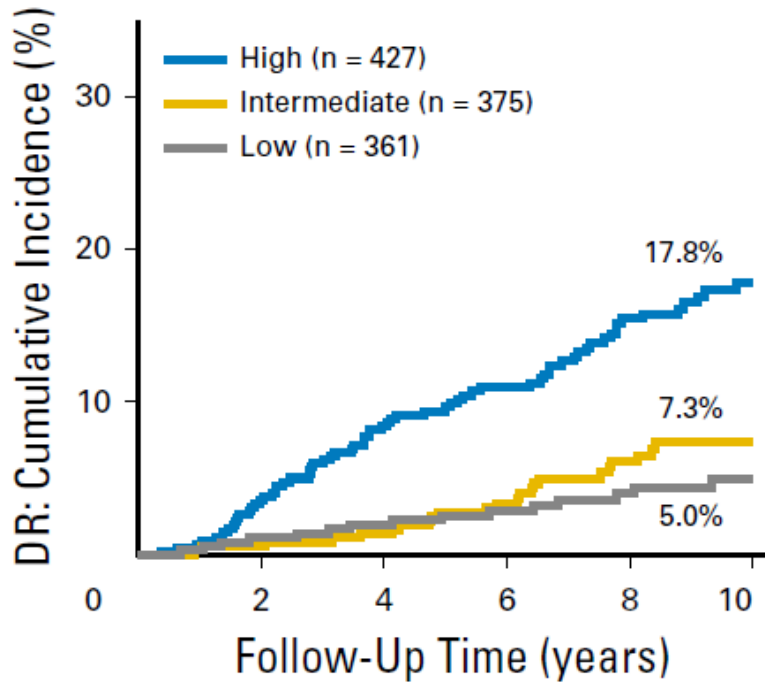


Two Nodes

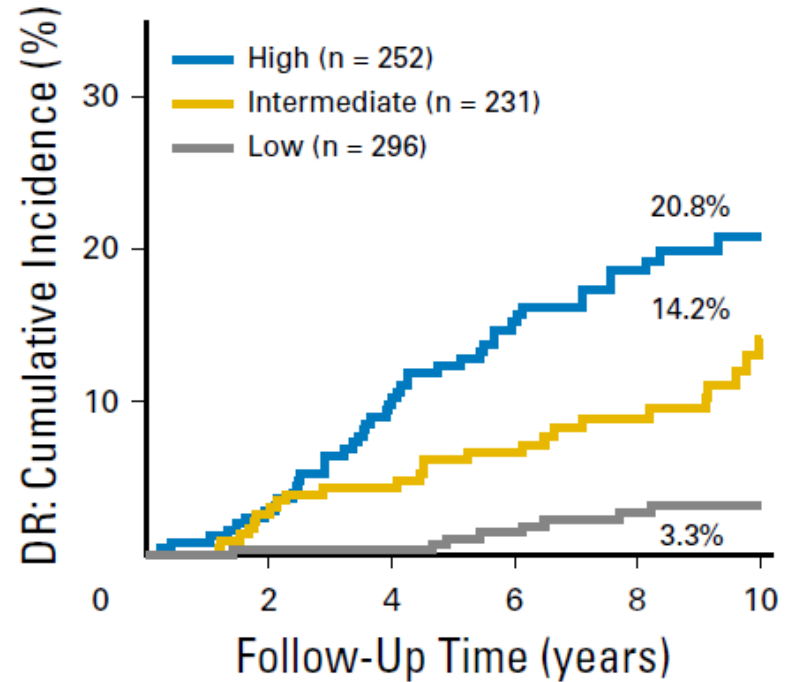


Three Nodes

# Prosigna (ROR): Danish Cohort

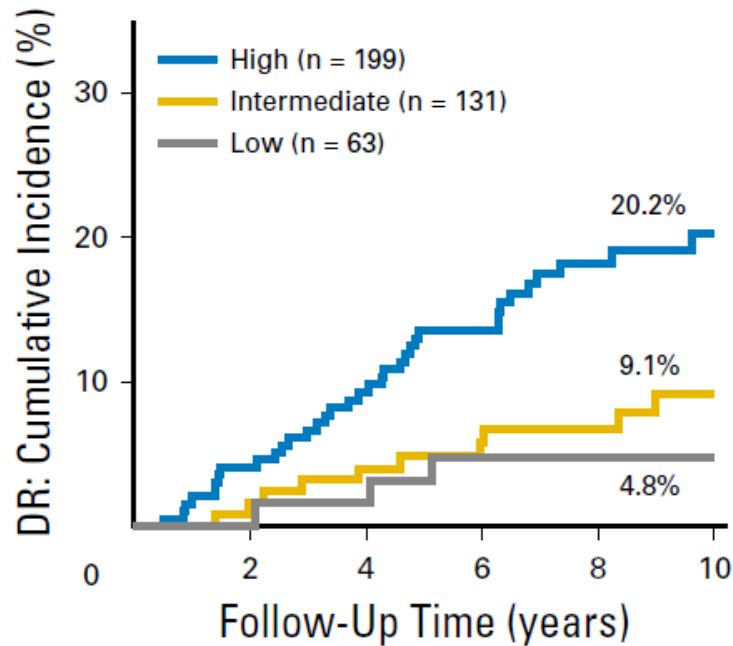


Zero Node

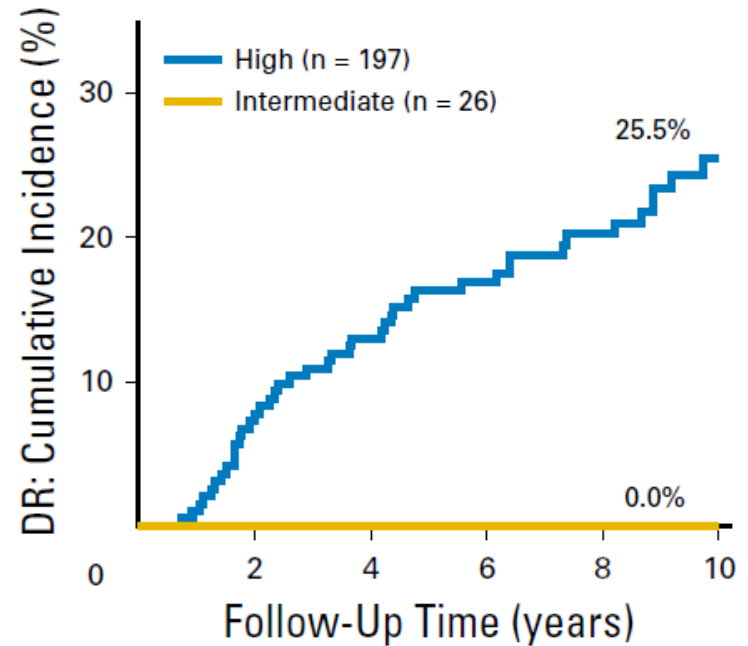


One Node

# Prosigna (ROR): Danish Cohort

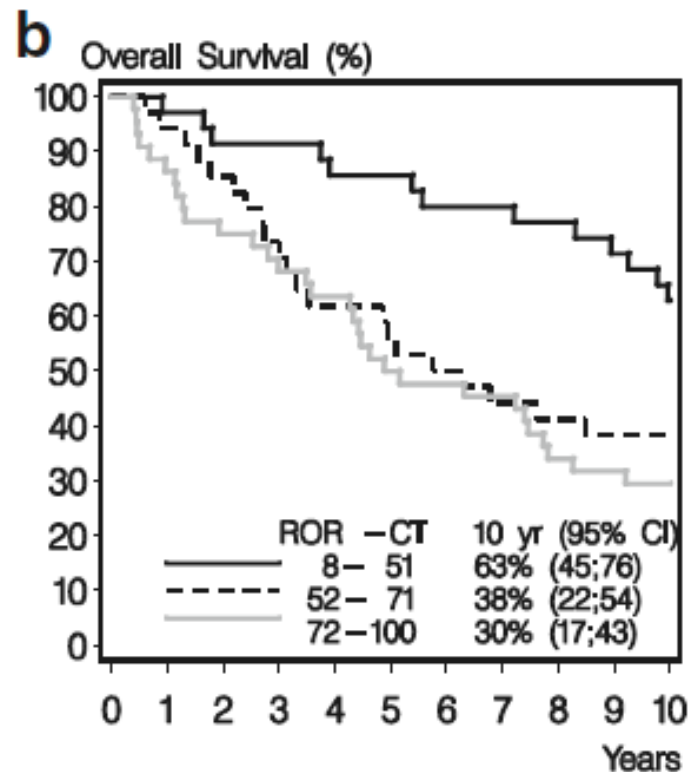
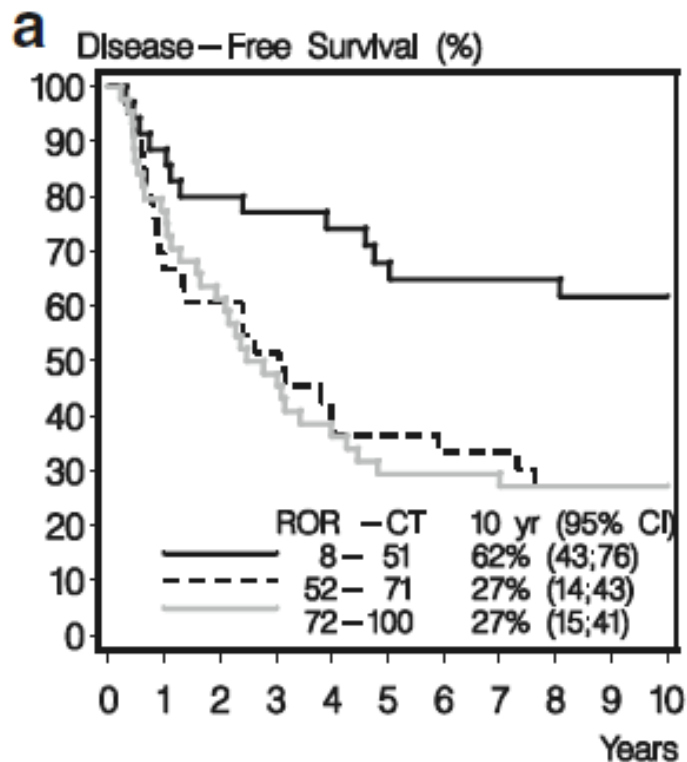


Two Node



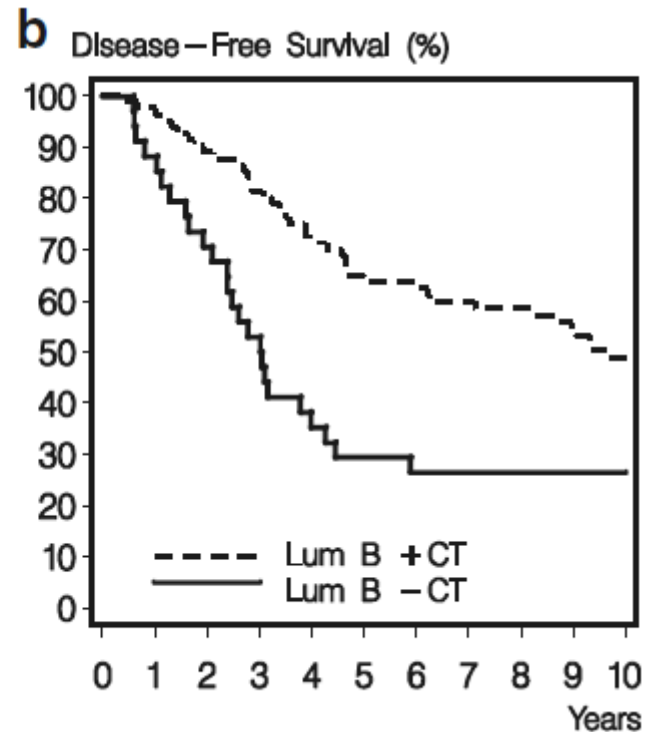
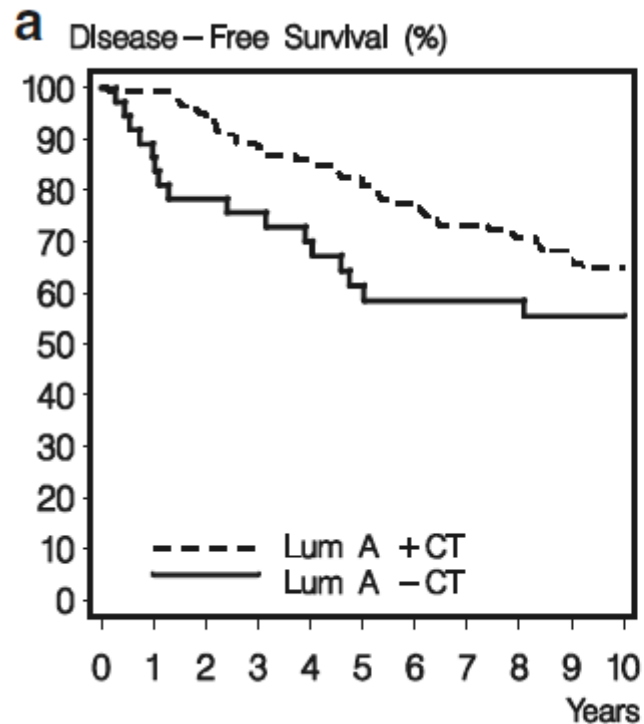
Three Nodes

# Prosigna (ROR): Danish Cohort



Premenopausal

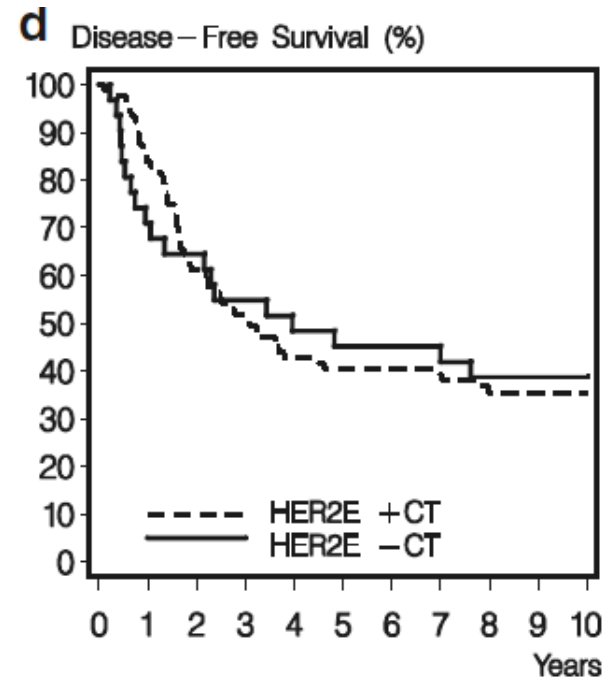
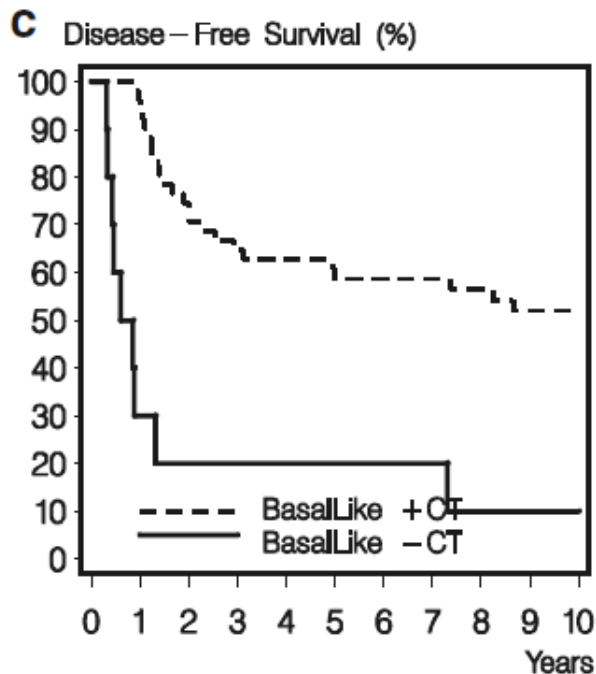
# Prosigna (ROR): Predictive



Premenopausal – C/CMF Therapy

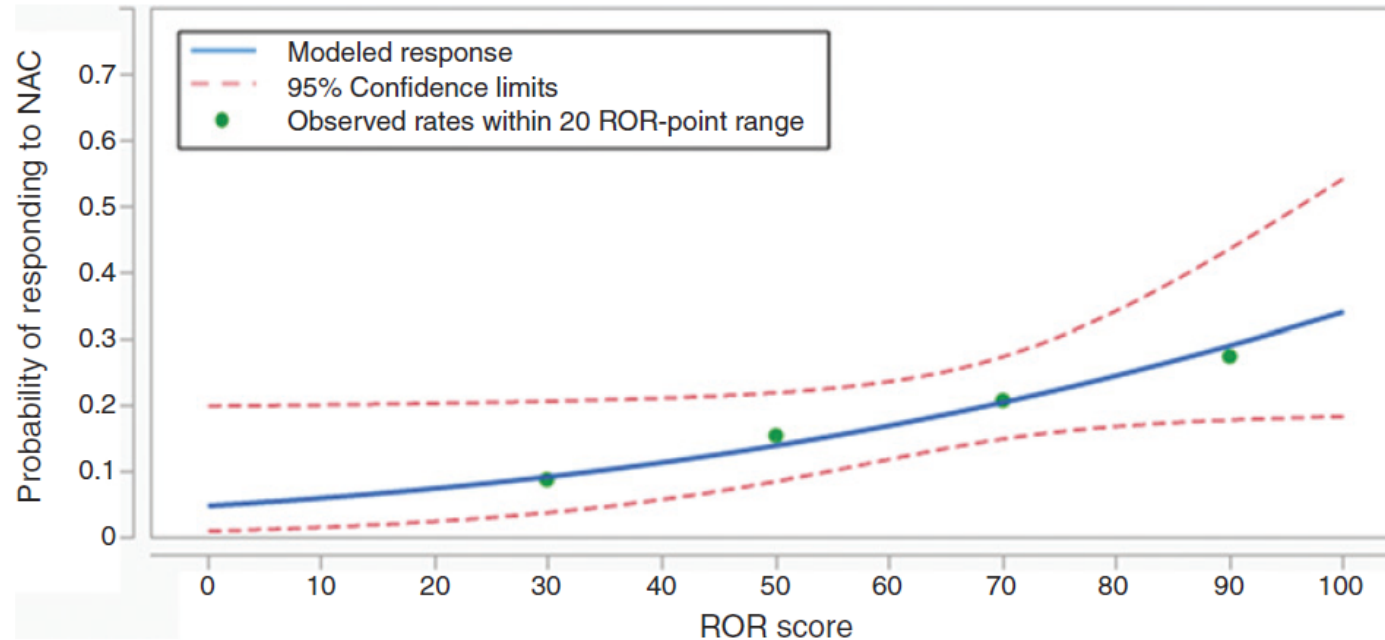


# Prosigna (ROR): Predictive



Premenopausal – C/CMF Therapy

# Prosigna (ROR): Neoadjuvant Prat et al., 2015



**Table 5.** Chemo-predictive value of ROR score and intrinsic subtype

<b>Predictor</b>	<b>Chemo-prediction OR</b>	<b>Validation study <i>P</i></b>
ROR score		0.047
10 point increase	1.261	
20 point increase	1.591	
<i>P</i> score	1.416	0.005
Subtype		
Luminal A versus other	0.341	0.037

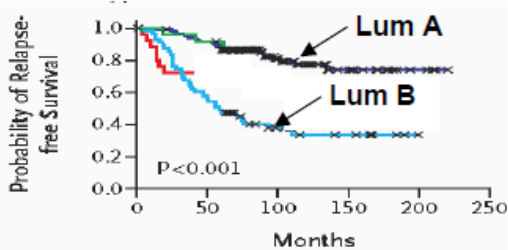
# Summary:

**2000** Perou CM **Nature**  
*Molecular portraits...*

**2002** van 't Veer LJ **Nature**  
*Gene-expression profiling predicts..*

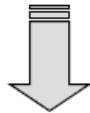
**2004** Paik S **NEJM**  
*A multi-gene assay...*

**A. Intrinsic Subtype**



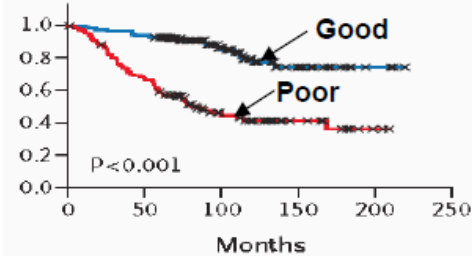
**PAM50** → **Prosigna™**

**2009+**



Approved by Health Canada  
April 2014

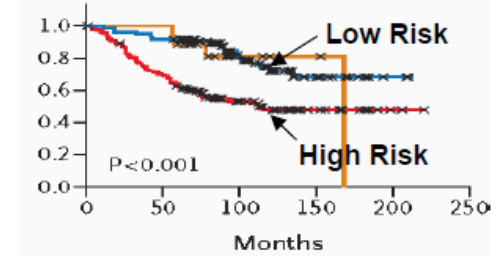
**B. 70 - gene profile**



**MammaPrint™**  
(\$4200 USD) Agendia

**2007**

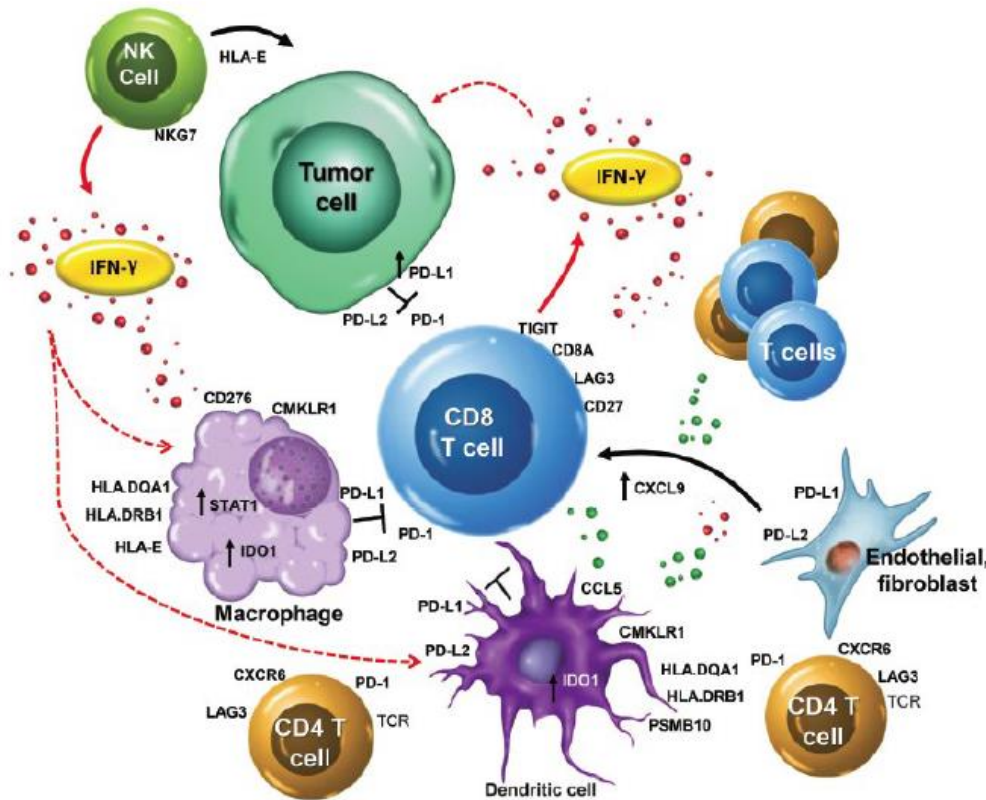
**C. Recurrence Score**



**Oncotype Dx™**  
(\$4200 USD) Genomic Health

**2004**

# Tumour Inflammation Signature:



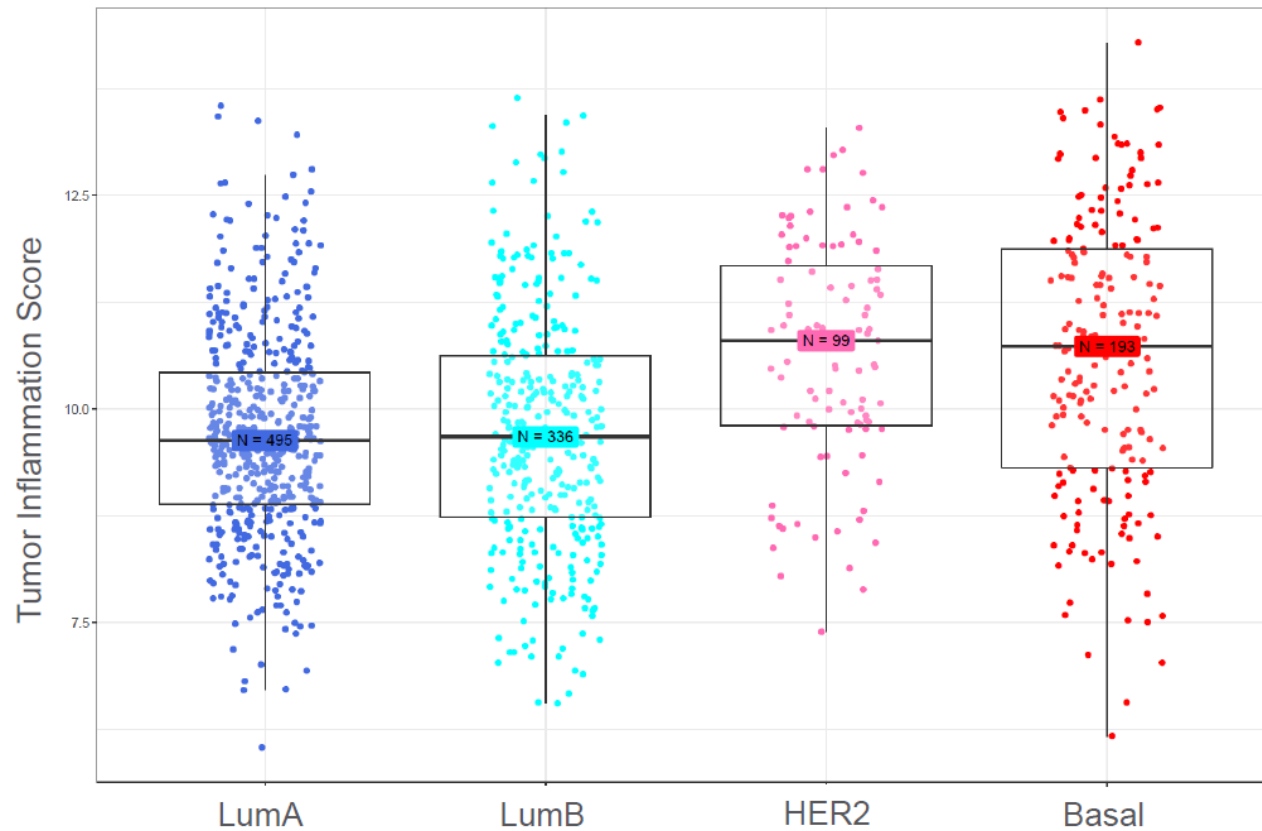
IFN $\gamma$ Biology	T Cell Exhaustion
CCL5	TIGIT
CXCL9	CD8A
CD27	LAG3
CXCR6	PD-L1
IDO1	PD-L2
STAT1	CD276

T Cell/NK Signature	Antigen Presenting Cell Signature
HLA-E	PSMB10
NKG7	HLA-DQA1
	HLA-DRB1
	CMKLR1

18 functional genes, 10 housekeeper genes to run the TIS Algorithm

TIS Predicts Response to PD-1 Pathway Blockade by Measuring 4 Areas of Immune Biology

# Tumour Inflammation Signature:

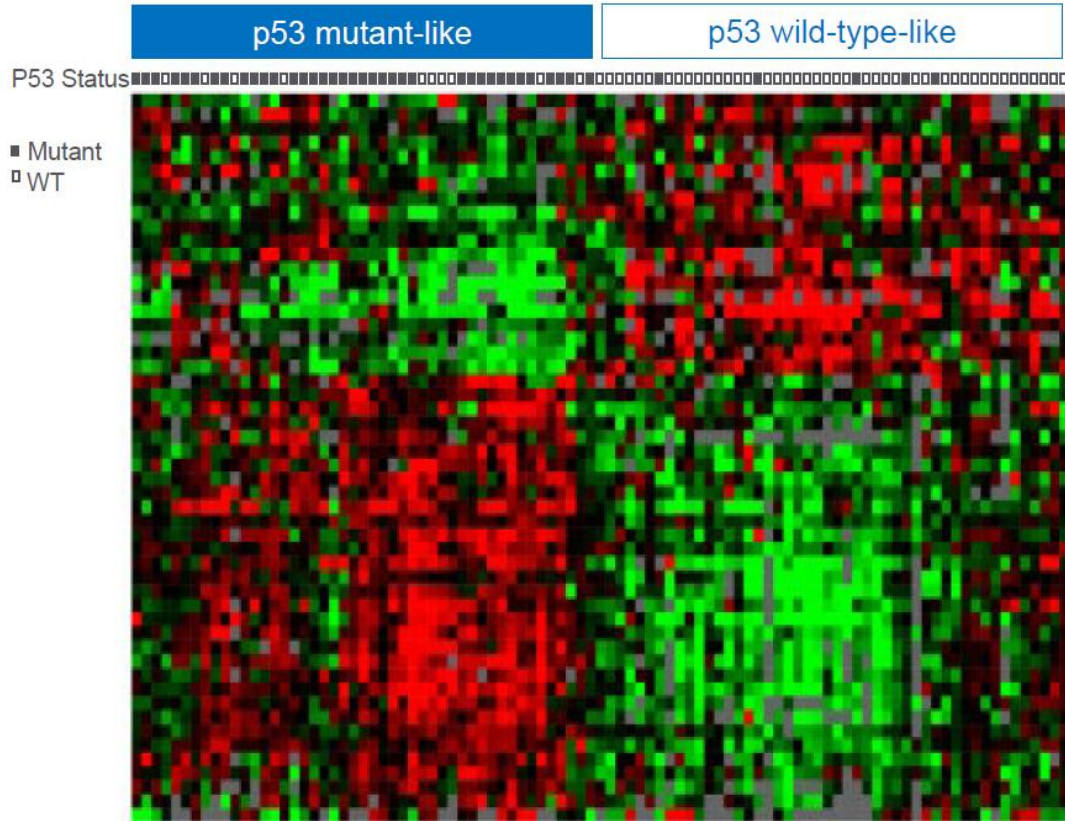


- TNBC breast cancer is a heterogeneous disease characterized by aggressive biology and poor prognosis
- Tumor-infiltrating lymphocytes are correlated to favorable breast cancer outcome in ER- tumors
- TILs were significantly associated with better survival outcome in early TNBC and may serve as an additional prognostic factor for these patients
- While PD-L1 protein expression is rare in breast cancer, it is enriched in basal-like tumors

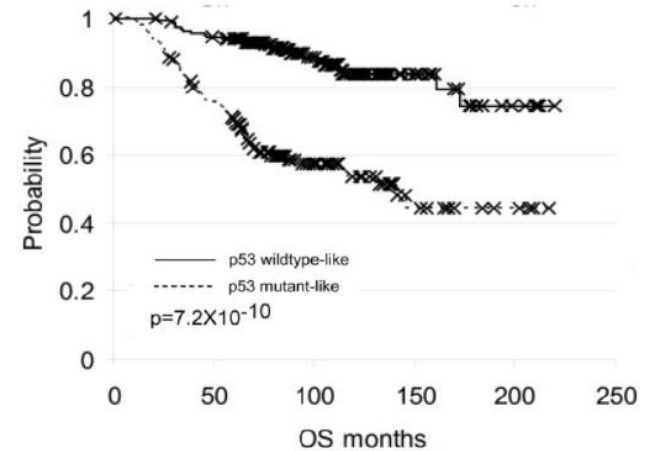
Source: Ali HR, et al. Ann Oncol. 2015; Ibrahim EM, et al. Breast Cancer Res Treat. 2014; Matsumoto H, et al. Clinical Pathology, 2015



# TP53 Signature:

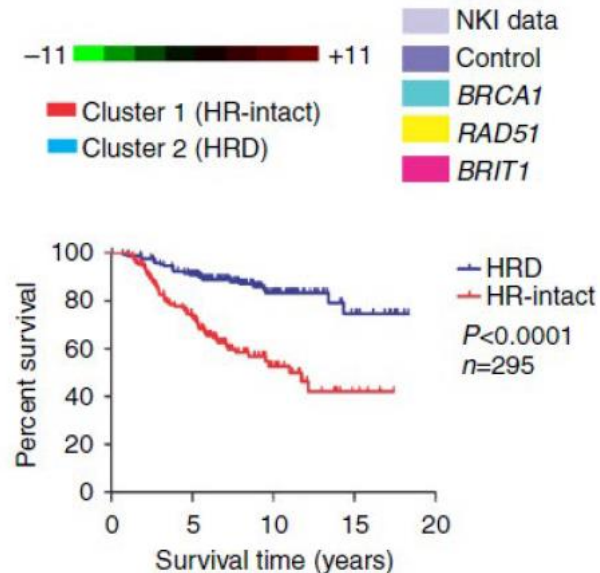
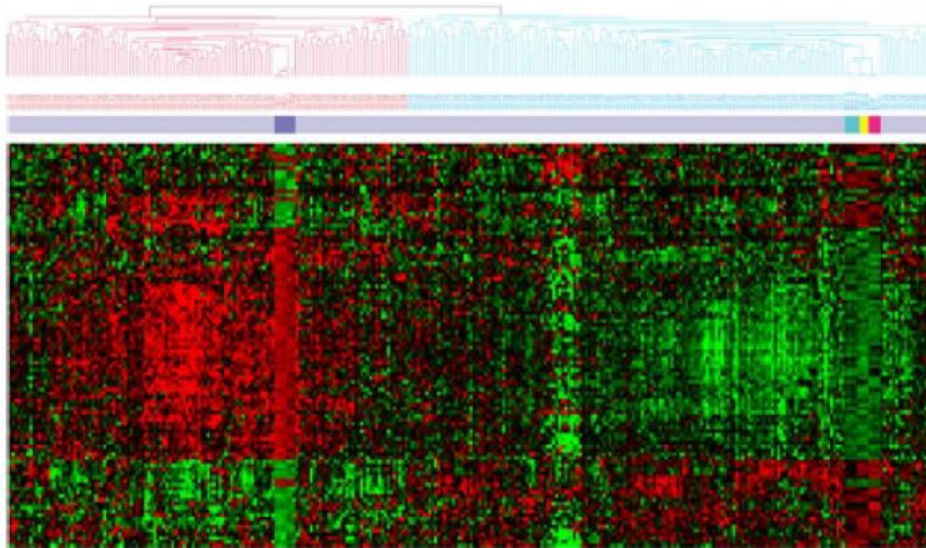


- Fifty-two gene signature based on p53 status
- Signature is significantly associated with overall survival in breast cancer



Troester MA, Herschkowitz JI, Oh DS, et al. Gene expression patterns associated with p53 status in breast cancer. BMC Cancer. 2006;6:276.

# HRD Signature:

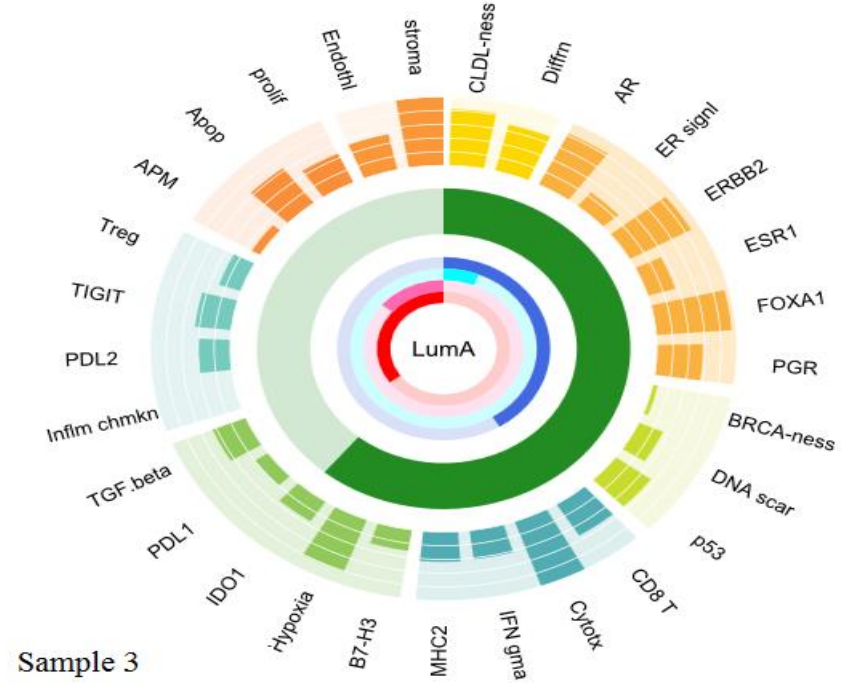
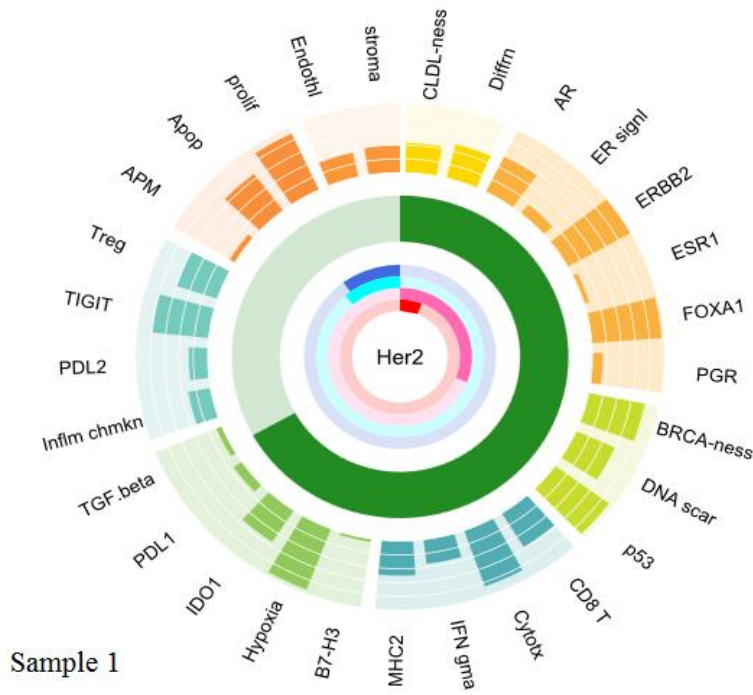


- **HRD gene signature used to functionally assess homologous recombination repair status**
  - Common molecular changes associated with defective homologous recombination repair
  - Predicts homologous recombination status and sensitivity to PARP inhibitors
- **Initial development compared homologous recombination-deficient cell lines and parental cell lines to determine 230 gene signature**
  - Captures cell cycle regulation, DNA replication and DNA recombination and repair pathways
  - Clinical assessment shows that HRD gene signature predicts overall survival in two independent breast cancer patient cohorts and a lung cancer patient cohort<sup>1</sup>

Peng G, Lin CC, et al. Genome-wide transcriptome profiling of homologous recombination DNA repair. Nature Comm. 2014; (5) 3361.



# Multi Signatures:



*Thank You*

