Gene Expression Profiling and Treatment Decision-Making in Breast Cancer

Mohammad R. Akbari, M.D., Ph.D.
Scientist, Women's College Research Institute
Associate Professor, Dalla Lana School of Public Health
University Of Toronto

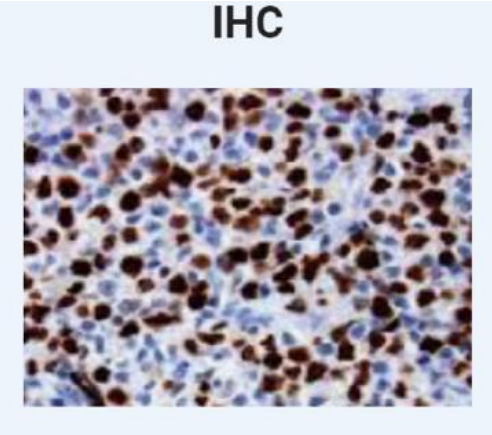
akbarilab.utoronto.ca

mohammad.akbari@utoronto.ca

January 30, 2022

Breast Cancer

- 13% of all cancers diagnosed in Iran in 2020 (~17,000 cases)
- 25% of all cancers diagnosed in Canada in 2020 (~27,000 cases)
- A heterogenous disease (molecular, histological and clinical)
- The goal of breast cancer classification:
  - To determine the optimal treatment plan for the patients
- Current BC classification:
  - IHC of ER, PR, and HER2
  - ER+, HER2+ and TNBC subtypes



Gene Expression Profiling Tests

- PAM50 (Prosigna)
- MammaPrint
- Oncotype
- EndoPredict
- Breast Cancer Index

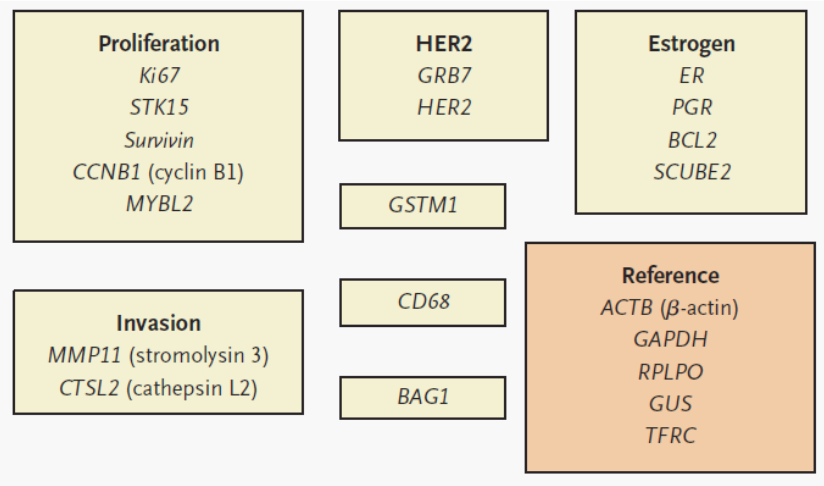
- GEP tests are recommended by:

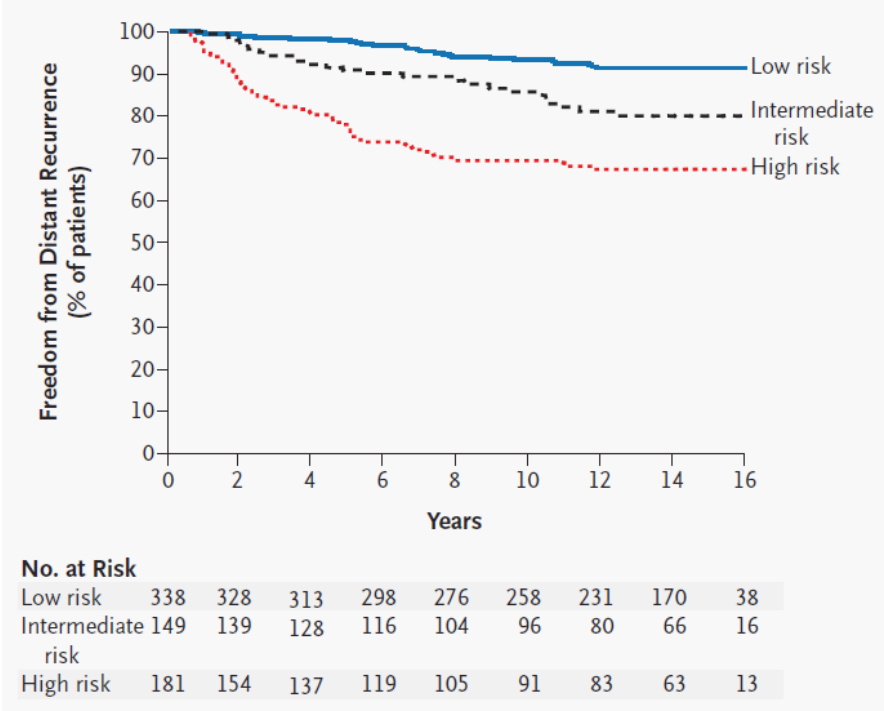
  - American Society of Clinical Oncology (ASCO)
  - National Comprehensive Cancer Network (NCCN)
  - St. Gallen International Experts Consensus
  - European Society of Medical Oncology
  - National Institute for Health and Care Excellence (NICE)

Oncotype

Oncotype: First Report

- NSABP B14 Trial
- 668 ER+/HER2- node - BC patients treated with Tamoxifen

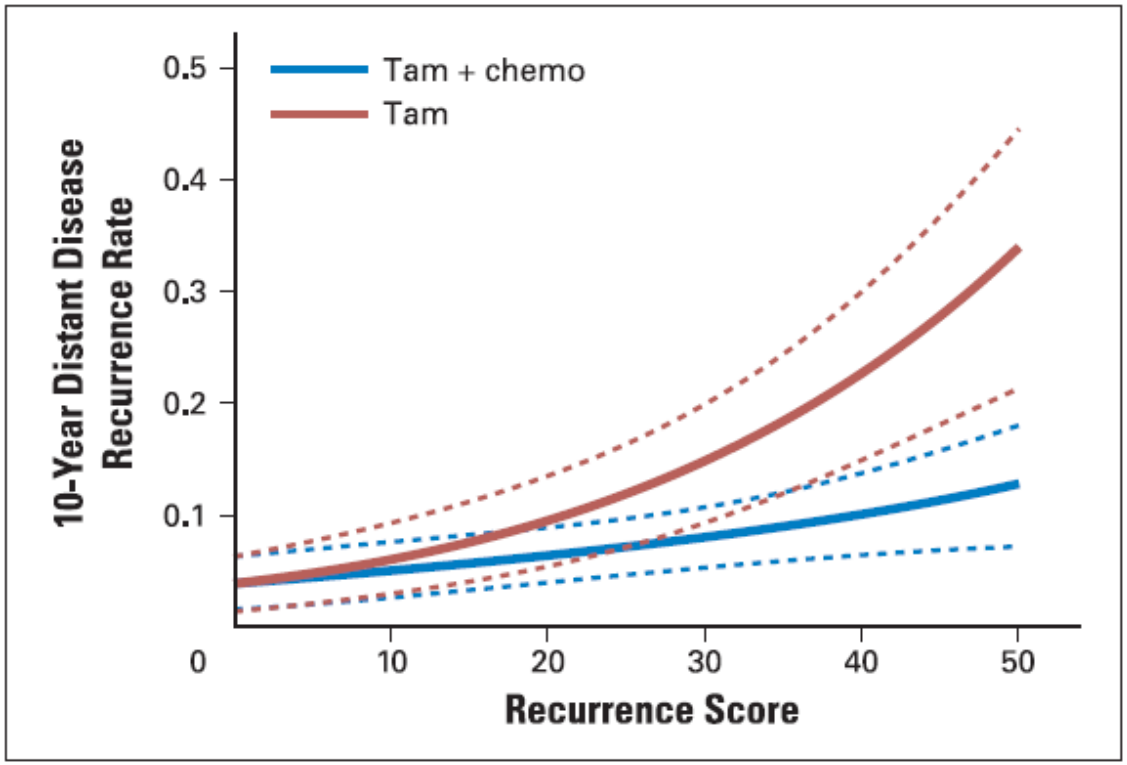




Paik et al., NEJM 2004

Oncotype: First Clinical Trial

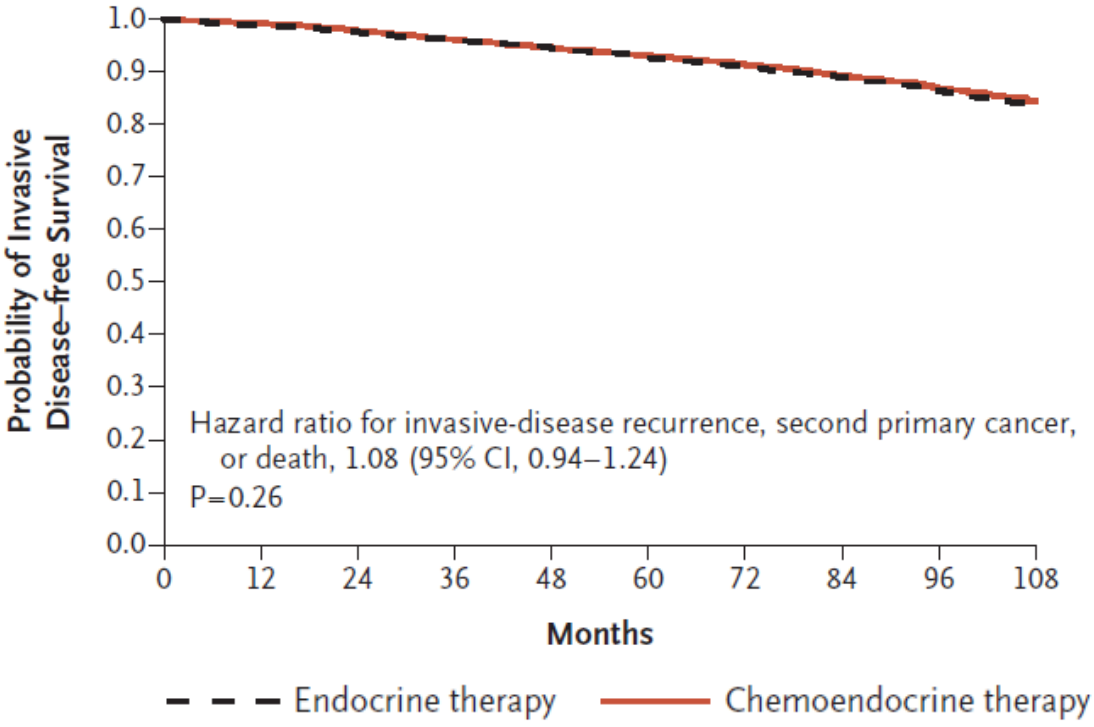
- NSABP B20 Trial
- 651 ER+/HER2- node- BC patients randomly assigned to chemo and chemoendocrine therapy



Paik et al., JCO 2006

Oncotype: Intermediate RS

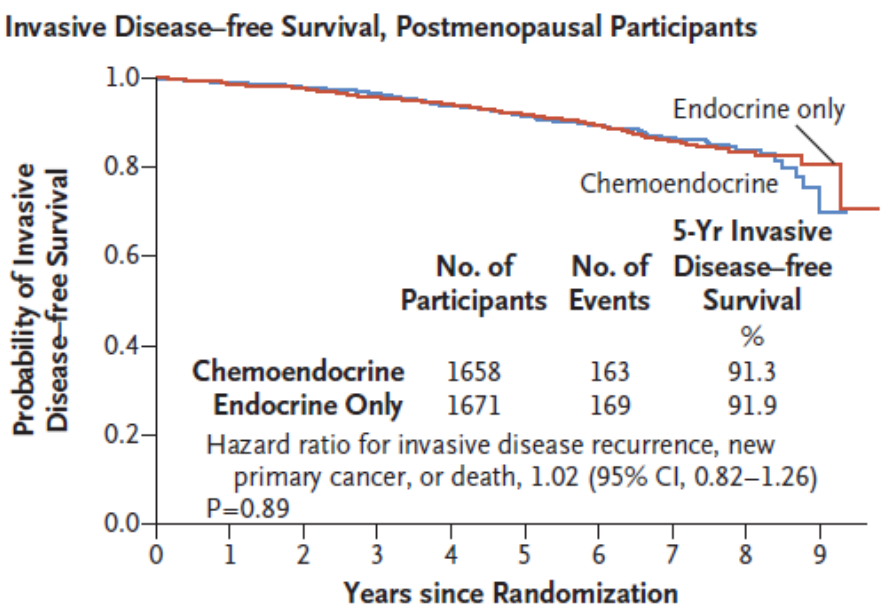
- TAILORx Trial
- 6711/9719 ER+/HER2- Node- BC patients with intermediate RS (16-25)
- Randomized for endocrine or chemoendocrine therapy

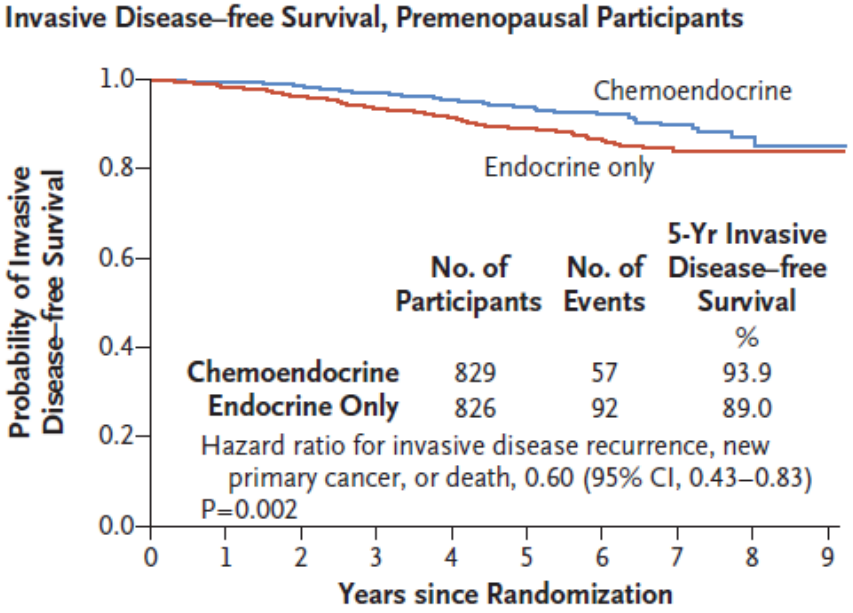


Sparano et al., NEJM 2018

Oncotype: Node+ patients

- RxPONDER Trial
- 5018 ER+/HER2- Node+ BC patients with low or intermediate RS (0-25)
- Randomized for endocrine or chemoendocrine therapy

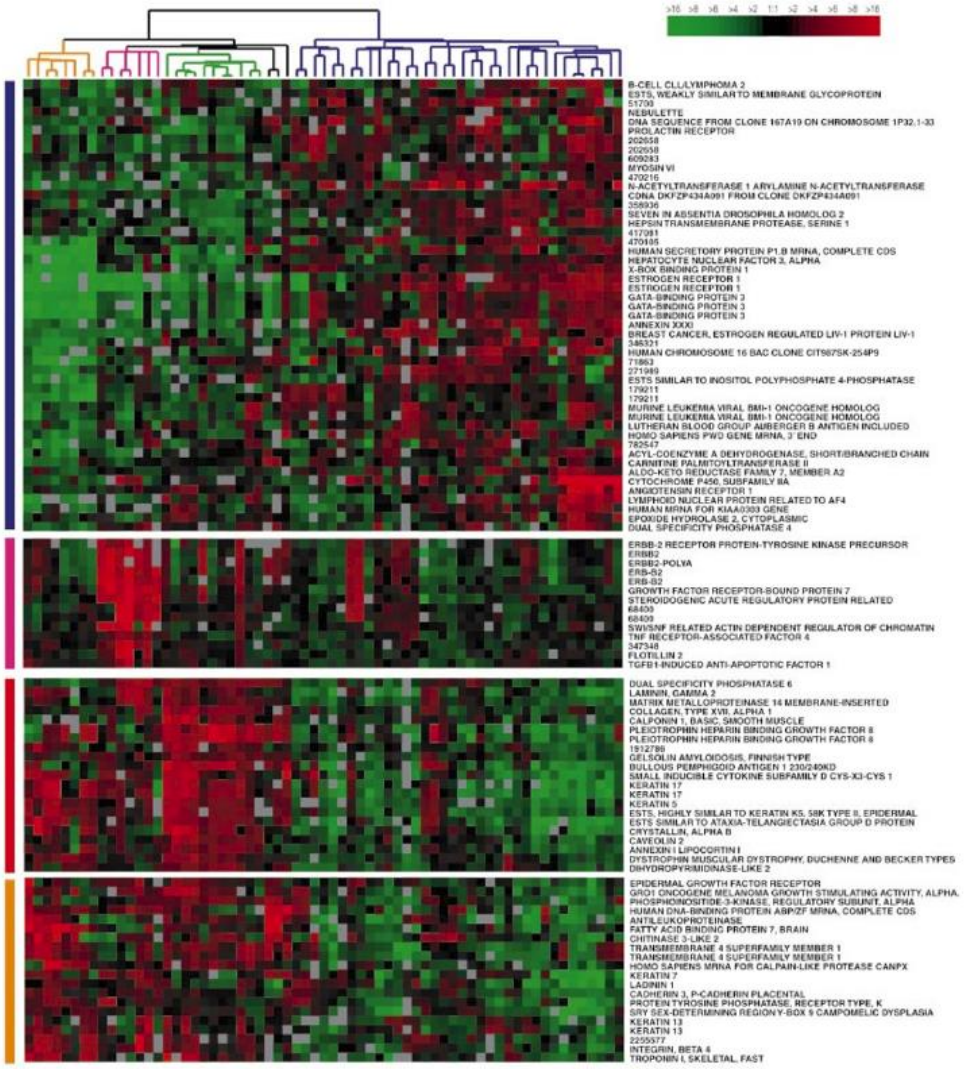




Kalinsky et al., NEJM 2021

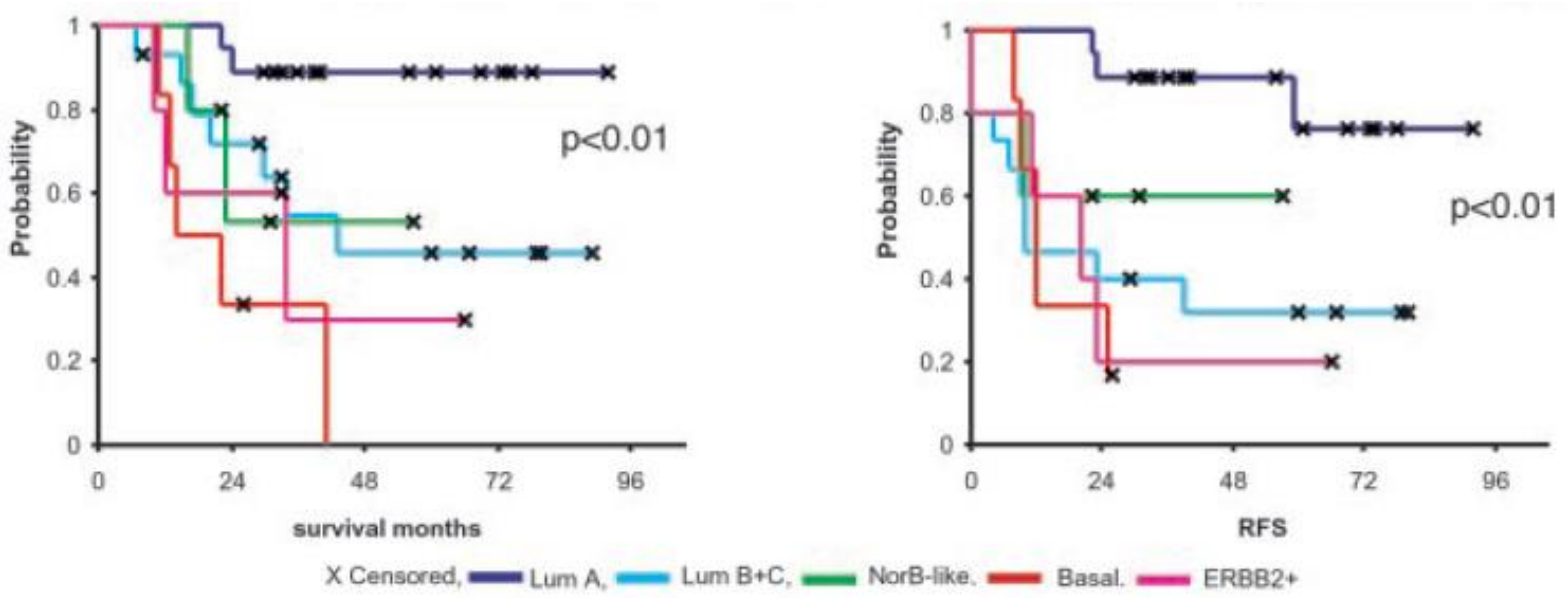
PAM50 (Prosigna)

Start of Gene Expression Profiling



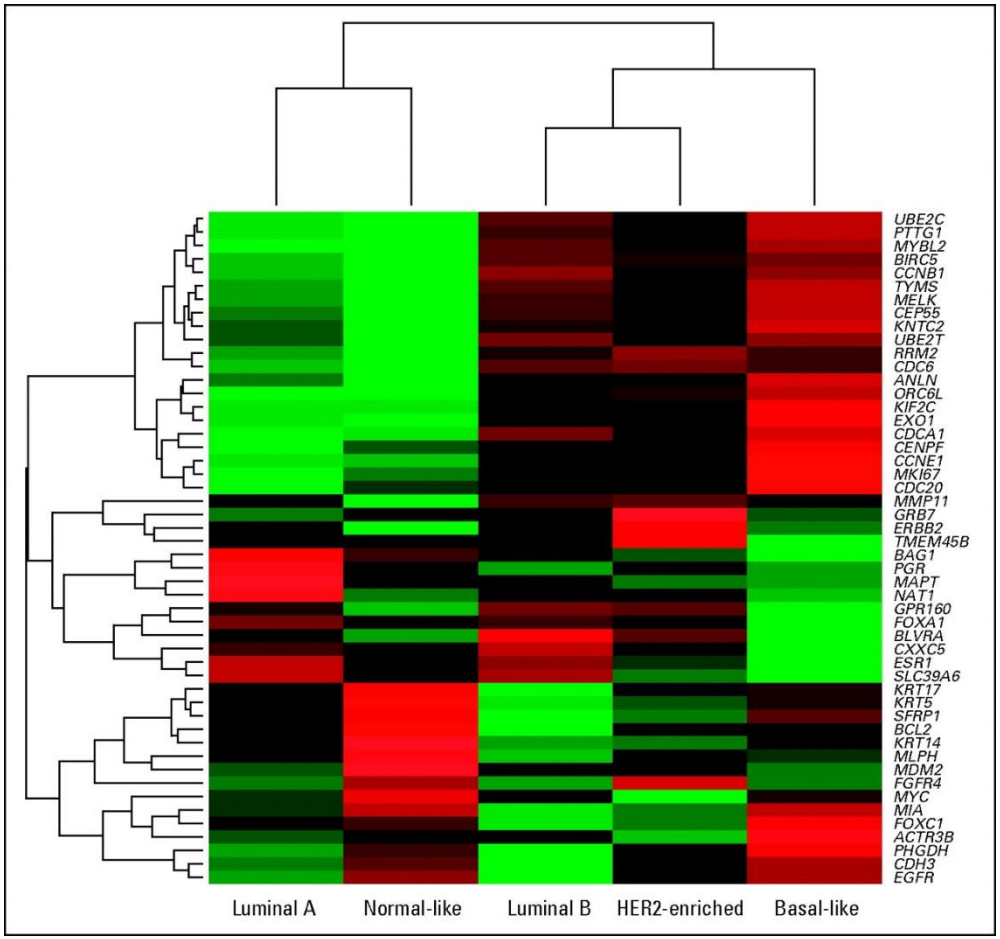
Perou et al., Nature 2000

Gene Expression Profiling and Outcome



Sorlie et al., PNAS 2001

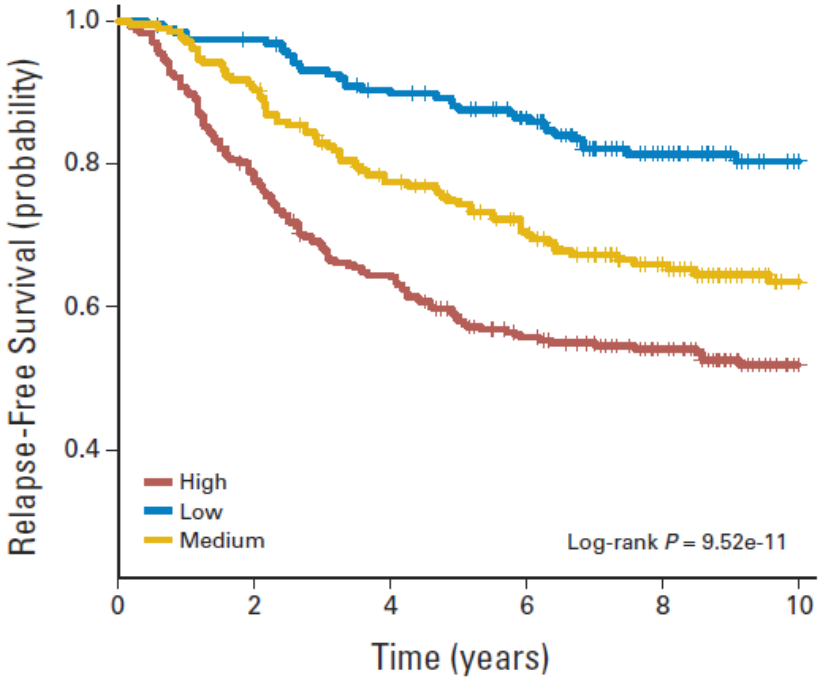
PAM50: Prediction Analysis of Microarray 50



Parker et al., JCO 2009

PAM50: Risk of Recurrence Score (ROR)

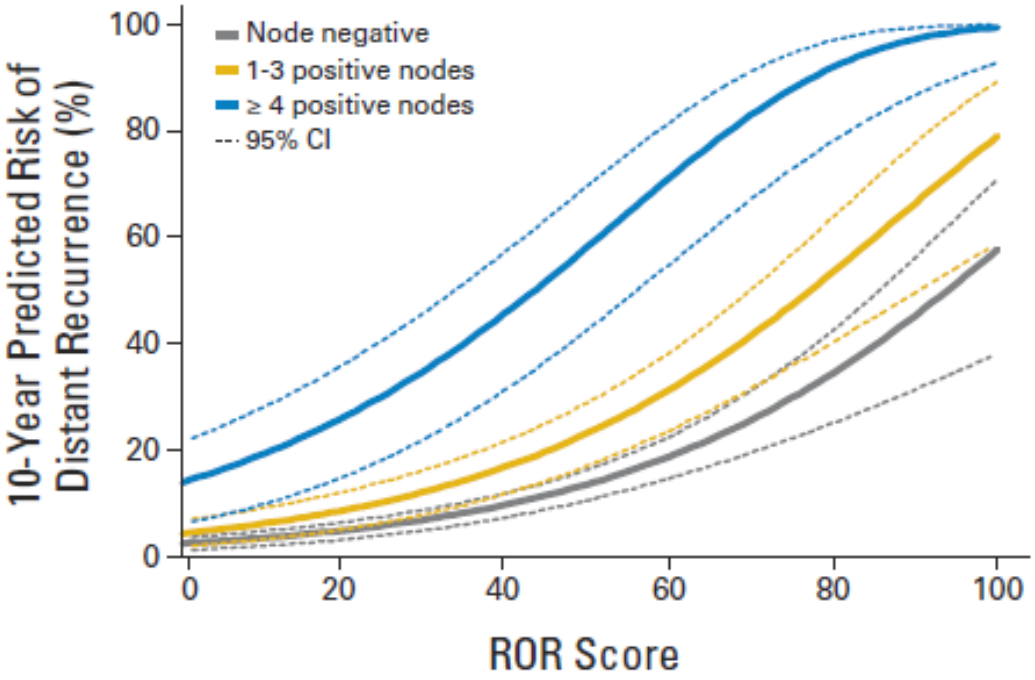
- Molecular Subtype
- Tumour Proliferation Score
- Tumour Size (=<2 or >2 cm)



Parker et al., JCO 2009

PAM50: First Study

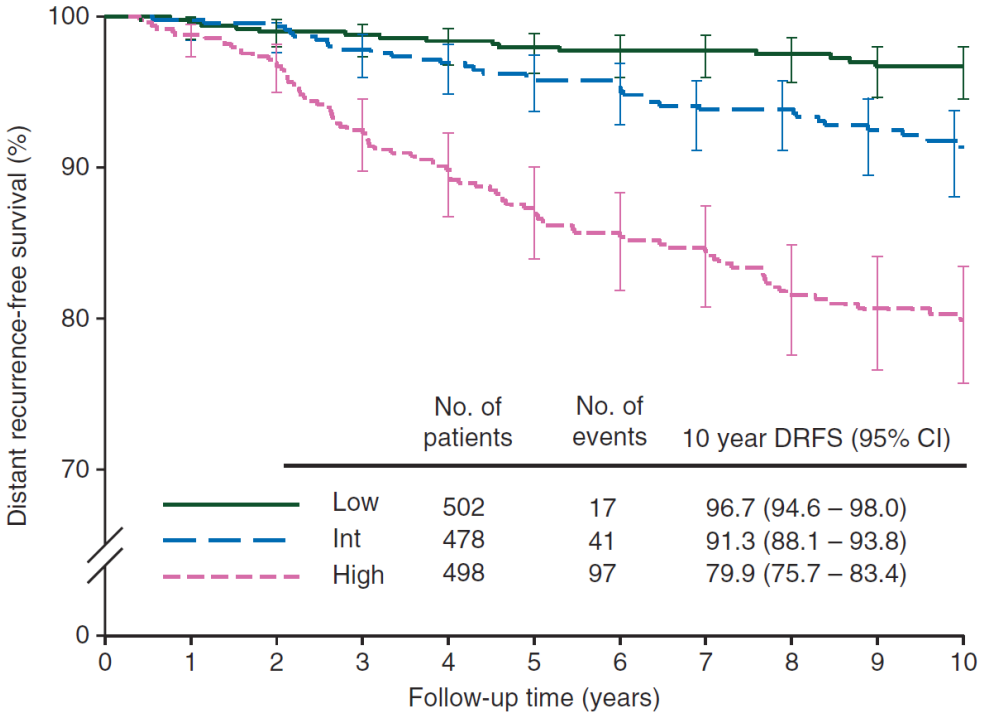
- ATAC Trial
- 1017 ER+/HER2- BC patients treated with Tamoxifen/Anastrozole



Dowsett et al., JCO 2013

PAM50: Second Study

- ABCSG Trial
- 1478 ER+/HER2- BC patients treated with Tamoxifen/T+Anastrozole

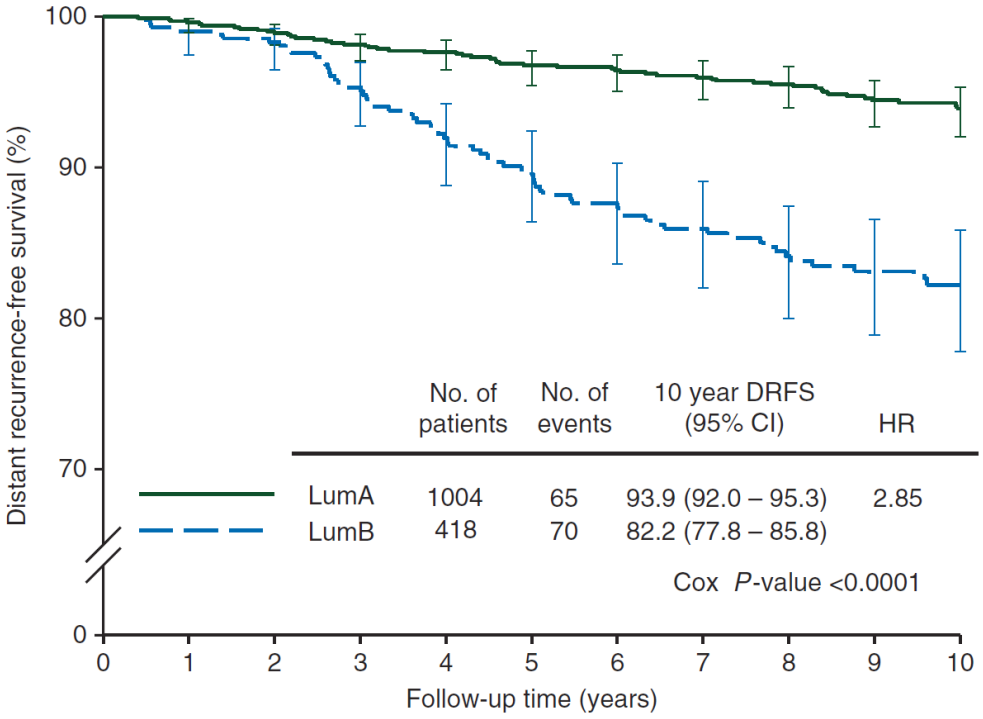


HR : 6.1 (High vs Low)

Gnant et al., Annals of Oncology 2014

PAM50: Second Study

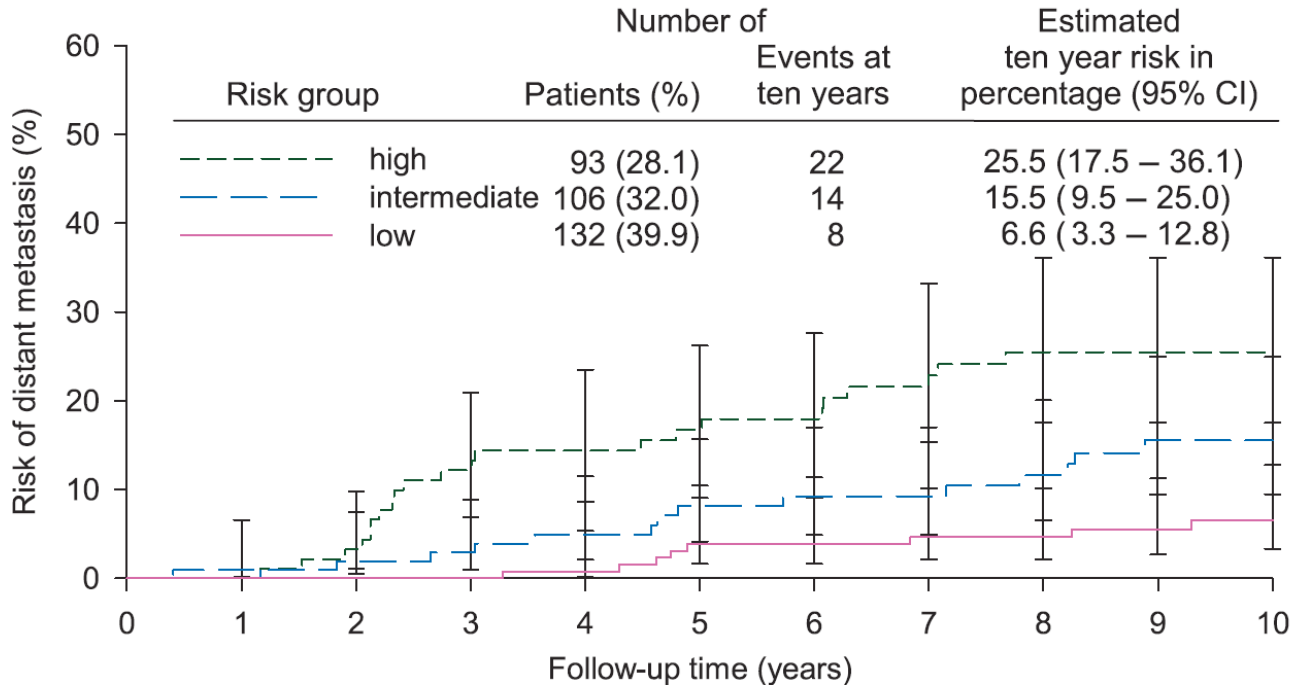
- ABCSG Trial
- 1478 ER+/HER2- BC patients treated with Tamoxifen/T+Anastrozole



Gnant et al., Annals of Oncology 2014

PAM50: Node-Positive Patients

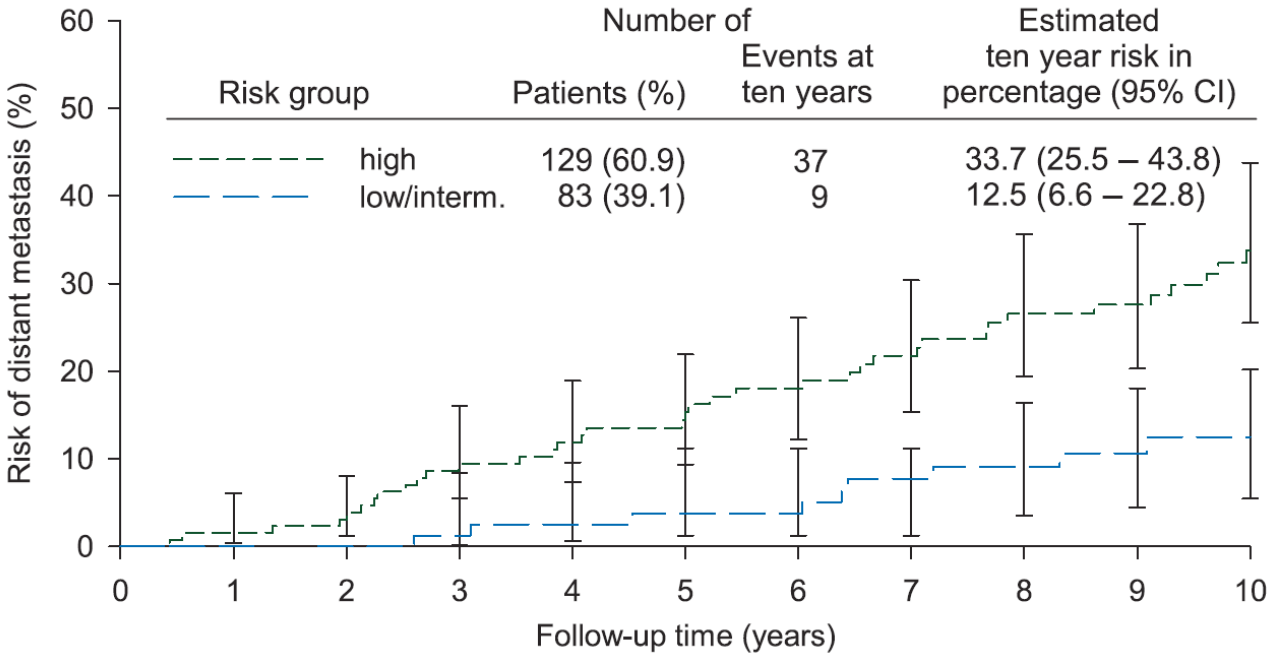
- ABCSG and ATAC Trials
- 331 ER+/HER2- 1 Node+ BC patients with 5-year hormone therapy



Gnant et al., Annals of Oncology 2015

PAM50: Node-Positive Patients

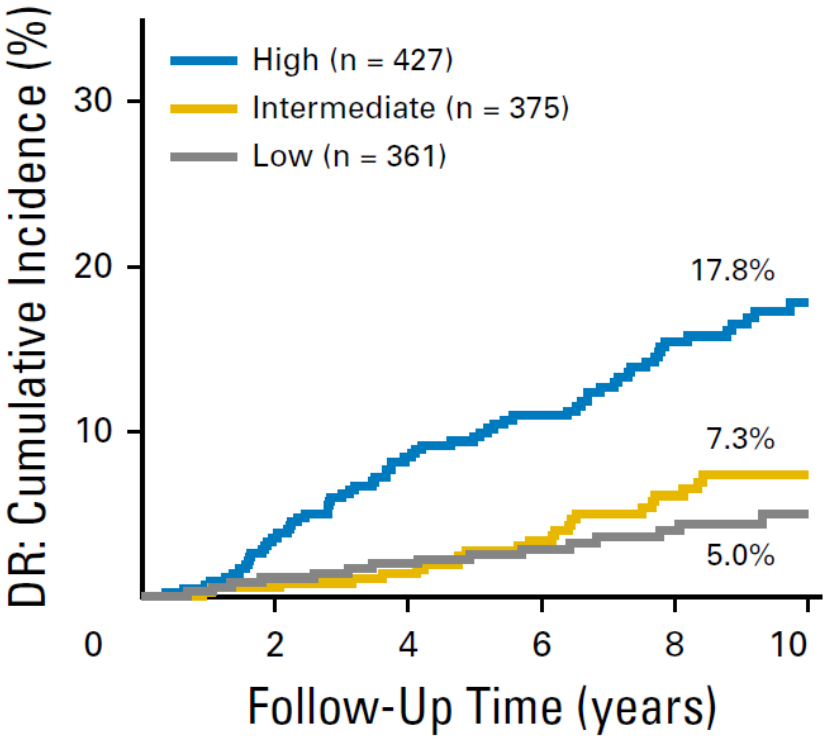
- ABCSG and ATAC Trials
- 212 ER+/HER2- 2-3 Node+ BC patients with 5-year hormone therapy



Gnant et al., Annals of Oncology 2015

PAM50: Danish Study

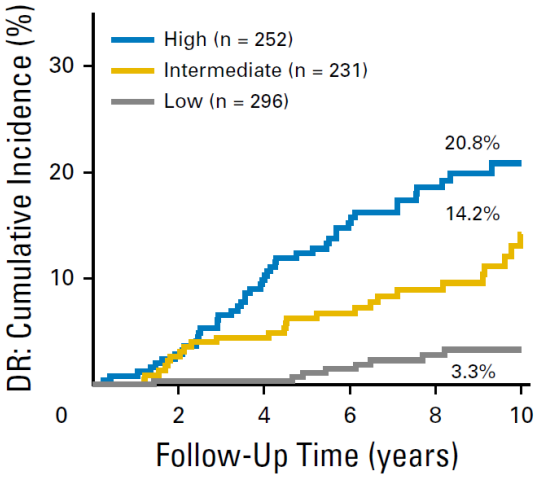
- 1163 ER+/HER2- Node- BC patients with 5-year hormone therapy



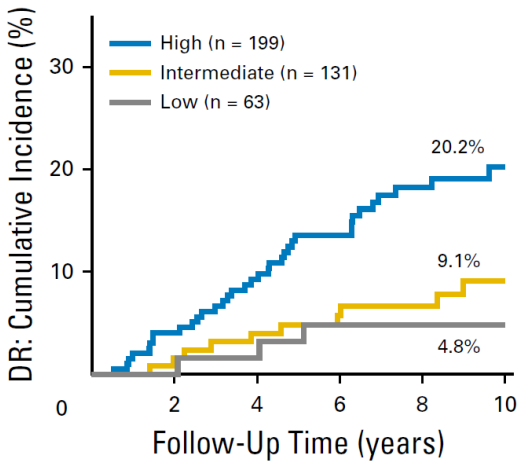
Lankholm et al., JCO 2018

PAM50: Danish Study

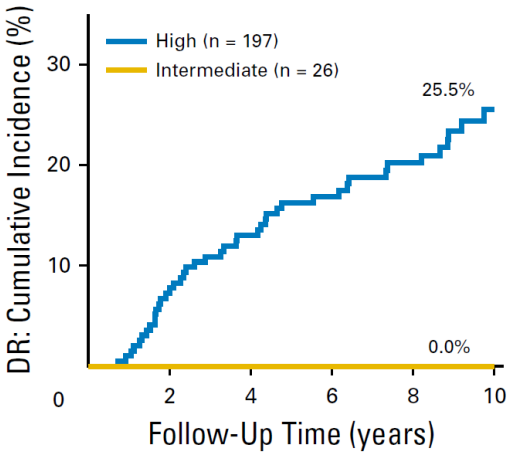
- 1395 ER+/HER2- Node+ BC patients with 5-year hormone therapy



1 node+



2 nodes+

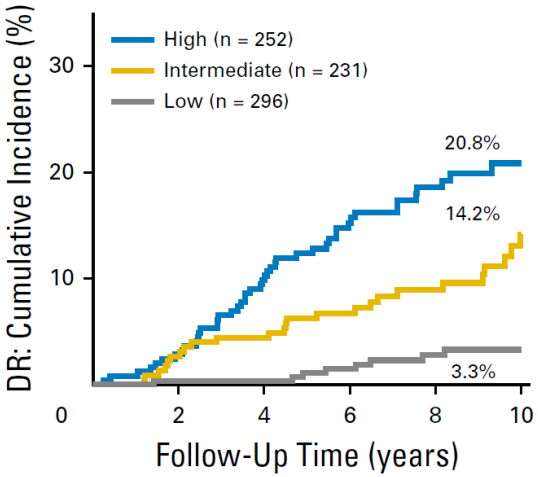


3 nodes+

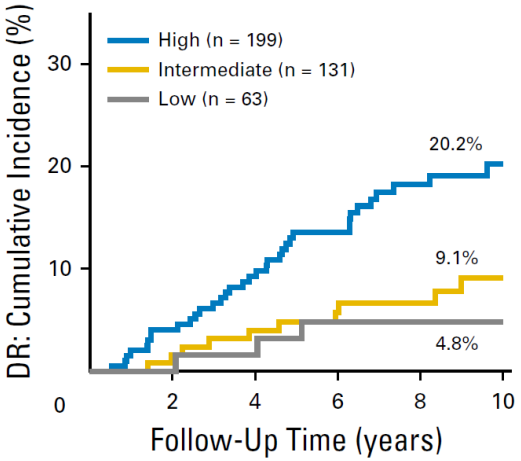
Lankholm et al., JCO 2018

PAM50: Danish Study

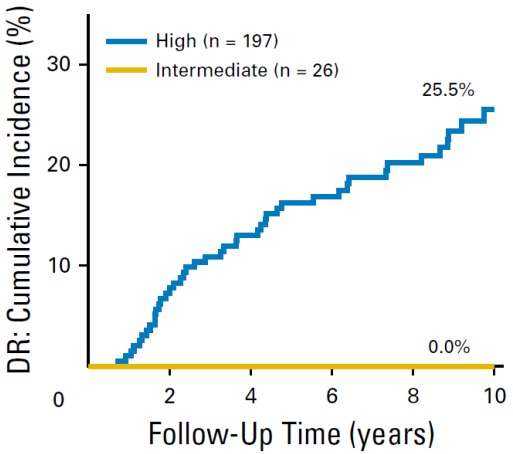
- 1395 ER+/HER2- Node+ BC patients with 5-year hormone therapy



1 node+



2 nodes+



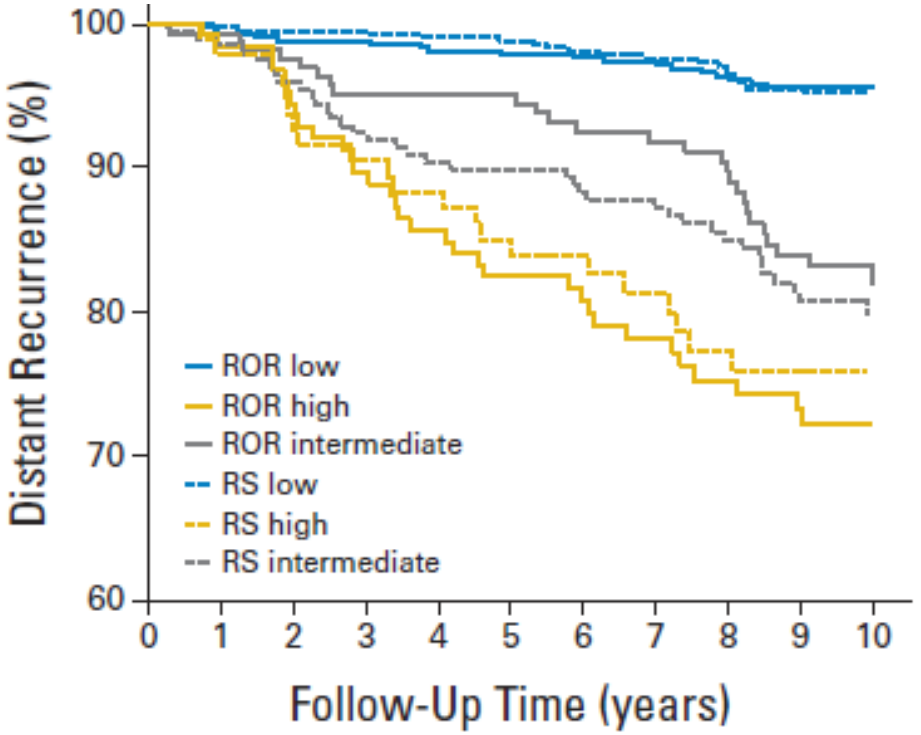
3 nodes+

Lankholm et al., JCO 2018

PAM50 vs Oncotype

PAM50 ROR vs Oncotype RS

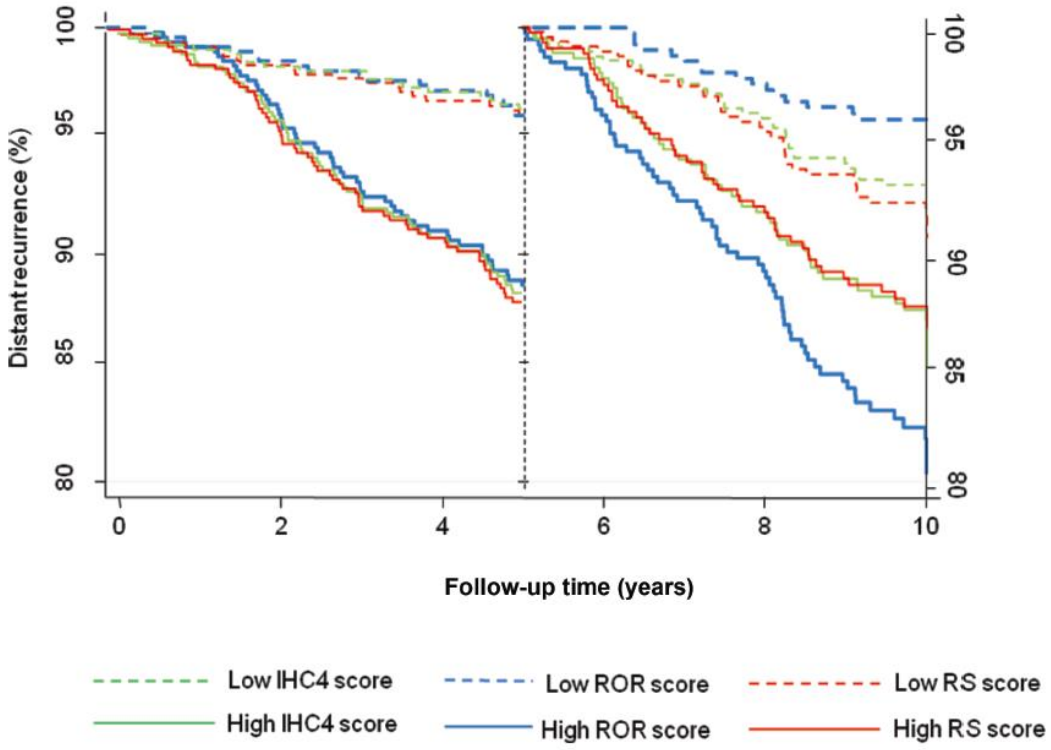
- ATAC Trial
- 1017 ER+/HER2- BC patients with 5-year Tamoxifen/Anastrozole



Dowsett et al., JCO 2013

PAM50 ROR vs Oncotype RS

- ATAC Trial
- 1017 ER+/HER2- BC patients with 5-year Tamoxifen/Anastrozole



Sestak et al., JNCI 2013

PAM50 ROR vs Oncotype RS

- 774 ER+/HER2- BC patients with 5-year hormone therapy

Table 1. Univariate HRs and C Indexes for All Prognostic Signatures According to Nodal Status During Years 0 to 10

Gene Signature	Patient Group			
	Node-Negative Disease (n = 591)		Node-Positive Disease (n = 227)	
	HR (95% CI)[a]	C Index (95% CI)	HR (95% CI)[a]	C Index (95% CI)
CTS	1.99 (1.58-2.50)	0.721 (0.668-0.774)	1.63 (1.20-2.21)	0.640 (0.554-0.726)
IHC4	1.95 (1.55-2.45)	0.725 (0.665-0.785)	1.33 (0.99-1.78)	0.601 (0.511-0.690)
RS	1.69 (1.40-2.03)	0.667 (0.585-0.750)	1.39 (1.05-1.85)	0.603 (0.513-0.693)
BCI	2.46 (1.88-3.23)	0.762 (0.704-0.820)	1.67 (1.21-2.29)	0.652 (0.566-0.739)
ROR	2.56 (1.96-3.35)	0.764 (0.707-0.821)	1.58 (1.16-2.15)	0.636 (0.552-0.719)
EPclin	2.14 (1.71-2.68)	0.765 (0.716-0.814)	1.69 (1.29-2.22)	0.671 (0.590-0.752)

Sestak et al., JAMA Oncology 2018

PAM50 ROR vs Oncotype RS

- 100 ER+/HER2- BC patients with 5-year hormone therapy
- 29% Chemotherapy and 57% Radiotherapy

Agreement in risk group assignment between ODX RS and Prosigna ROR.

	Oncotype Recurrence Score			
	Low (<18)	Intermediate (18–30)	High (>31)	Total
Prosigna risk groups				
Low (<40)	43	22	2	67
Intermediate (40–60)	8	8	1	17
High (61–100)	6	9	1	16
Total	57	39	4	100

Abdelhaka et al., Can Treat and Research Com 2021

PAM50 ROR vs Oncotype RS

- 100 ER+/HER2- BC patients with 5-year hormone therapy
- 3/100 had recurrence

ODX, Prosigna, and Ki67 scores in three cases with confirmed recurrence at different sites and their clinical characteristics.

ODX RS scoreAnd category		Prosigna ROR score and category		Ki67(%) and proliferative labeling index		Recurrence regional and distant (site)	Time to recurrence	Age	Grade	Node	Menopause	Surgery	Hormonal	Chemotherapy	Radiotherapy
17	Low	66	High	30	High	(chest wall)	6 years	51	2	N	Peri-menopausal	Mastectomy	Y	N	Y
11	Low	70	High	30	High	(left breast)	17 years	70	2	N	Postmenopausal	Lumpectomy	Y	Y	N
20	Intermediate	80	High	30	High	(liver)	5 years	68	3	N	Postmenopausal	Mastectomy	Y	N	N

Abdelhaka et al., Can Treat and Research Com 2021

PAM50 ROR vs Oncotype RS

- 12 ER+/HER2- BC patients recently diagnosed
- All had Oncotype test (Genomic Health Inc.)

Sample ID	Age at Diagnosis	ER Status	PR Status	HER2 Status	Tumour Size	Lymph Node Status	Oncotype RS	Oncotype 10 years Distance Recurrence Risk	PAM50 Molecular Subtype	PAM50 ROR	PAM50 10 years Distance Recurrence Risk
1	44	Positive	Positive	Negative	>2cm	Negative	16	4%	Luminal A	25	4%
2	59	Positive	Positive	Negative	<=2cm	Micromets	11	13%	Luminal B	55	24%
3	48	Positive	Positive	Negative	>2cm	Negative	7	3%	Luminal B	54	11%
4	47	Positive	Positive	Negative	<=2cm	Negative	18	5%	Luminal B	55	11%
5	41	Positive	Positive	Negative	<=2cm	Negative	18	5%	Luminal A	28	4%
6	48	Positive	Positive	Negative	<=2cm	Negative	11	3%	Luminal A	44	11%
7	63	Positive	Positive	Negative	<=2cm	Negative	20	6%	Luminal A	34	4%
8	30	Positive	Positive	Negative	>2cm	Negative	41	29%	Luminal B	72	22%
9	34	Positive	Positive	Negative	>2cm	Negative	22	8%	Luminal A	23	4%
10	52	Positive	Positive	Negative	<=2cm	Negative	12	3%	Luminal A	28	4%
11	53	Positive	Positive	Negative	<=2cm	Negative	17	5%	Luminal A	26	4%
12	37	Positive	Positive	Negative	<=2cm	Negative	20	6%	Luminal A	19	4%

Test Reports

Oncotype Report

Recurrence Score® (RS) Result

17

Distant Recurrence Risk at 9 Years

With AI or TAM Alone

5%

95% CI (4%, 6%)

TAILORx

Group Average Absolute Chemotherapy (CT) Benefit*

RS 11-25 All Ages

<1%

95% CI (-1%, 2%)

TAILORx

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors.

AI = Aromatase Inhibitor / TAM = Tamoxifen
CI = Confidence Intervals

*For estimated CT benefit for individual RS results, see page 2.

Quantitative Single-Gene Scores[1]

Oncotype Report

Recurrence Score® (RS) Result

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors.

Distant Recurrence Risk at 9 Years

With TAM Alone

29%

95% CI (22%, 37%)

NSABP B-14

TAM = Tamoxifen
CI = Confidence Intervals

Group Average Absolute Chemotherapy (CT) Benefit*

RS 26-100 All Ages

>15%

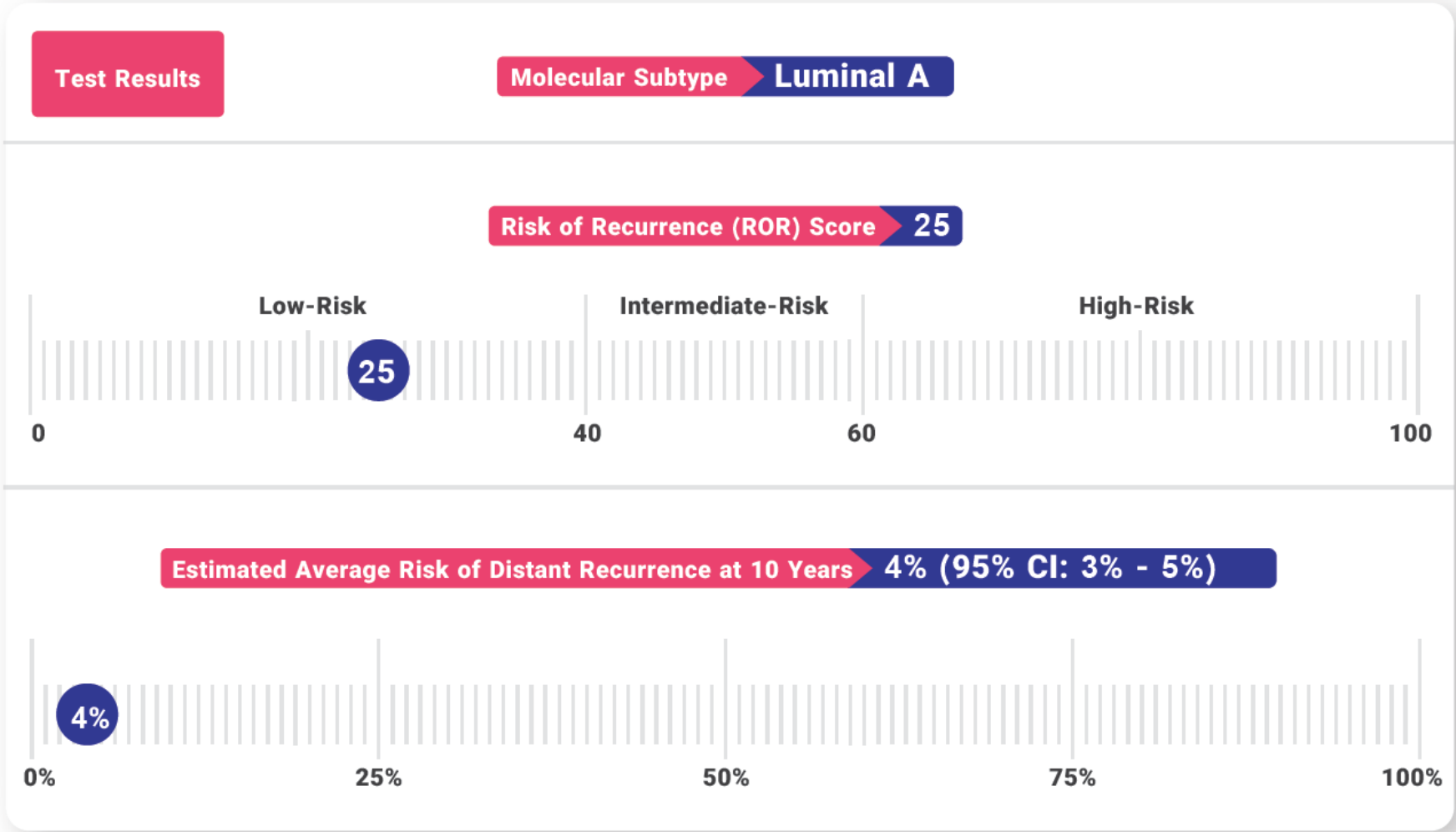
95% CI (9%, 37%)

NSABP B-20

*For estimated CT benefit for individual RS results, see page 2.

Quantitative Single-Gene Scores[1]

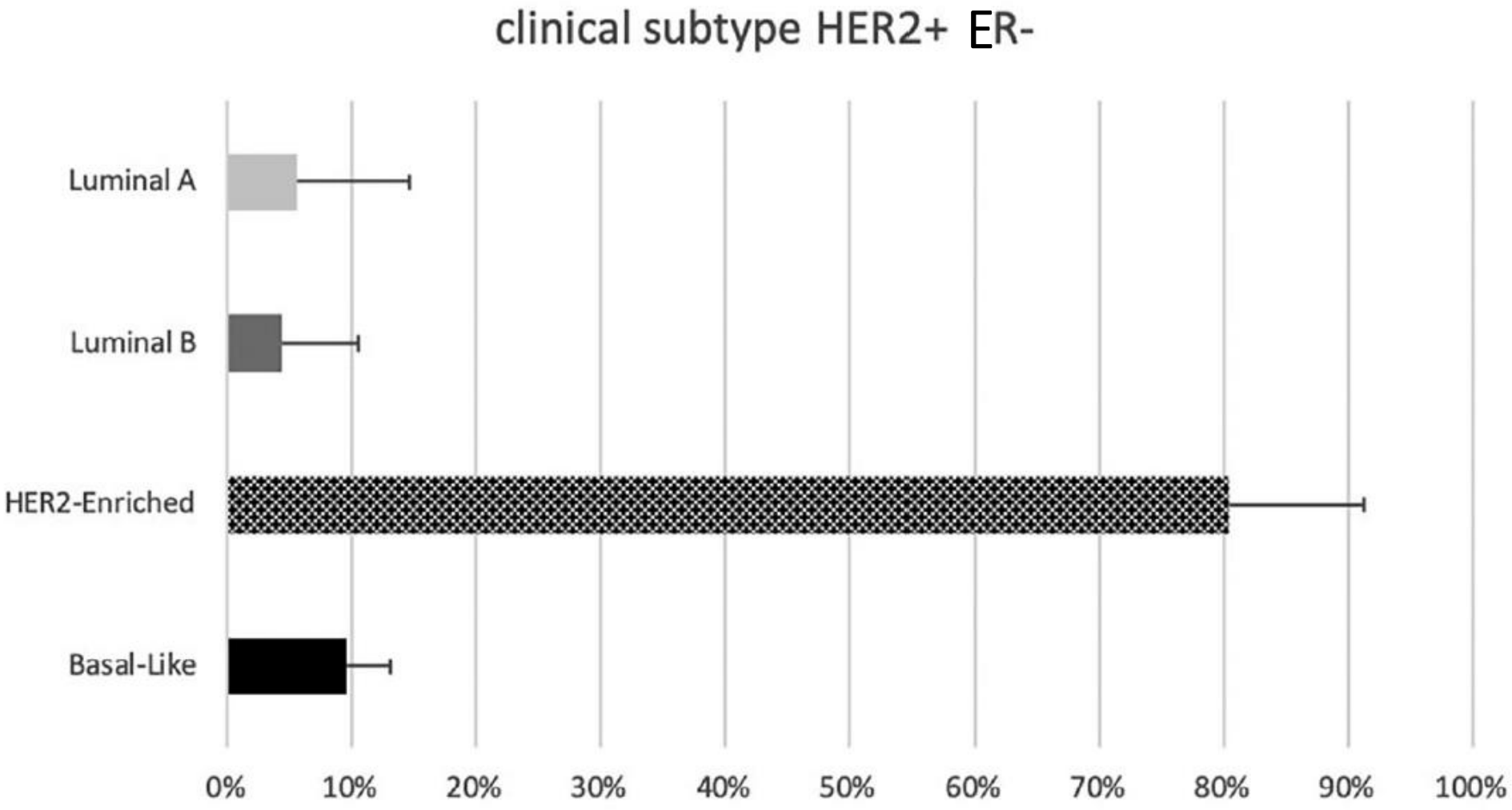
PAM50 Report: Node-Negative



PAM50 Report: Node-Positive

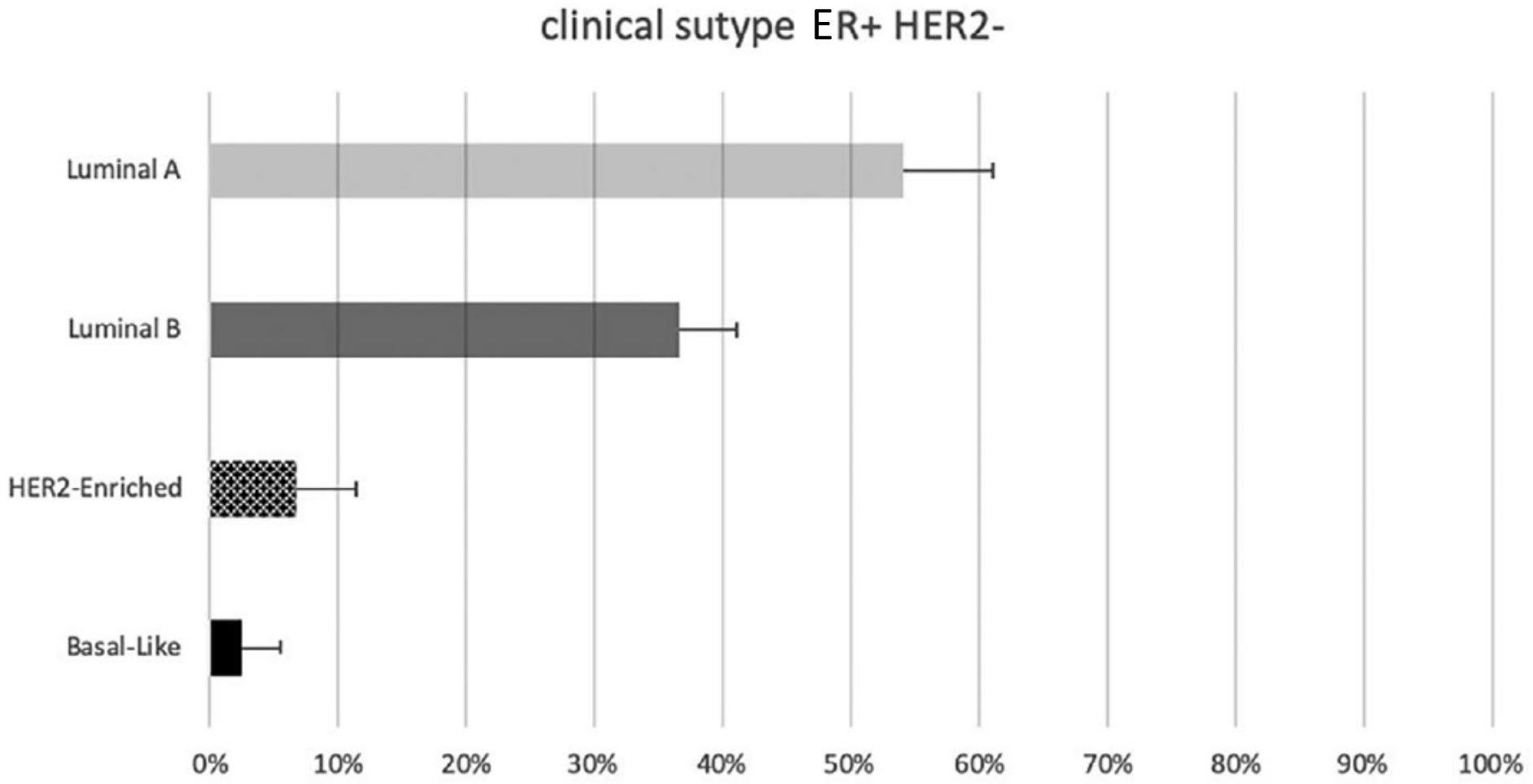
Molecular Subtypes Implications

Discordance of HER2+ and HER2-Enriched Subtypes



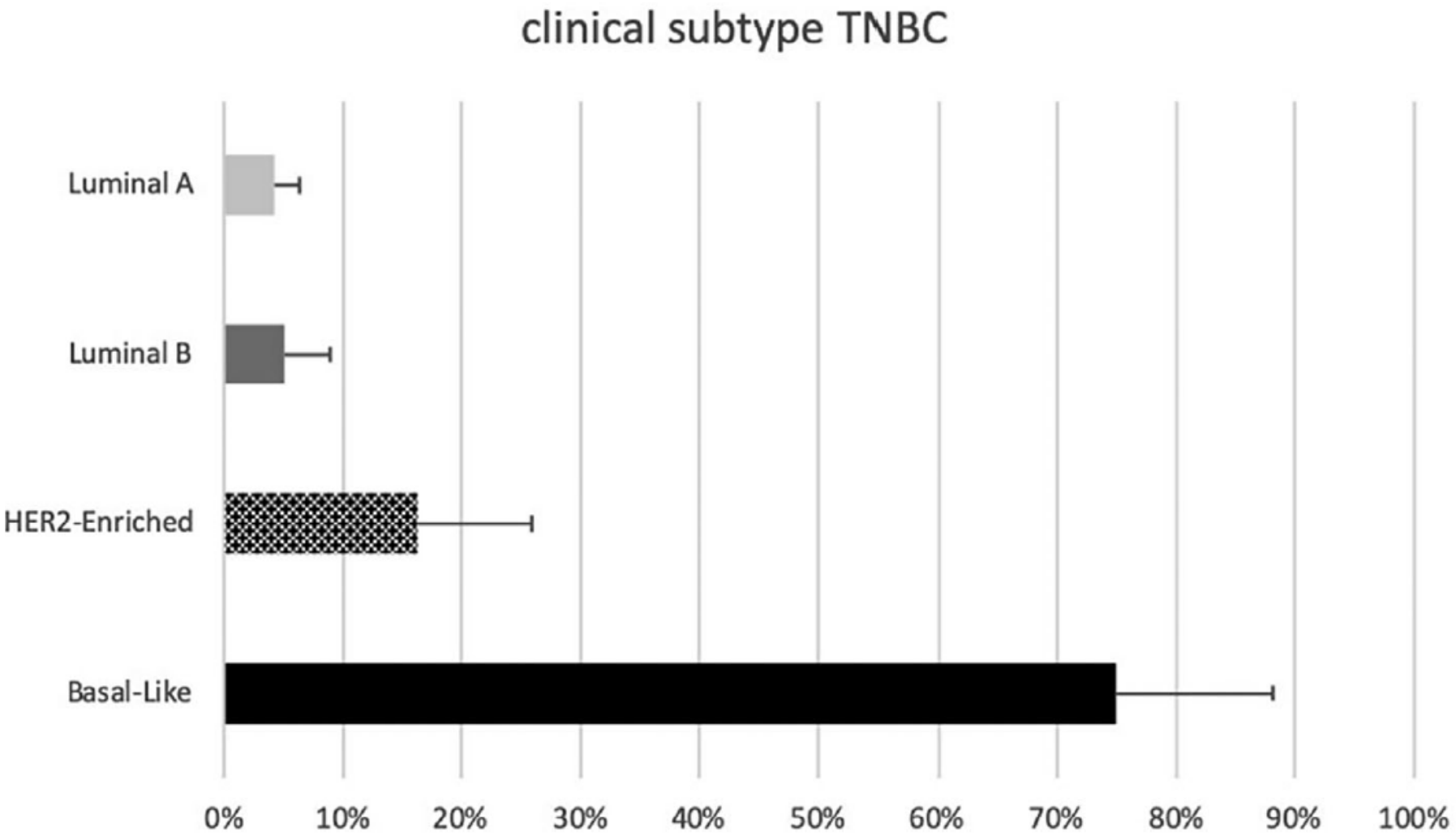
Based on 1,237 HER2+ patients

Discordance of ER+ and Luminal Subtypes



Based on 4,402 ER+ patients

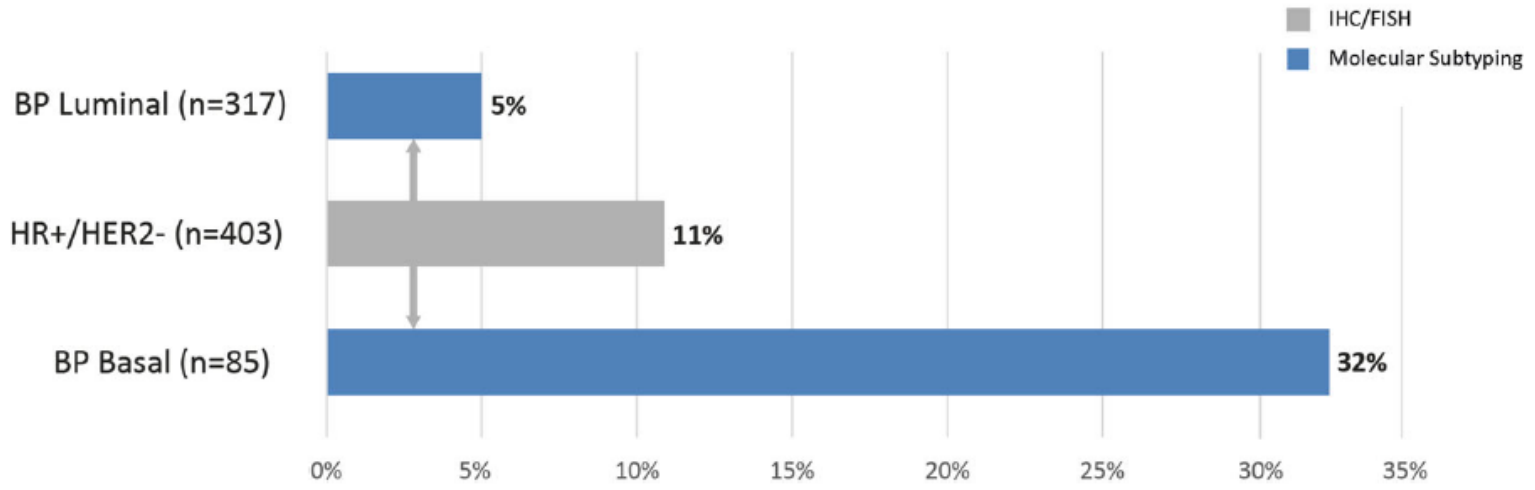
Discordance of TNBC and Basal-Like Subtypes



Based on 3,931 TNBC patients

pCR in Molecular Subtypes of ER+ Patients

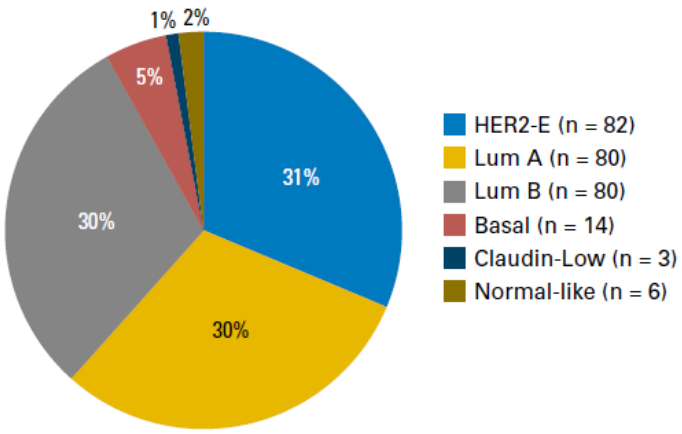
- 474 ER+ patients
- pCR rate after neoadjuvant chemotherapy

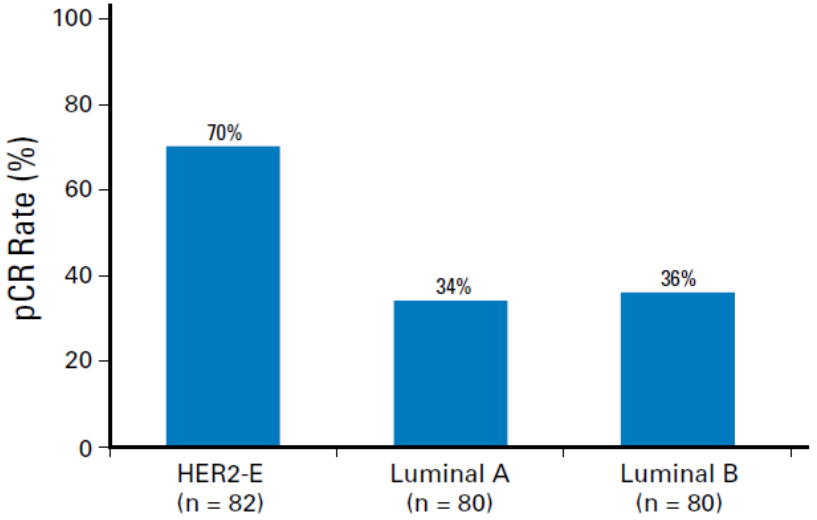


Whitworth et al., Annals of Surgical Oncology 2017

Response to Anti-HER2 among HER2-Enriched Patients

- CALGB 40601 Clinical Trial
- 305 HER2+ patients
- Neoadjuvant (Taxol, Trastuzumab, Lapatinib)
- pCR among HER2-Enriched vs nonHER2-Enriched: 70% vs 34-36%

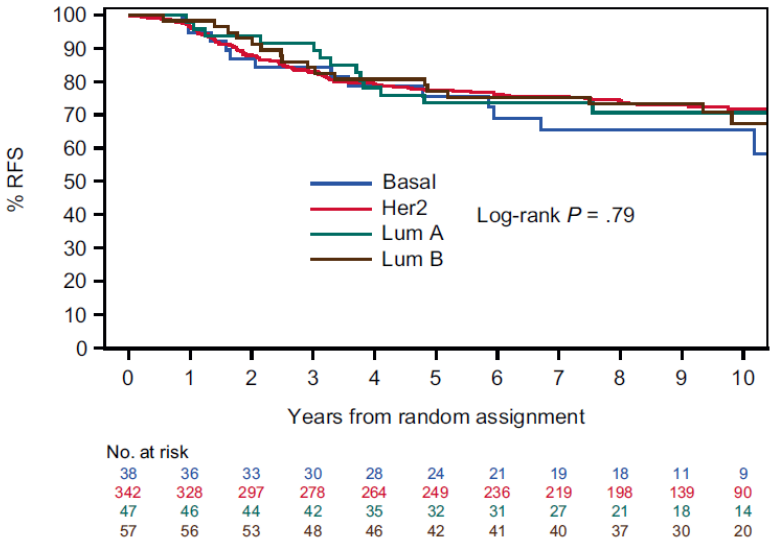




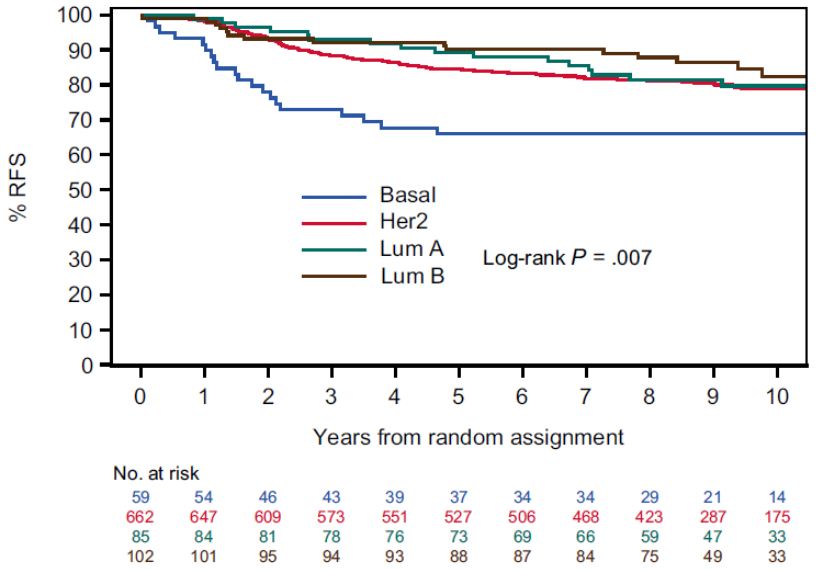
Carey et al., JCO 2016

Response to Anti-HER2 among HER2-Enriched Patients

- NCCTG (Alliance) N9831 Clinical Trial
- 1,392 HER2+ patients
- Adjuvant chemotherapy with (908) or without (484) Trastuzumab
- 1,003 (72%) were HER2-Enriched and 97 (7%) were Basal-Like



Chemotherapy alone

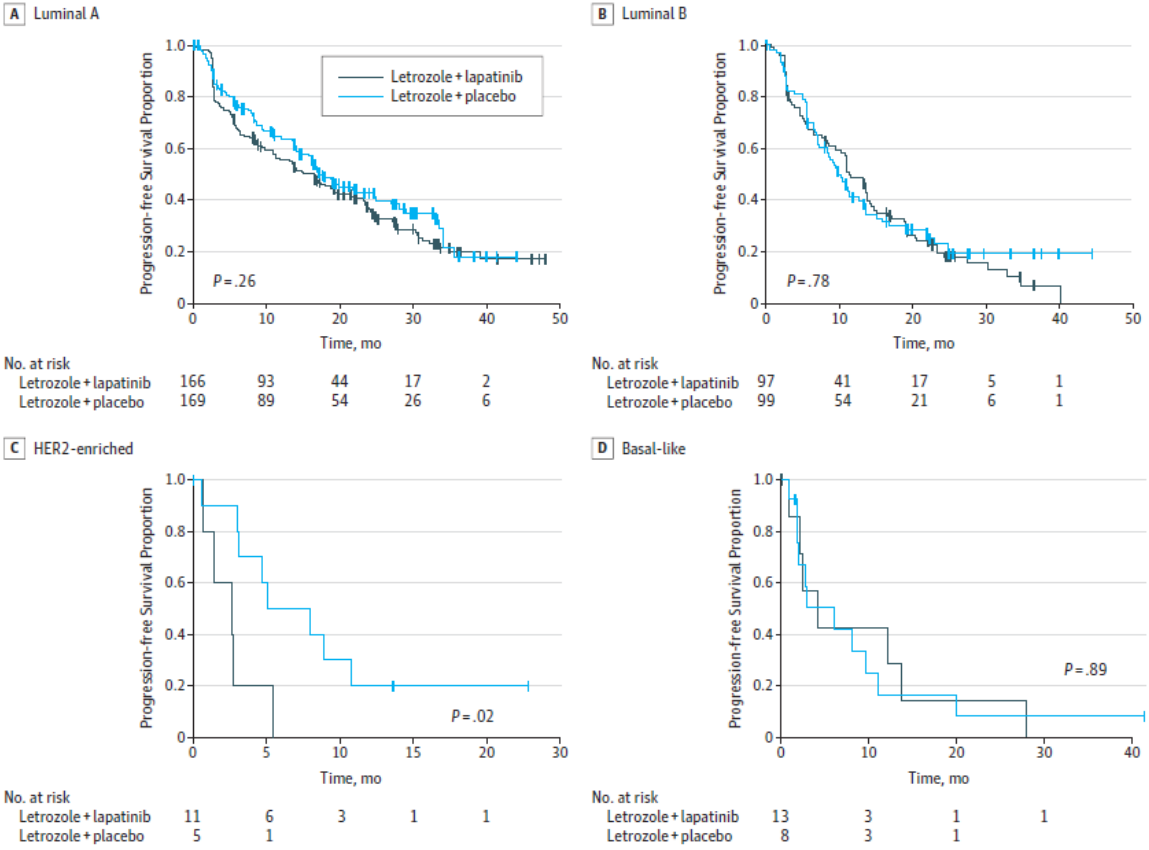


Chemotherapy with Trastuzumab

Perez et al., JNCI 2017

Response to Anti-Her2 in ER+/HER2-Enriched Patients

- EGF30008 clinical trial
- 568 ER+/HER2- patients were randomized on Letrozole with or without Lapatinib
- Median progression-free survival for HER2-Enriched (6.5 m vs 2,6 m, HR : 0.24, p : 0.02)



Prat et al., JAMA Oncology 2016

Received: 17 November 2020 | Revised: 12 December 2020 | Accepted: 14 December 2020

DOI: 10.1111/cge.13900

CLINICAL GENETICS WILEY

REVIEW

Molecular intrinsic versus clinical subtyping in breast cancer: A comprehensive review

Agata Szymiczek[1] | Amna Lone[1] | Mohammad R. Akbari[1,2,3]

[1]Women's College Research Institute, University of Toronto, Toronto, Ontario, Canada

[2]Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

[3]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Correspondence
Mohammad R. Akbari, Women's College Hospital, 76 Grenville Street, Room 6421, Toronto, ON, M5S 1B2.
Email: mohammad.akbari@utoronto.ca

Funding information
Canadian Institute for Health Research (CIHR), Grant/Award Number: 152939

Abstract

Breast cancer is a heterogeneous disease manifesting diversity at the molecular, histological and clinical level. The development of breast cancer classification was centered on informing clinical decisions. The current approach to the classification of breast cancer, which categorizes this disease into clinical subtypes based on the detection of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and proliferation marker Ki67, is not ideal. This is manifested as a heterogeneity of therapeutic responses and outcomes within the clinical subtypes. The newer classification model, based on gene expression profiling (intrinsic subtyping) informs about transcriptional responses downstream from IHC single markers, revealing deeper appreciation for the disease heterogeneity and capturing tumor biology in a more comprehensive way than an expression of a single protein or gene alone. While accumulating evidences suggest that intrinsic subtypes provide clinically relevant information beyond clinical surrogates, it is imperative to establish whether the current conventional immunohistochemistry-based clinical subtyping approach could be improved by gene expression profiling and if this approach has a potential to translate into clinical practice.

KEYWORDS

breast cancer, gene expression profiling, hormone receptor, intrinsic subtyping, prognosis, response to treatment

Thank You