MAMMAPRINT

FELIPE ZERWES

Mastologista

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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SPECIAL ARTICLE

De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

G. Curigliano[1*,†], H. J. Burstein[2†], E. P. Winer[2], M. Gnant[3], P. Dubsky[3,4], S. Loibl[5], M. Colleoni[1], M. M. Regan[6], M. Piccart-Gebhart[7], H.-J. Senn[8] & B. Thürlimann[9], on behalf of the Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017

MENOS
ESVAZIAMENTOS

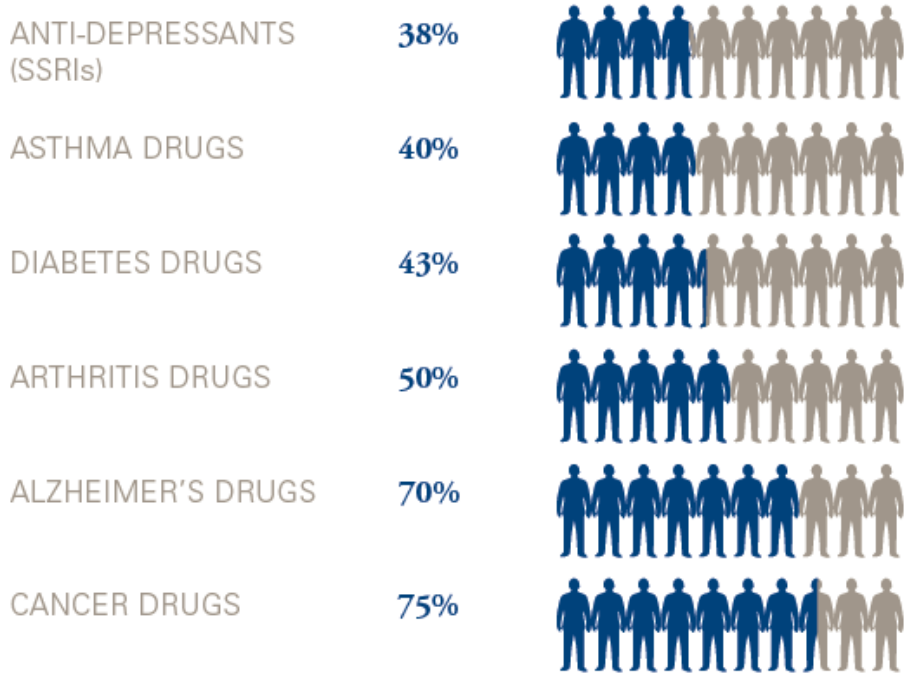
CIRURGIAS MENOS
MUTILANTES

RADIOTERAPIA PARCIAL

HIPOFRACIONAMENTO

The Current Situation:

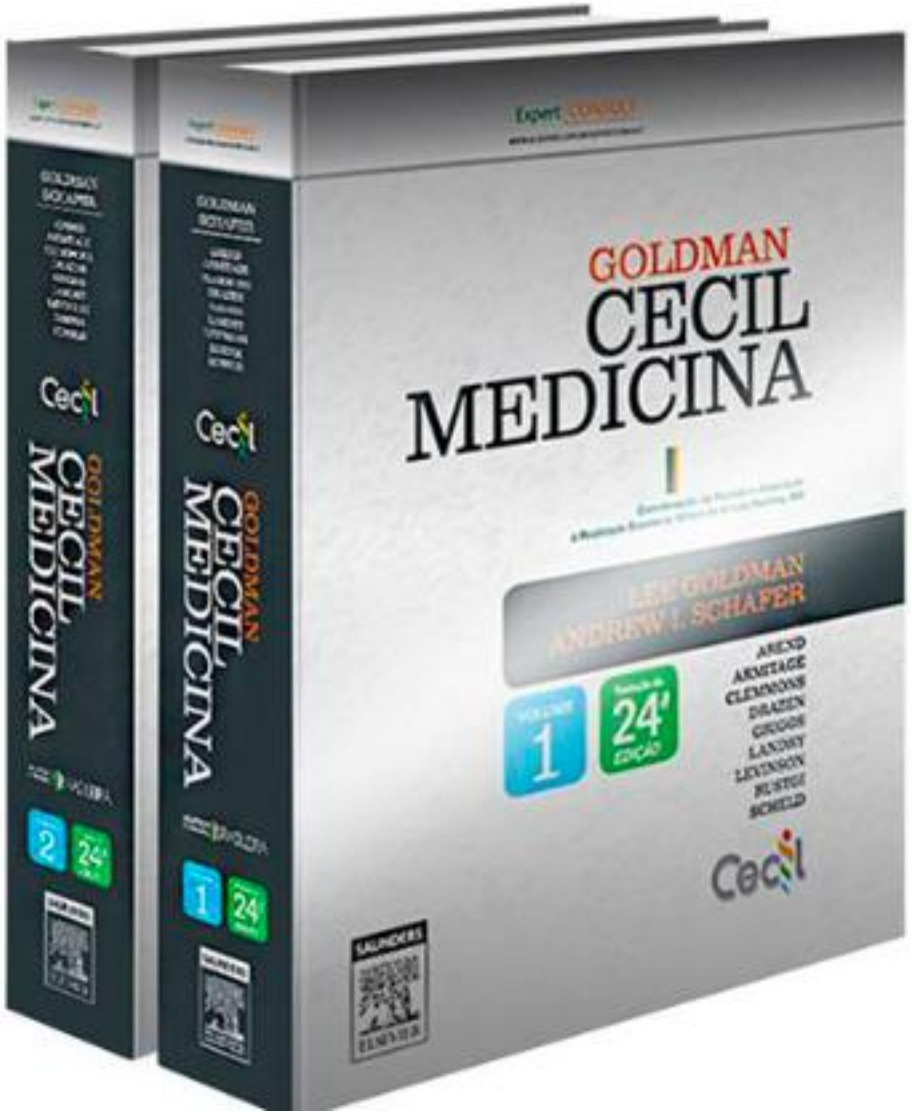
Only one in four cancer patients derive significant benefit from their treatment



37 of 49 billion dollars spent on cancer drugs globally are only causing toxicity for patients and deliver no benefit

TABLE 1. Summary of Available Multiparameter Genomic Assays for Decision Making in Early Breast Cancer

Name	Description	Results	References
Breast Cancer Index	HoxB13/IL17BR plus molecular-grade index	Low vs. high risk for both prognosis and prediction	13,14,17
EndoPredict	11-gene signature	Low vs. high risk	15,18,19
uPA/PAI-1 (Femtelle)	Urokinase plasminogen activator plus plasminogen activator inhibitor type 1	Low vs. high risk	20
70-gene breast cancer recurrence assay (MammaPrint)	70-gene signature	Low vs. high risk	
Mammostrat	5-gene signature	Low vs. moderate vs. high risk	
21-gene recurrence score assay (Oncotype DX)	21-gene signature	Low vs. intermediate vs. high risk	6,7,21
PAM50 risk of recurrence score (Prosigna)	46-gene signature plus 18-gene proliferation score plus tumor size	Low vs. intermediate vs. high risk	12,22,23



SEÇÃO II

PRINCÍPIOS
DA AVALIAÇÃO
E TRATAMENTO

CAP. 9 : Usando a informação para tomada de decisões clínicas.

Antes de solicitar um teste ou exame, os clínicos devem considerar se o resultado do teste iria **modificar** sua conduta.

QUAL O MELHOR TESTE ?

- Se um clínico decidir que são necessárias mais informações para reduzir a incerteza e for possível que os testes gerem mudanças nas estratégias, a pergunta que deve ser feita é:

QUAL O TESTE MAIS APROPRIADO ?

“ If we have data, let’s look at data. If all we have are opinions, let’s go with mine”

Jim Barksdale

former Netscape CEO

Evidências Científicas....

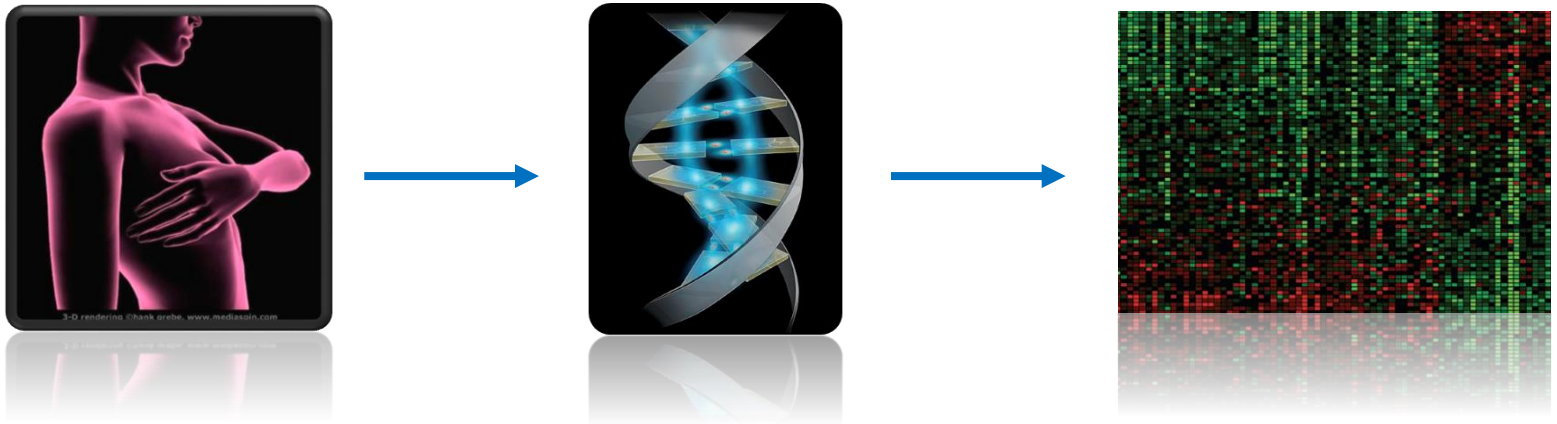
ECRs

Prospective, Randomized Trials of Genomic Assays in Breast Cancer

- TAILORx - LN negative
  - Observational, Non-randomized cohort @ 5 years - reported
  - Randomized cohort of RS 11-25 – not yet reported
  - *No further randomized data forthcoming for RS over 25*
- RxPonder – LN 1-3 positive
  - Randomized cohort ≤ 25
  - Not yet reported

- MINDACT
  - Observational and Randomized cohorts @ 5 years - reported

The Basis for the MINDACT Study



Designed to answer the question:

Can ***genomic profiling*** of breast cancers

with ***high-risk clinical and pathologic features***

identify women who can ***safely avoid chemotherapy***?

The NEW ENGLAND JOURNAL of MEDICINE

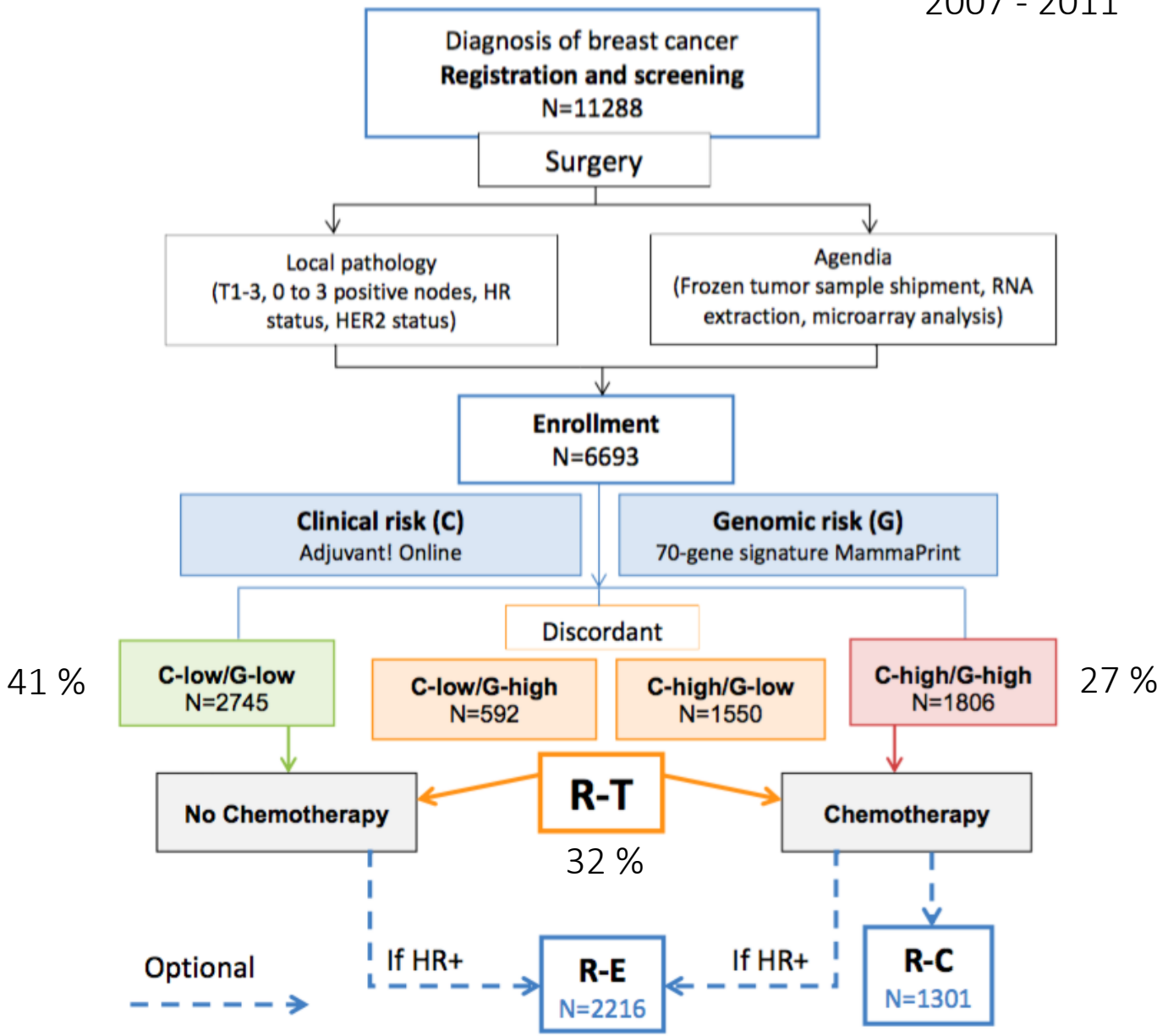
ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

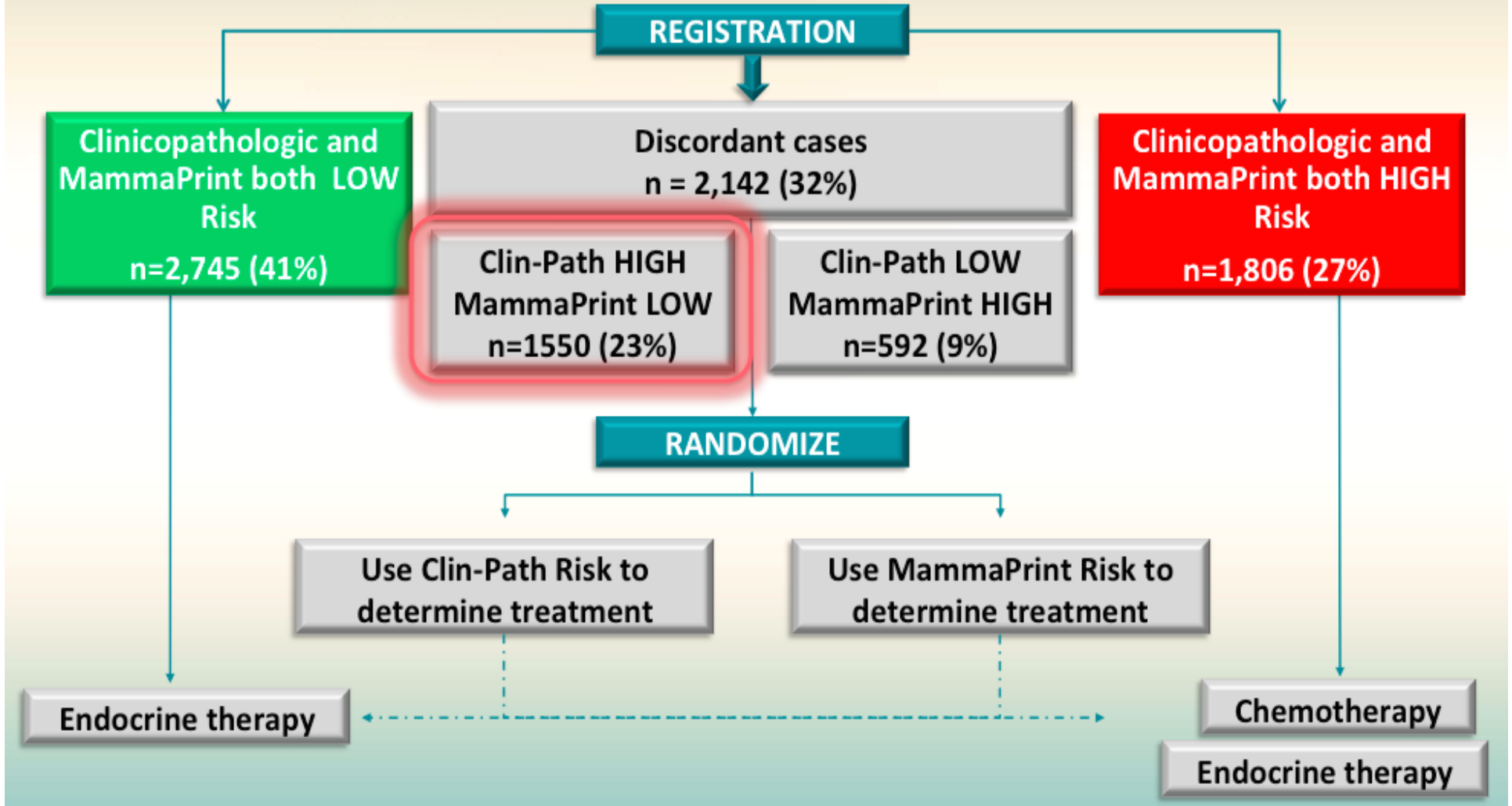
Figure S 7: The MINDACT study design.

2007 - 2011

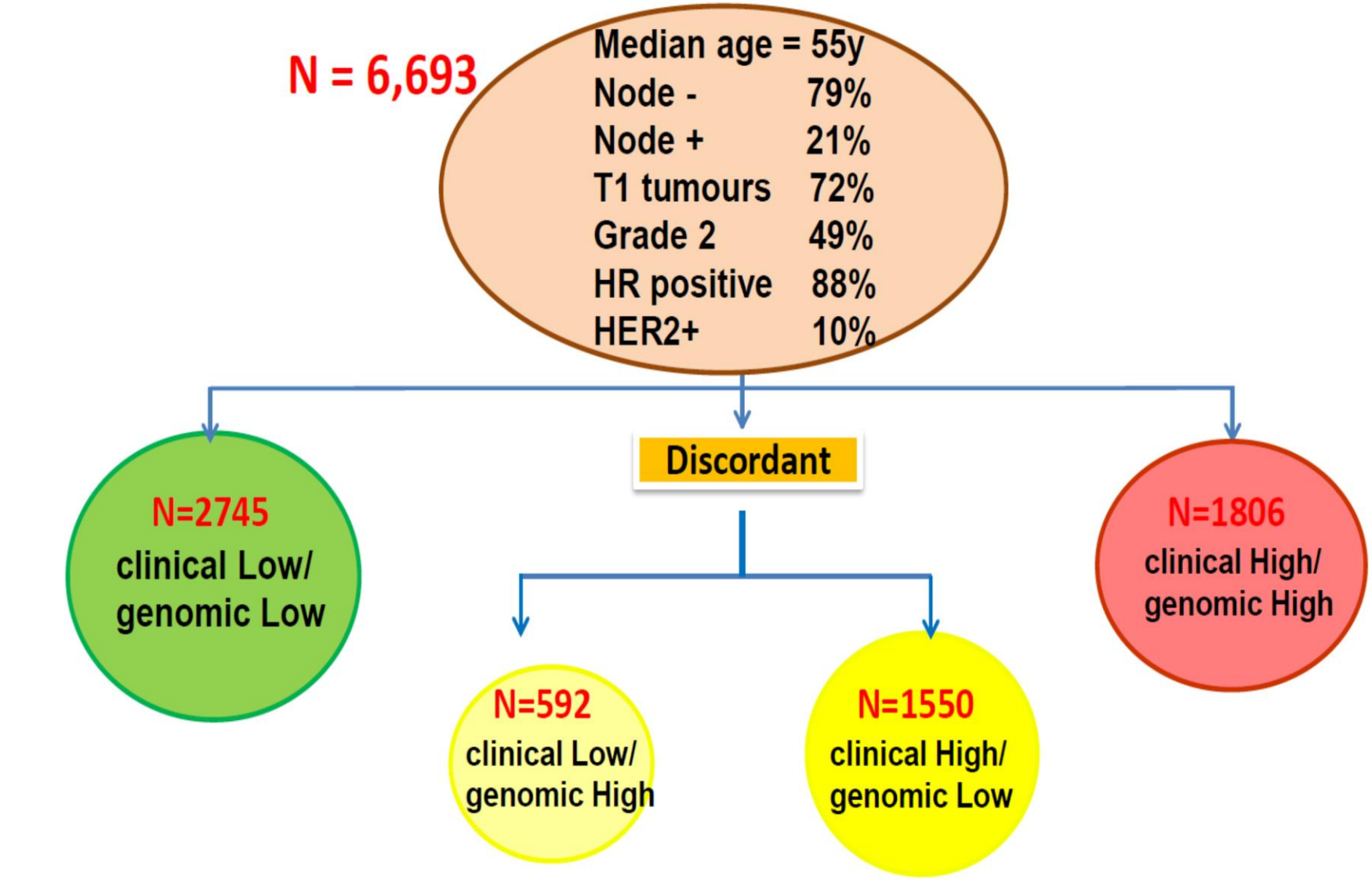


MINDACT Trial Design (n = 6,693)

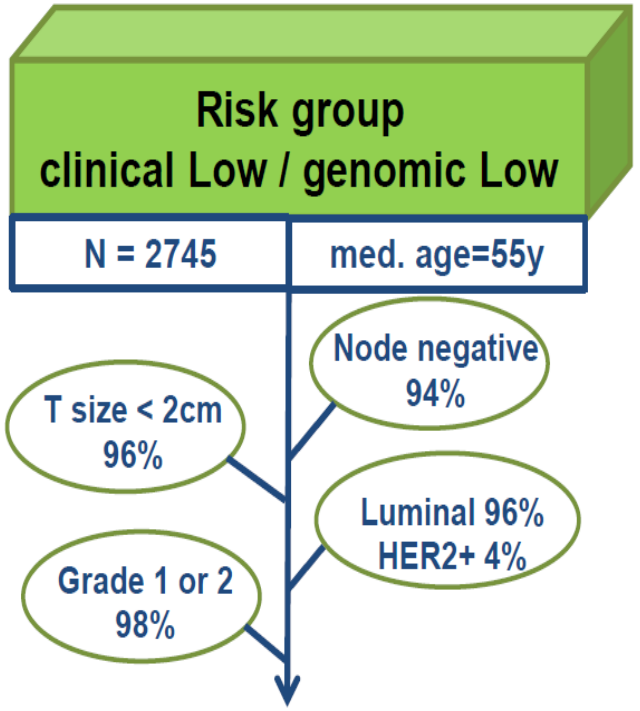
Node negative & 1-3 positive nodes



The MINDACT study: Patient demographics



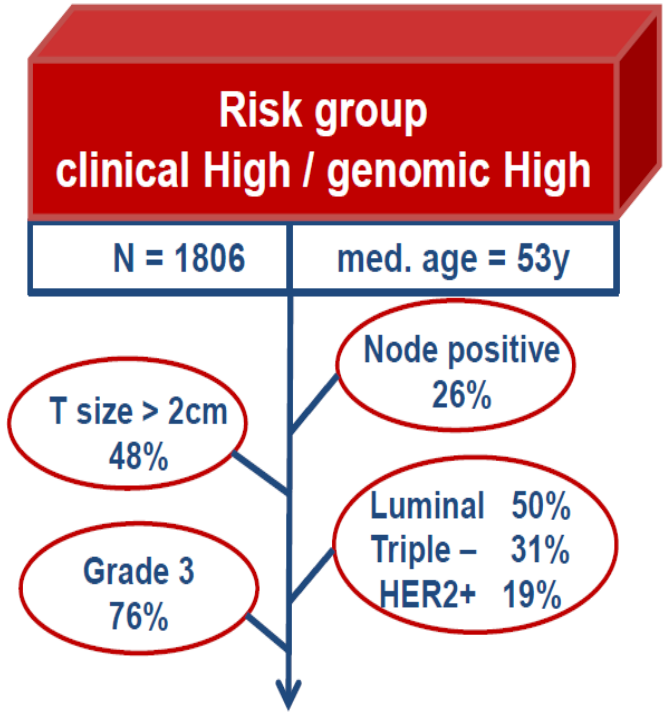
MINDACT: patient demographics and compliance with assigned therapy



Assigned:
NO CHEMOTHERAPY

Compliance = 99%

(Received Endocrine therapy: 79%)



Assigned:
CHEMOTHERAPY

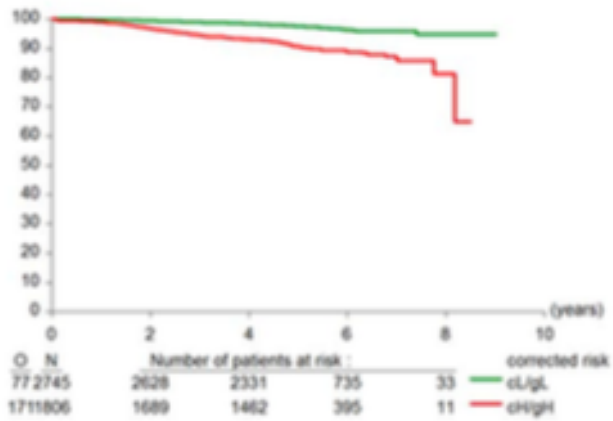
Compliance = 96%

(Received Endocrine therapy: 59%
Received trastuzumab: 15%)

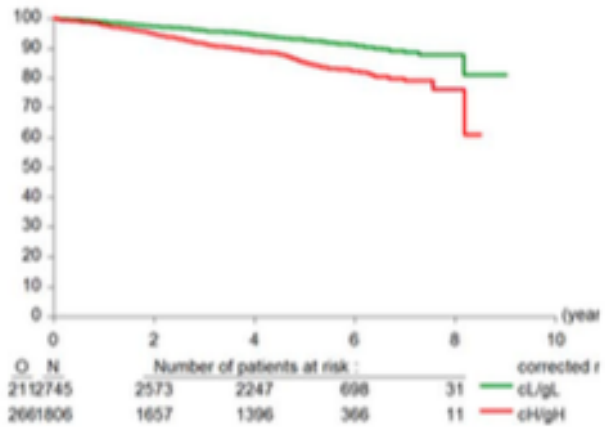
Clinical outcome of the MINDACT population at 5y median follow-up

A) CONCORDANT RISK GROUPS (using corrected risk)

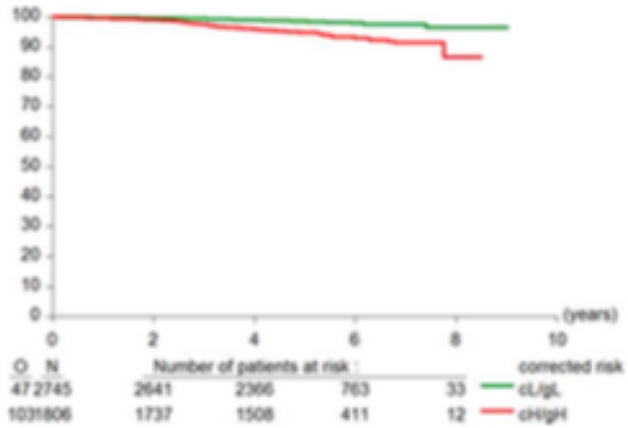
DMFS



DFS

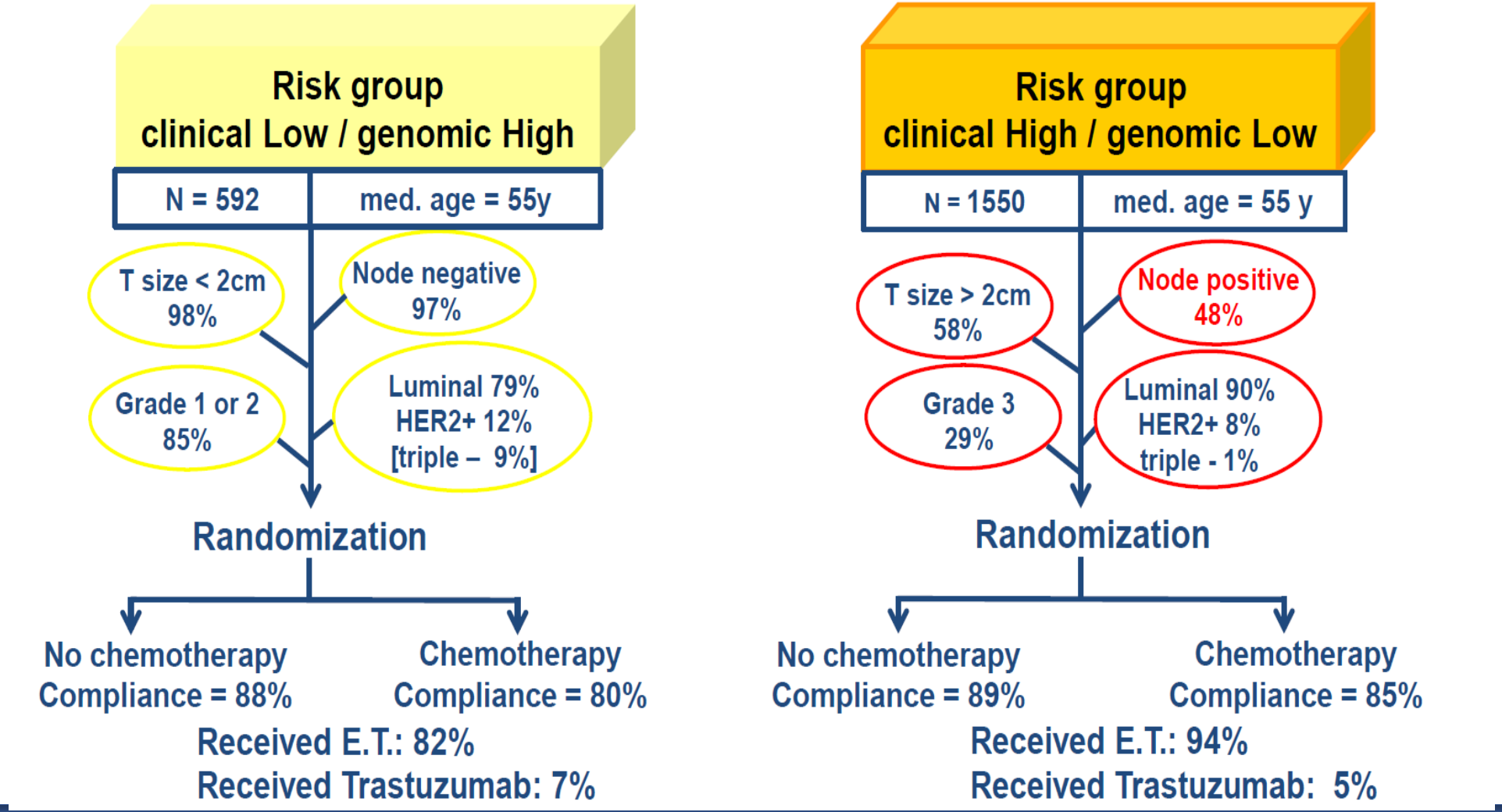


OS



	% at 5y (95% CI)	**% at 5y**	**% at 5y**
cL/gL	**97.6** (96.9 – 98.1)	**92.8** (91.7 – 93.7)	**98.4** (97.8 – 98.9)
cH/gH	**90.6** (89.0 – 92.0)	**85.3** (83.4 – 87.0)	**94.7** (93.4 – 95.7)

MINDACT: patient demographics and compliance with assigned therapy



13 Clinical risk assessment according to modified Adjuvant!Online

Table S 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
ER negative	HER2 negative	well differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		moderately differentiated OR poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	Any	Any size	C-high

C-low

RH	HER-2	GRAU	N	T
+	NEG	1	0	≤ 3 cm
+	NEG	1	1-3	≤ 2 cm
+	NEG	2	0	≤ 2 cm
+	NEG	3	0	≤ 1 cm
+	POS	1/2	0	≤ 2 cm
+	POS	3	0	≤ 1 cm
-	POS	1/2	0	≤ 1 cm
-	NEG	1	0	≤ 2 cm
-	NEG	2/3	0	≤ 1 cm

C-low

RH	HER-2	GRAU	N	T
+	NEG	1	0	≤ 3 cm
+	NEG	1	1-3	≤ 2 cm
+	NEG	2	0	≤ 2 cm
+	NEG	3	0	≤ 1 cm

C-low

RH	HER-2	GRAU	N	T
+	NEG	1	0	≤ 3 cm
+	NEG	1	1-3	≤ 2 cm
+	NEG	2	0	≤ 2 cm
+	NEG	3	0	≤ 1 cm

LUMINAIS

T1 N0	G1/2
T1b N0	G3
T1 N1(1-3)	G1
T2(≦3cm) N0	G1

RH	HER-2	G	N	T (cm)
+	NEG	1	0	3,1 – 5,0
+	NEG	1	1-3	2,1 - -5,0
+	NEG	2	0	2,1 – 5,0
+	NEG	2	1-3	ANY
+	NEG	3	0	1,1 – 5,0
+	NEG	3	1-3	ANY
+	POS	1/2	0	2,1 – 5,0
+	POS	1/2	1-3	ANY
+	POS	3	0	1,1 – 5,0
+	POS	3	1-3	ANY
-	POS	1/2	0	1,1 – 5,0
-	POS	1/2	1-3	ANY
-	POS	3	ANY	ANY
-	NEG	1	0	2,1 – 5,0
-	NEG	1	1-3	ANY
-	NEG	2/3	0	1,1 – 5,0
-	NEG	2/3	1-3	ANY

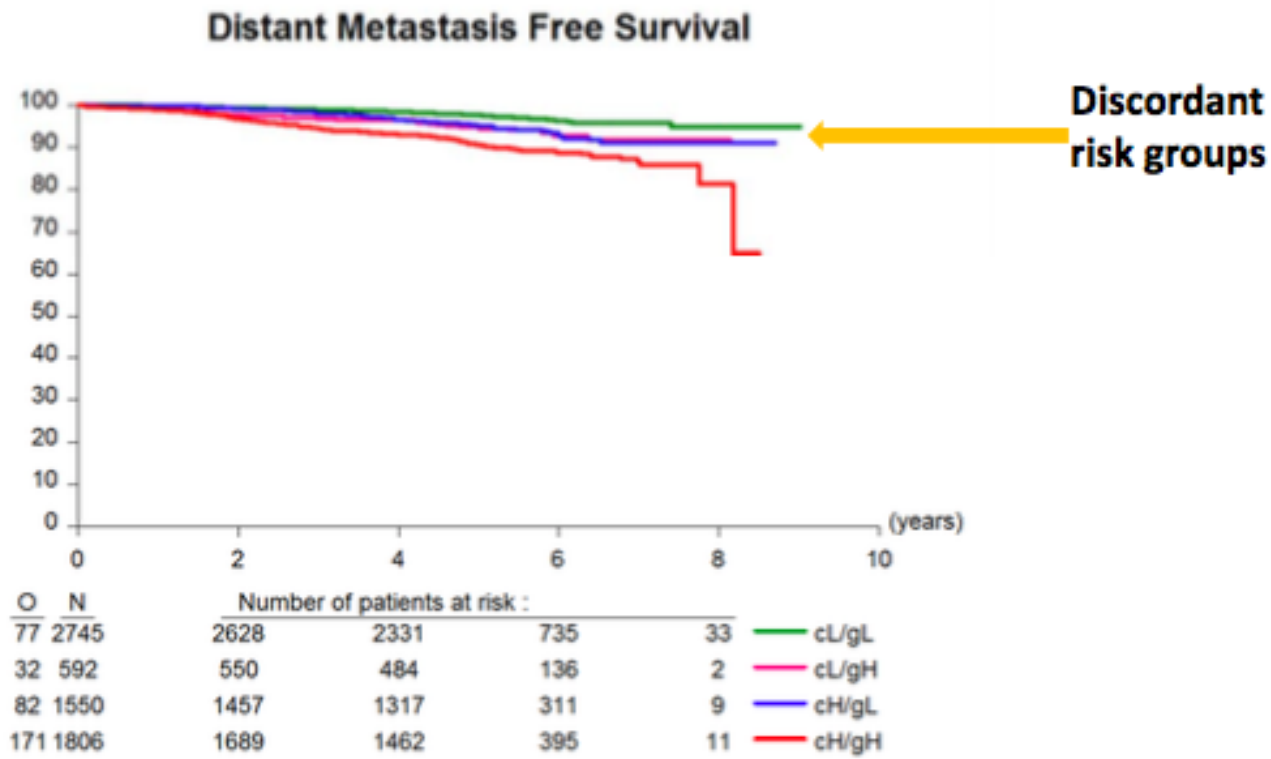
Study End Points

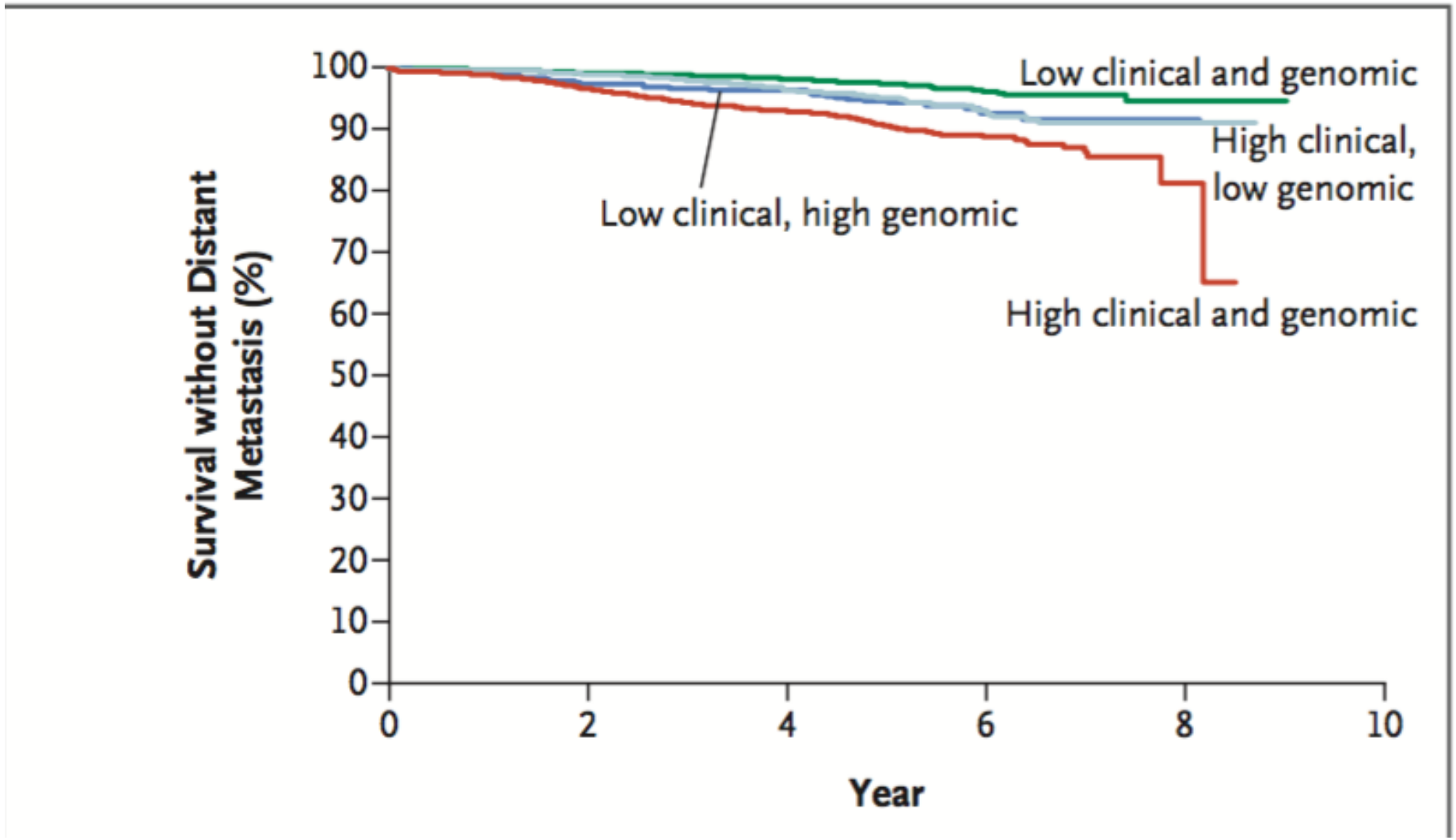
- EP primário
  - Sobrevida sem metástases a distância

- EP secundário
  - Proporção de pacientes que receberam QT de acordo com o risco clínico, comparado ao risco genômico
  - Sobrevida global
  - Sobrevida livre de doença

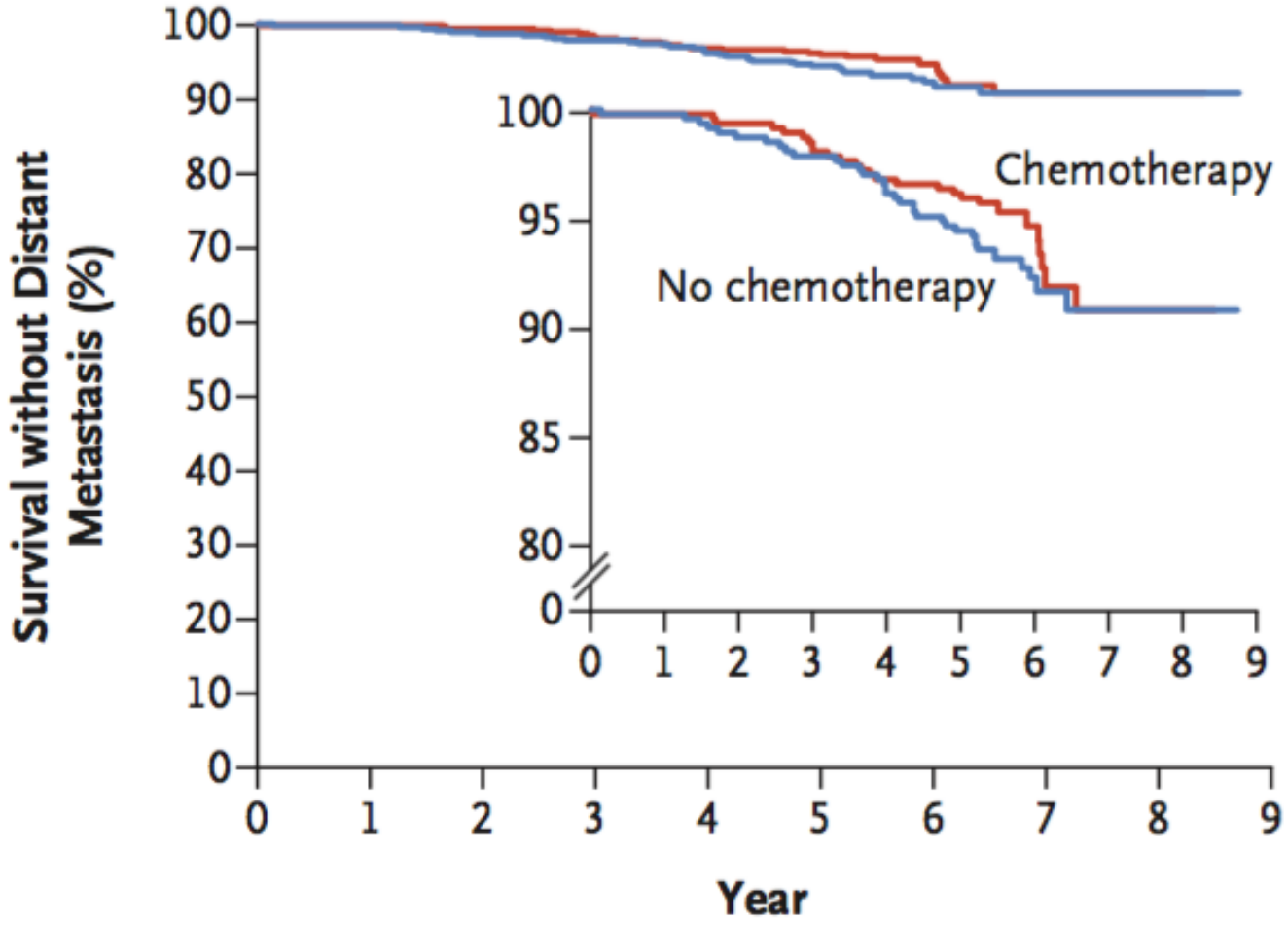
Clinical outcome of the MINDACT population at 5y median follow-up

DMFS IN ALL 4 RISK GROUPS




Survival without Distant Metastasis (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Year
Low clinical and genomic
High clinical, low genomic
Low clinical, high genomic
High clinical and genomic

A **High Clinical Risk, Low Genomic Risk**



No. at risk

Chemotherapy	749	714	698	677	611	346	145	41	3
No chemotherapy	748	727	708	696	655	424	160	41	4

cH/gL: CT versus no CT per protocol

cH/gL ACT vs no ACT per protocol population						
	Treatment received	Patients	Observed Events	% at 5 Year(s) (95% CI)	Hazard Ratio (adjusted Cox model) (95% CI)	p-value (adjusted logrank)
DMFS	ACT	592	22	**96.7** (94.7, 98.0)	**0.65** (0.38,1.10)	0.106
	no ACT	636	37	**94.8** (92.6, 96.3)	1.00	
DFS	ACT	592	39	**93.3** (90.7, 95.2)	**0.64** (0.43,0.95)	0.026
	no ACT	636	66	**90.3** (87.6, 92.4)	1.00	
OS	ACT	592	10	**98.8** (97.4, 99.5)	**0.63** (0.29,1.37)	0.245
	no ACT	636	18	**97.3** (95.6, 98.4)	1.00	

EORTC
The future of cancer therapy

BIG
Breast International Group

TRANSBIG

cL/gH: CT versus no CT per protocol

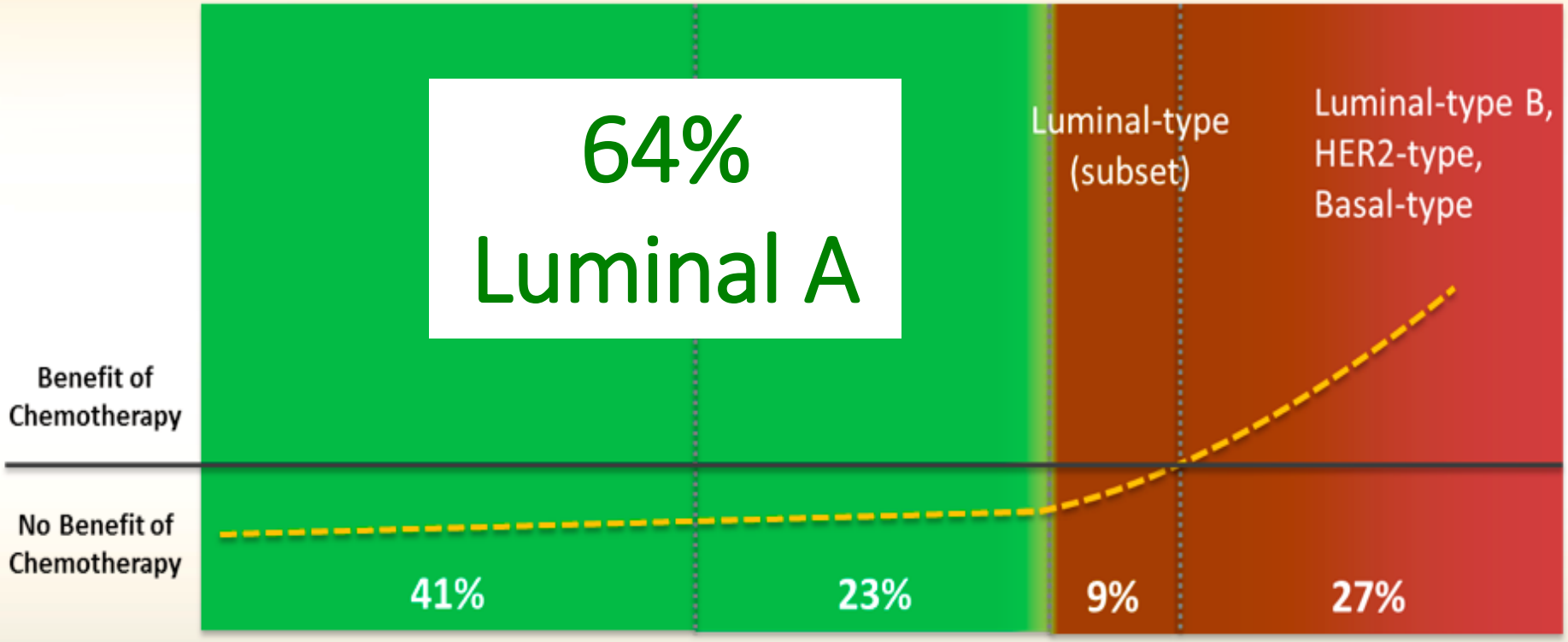
cL/gH ACT vs no ACT per protocol population						
	Treatment received	Patients	Observed Events	% at 5 Year(s) (95% CI)	Hazard Ratio (adjusted Cox model) (95% CI)	p-value (adjusted logrank)
DMFS	ACT	224	11	**96.1** (92.4, 98.1)	**0.90** (0.40,2.01)	0.798
	no ACT	254	14	**93.9** (89.6, 96.5)	1.00	
DFS	ACT	224	17	**92.7** (87.9, 95.7)	**0.74** (0.40,1.39	0.355
	no ACT	254	25	**90.5** (85.7, 93.8)	1.00	
OS	ACT	224	5	**98.1** (94.9, 99.3)	**0.72** (0.23,2.24)	0.572
	no ACT	254	8	**97.0** (93.8, 98.6)	1.00	

EORTC

BIG

TRANSBIG

The Chemotherapy Benefit Continuum



	cL/MP Low	cH/MP Low	cL/MP High	cH/MP High
MINDACT 5-year DMFS	97.6% no ACT	94.7% no ACT	93.9% no ACT	90.6% ACT

6693 mulheres no estudo

3356

C-high

6693 mulheres no estudo

Antes de solicitar um teste ou exame, os clínicos devem considerar se o resultado do teste iria **modificar** sua conduta.

TAILORx

- 04/ 2006 - 10/2010
- 10253 pacientes

Oncotype - DX

- 1626 (15,9 %) LOW RISK (RS 0 – 10)
- 6897 (67,3 %) INT. RISK (RS 11 – 25)
- 1730 (16,9 %) HIGH RISK (RS > 26)

Research

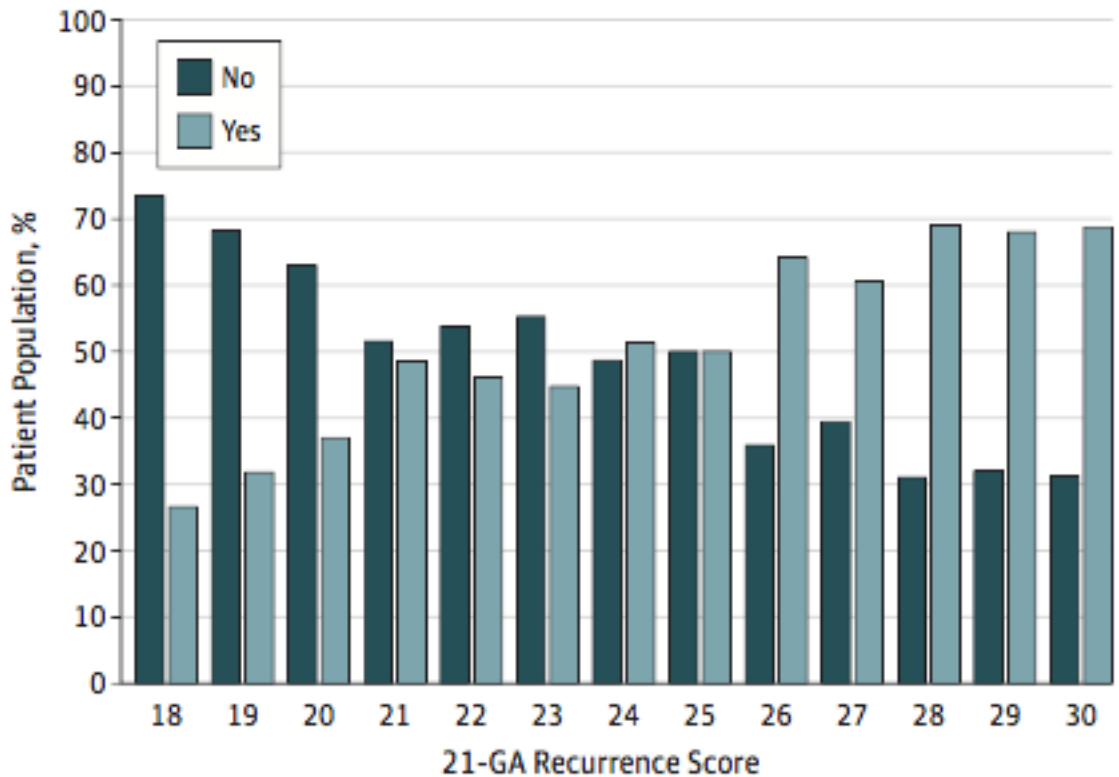
JAMA Oncology | Original Investigation

Association of 70-Gene Signature Assay Findings With Physicians' Treatment Guidance for Patients With Early Breast Cancer Classified as Intermediate Risk by the 21-Gene Assay

Michaela Tsai, MD; Shelly Lo, MD; William Audeh, MD; Rubina Qamar, MD; Raye Budway, MD; Ellis Levine, MD; Pat Whitworth, MD; Blanche Mavromatis, MD; Robin Zon, MD; Dwight Oldham, MD; Sarah Untch, MS; Tina Treece, PhD; Lisa Blumencranz, PhD; Hatem Soliman, MD

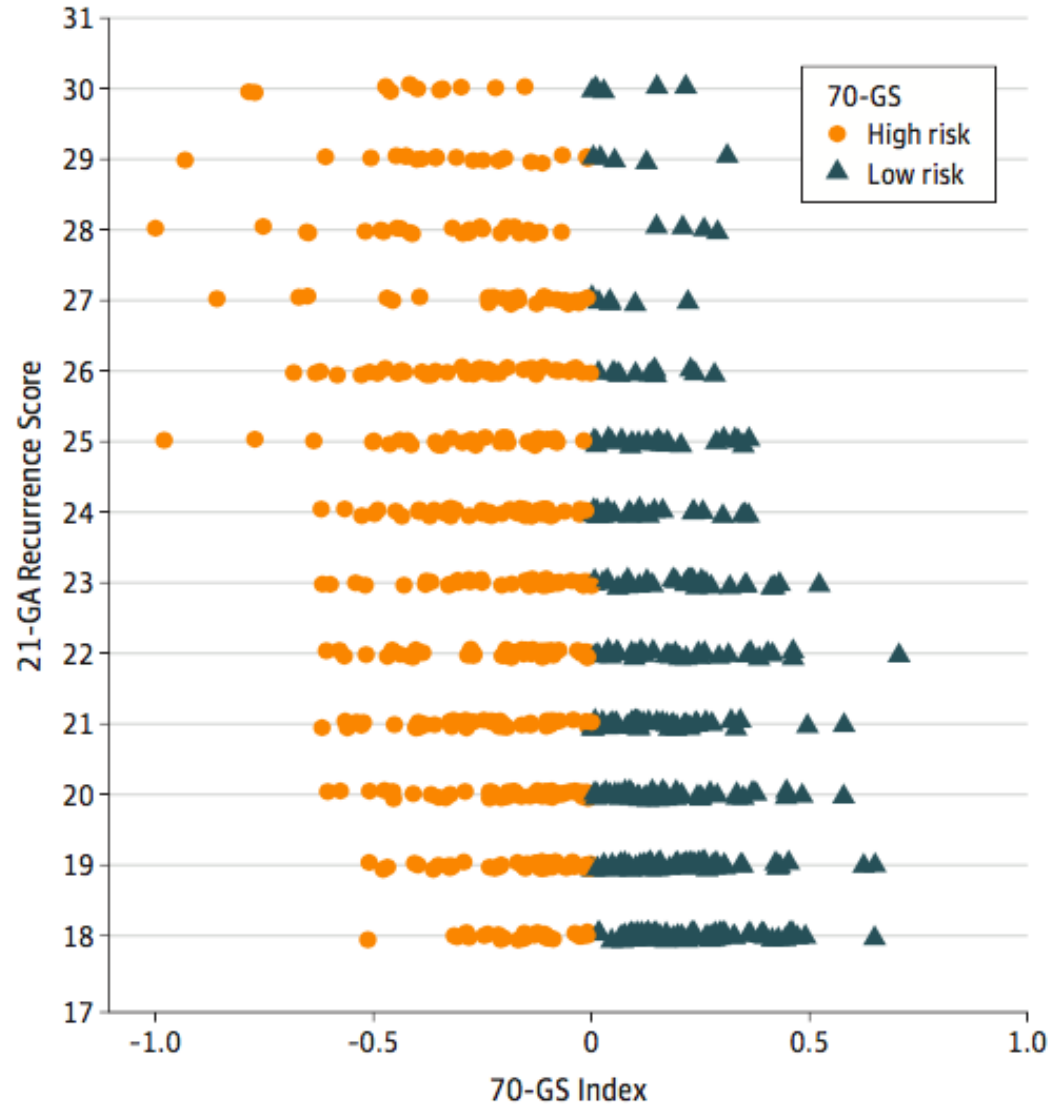
JAMA Oncology Published online October 26, 2017

Figure 1. Recommendation to Receive Chemotherapy Based on 21-Gene Assay (21-GA) Recurrence Score in 840 Patients



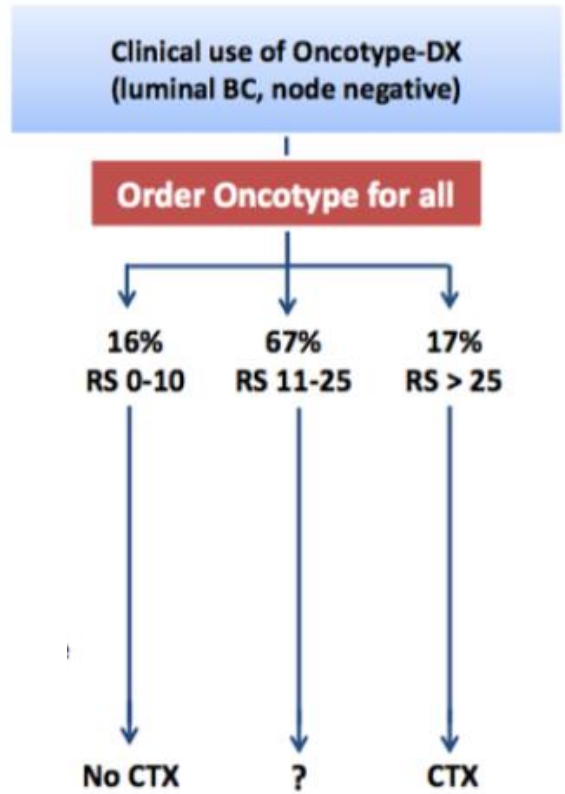
21-GA scores ranging from 18 to 30 were considered to indicate intermediate risk for this study.

Figure 2. Scatterplot of 70-Gene Signature (70-GS) Index vs 21-Gene Assay (21-GA) Recurrence Score

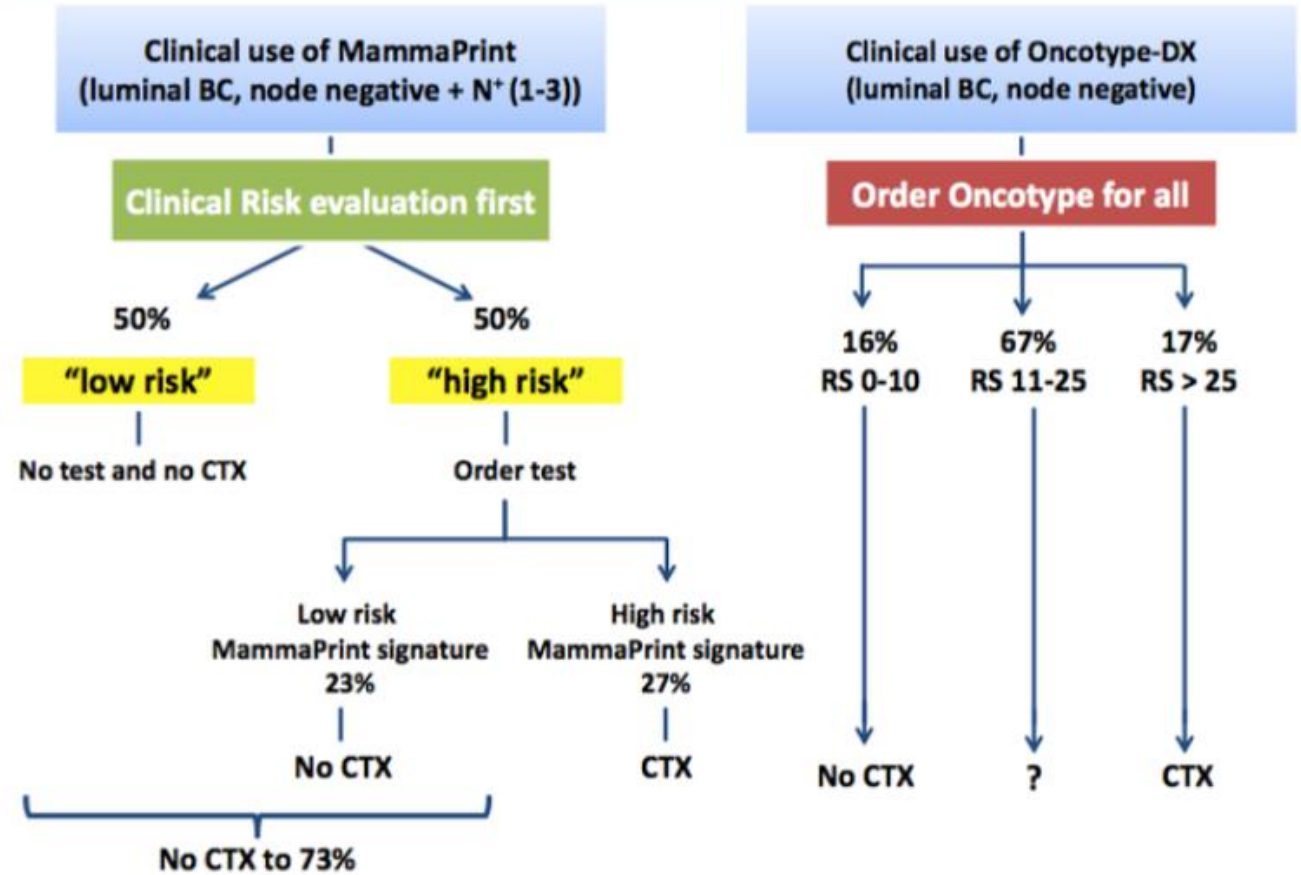


Data points indicate 70-GS risk classification result.

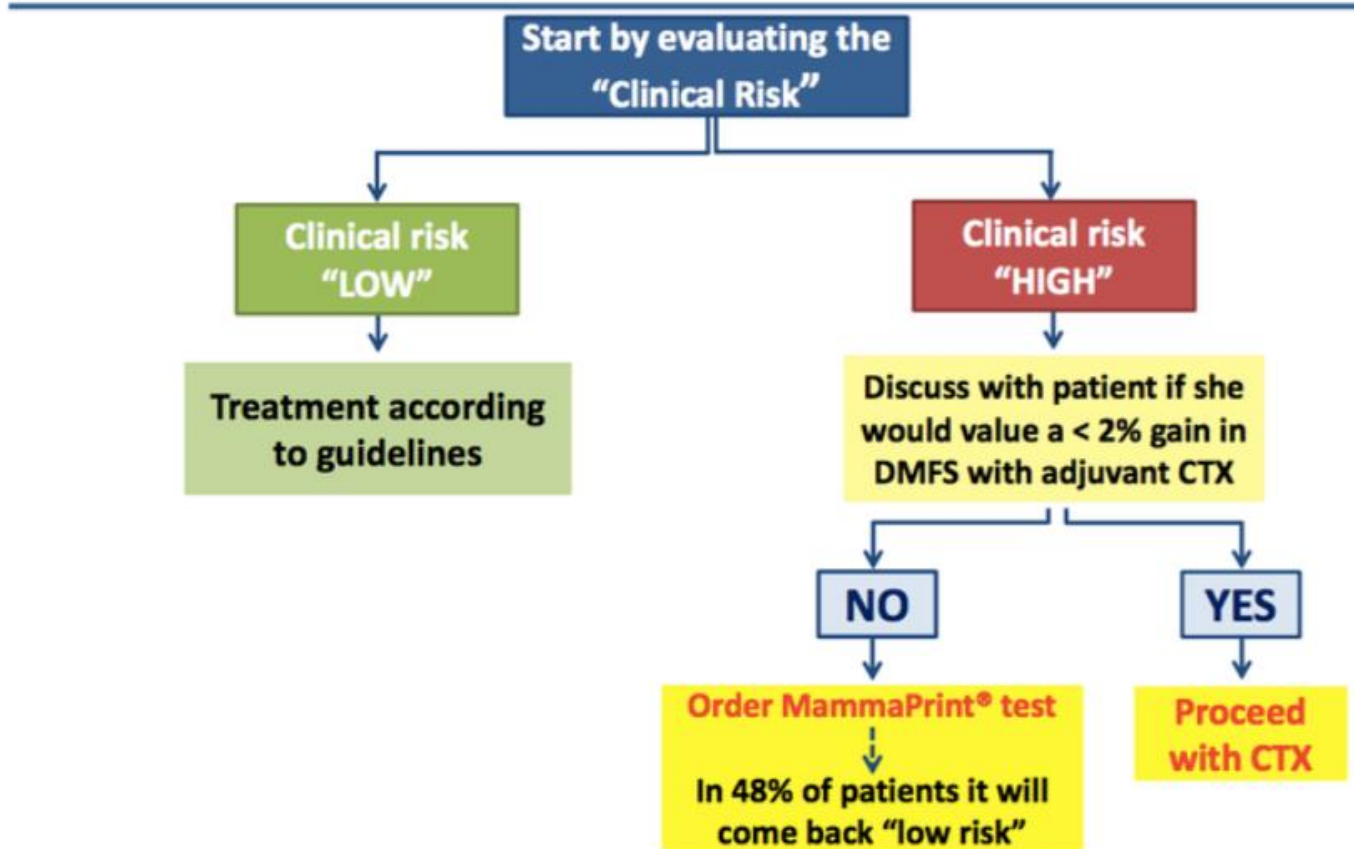
Use of gene expression signatures in the clinic today



Use of gene expression signatures in the clinic today



How to use 70-gene array
Integrating clinical parameters



Avaliando os 2 ECR....

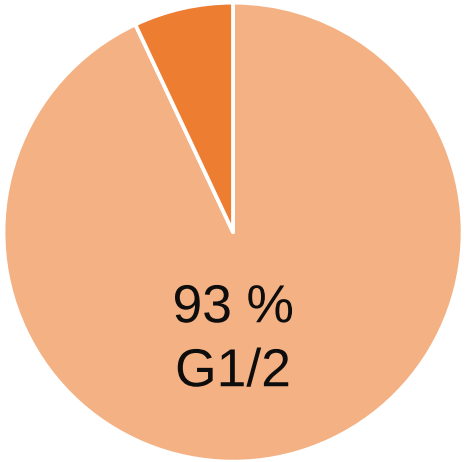
- Mulheres com baixo risco clínico (conforme critérios do Mindact) não necessitam realizar Mammaprint;

- TailorX somente confirmou (por enquanto) que RS <10 no Oncotype não necessita Qt (será que necessita testar ???)

Mediana pacientes Tailor X

58 anos

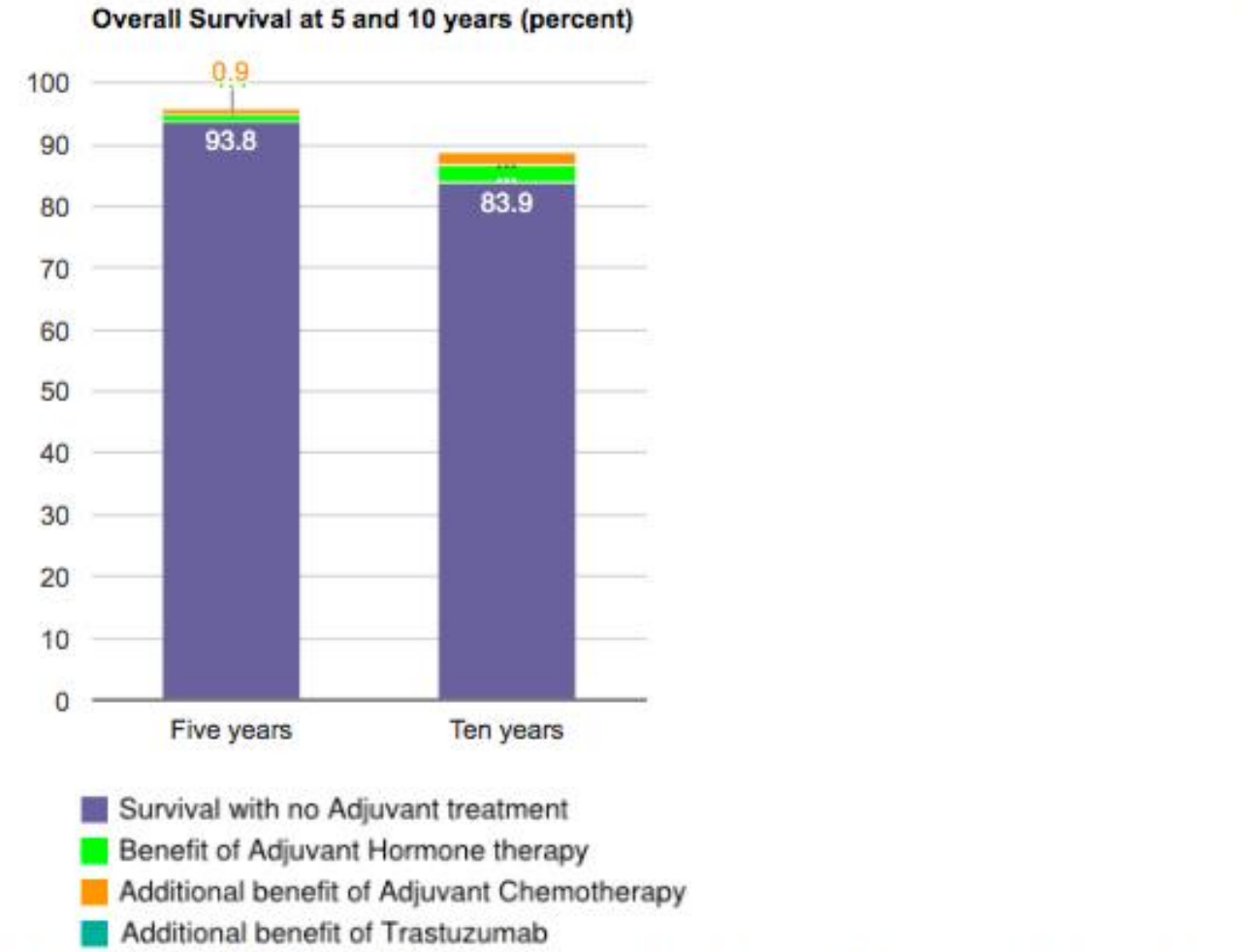
1.5 cm



PREDICT Tool Version 2.0: Breast Cancer Survival; Input

Age at diagnosis:	58		
Mode of detection:	○ Screen-detected	● Symptomatic	○ Unknown
Tumour size in mm:	15 (blank if unknown)		
Tumour Grade:	○ 1	● 2	○ 3
Number of positive nodes:	0 (blank if unknown)		☐ Micromet
ER status:	● Positive	○ Negative	
HER2 status:	○ Positive	● Negative	○ Unknown
KI67 status:	● Positive	○ Negative	○ Unknown
Gen chemo regimen:	○ No chemo	○ Second	● Third

Five year survival
94 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy
Ten year survival
84 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 3 out of 100 women treated are alive because of hormone therapy
An extra 5 out of 100 women treated are alive because of hormone therapy & chemotherapy



- Mulheres com alto risco clínico (Mindact), após orientadas sobre pequena diferença (não significativa) de desfecho podem optar por realizar Mammaprint e tentar evitar Qt.

- Nenhum teste dá “segurança absoluta” em relação à recidiva tumoral.

Research

JAMA Oncology | Original Investigation

Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades

Laura J. Esserman, MD, MBA; Christina Yau, PhD; Carlie K. Thompson, MD; Laura J. van 't Veer, PhD; Alexander D. Borowsky, MD; Katherine A. Hoadley, PhD; Nicholas P. Tobin, PhD; Bo Nordenskjöld, MD, PhD; Tommy Fornander, MD, PhD; Olle Stål, PhD; Christopher C. Benz, MD; Linda S. Lindström, PhD

STO-3 STUDY – Stockholm Tamoxifen Trial 1976 – 1990

1780 mulheres
Pós-menopausa
T ≦ 3 cm
N0

→

2 anos TMX
X
NADA

- 3 ANOS (35 %)
- NADA (65%)

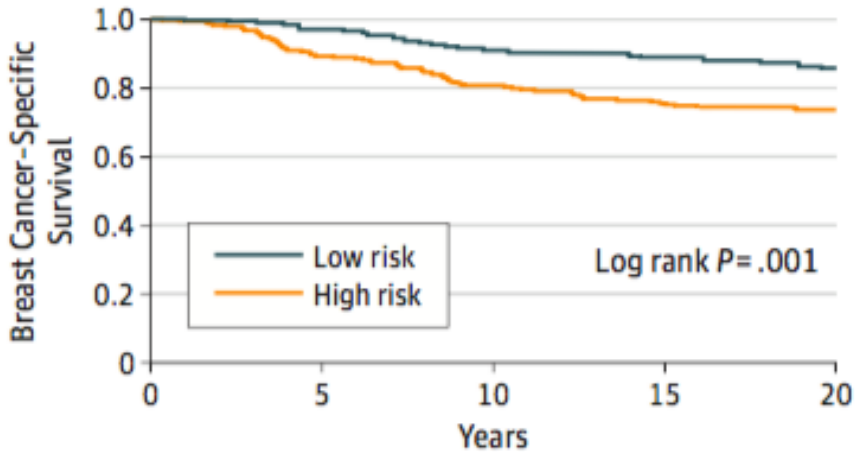
652 pacientes - MAMMAPRINT

98 (15 %) **ULTRALOW RISK**

≦ 0.355

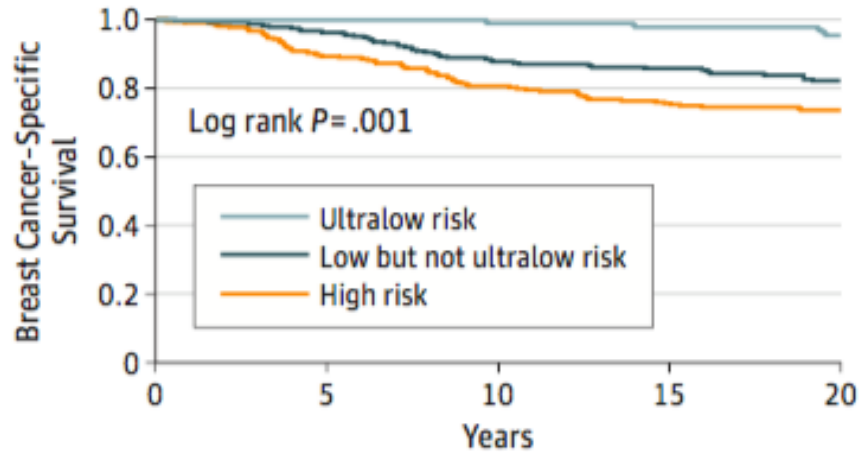
Figure 2. Kaplan-Meier Plots of Breast Cancer–Specific Survival

A 652 Total patients



No. at risk					
Low risk	377	348	292	238	163
High risk	275	227	183	150	121

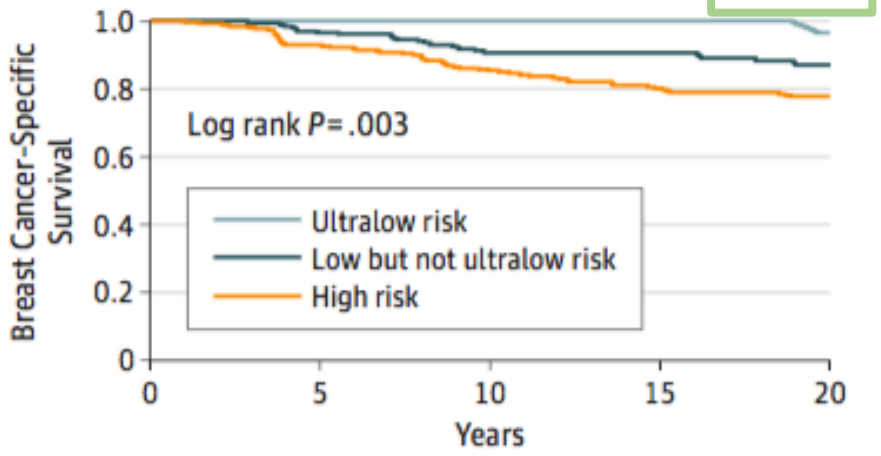
B 652 Total patients



No. at risk					
Ultralow risk	98	95	84	69	47
Low but not ultralow risk	279	253	208	169	116
High risk	275	227	183	150	121

C 339 Tamoxifen-treated patients

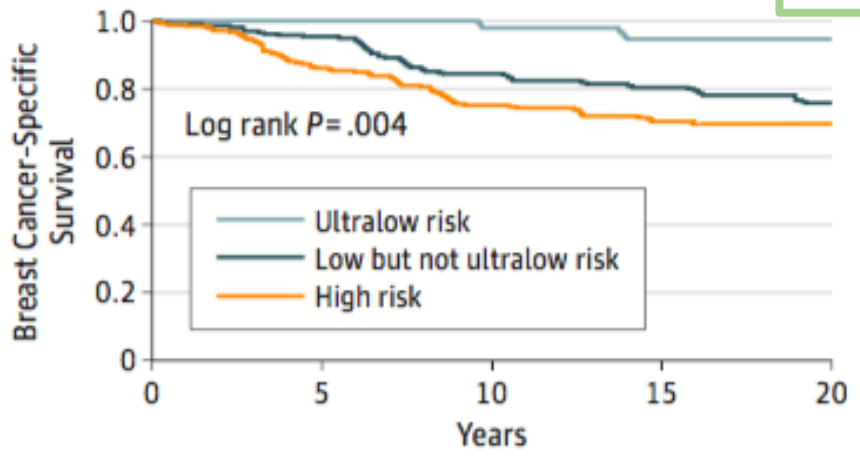
97 %



No. at risk					
Ultralow risk	54	52	48	39	28
Low but not ultralow risk	148	136	116	92	63
High risk	137	115	97	80	63

D 313 In untreated arm

94 %

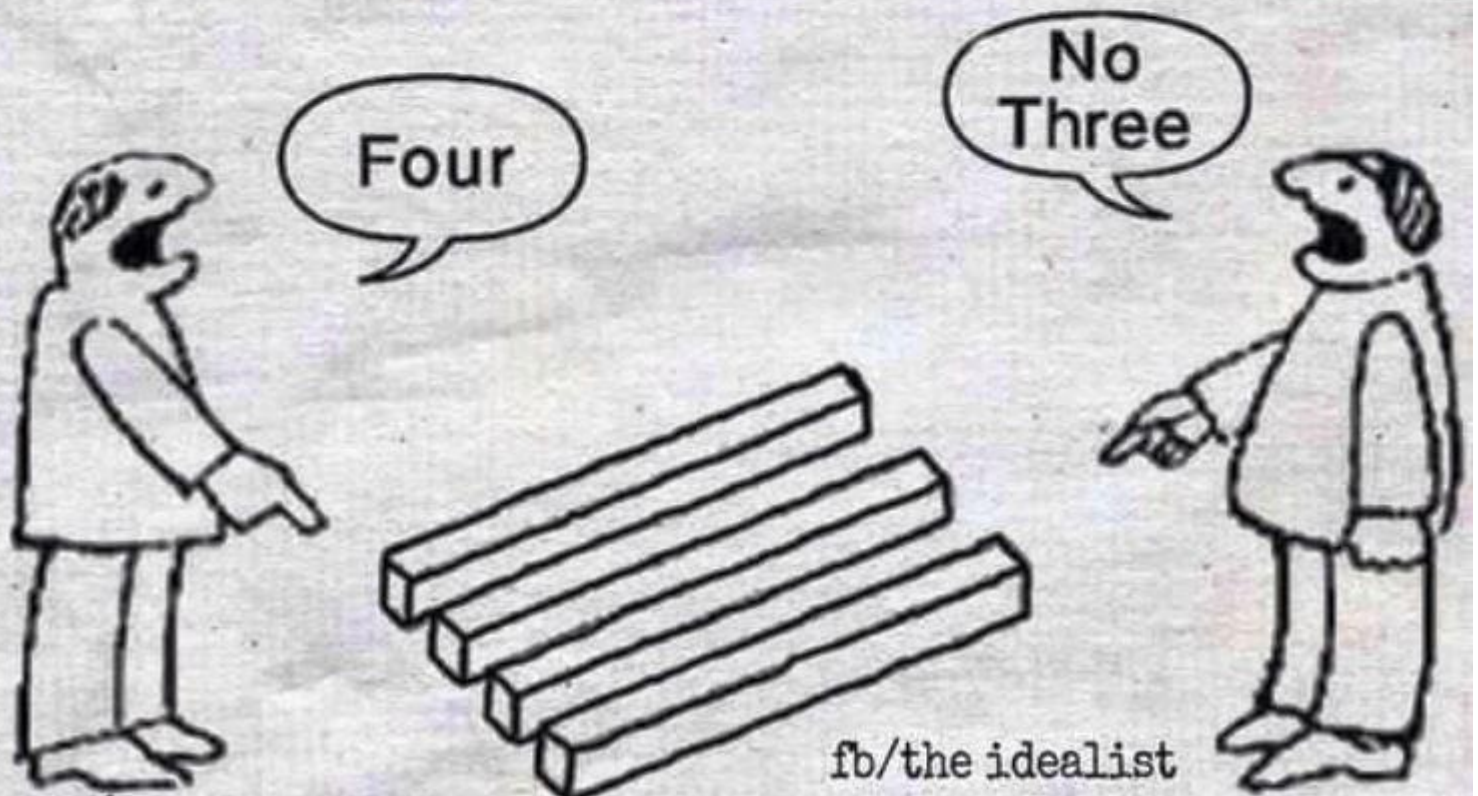


No. at risk					
Ultralow risk	44	43	36	30	19
Low but not ultralow risk	131	117	92	77	53
High risk	138	112	86	70	58

Meaning The ultralow-risk threshold can identify patients whose long-term risk of dying from breast cancer is exceedingly low.

"Everything we hear
is an opinion, not a fact.
Everything we see
is a perspective, not the truth."

- Marcus Aurelius



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