La predizione del rischio basata sui tests di espressione genica

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Precision Medicine:
Prognostic and Predictive Factors

	Definition	Aim
Prog Fact		sary
Predictive Factors	Provide information on probability of benefit or toxicity from a specific therapy	To spare ineffective treatments

Prognosis:
telling the future is useless unless we can modify the outcome

Adjuvant Systemic Therapy for EBC
Summary of the Evidence

Subgroup	Treatment	Comparator	Risk reduction for recurrence
HR+	**TAM for 5y**	No TAM	**39%**
	AI (upfront or sequence)	5y TAM	**23-29%**
	Extended adjuvant ET	5y TAM	**15-43%**
All	**Polychemotherapy**	No chemo	**~ 24%**
	Anthra regimens	CMF	**20%**
	Anthra+Taxane regimens	Anthra	**12%**
HER2+	**Trastuzumab + Chemo**	Chemo	**40%**

Precision Medicine:
Prognostic and Predictive Factors

Prognosis:
telling the future is useless unless we can modify the outcome

Prognostic Factors	outcome regardless of therapy	treatments
Pre… Fa…		

This is not the case !
Adjuvant therapies can reduce the risk of relapse up to 80%

Precision Medicine:
Prognostic and Predictive Factors

Prediction:
therapies are useless unless we know who to treat

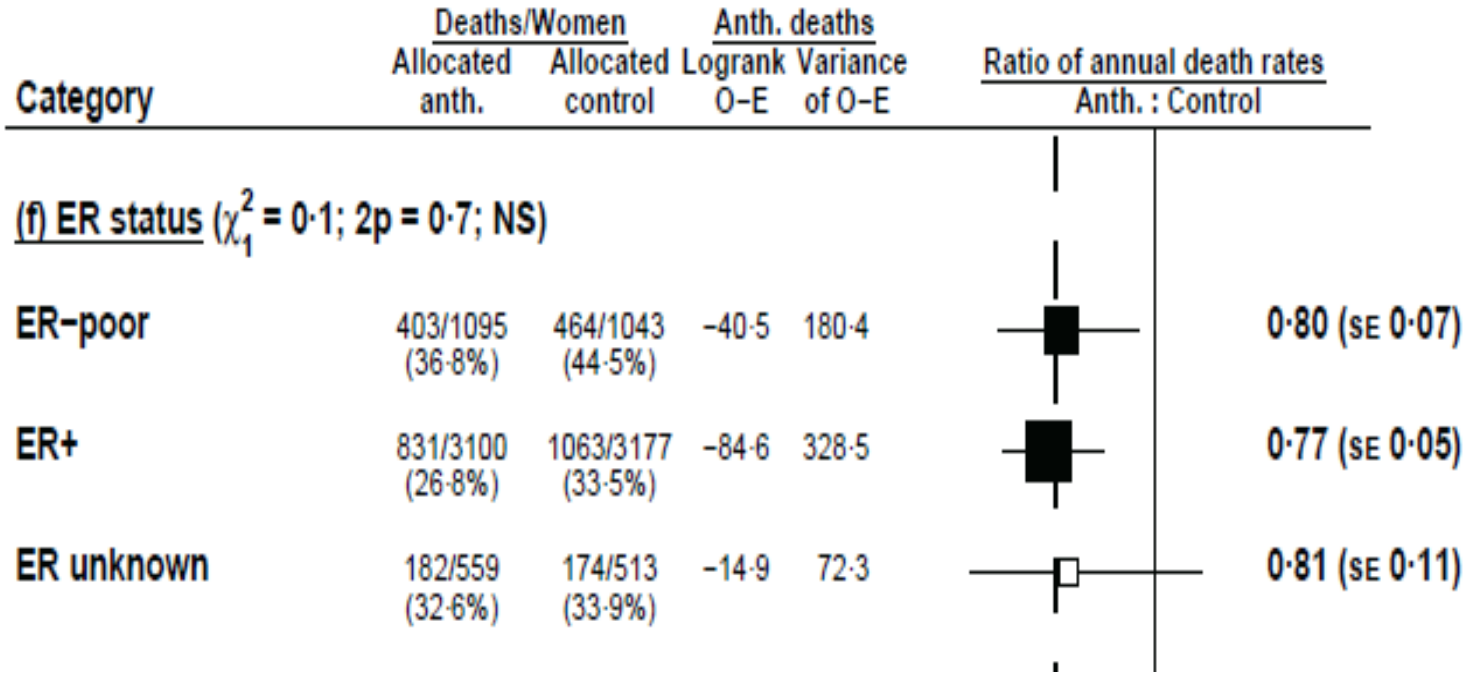
Prognostic Factors	Provide information on outcome regardless of therapy	To spare unnecessary treatments
Predictive Factors	Provide information on probability of benefit or toxicity from a specific therapy	To spare ineffective treatments

Number of patients with EBC needed to treat with Adjuvant Therapy to prevent ONE recurrence

Comparison	Absolute reduction in Recurrence %	**NNT**
Tamoxifen *vs.* Nil ^	11.8	**8**
Aromatase Inhibitors vs TAM*	3- 5.3	**19 - 33**
Aromatase Inhibitors vs Nil˚	~ 16	**~ 6**
Polychemo *vs.* Nil (< 50)^	12.3	**8**
Polychemo *vs.* Nil (50+)^	4.2	**23**
Anthra vs CMF^	4.0	**25**
Taxanes *vs.* Anthra§	~ 5	**20**
3rd gen taxane regimen vs Nil˚	~ 23	**~ 4**
ChemoRx + Trastuzumab vs ChemoRx	6.3 - 18	**6 - 15**
ChemoRx + Trastuzumab vs Nil+	13 - 35	**2-3**

^ 15 yrs,EBCTCG 2005
* 3-6 y from RCTs, postmenopause
˚ 10 yrs, estimated from Adjuvant!
§ 10 yrs, Peto, SABCS 2007
+ 3 yrs, estimated from RCTs

Breast cancer mortality ratio: any anthracycline-based regimen (eg, standard 4AC) vs no adjuvant chemotherapy, by ER STATUS and subsets of ER+



Adjuvant Therapy for EBC: the Price of Success

- **More effective adjuvant ET:**
  AIs > TAM
  10y ET > 5y TAM

- **Polychemotherapy:**
  effective independently from HR status

- **Improved prognosis over time:**
  more early stages
  multiple effective therapies

Precision Medicine:
Prognostic and Predictive Factors

Prediction:
therapies are useless unless we know who to treat

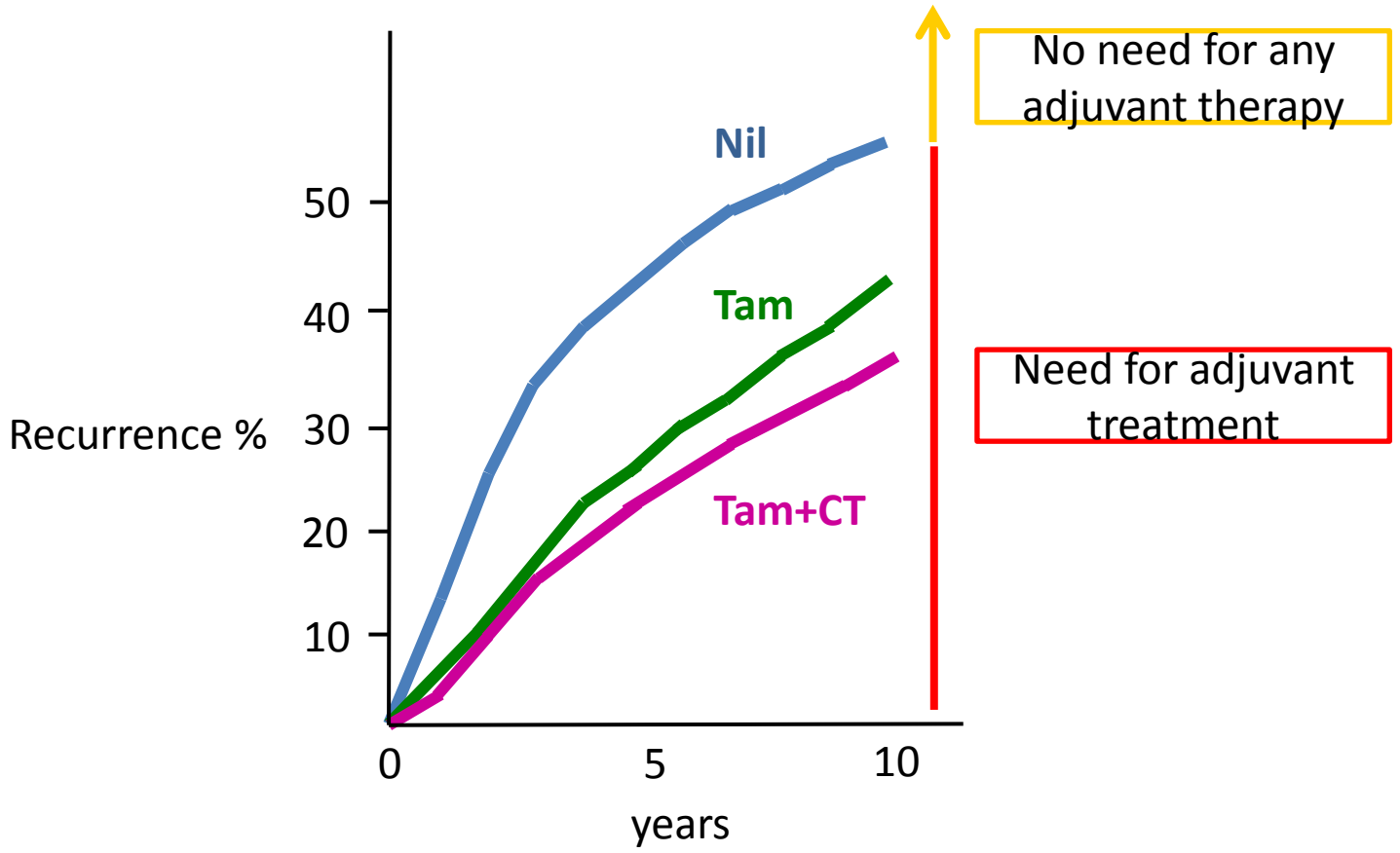
Prognostic Factors	outcome regardless of therapy	ssary treatments
Pre Fac		

Negative Prediction:
good enough to predict who will NOT respond to ET and antiHER2 therapy.
No good predictor for chemotherapy.

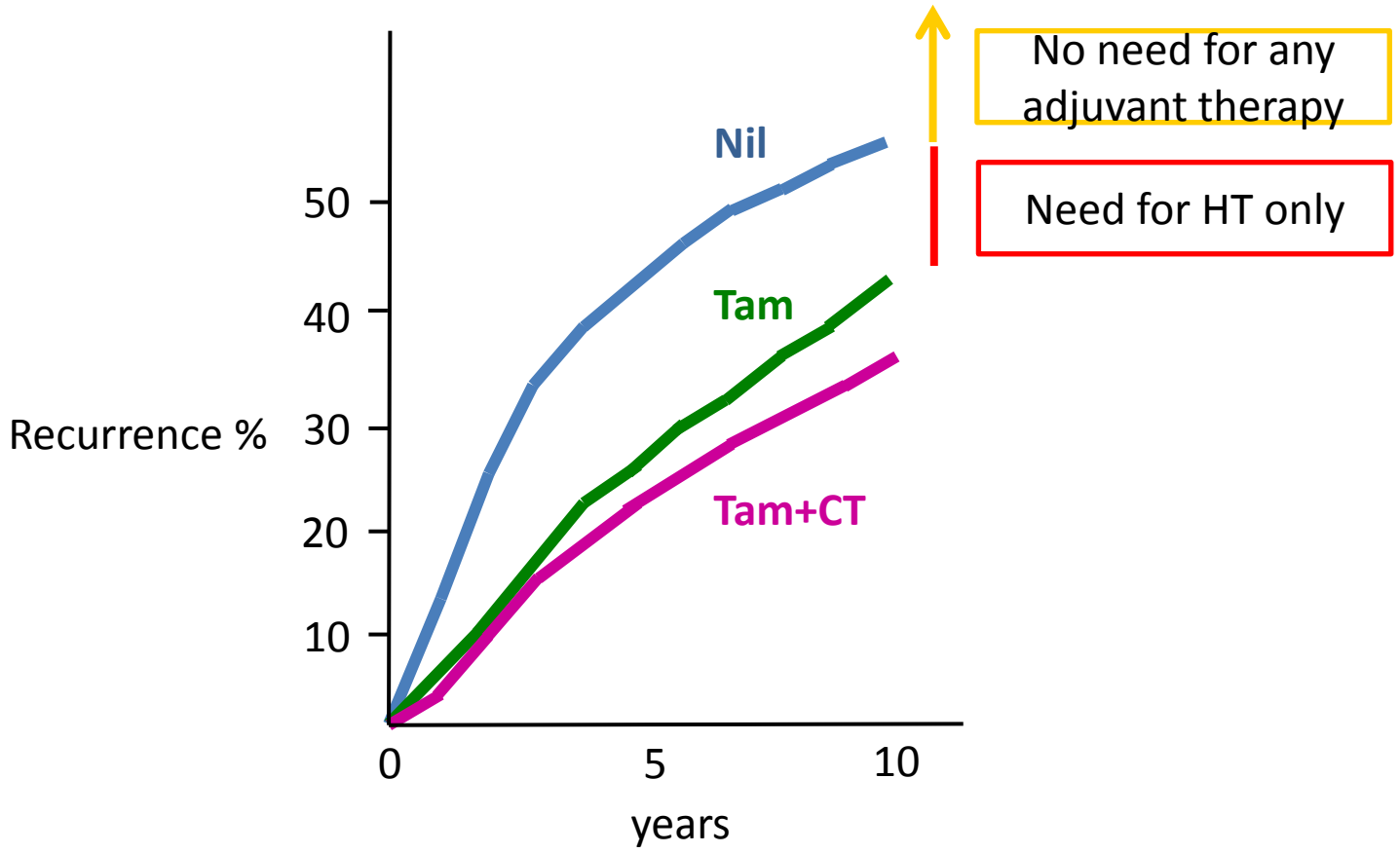
HR+ EBC: the quest for precision cancer medicine ….

prognosticators of distant relapses
predictors of chemotherapy benefit

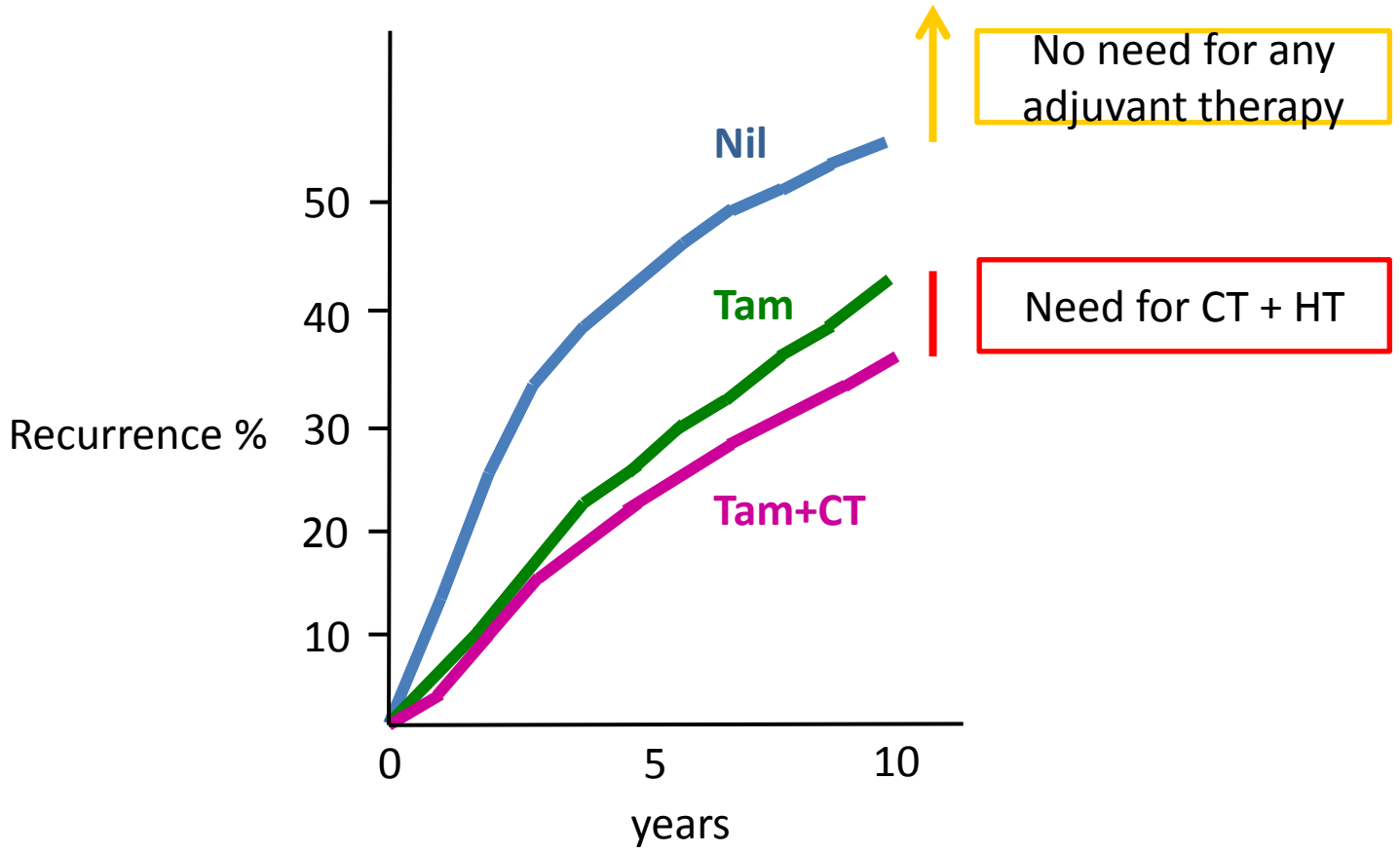
ER+ N+: Outcome by treatment adapted from EBCTCG metanalysis 2011



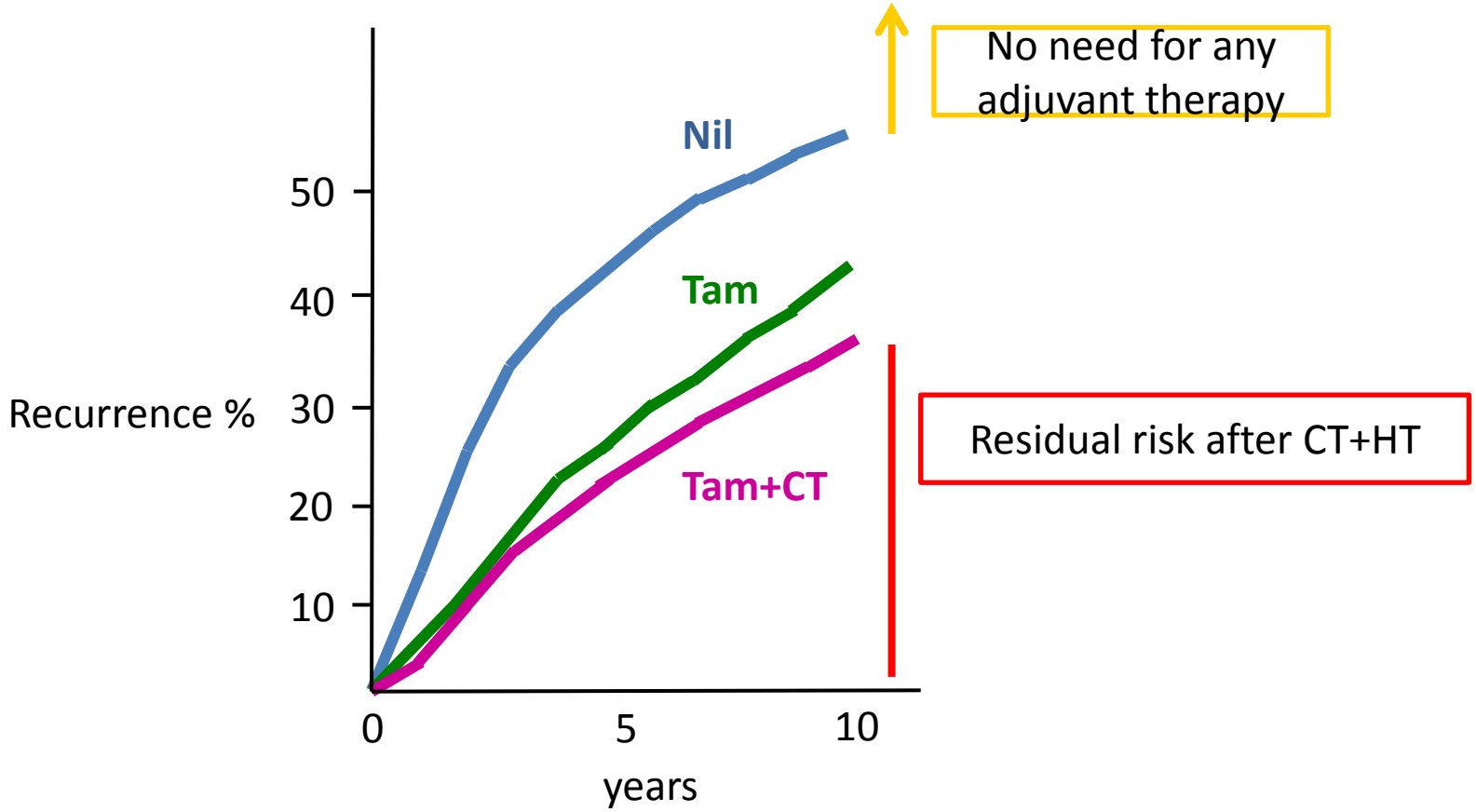
ER+ N+: Outcome by treatment adapted from EBCTCG metanalysis 2011



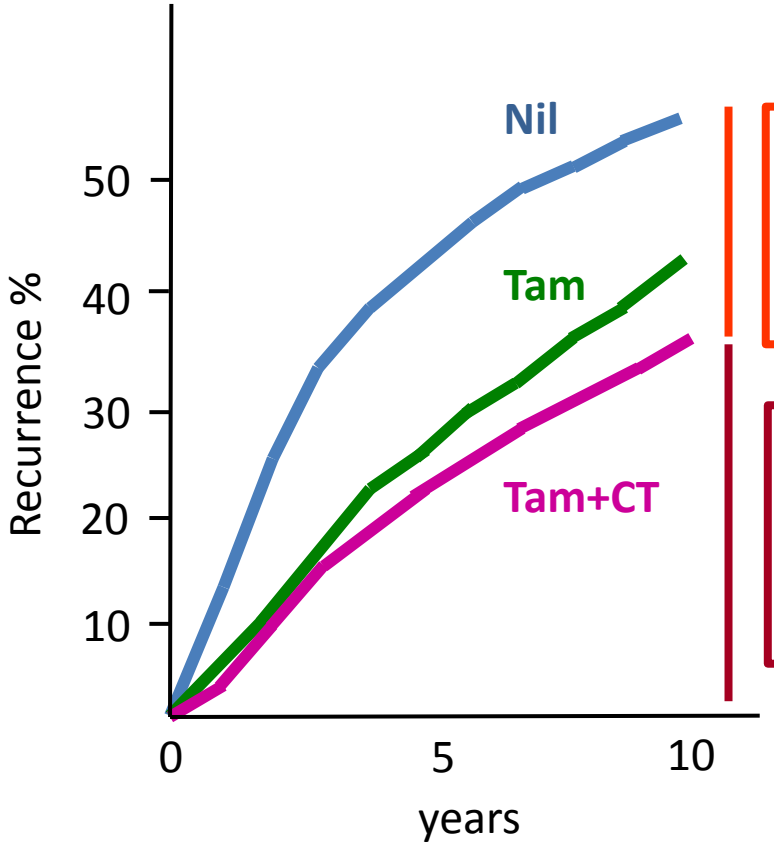
ER+ N+: Outcome by treatment adapted from EBCTCG metanalysis 2011



ER+ N+: Outcome by treatment adapted from EBCTCG metanalysis 2011



ER+ N+: Outcome by treatment adapted from EBCTCG metanalysis 2011



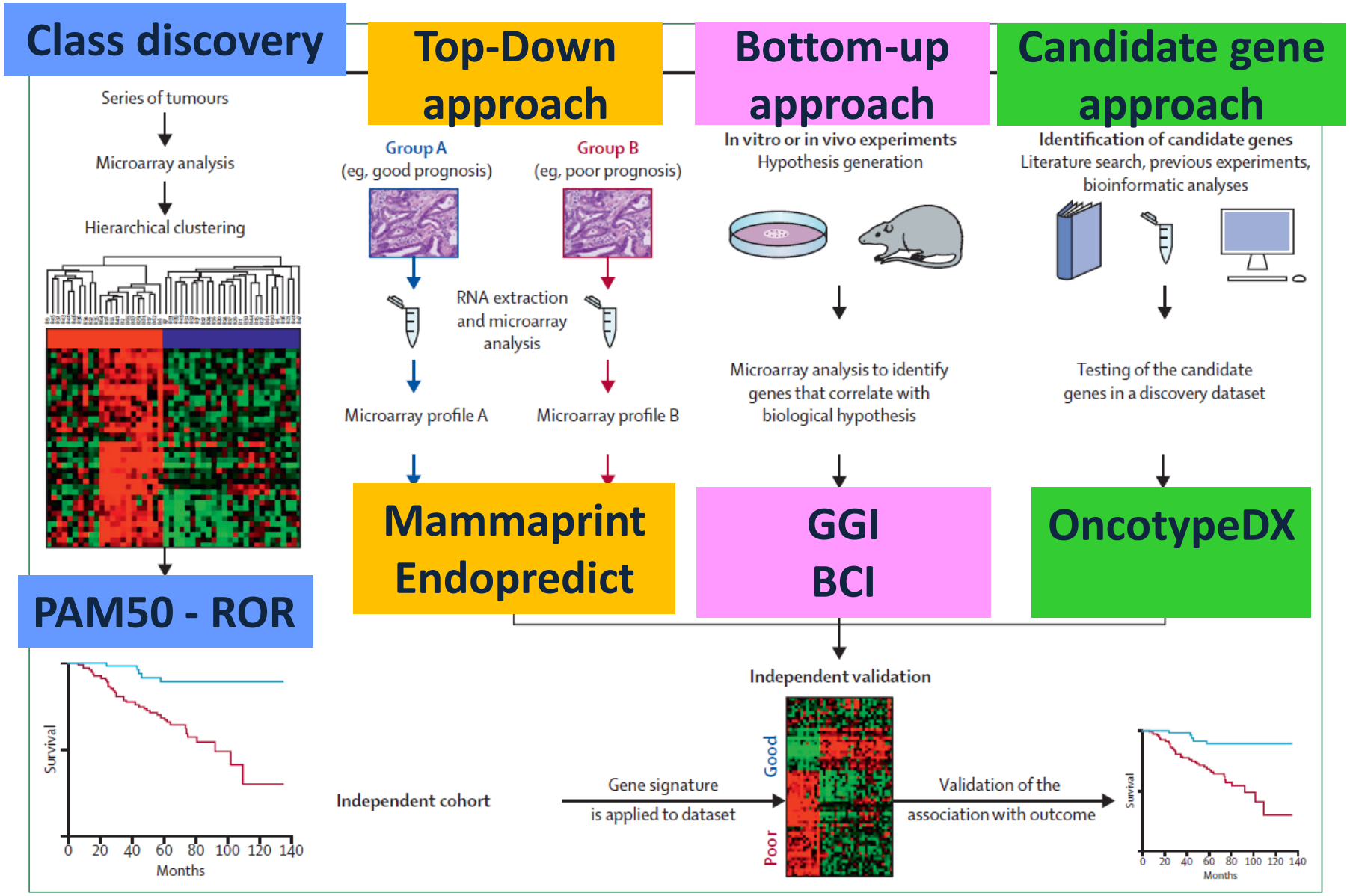
WHO CAN BE SPARED ADJUVANT CT?

WHICH PATIENTS ARE STILL AT RISK AFTER HT+CT?

WHO DESERVES EXTENDED ADJUVANT HT?

Personalised Cancer Medicine

- Understand the biology of each specific tumor
  - Dissect tumor heterogeneity
  - Determine pathways driving cancer growth and treatment resistance
  - Identify potential targets
- Assess the risk of recurrence
- Assess treatment benefit
  - Identify patients more likely to benefit from toxic treatments
  - Identify patients who may be spared unnecessary toxicity
  - Select the most appropriate treatment



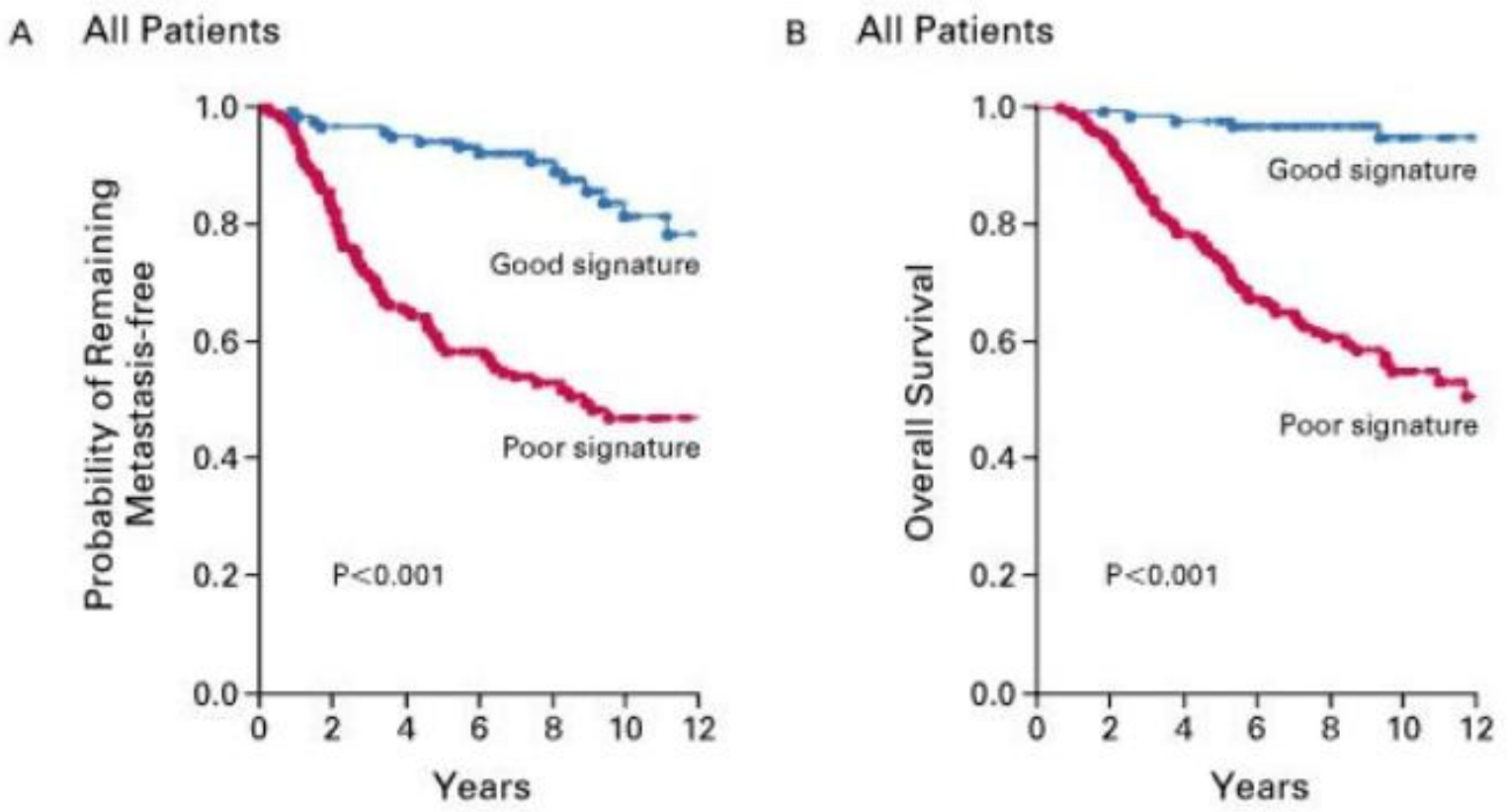
Reis-Filho J, Lancet 2011

First-generation prognostic signatures: common features

- ER-related and proliferation genes are the two most powerful molecular processes associated with outcome
  - ER has a broad transcriptional footprint and cell proliferation requires the expression of hundreds of genes→ large number of minimally overlapping models
- Relatively good overall concordance, however substantial discordances (20 to 30%) in risk assignment at the individual case level may be observed across multiple models
- Correlation with chemosensitivity (high proliferation)
- No molecular marker associated with stage is included
  - T and N provide INDEPENDENT prognostic information
- Prognostic information above the IHC-derived information are limited
  - in particular when IHC features are evaluated in a centralized and standardized fashion

Mammaprint: independent cohort

295 consecutive patients with stage I or II breast cancer, < 53 years old; 151 had lymph-node-negative disease, and 144 had lymph-node-positive disease



Van de Vijver MJ, et al,
NEJM 347:1999-2009, 2002

Mammaprint

CONs

- General limitations of first-generation signatures can be applied

- Previously: fresh or frozen samples required

PROs

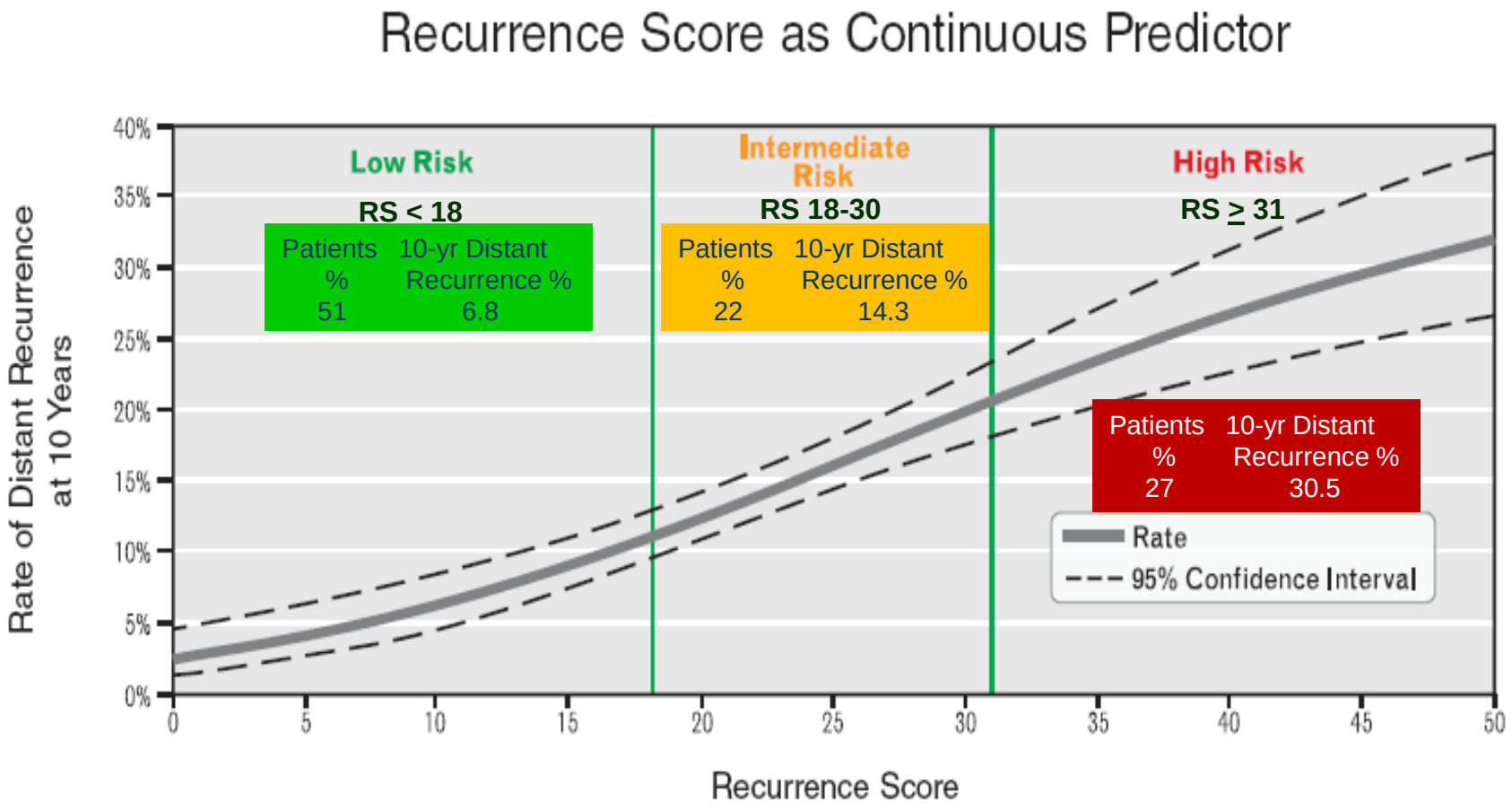
- Dichotomous, no «grey zone» (does it truely reflect the continuum of biology?)

- Recent versions of the test allow the use of FFPE samples

Oncotype DX

- **Prognostic value**
  - Is the risk of relapse low enough to avoid chemo?
- **Prediction of chemotherapy benefit**
- **Recurrence score vs «the rest of the world»**
  - Clinico-pathologic factors
  - IHC4 score
- **Decision Impact Studies**
  - The ongoing Breast-DX Italian study

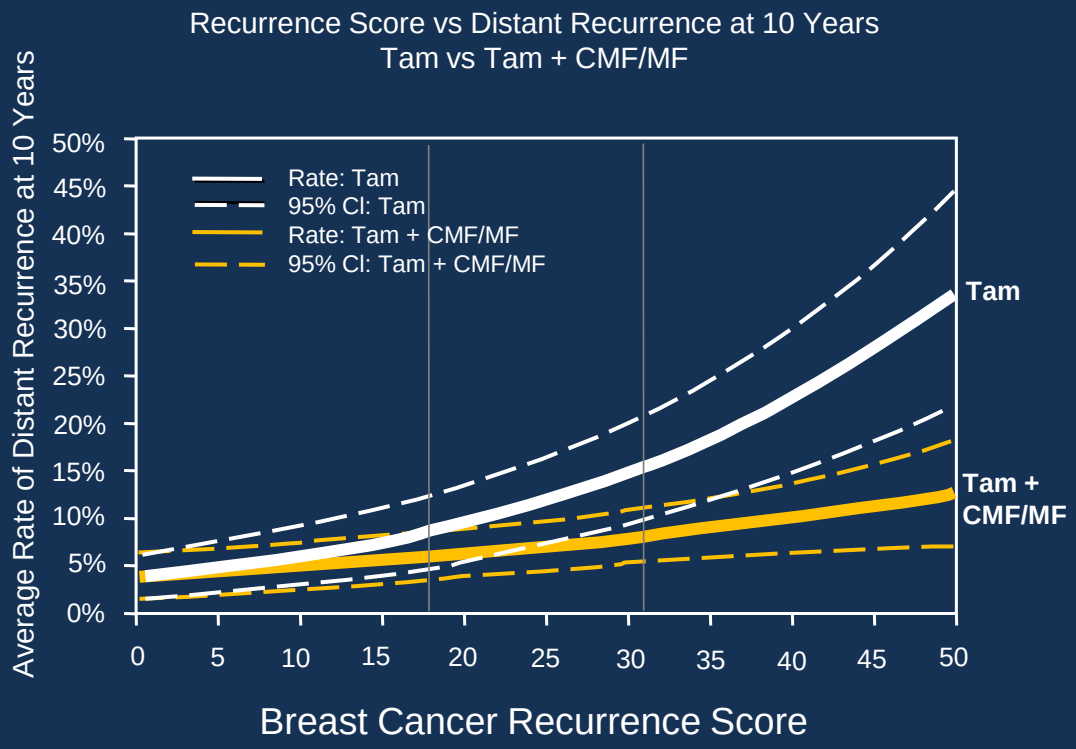
The RS® is a Continuous Predictor of the Risk of Distant Recurrence

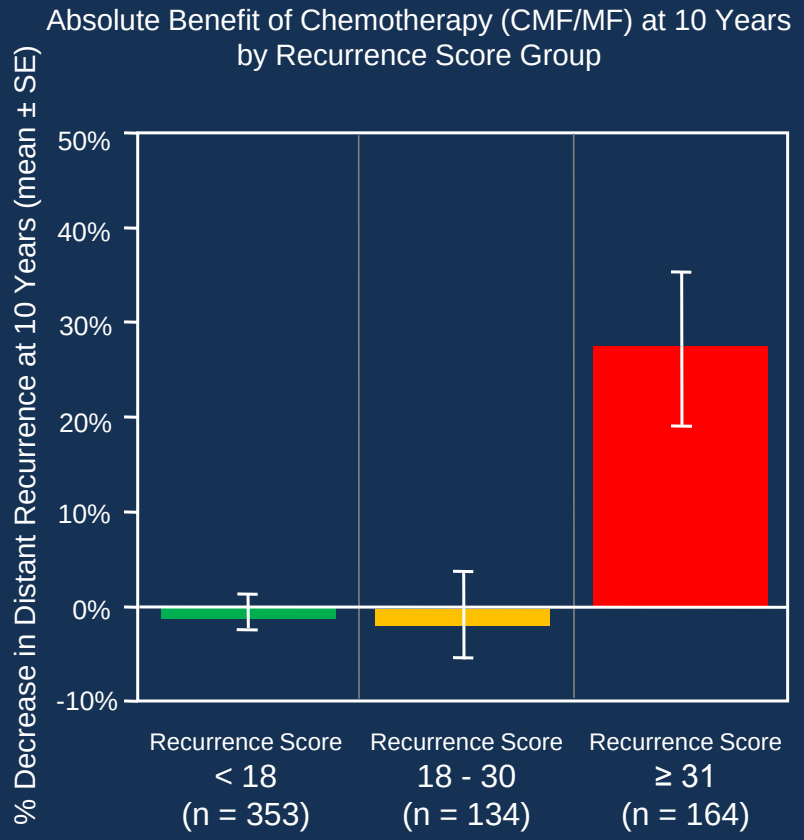


Paik S, NEJM 351(27):2817, 2004

High Recurrence Score® Disease Is Chemo-sensitive Whereas Low Recurrence Score Disease is Not (NSABP B-20)

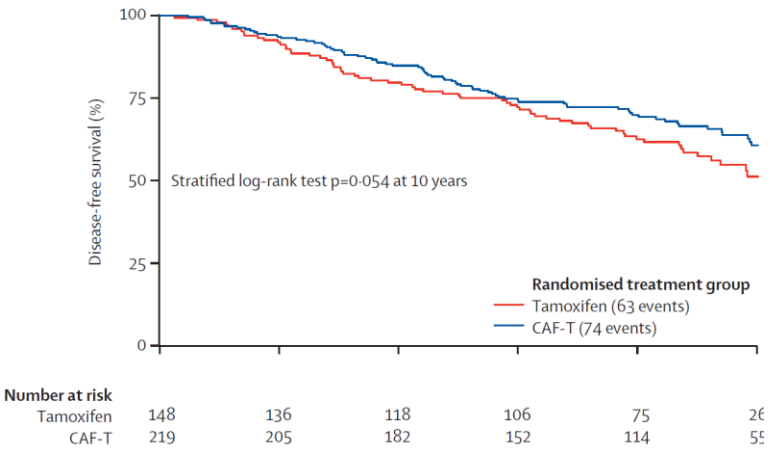
Node Negative, ER-Positive Breast Cancer Chemotherapy Benefit





Recurrence Score: prediction of chemotherapy benefit in ER+ N+ patients

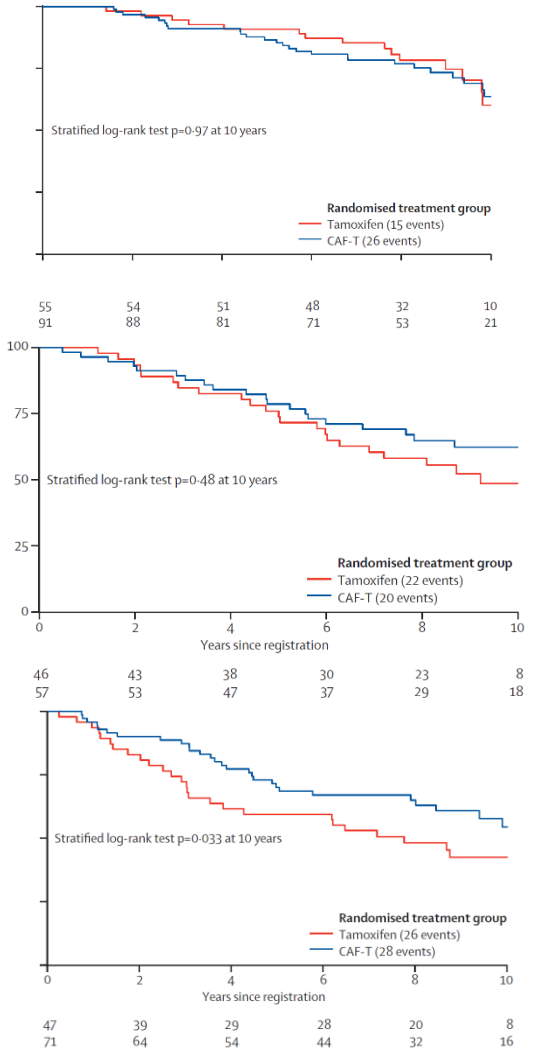
SWOG-8814 trial
(ER+, node positive)
Tamoxifen versus CAF→TAM



RS<18

RS 18-30

RS ≥31



Albain KS Lancet Oncol 2010

Anatomy and Biology: two complementary sides of breast cancer prognostication

Covariate	NSABP B-14 (n = 647)		TransATAC (n = 1,088)	
	Hazard Ratio	Wald Test	Hazard Ratio	Wald Test
RS linear component	5.344*	< .001	2.766*	.02
RS nonlinear component		.004		.37
Tumor poorly differentiated	2.845	.008†	2.477	.012†
Tumor moderately differentiated	1.223	.50†	1.625	.14†
Tumor size	1.266‡	.006	1.72‡	< .001
Age at surgery	0.892§	.22	0.933§	.53
Treatment (anastrozole *v* tamoxifen)	—	—	0.886	.48
1-3 positive nodes (N1-3)	—	—	1.429	.083
4+ positive nodes (N4+)	—	—	4.548	< .001

- Pathologic variables (i.e. grade, tumor size and nodal status) retained an independent prognostic value which is not captured by the molecular signature

Which are the practical implications?

Gong G JCO 2011

Graphical Printout | **RSPC** (Recurrence Score - Pathology-Clinical)

RSPC Assessment of Node Negative , ER Positive Distant Recurrence Risk

User Input

Oncotype DX® Breast Cancer Assay Recurrence Score®:	22
Planned Hormonal Treatment:	Aromatase Inhibitor
Patient age at surgery:	60
Tumor size (cm):	1.5
Tumor grade (differentiation):	Grade 2 (Moderate)

Results

Risk of distant recurrence at 10 years:	9% (6%-11%)

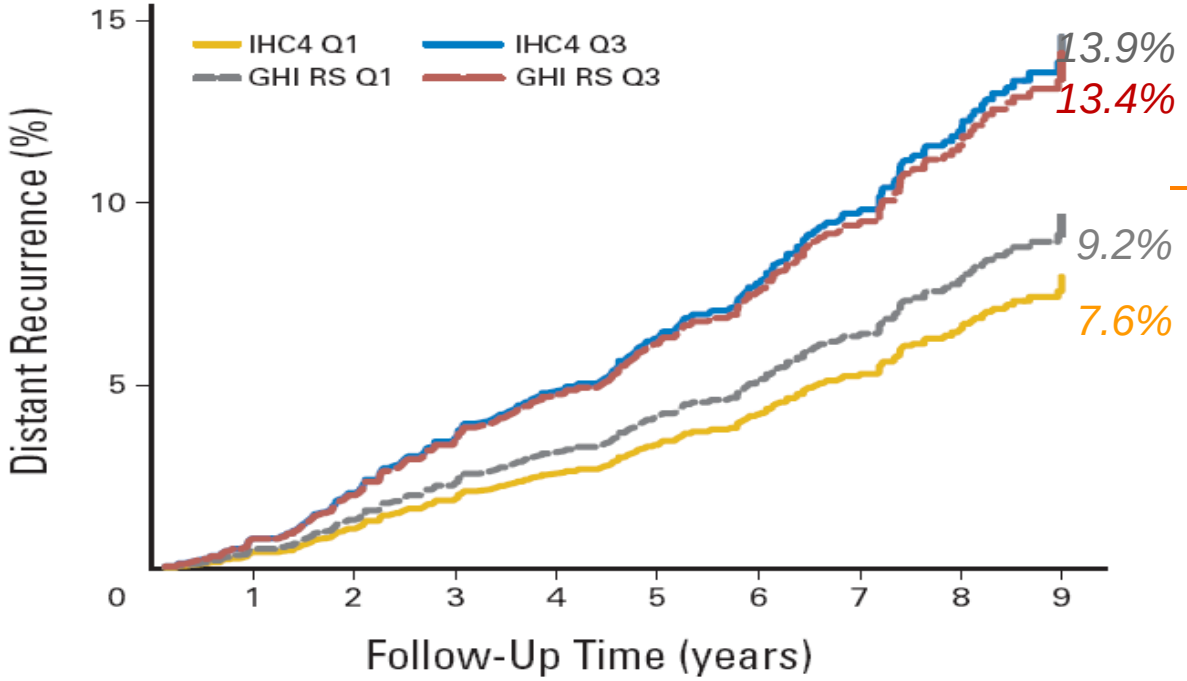
Graphical Printout | **RSPC** (Recurrence Score - Pathology-Clinical)

RSPC Assessment of Node Negative , ER Positive Distant Recurrence Risk

User Input	
Oncotype DX® Breast Cancer Assay Recurrence Score®:	22
Planned Hormonal Treatment:	Aromatase Inhibitor
Patient age at surgery:	50
Tumor size (cm):	1.5
Tumor grade (differentiation):	Grade 3 (Poor)
Results	
Risk of distant recurrence at 10 years:	18% (13%-24%)

T, N and G need to be accurately determined!!!

IHC4 score vs GHI-RS



Predicted TTDR for a ≥65ys patient with node-neg, 1-2cm poorly differentiated tumor receiving anastrozole.

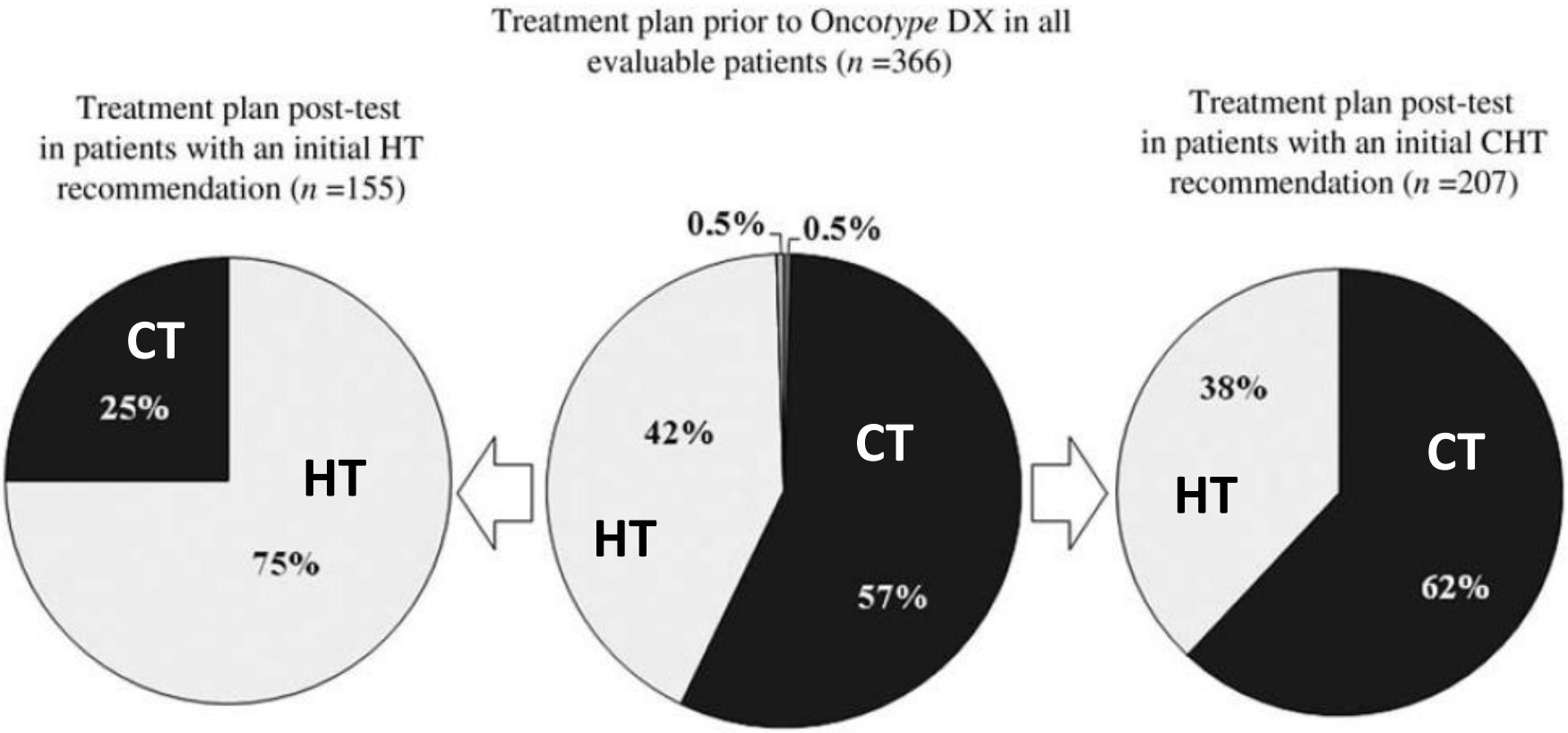
Kaplan Meyer curves for either the 25˚or 75˚percentile of each score .

The amount of prognostic information provided by the IHC4 score in addition to the clinical score is similar to that provided by the GHI-RS.
Using both scores together, in addition to clinical score, provided only slightly more information than using either of the scores individually added to clinical variables.

BUT:
methodological issues, Ki67 reproducibility, no prediction on chemo efficacy

Cuzick J et al, JCO 2011

The German Decision Impact study



Relative reduction of actual CT use: 29% for N0 and 38% for N1-3 patients

Eiermann, Ann Oncol 2012

I.O.V.
ISTITUTO ONCOLOGICO VENETO I.R.C.C.S.

REGIONE DEL VENETO

Breast-DX Italy

Impact of the Oncotype DX® Breast Cancer Assay on Resources Optimization and Treatment Decisions for Women with Estrogen Receptor-Positive, Node-Negative and Node-Positive Breast Carcinoma: a prospective Italian multicenter study.

PROGRAMMA PER LA RICERCA INNOVAZIONE E HTA (PRIHTA) – REGIONE DEL VENETO

Coordinatore: Istituto Oncologico Veneto IRCCS, Padova
PI: Prof. PierFranco Conte

Breast-DX Italy

- Prospective, multicenter study (Rete Oncologica Veneta)

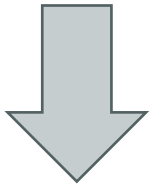
- To evaluate the impact of Onco*type* DX® on the decision making processes of physicians in recommending adjuvant therapy and on resources optimization in an Italian setting

Both N0 and N1 patients will be included.

Breast-DX Italy

OBSERVATIONAL PHASE:
ALL CONSECUTIVE ER+, HER2-, N0-3, T1-3 PATIENTS

-Data collection
-Physician's perception of Oncotype DX utility



Low-Risk at least 4 of the following:

- G1
- T1a-b
- Ki67 <15%
- N negative
- ER >80%

EXCLUDED

CLINICAL PHASE:
SUBGROUP OF PTS FROM THE OBSERVATIONAL PHASE

-Pre-test Physician decision
-Test
-Post-test Physician decision + post-test perception of utility
-Treatment started

High-Risk at least 4 of the following:

- G3
- T≥2
- Ki67 >30%
- N pos
- ER <30%

EXCLUDED

Oncotype DX Request for pts not eligible for the Clinical Phase will not be processed by GH.

Future directions:

- **Mindact, TAILORx and RxPONDER will establish the CLINICAL UTILITY of GEPs**

- **Predictive role of first-generation prognostic signatures** in patients treated with modern chemotherapy regimens

- **Second generation prognostic signatures**
  - developped in specific breast cancer subtypes
  - prognosis of ER- and/or highly proliferating ER+ BC patients (i.e. immune modules)

- **Residual risk after adjuvant treatment**
  - Patients at high risk after 5 years of adjuvant endocrine treatment to offer extended endocrine therapy

  - Patients at high risk after chemotherapy+endocrine treatment to offer clinical trials with new agents