Endopredict score per la stima del rischio residuo di ripresa di malattia nelle pazienti ER+ trattate con 5 anni di ormonoterapia adiuvante e confronto con il RS (OncotypeDX)

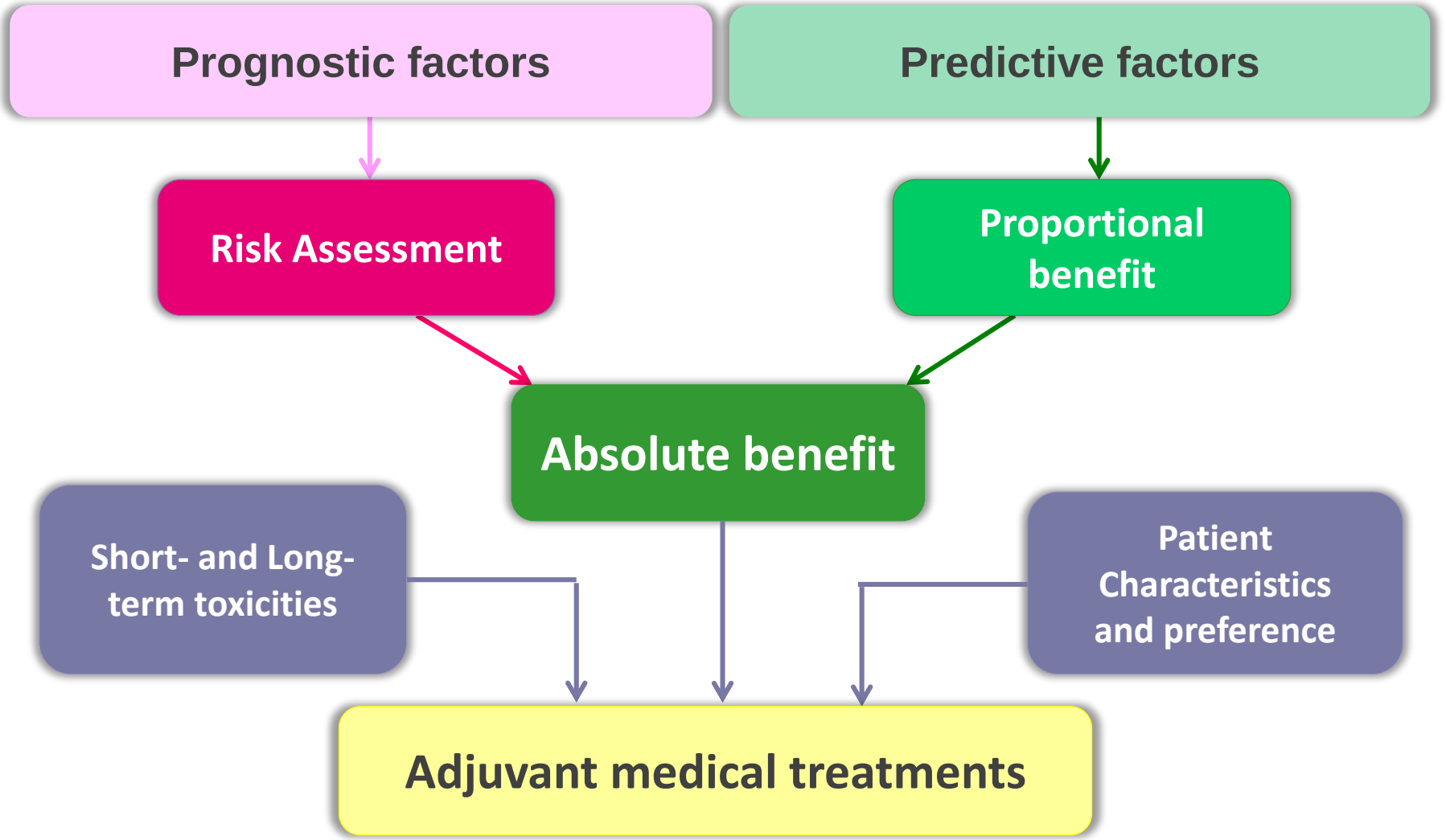
Maria Vittoria Dieci
Università di Padova
Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche
Istituto Oncologico Veneto I.R.C.C.S.

UNIVERSITAS STUDII PADUANI MCCX XII

REGIONE DEL VENETO

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

Adjuvant Rx of EBC
Decision-making Algorithm



Clinical validity and utility of a prognostic biomarker

Clinical validity — **Predict baseline prognosis**

Clinical utility — **Who can be spared chemotherapy?**

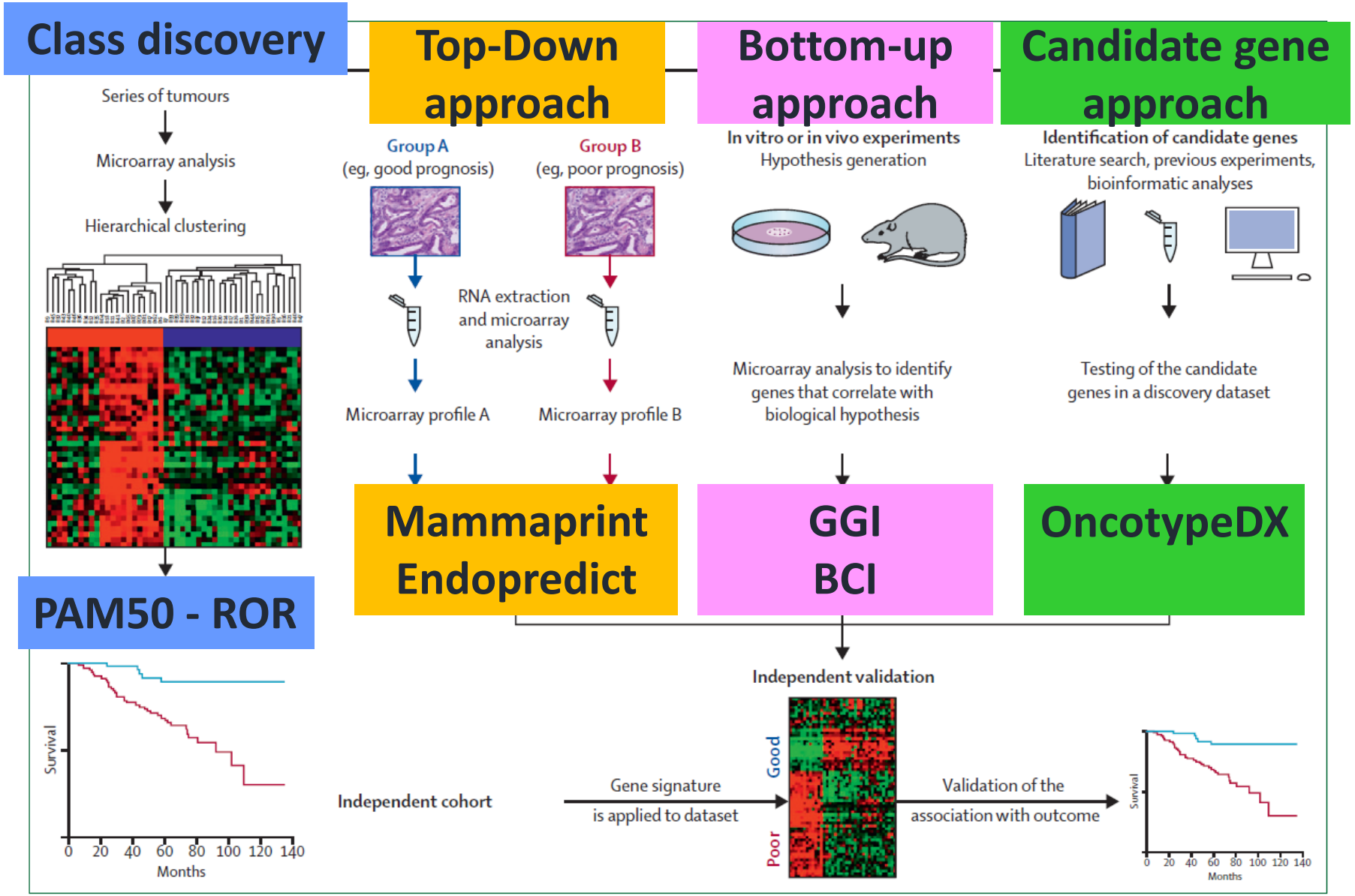
ABSOLUTE RISK at a pre-defined time point

Prognosis is so good that the relative benefit, if any, would translate into a not clinically relevant absolute gain

Target pts — **(VERY) LOW RISK**

(don't mind what the relative benefit would be)

Prognostic GEP



Reis-Filho J, Lancet 2011

The Oncotype DX® 21 Gene Recurrence Score (RS) Assay: continuous predictor

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

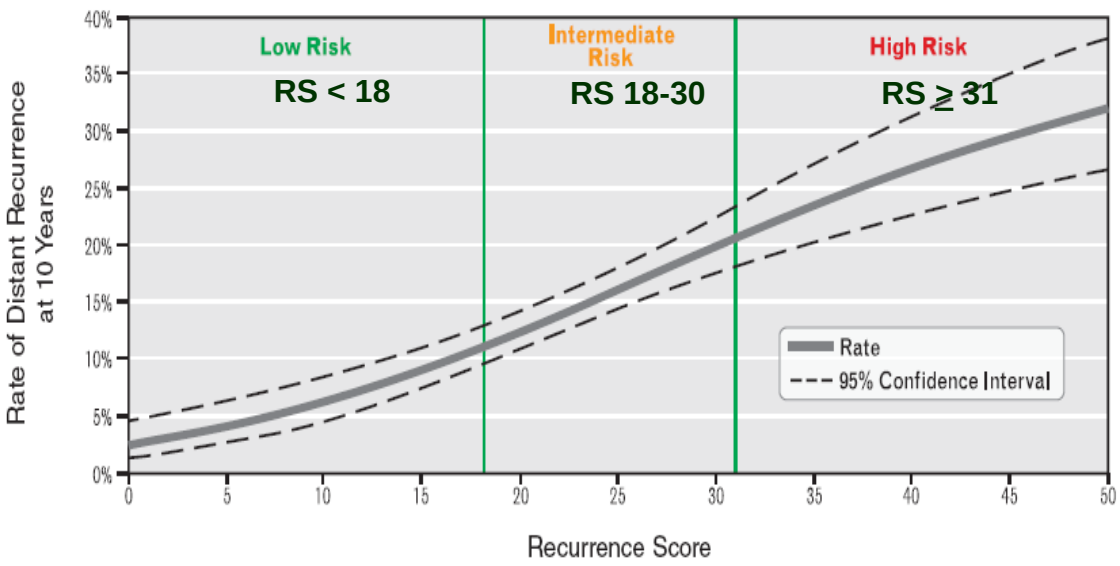
INVASION
Stromolysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS = + 0.47 x HER2 group core
- 0.34 x HR group score
+ 1.04 x proliferation group score
+ 0.10 x invasion group score
+ 0.05 x CD 68
- 0.08 x GSTM1
- 0.07 x BAG1



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

The EP and EPClin scores

EP training: 964 ER+/HER2- tamoxifen (TAM)-treated pts, top-down.

EP validation: ER+/HER2- pts included in the Phase III **ABCSG-6** (n=378) and **ABCSG-8** (n=1,324) trials (TAM x 5 yrs or TAM2yrs → AI3yrs).

EPclin: predefined score incorporating EP, tumor size and nodal status.

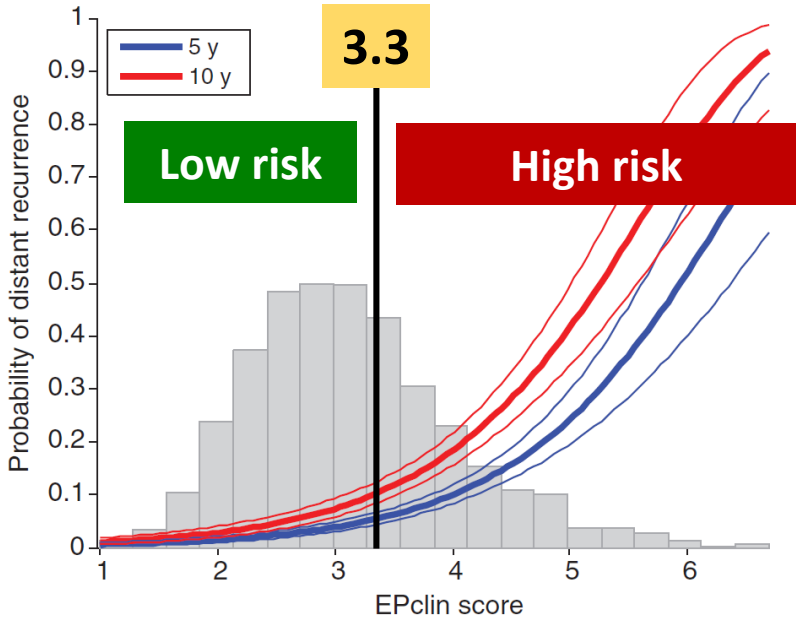
EP

Reference genes		
CALM2	Member 1	*BIRC5*
		RBBP8
OAZ1	Member 2	*UBE2C*
		IL6ST
RPL37A	Member 3	*AZGP1*
		DHCR7
	Member 4	*MGP*
		STC2

High/low risk cutoff: 5.0

+ T
(≤1,1-2,2-5,>5cm)
+ N
(0,1-3,4-10,>10)

EPclin



Filipits M et al., Clin Cancer Res 2011

EndoPredict (EPclin) score for estimating residual distant recurrence (DR) risk in ER+/HER2- breast cancer (br ca) patients treated with 5 years adjuvant endocrine therapy alone: Validation and comparison with the OncotypeDX recurrence score (RS)

Dowsett M[1], Sestak I[2], Buus R[1], Kronenwett R[3], Denkert C[4], Krappmann K[3], Scheer M[3], Petry C[3], Dubsky P[5], Cuzick J[2]

1. Royal Marsden Hospital/The Breast Cancer Now Toby Robins Research Centre, Institute of Cancer Research, London, UK
2. Queen Mary University of London, London, UK
3. Sividon Diagnostics, Cologne, Germany
4. Charité Universitätsmedizin Berlin, Berlin, Germany
5. Medical University Vienna, Vienna, Austria

Aims

- To assess the prognostic value of the EP and EPClin scores in patients with ER+ve HER2-ve primary breast cancer in TransATAC

- To compare the prognostic value of the scores with that of Oncotype DX and the clinical treatment score (CTS)

The TransATAC clinical platform

ATAC
randomized phase III (Tam vs Ana vs Tam+Ana x5 yrs for postmeopausal BC pts)
n=9366

Eligible for TransATAC:
Monotherapy and HR+
n=5880

Blocks received
n=2006

RS
n=1230, HR+
Dowsett M, JCO 2010

RS, IHC4, CTS
n=1125, HR+
Cuzick, JCO 2011

RS and RSPC
n=1088, ER+
Tang, JCO 2011

RS, PAM50, CTS, IHC4
n=940, ER+
Dowsett, JCO 2013

RS, BCI, IHC4, CTS
n=665, ER+/N0
Sgroi, Lancet Oncol 2013

RS, EP/EPClin, CTS
n=928
Dowsett, SABCS 2015

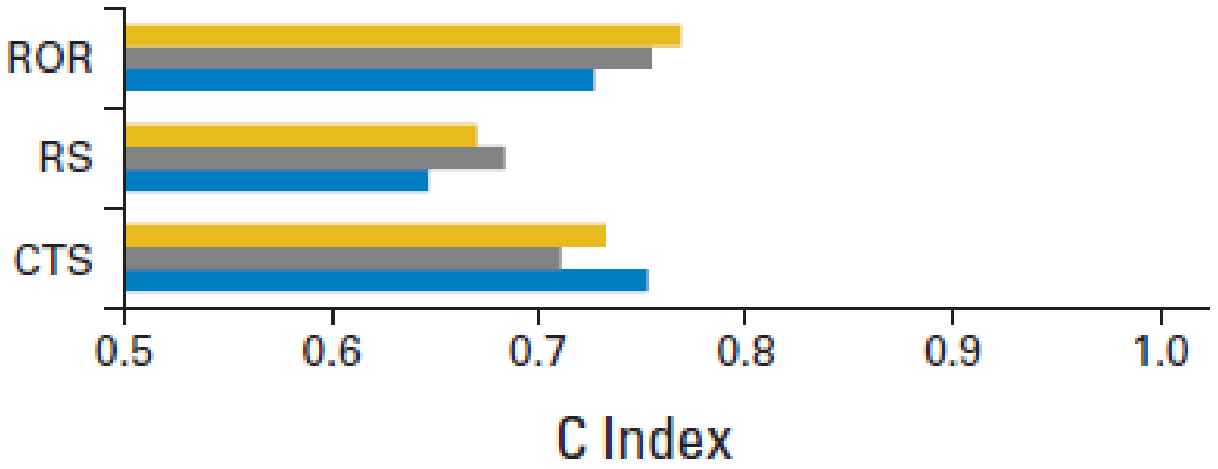
The CTS score

Cuzick, JCO 2011
n=1125, HR+

TRAINED IN TRANSATAC

$$\text{clinical score} = 100 \times \{0.417N_{1\text{-}3} + 1.566N_{4+} + 0.930(0.497T_{1\text{-}2} + 0.882T_{2\text{-}3} + 1.838T_{>3} + 0.559Gr_2 + 0.970Gr_3 + 0.130Age_{\geq 65} - 0.149Ana)\},$$

Dowsett, JCO 2013



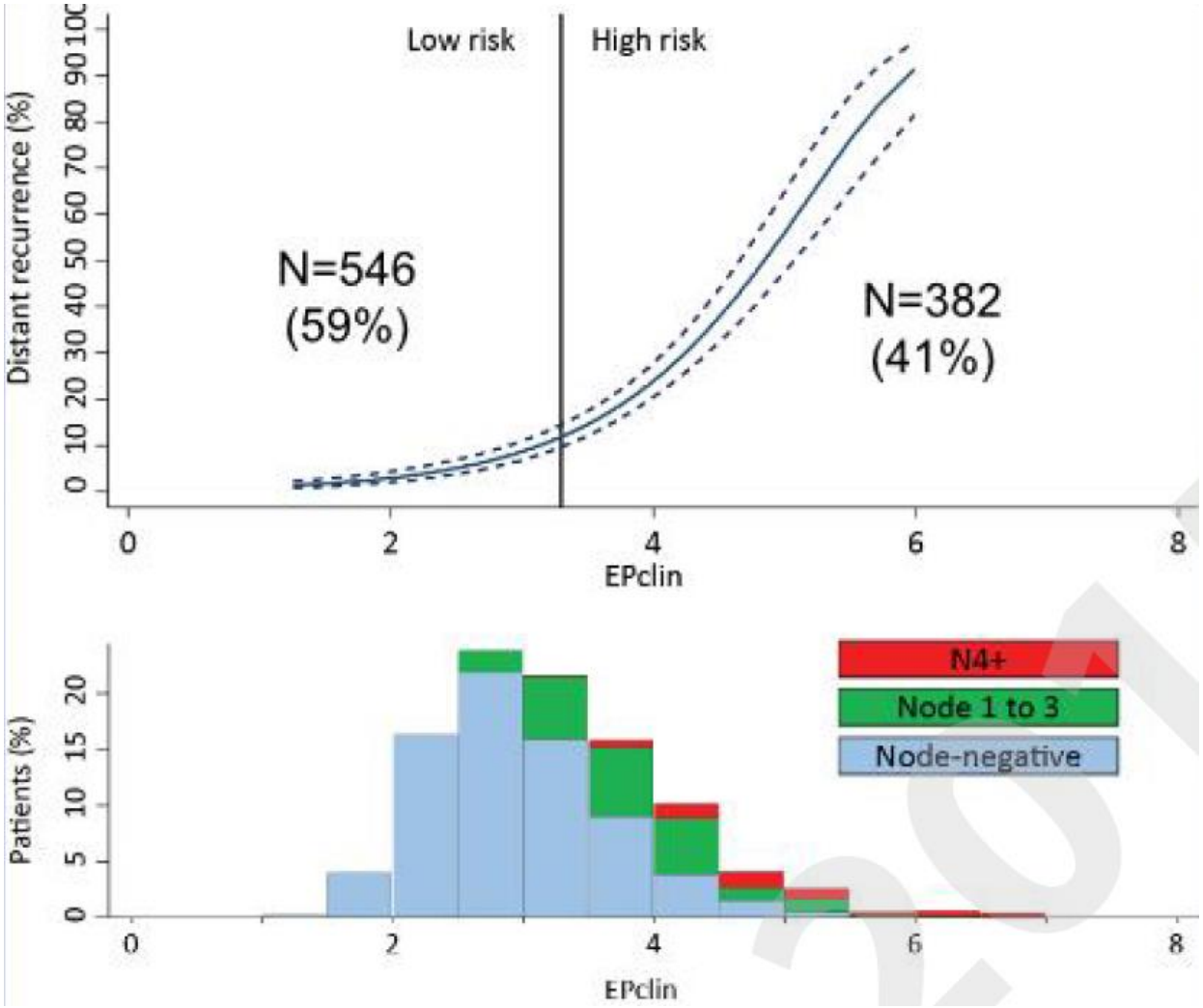
Statistical plan

- Does EP/EPclin have significant prognostic information in TransATAC?
- Does EP/EPClin add significant information to RS?
- Does EP/EPClin add significant information to CTS?

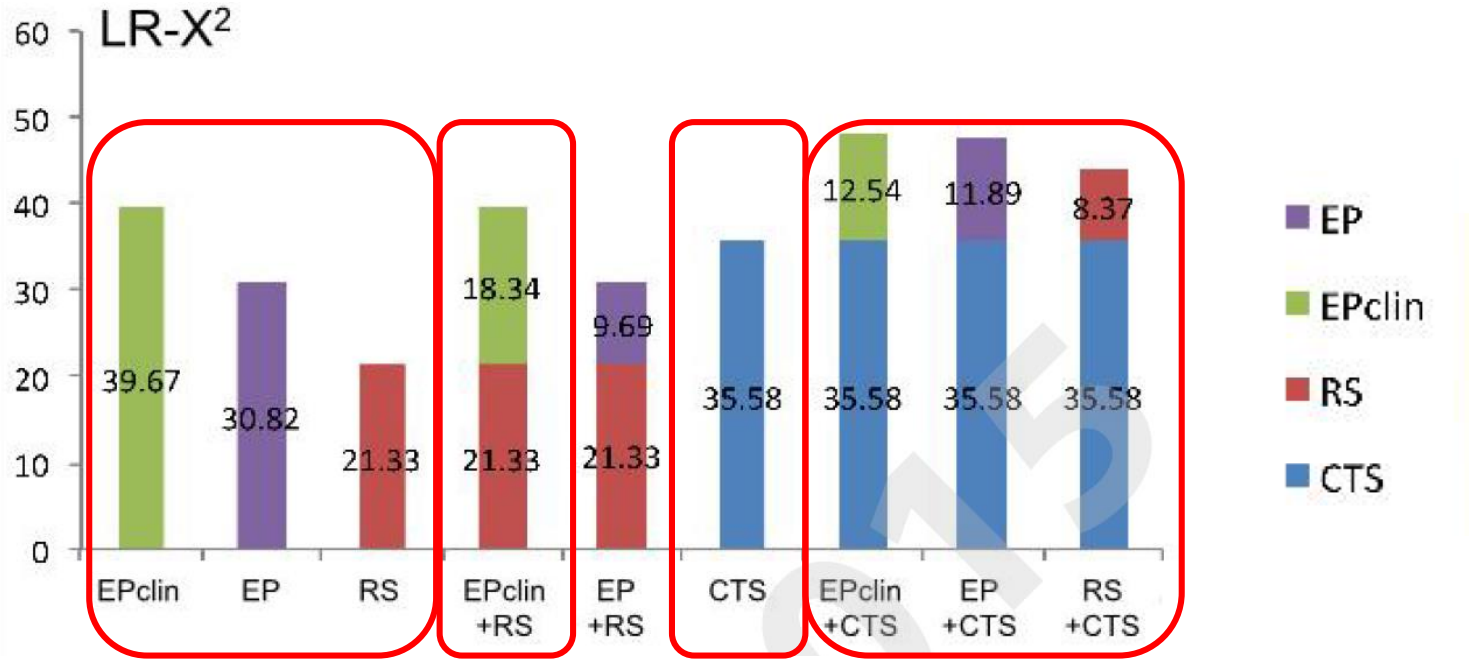
Patients characteristics

All ER+/HER2-	n=928
Age, mean	64.7 yrs (SD=8.3)
N	
Neg	680 (73.3%)
1-3	198 (21.3%)
4 or more	50 (5.4%)
T	
<1cm	130 (14%)
1-2cm	489 (53.7%)
2-5cm	290 (31.3%)
>5cm	19 (2.1%)
Grade	
1	244 (26.3%)
2	497 (53.6%)
3	147 (15.8%)
Tx	
RT	649 (69.9%)
Mastectomy	363 (39.1%)
CT	0

Clinical validity of EPClin confirmed in TransATAC

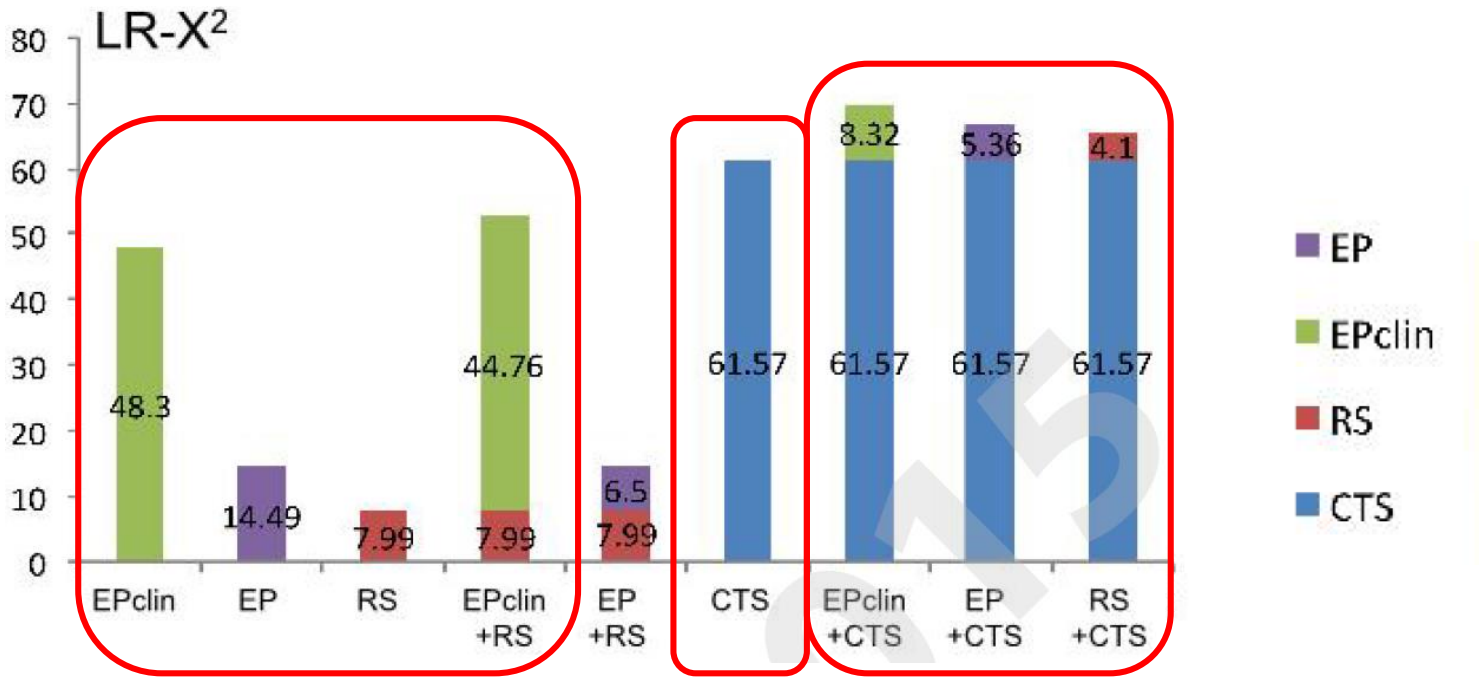


Prognostic info provided by EPClin/EP/RS/CTS: N-



- EpClin, EP, RS: relevant prognostic info
- EpClin>RS, additional info beyond RS
- CTS substantial prognostic info
- GEPs add but modestly beyond CTS

Prognostic info provided by EPClin/EP/RS/CTS: N+

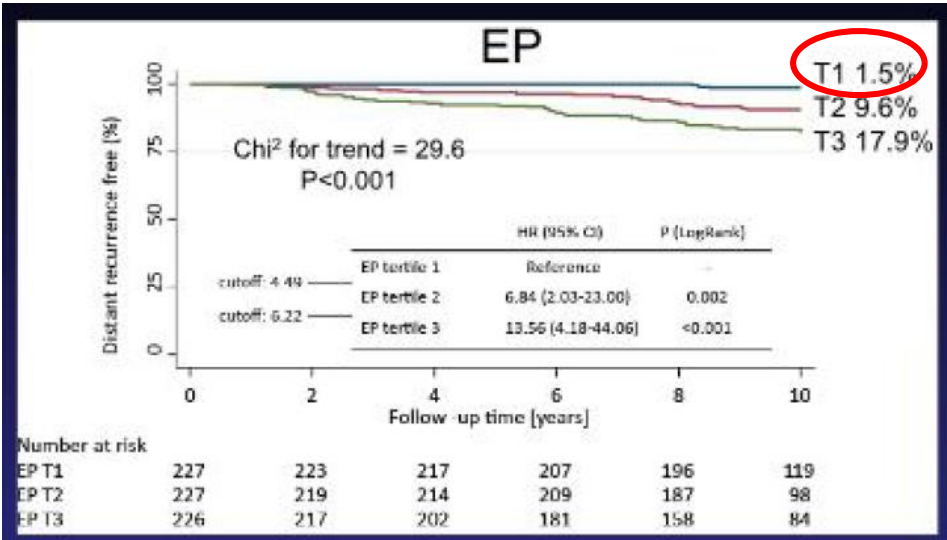


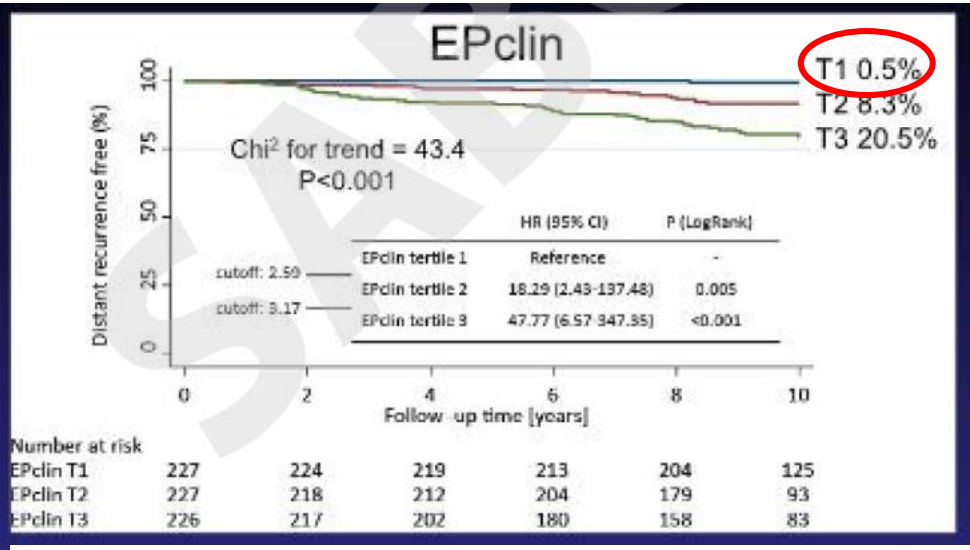
- EpClin>>>RS, EP; high amount of info beyond RS: Categories of N+
- CTS: highly performant (trained in TransATAC, N+ categories)
- GEP add little info beyond CTS

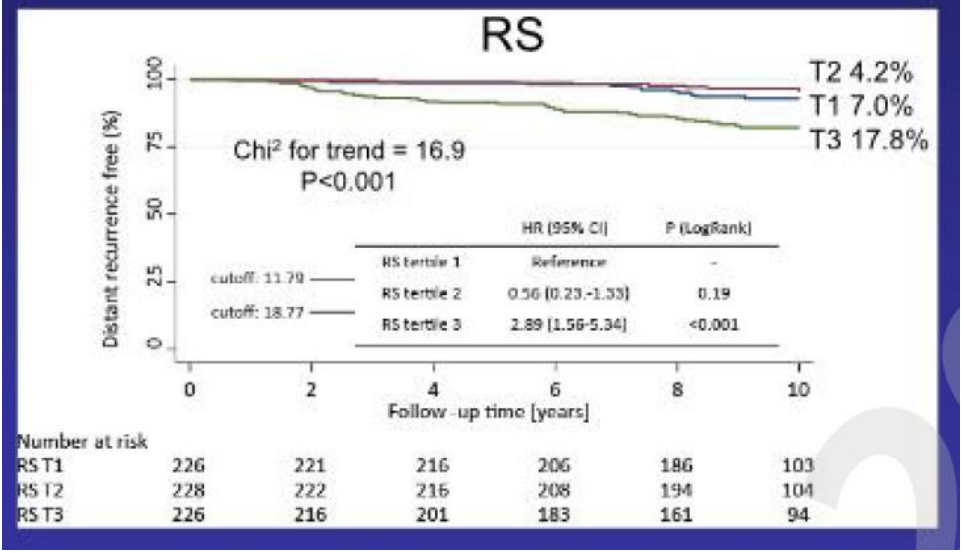
Distant recurrence-free survival according to pre-defined EP/EPClin/RS cut-offs in TransATAC

		EP-low <5.0	EP-high >5.0	EPClin-low <3.3	EPClin-high >3.3	RS-low <18	RS-non low >18
All	n	386	542	546	382	-	-
	10yrs DFRS%	7.3%	20.8%	5.8%	28.8%	-	-
	HR (95%CI)	2.98 (1.94-4.58)		5.99 (3.94-9.11)		-	-
N-	n	292	388	499	181	432	248
	10yrs DFRS%	3%	14.6%	5.9%	20%	5.3%	17.1%
	HR (95%CI)	5.15 (2.55-10.85)		3.90 (2.33-6.52)		3.72 (2.17-6.39)	
N+	n	94	154	47	201	-	-
	10yrs DFRS%	25.1%	36.4%	5%	36.9%	-	-
	HR (95%CI)	1.78 (1.04-3.04)		9.49 (2.33-38.75)		-	-

EP/EPClin vs RS: tertiles, N-

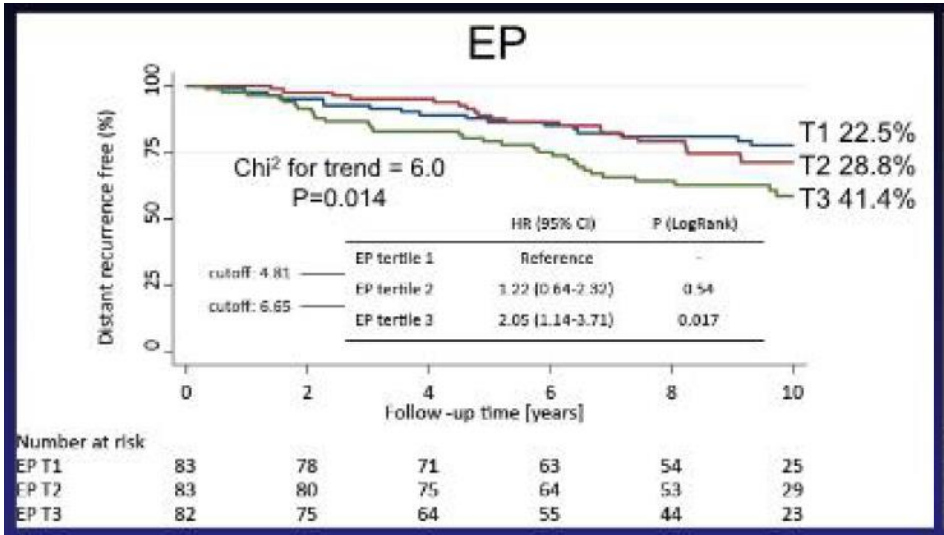


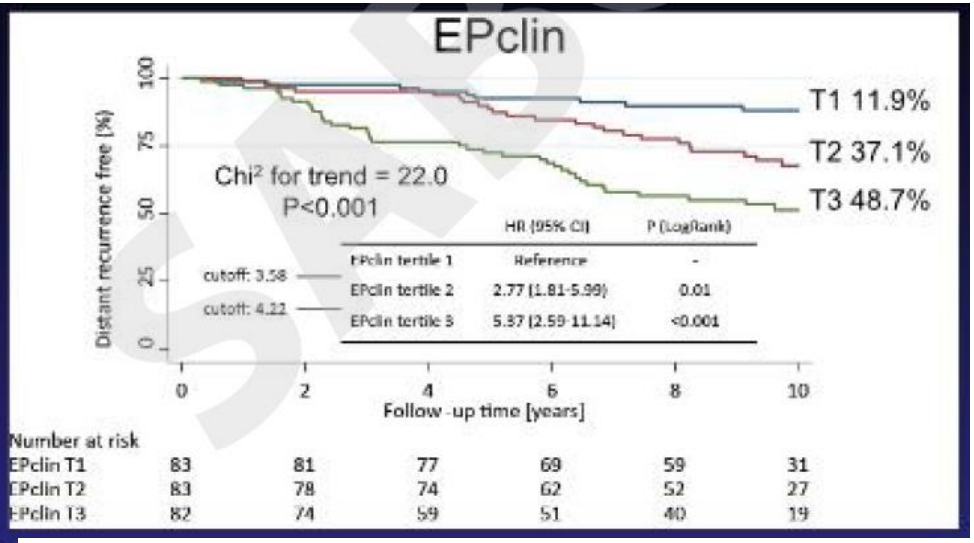


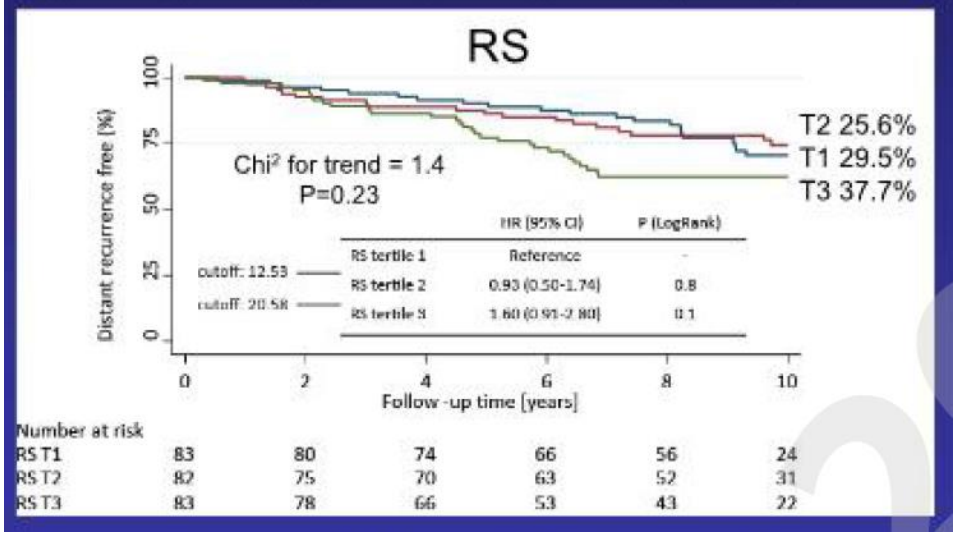


	EP	EPClin	RS
T1	<4.49	<2.59	<11.79
T2	4.49-6.22	2.59-3.17	11.79-18.77
T3	>6.22	>3.17	>18.77

EP/EPClin vs RS: tertiles, N+







	EP	EPClin	RS
T1	<4.81	<3.58	<12.53
T2	4.81-6.65	3.58-4.22	12.53-20.58
T3	>6.65	>4.22	>20.58

Conclusions

- EPclin identified a low risk group of patients who may be spared chemotherapy (validated cut-off)
- EPclin provided more accurate prognostic information than the RS - partly but not entirely due to the EPclin including tumour size and nodal status
- Differences between EPclin and RS were greatest in node positive patients
- The bottom tertile of EPclin in node negative patients identified a group with extremely good prognosis

Controversial value of tertiles analyses:

- Ep/EPClin and RS are continuous scores, with validated cut-offs
- EP/Epclin: pre-specified cut-off identifies 2 categories

What was the aim? Was the methodology correct?

Discussion

- **Do we need a GEP beyond classical features?**
  - GEPs add modestly to CTS (need for validation, trained in TransATAC)
  - IHC markers were not included

- **Different tests developed to answer the same question, how to choose?**

  1. The clinical question MUST be clear
    - Are we looking for the 0% relapse subgroup (i.e. subgroup with the lowest risk of relapse, even if it is very small)?
      - If so, what about pts at 3,5…10% relapse risk?
    - Are we looking for a subgroup with an absolute baseline risk low enough to avoid CT (i.e., the largest group of patients with a predefined low risk of relapse)?
      - If so, define the acceptable upper limit of risk

  2. When the question is clear, define the priority of «statistical measures» to consider
    - Absolute 10yrs DRFS %, size of low-risk group, HR