Endopredict score per stima del rischio di ricaduta oltre il 5° anno. Quale sarà il ruolo nella pratica clinica?

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Istituto Nazionale per la Ricerca sul Cancro

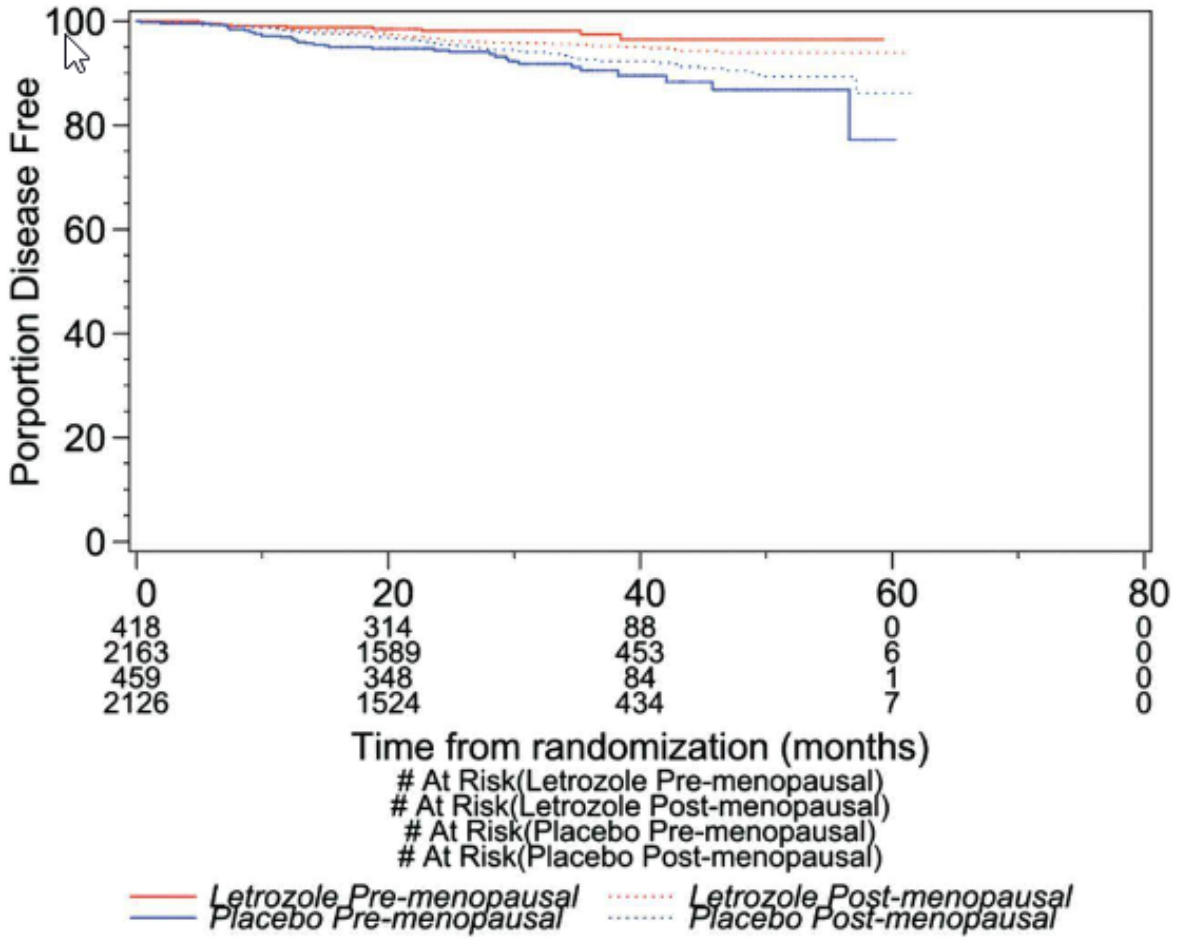
Benefit of Extended Adjuvant Tamoxifen in ATLAS and aTTom

	Breast Cancer Mortality	Overall Survival
Years 5-9	0.97 (0.84-1.15)	0.99 (0.89-1.10)
Years 10+	0.75 (0.65-0.86)*	0.84 (0.77-0.93)*
All years	0.85 (0.77-0.94)*	0.91 (0.84-0.97)*

* P < 0.05 favoring 10 years

Gray et al, ASCO, 2013

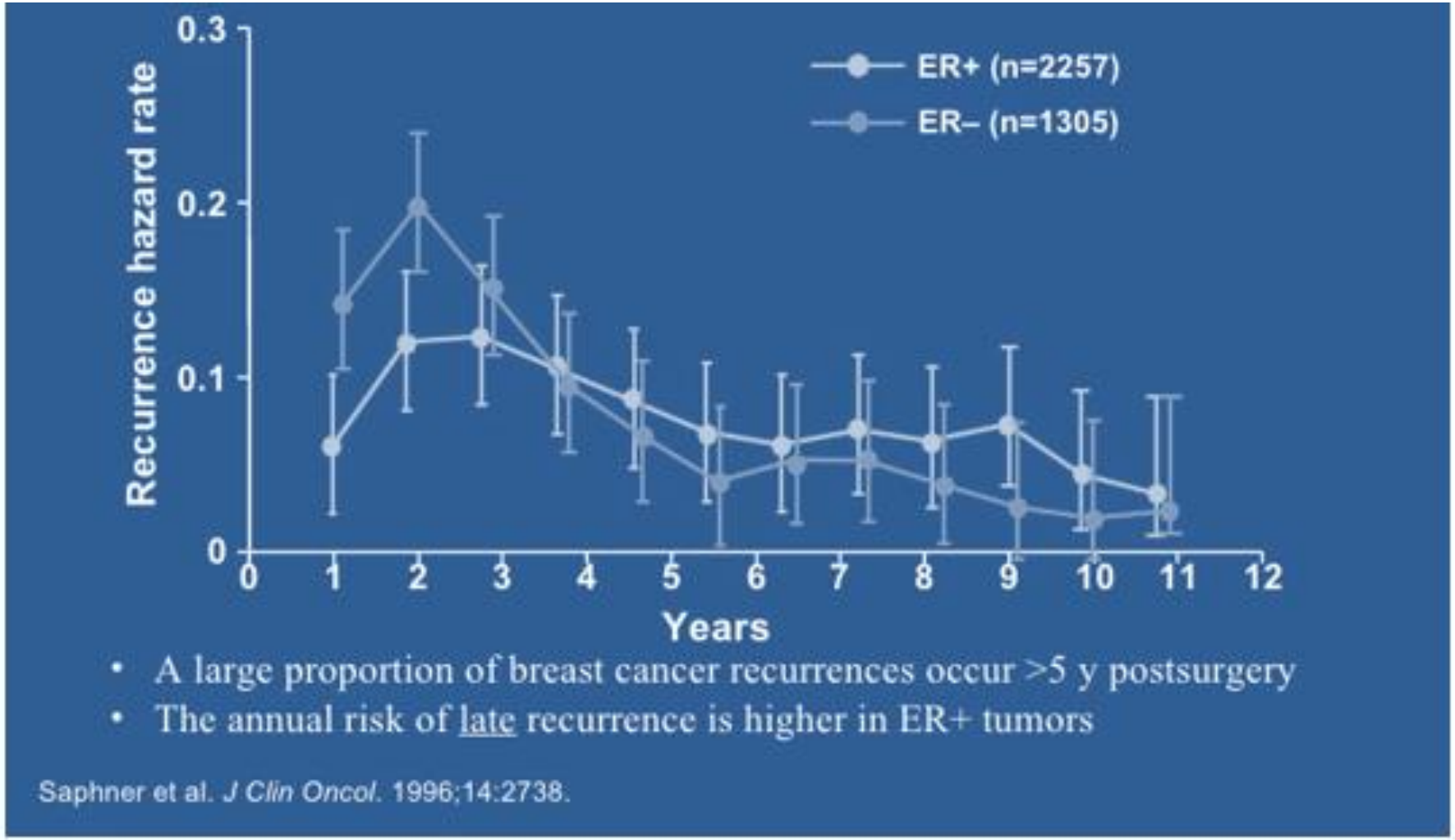
Benefit of Extended Adjuvant Letrozole in MA-17



Notable benefit for women who were premeno-pausal at time of diagnosis and became postmeno-pausal during tamoxifen

Goss et al. Ann Oncol, 2013

Annual risk of recurrence by hormonal receptors



Some Potential Factors to Support Use of Extended Adjuvant Endocrine Therapy

- Higher stage at diagnosis
- Limited or absent toxicity
- Absence of life-threatening comorbidities
- Younger age
- Patient preference
- **Biomarkers for late recurrence?**

Potential Molecular Tests for Late Recurrence

Test	Abbreviation	Description
Clinical Treatment Score	CTS	T, N, grade, age, treatment
Immunohistochemical Score 4	IHC4	IHC for ER, PR, Ki67, HER-2
Oncotype Dx	RS	21 gene assay
Prosigna Risk of Recurrence	ROR	PAM50
Breast Cancer Index	BCI	HOXB13/IL17BR
EndoPredict	EPClin	12 gene assay

Adapted from Sestak et al, J Clin Oncol, 2014

Validità clinica

- definisce la capacità di un determinato test di indentificare o predire in modo accurato e riproducibile il rischio dell'outcome di interesse, nel caso specifico il rischio di ricaduta a distanza o di morte a 5-10 anni dopo la chirurgia in pazienti con diagnosi di carcinoma mammario operato. Esso si riferisce all'abilità prognostica del test e coincide con la sensibilità e la specificità clinica.

Utilità clinica

- definisce la capacità del test di discriminare le pazienti che possono trarre un maggior o minor beneficio clinico da un determinato intervento terapeutico, nel caso specifico il beneficio derivante dalla chemioterapia adiuvante in pazienti con carcinoma mammario operato. Viene valutata attraverso i seguenti outcome:

- L'impatto del test sul decision-making
- L'abilità predittiva del test
- L'impatto sulla qualità di vita

Utility of prognostic genomic tests in breast cancer practice: The IMPAKT 2012 Working Group Consensus Statement†

H. A. Azim Jr[1], S. Michiels[1], F. Zagouri[2], S. Delaloge[3], M. Filipits[4], M. Namer[5], P. Neven[6], W. F. Symmans[7], A. Thompson[8], F. André[3*], S. Loi[1*] & C. Swanton[9,10]

	Oncotype DX	Mammaprint	PAM50	EndoPredict
Validità analitica	Convincente	Convincente	Necessità di ulteriori dati	Necessità di ulteriori dati
Validità clinica	Convincente	Convincente	Necessità di ulteriori dati	Necessità di ulteriori dati
Utilità clinica	Non convincente	Non convincente	Non convincente	Non convincente

Ann Oncol 2013

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	Oncotype DX	Mammaprint	PAM50	EndoPredict
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Validità clinica	Convincente	Convincente	Necessità di ulteriori dati	~~Necessità di ulteriori dati~~ Convincente
Utilità clinica	Non convincente	Non convincente	Non convincente	Non convincente

Ann Oncol 2013

Clinical Cancer Research

A New Molecular Predictor of Distant Recurrence in ER-Positive, HER2-Negative Breast Cancer Adds Independent Information to Conventional Clinical Risk Factors

Martin Filipits[1], Margaretha Rudas[2], Raimund Jakesz[3], Peter Dubsky[3], Florian Fitzal[3], Christian F. Singer[4],

Gene symbol	Full name	GO terms (biological process)	Association with ER expression
AZGP1	alpha-2-glycoprotein 1, zinc-binding	cell adhesion	correlation with ER [LS13]
BIRC5	baculoviral IAP repeat-containing 5	anti-apoptosis	
		cell division	
		cytokinesis	
		G2/M transition of mitotic cell cycle	
		establishment of chromosome localization	
DHCR7	7-dehydrocholesterol reductase	cholesterol biosynthetic process	
IL6ST	interleukin 6 signal transducer	cytokine-mediated signaling pathway	coregulated with ER [LS14]
		leukemia inhibitory factor signaling pathway	
		negative regulation of interleukin 6-mediated signaling pathway	
		positive regulation of cell proliferation	
		positive regulation T cell proliferation	
		positive regulation of JAK-STAT cascade	
		response to cytokine stimulus	
MGP	matrix Gla protein	regulation of transcription (no experimental evidence)	induced by estrogen [LS15]
RBBP8	retinoblastoma binding protein 8	DNA repair	correlation with ER [LS16]
STC2	stanniocalcin 2	cell-cell signaling (no experimental evidence)	coregulated with ER [LS14]
UBE2C	ubiquitin-conjugating enzyme E2C	ubiquitin-dependent protein catabolic process	
		protein ubiquitination	
		exit from mitosis	
		positive regulation of exit from mitosis	
		cyclin catabolic process	

Table S8. Baseline characteristics of patients from ABCSG Trials 6 and 8 according to EP risk groups

Characteristic	Total n = 1702	EP score ≤ 5 n = 832	EP score > 5 n = 870	*P**
Age				0.68
Median, years	63.8	63.8	63.9	
Range, years	41.5 - 80.7	45.5 - 80.7	41.5 - 80.5	
≤60 years	579 (34%)	279 (34%)	300 (35%)	
>60 years	1123 (66%)	553 (67%)	570 (66%)	
Tumor size				0.02
≤2 cm	1136 (67%)	582 (70%)	554 (64%)	
>2 cm - ≤5cm	539 (32%)	239 (29%)	300 (35%)	
>5cm	27 (2%)	11 (1%)	16 (2%)	
Nodal status				0.01
Negative	1165 (68%)	592 (71%)	573 (66%)	
1 - 3 positive nodes	454 (27%)	211 (25%)	243 (28%)	
>4 positive nodes	83 (5%)	29 (3%)	54 (5%)	
Tumor grade				<0.001
G1	379 (22%)	225 (27%)	154 (18%)	
G2	1252 (74%)	597 (72%)	655 (75%)	
G3	69 (4%)	9 (1%)	60 (7%)	
Unknown	2 (0.1%)	1 (0.1%)	1 (0.1%)	
Estrogen receptor				0.16
Low	177 (10%)	79 (10%)	98 (11%)	
Medium	553 (33%)	259 (31%)	294 (34%)	
High	972 (57%)	494 (59%)	478 (55%)	
Progesterone receptor				<0.001
Negative	353 (21%)	139 (17%)	214 (25%)	
Low	295 (17%)	119 (14%)	176 (20%)	
Medium	562 (33%)	293 (35%)	269 (31%)	
High	492 (29%)	281 (34%)	211 (24%)	
Ki67 (n =1638)				<0.001
≤11%	1271 (78%)	732 (92%)	539 (64%)	
>11%	367 (22%)	63 (8%)	304 (36%)	
Adjuvant therapy				0.69
Tamoxifen	1029 (61%)	499 (60%)	530 (61%)	
Tamoxifen+Anastrozole	673 (40%)	333 (40%)	340 (39%)	
Adjuvant!Online				0.001
Low risk	843 (50%)	446 (54%)	397 (46%)	
High risk	859 (51%)	386 (46%)	473 (54%)	

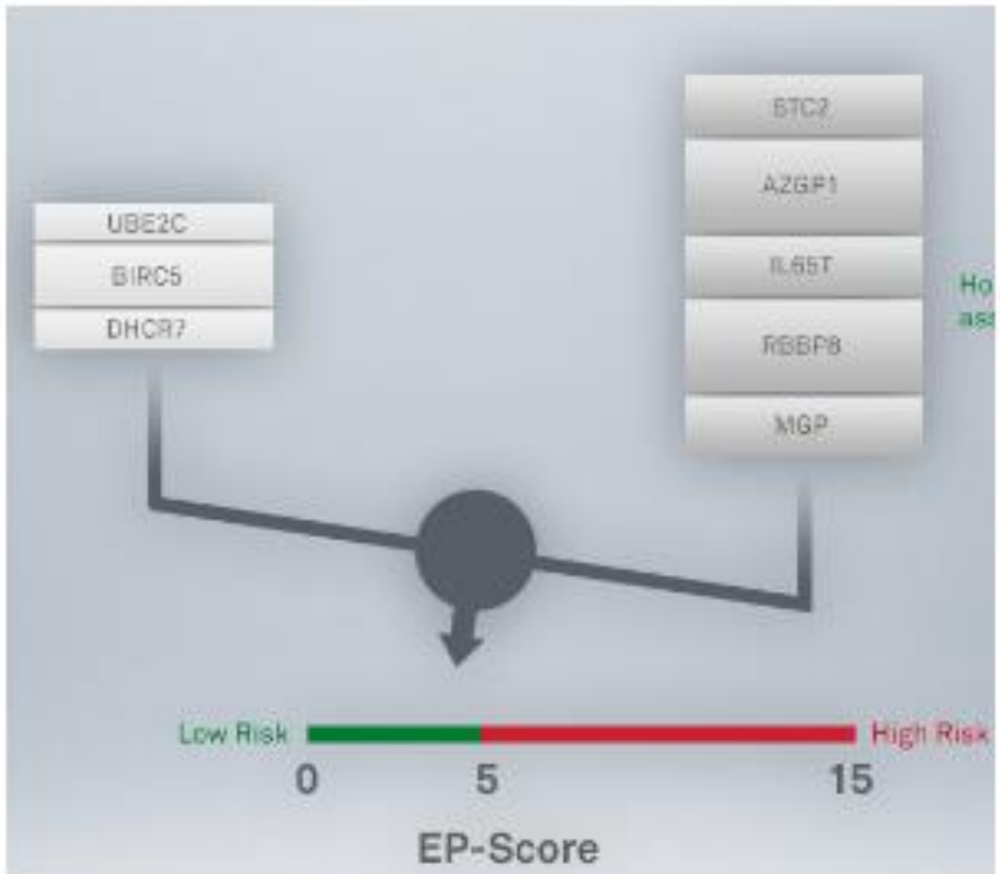
WHICH GENES ARE TARGETED?

12 GENES ARE MEASURED IN TRIPLICATE
PCR AMPLICONS 68-157 bp

GOOD ASSAY DESIGN

3 PROLIFERATION GENES
DHCR7, BIRC5, UBE2C

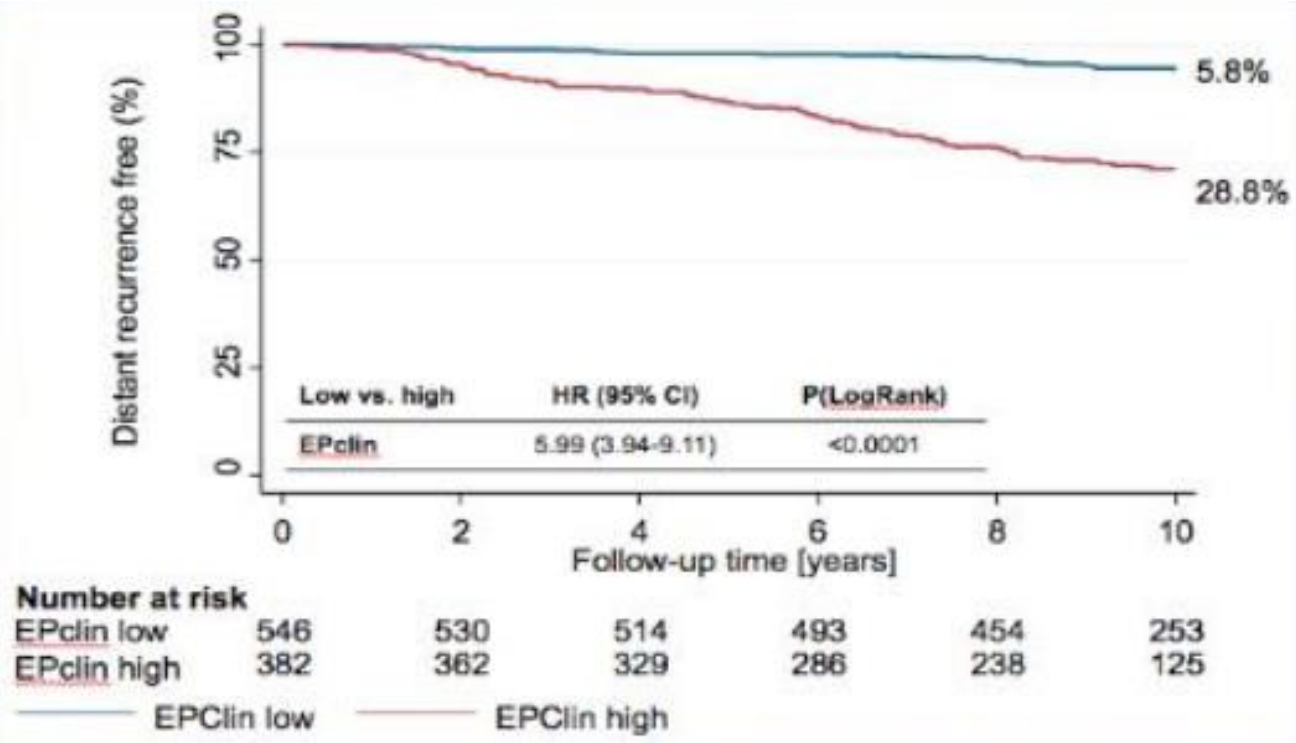
5 ER SIGNALING GENES
STC2, AZGP1, IL6ST, RBBP8, MGP



3 NORMALISATION GENES
0AZ1, CALM2, RPL37A

1 DNA TARGET GENE
HBB

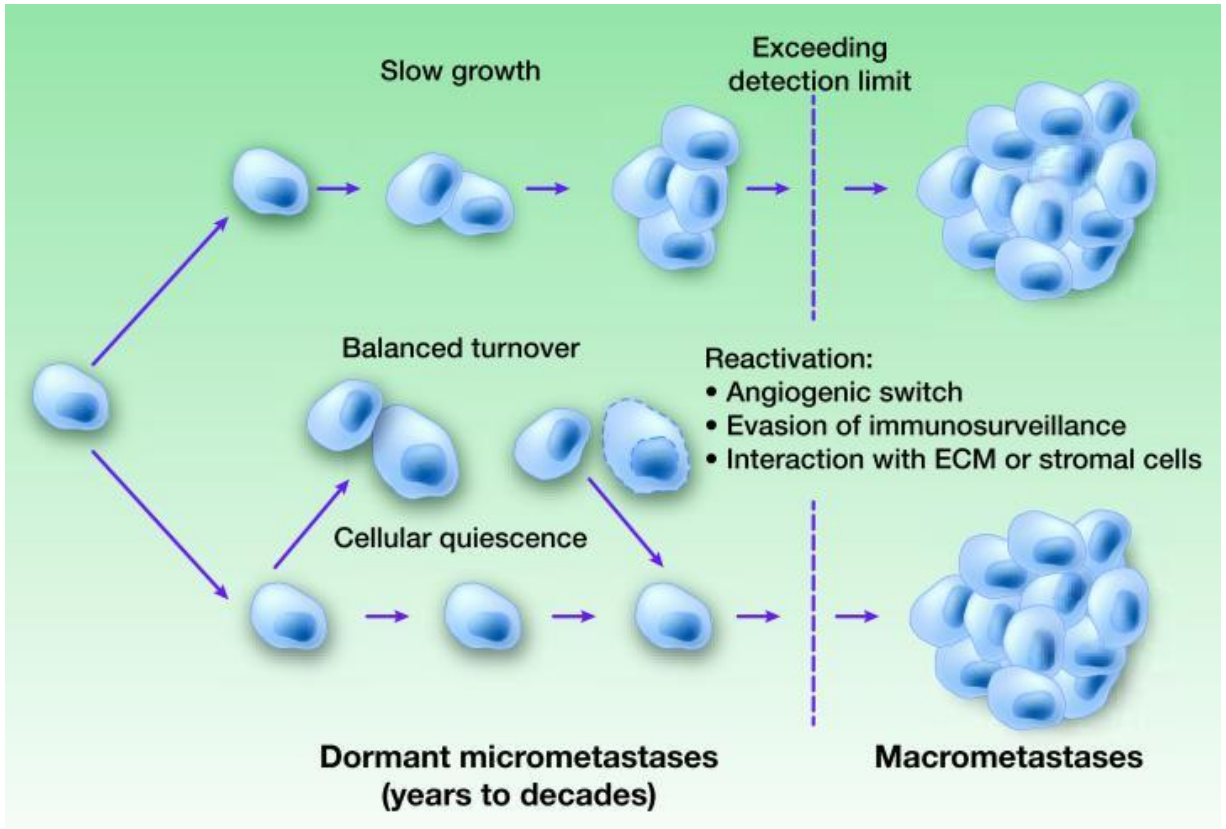
Endopredict



«EPclin identified a low risk group of patient who may be spared chemotherapy»

And hormonal therapy?

Limitations of primary tumours…



"The difficulty that all discussed molecular signatures have in common is that the information is derived from the primary tumor, assuming that driving forces for late recurrences are in these primary tumors. This might be true for early relapses but not necessarily for late recurrence."

Zhang et al,

Tumor biology is not all that matters…

"Non-clinical baseline factors, such as age or body mass index, may influence the prognostication of these signatures and furthermore may help to identify specific women who will benefit most from these tests."

Annals of Oncology 25 (Supplement 1): i8–i16, 2014
doi:10.1093/annonc/mdu066.1

Biomarkers in breast cancer

200 **ANALYSIS OF MOLECULAR SCORES FOR THE PREDICTION OF DISTANT RECURRENCE ACCORDING TO BODY MASS INDEX AND AGE AT BASELINE**

I. Sestak[1], M. Dowsett[2], S. Ferree[3], F.L. Baehner[4], J.W. Cowens[3], S. Butler[4], J. Cuzick[1]

[1]Wolfson Institute of Preventive Medicine, Queen Mary University, Centre for Cancer Prevention, London, UNITED KINGDOM
[2]Academic Biochemistry, Royal Marsden Hospital NHS Foundation Trust, London, UNITED KINGDOM
[3]Nanostring Technologies, NanoString Technologies, Seattle, WA, UNITED STATES OF AMERICA
[4]Genomic Health, Genomic Health, Redwood City, CA, UNITED STATES OF AMERICA

Background: Many trials have now shown the benefit of an aromatase inhibitor in postmenopausal women with hormone receptor positive breast cancer. Several molecular profiles (Clinical Treatment Score (CTS), IHC4) and gene signatures (Oncotype DX Recurrence Score (RS), ROR score (Prosigna™)) have been investigated for the prediction of (distant) recurrence in several trials and we have shown that these molecular markers significantly correlated with overall and also late distant recurrence. Here, we explore whether body mass index (BMI) and age affect the prediction of these molecular scores for distant recurrence in years 0–10 in the transATAC trial.

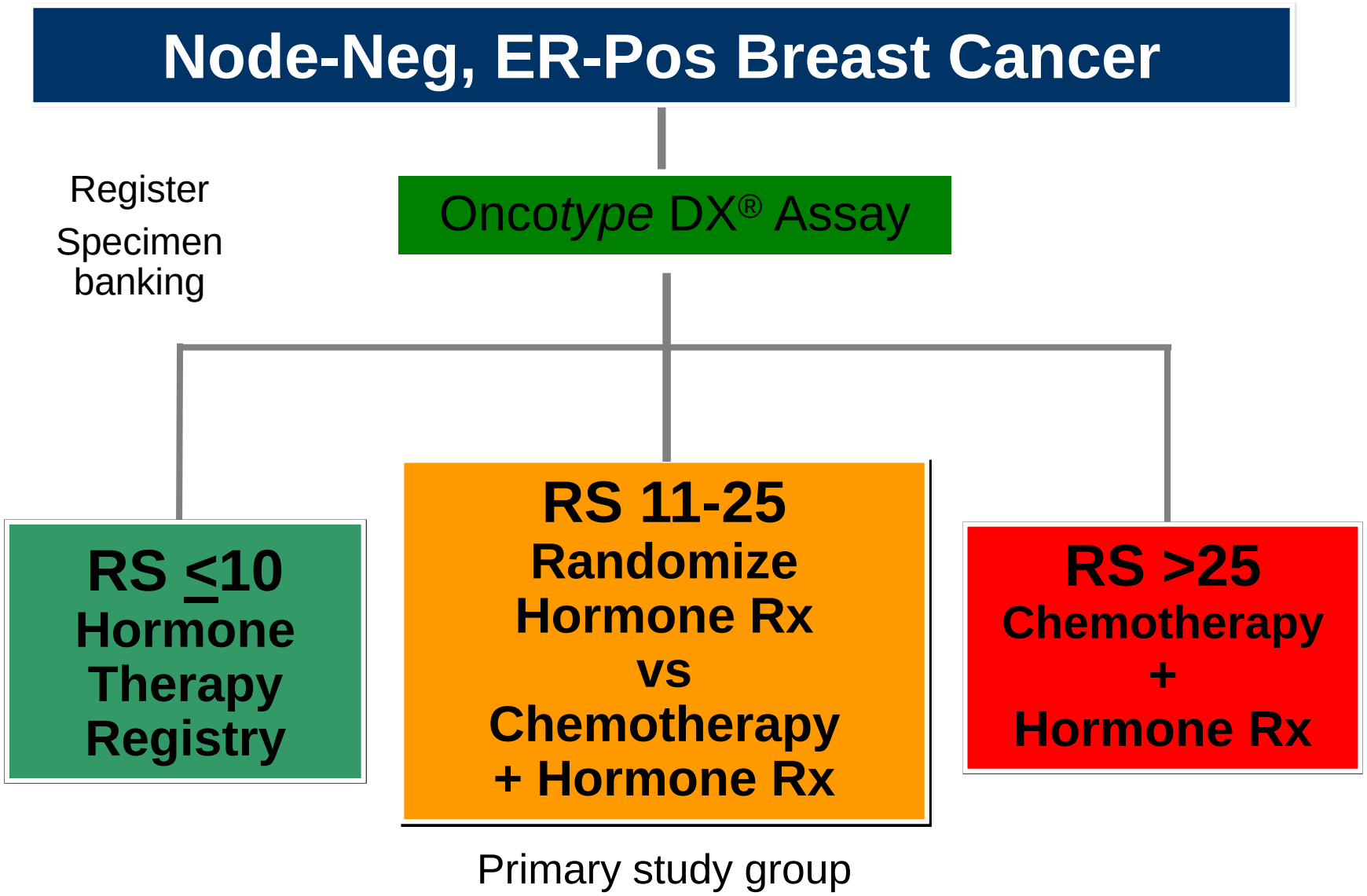
Methods: 940 postmenopausal women for whom all four scores were available were included in this analysis. Of these 865 (92.0%) had information on BMI and conventional BMI groups were used for the analysis (≤25, 25–30, >30 kg/m^2). Age at entry was available for all women and was split into equal tertiles. The primary endpoint was distant recurrence. Cox proportional hazard models were used to determine the effect of a molecular score for the prediction of distant recurrence according to BMI and age group.

Results: In this exploratory analysis, the CTS and ROR score added significant prognostic information in all three BMI groups, but tests for trend were not significant. The IHC4 provided most prognostic information in women with a BMI lower than 25 kg/m^2. The RS did not add prognostic information for distant recurrence in women with a BMI of 30 kg/m^2 or above, but a test for trend was non-significant. The effect size of the IHC4 and RS was strongest in women aged 59.8 years or younger. Trends tests for age were significant for the IHC4 and RS, but not for the CTS and ROR, for which most prognostic information was added in women aged 68 or older and those aged between 60 and 68, respectively. Further results for all scores in all patient sub-groups will be presented.

Conclusion: Molecular scores are increasingly used in women with breast cancer to tailor individual treatment decisions. We have shown that the effect size of the molecular scores is different across age groups and some non-significant differences were found for BMI. Our results may be incorporated in the identification of women who may benefit most from the use of these molecular scores.

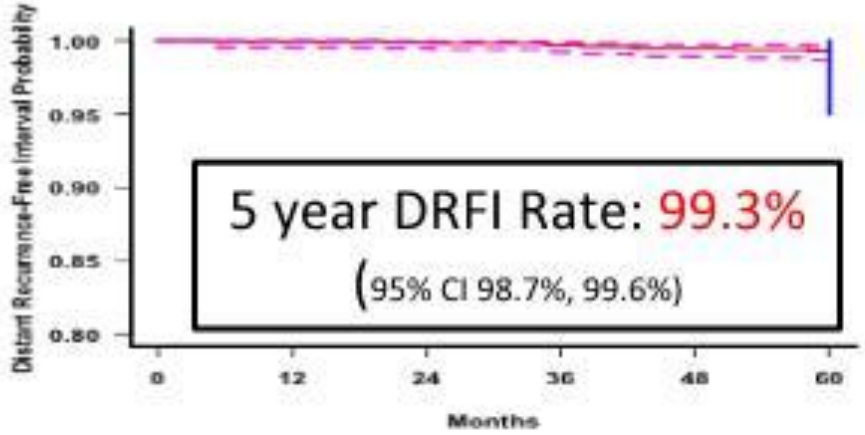
Disclosure: M. Dowsett: Prof Dowsett has received grant support from and is on the speaker's bureau for AstraZeneca. He acts as an adviser to Genoptix. S. Ferree: S. Ferree disclosed he is an employee of and shareholder in NanoString Technologies. F.L. Baehner: Dr Baehner disclosed that he is an employee Genomic Health. J. W. Cowens: Dr Cowens disclosed that he is an employee of and shareholder in Nano String Technologies. S. Butler: Dr Butler disclosed that he is an employee of Genomic Health. J. Cuzick: Prof Cuzick disclosed that he received grant support from and is on the speaker's bureau for AstraZeneca. All other authors have declared no conflicts of interest.

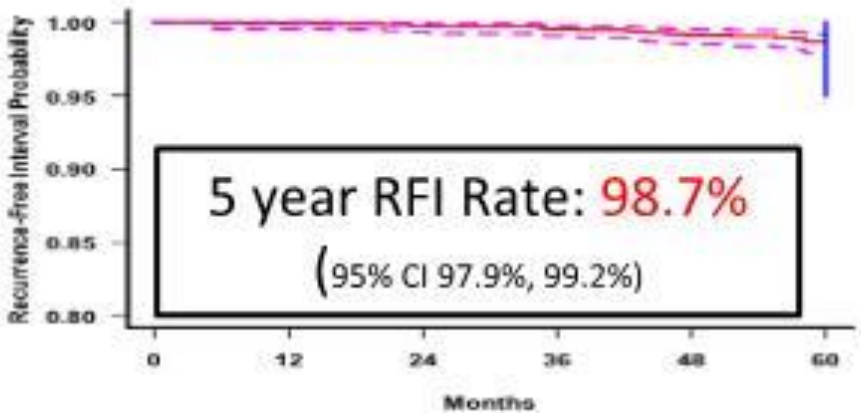
Schema: TAILORx

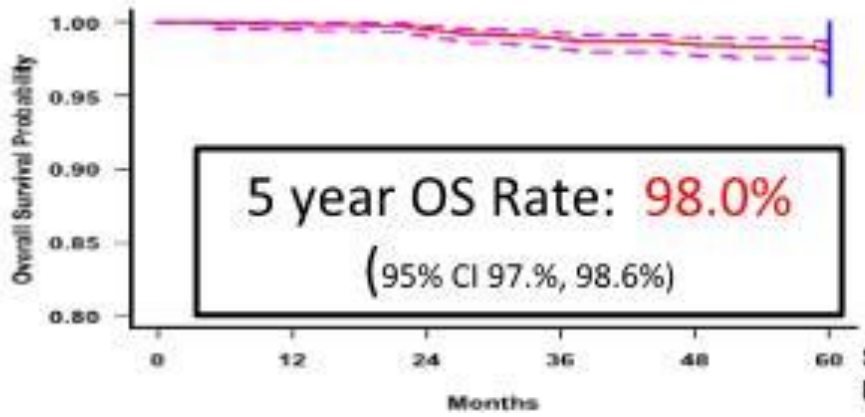


Results: Kaplan Meier Plots and 5 Year Event Rates

of events: 88 iDFS events & 30 deaths within 5 years of registration, including 18 recurrences (10 distant as first event), 15 2nd primary breast cancers, 43 other second primary cancers, 12 deaths without another event







Sparano et al, NEJM 2015

A 21-Gene Expression Assay in Breast Cancer

Table 1. Characteristics and Outcomes of Patients with a Very Low Ki-67 Proliferation Index (≤10%) Who Received Adjuvant Endocrine Therapy.*

Variable	Patients (N = 229)
Median age (interquartile range) — yr	60 (54–65)
Histologic grade of tumor — no.	
1	94
2	125
3	5
Not available	5
Events — no. (%)	
Freedom from recurrence	219 (95.6)†
Breast cancer–specific survival	226 (98.7)
Overall survival	211 (92.1)

* Data are from patients who received the primary diagnosis in 2005 or 2006. The follow-up analysis for survival occurred in July 2015. The main selection criteria were an age of 18 to 75 years and hormone receptor–positive, human epidermal growth factor receptor 2–negative, lymph node–negative tumors measuring 1 to 5 cm in the greatest dimension. The Ki-67 proliferation index is the percentage of cells that are positive for Ki-67.

† Six patients had locoregional relapse, and four patients had distant relapse.

the Ki-67 index may be an alternative to the recurrence score for the identification of patients with a low risk of recurrence.

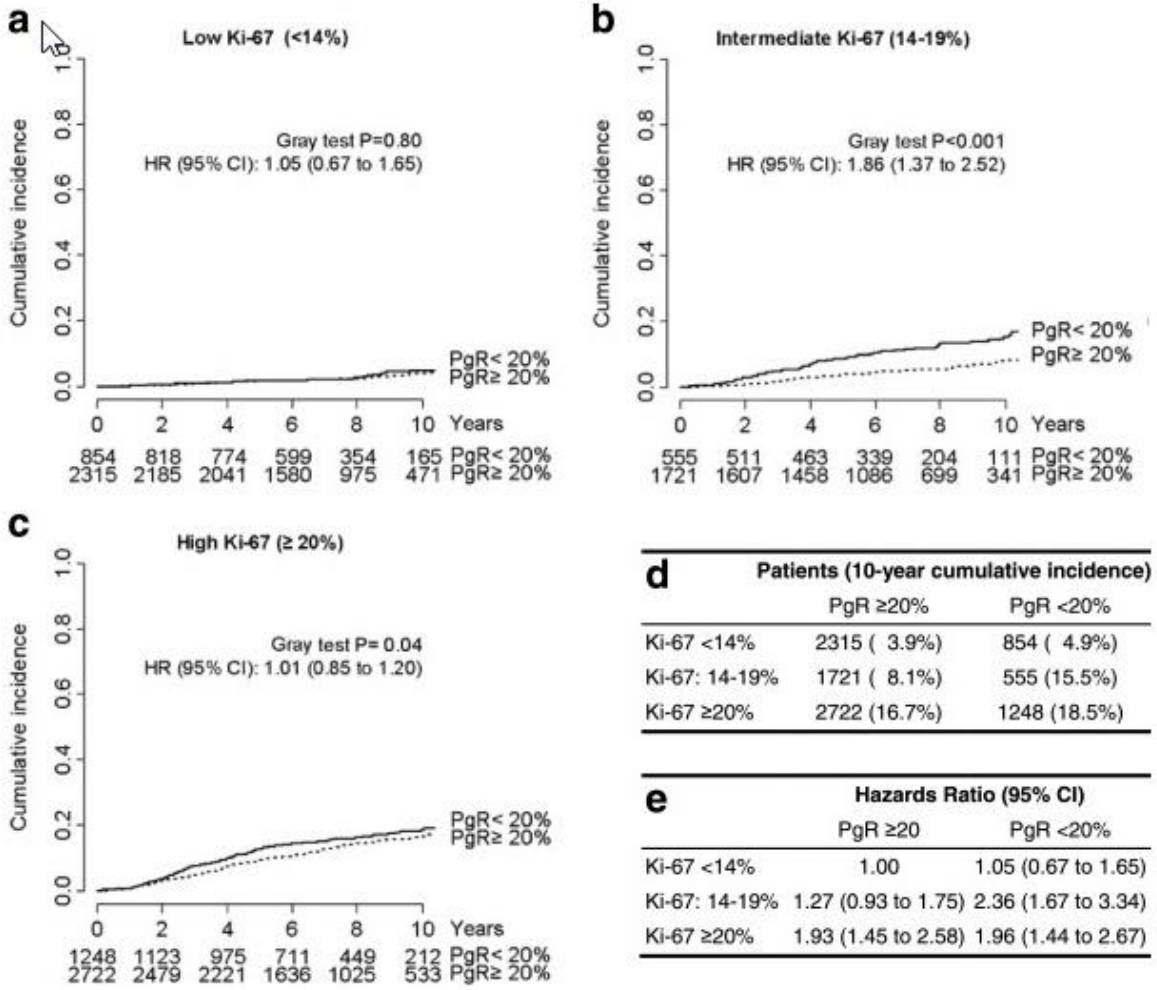
New proposal for surrogate definitions of intrinsic subtypes

Intrinsic subtypes	Clinicopathological surrogate definitions
Luminal A	"Luminal A–like"
	All of:
	ER-positive
	HER2-negative
	And at least one of:
	Ki-67 low expression (<14%)
	Ki-67 intermediate expression (14% to 19%) and PgR high expression (≥20%)
Luminal B (HER2-negative)	"Luminal B–like (HER2-negative)"
	All of:
	ER-positive
	HER2-negative
	And at least one of:
	Ki-67 intermediate expression (14% to -19) and PgR negative or low expression (<20%)
	Ki-67 high expression (≥20%)

Maisonneuve,
Breast Cancer Res 2014

New proposal for surrogate definitions of intrinsic subtypes

9415 pt
ER positive
Her2 negative



d

	Patients (10-year cumulative incidence)	
	PgR ≥20%	PgR <20%
Ki-67 <14%	2315 (3.9%)	854 (4.9%)
Ki-67: 14-19%	1721 (8.1%)	555 (15.5%)
Ki-67 ≥20%	2722 (16.7%)	1248 (18.5%)

e

	Hazards Ratio (95% CI)	
	PgR ≥20	PgR <20%
Ki-67 <14%	1.00	1.05 (0.67 to 1.65)
Ki-67: 14-19%	1.27 (0.93 to 1.75)	2.36 (1.67 to 3.34)
Ki-67 ≥20%	1.93 (1.45 to 2.58)	1.96 (1.44 to 2.67)

Maisonneuve,
Breast Cancer Res 2014

Take home message

…It is appropriate to suggest caution in the application of molecular features and gene expression score for tailoring extended ET but also to encourage continous research…