Méta-analyse et marqueurs biologiques : application chez les patientes atteintes de cancer du sein

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Trois exemples pronostiques

- Les lymphocytes infiltrant les tumeurs chez les patientes atteintes d'un cancer du sein triple négatif de stade précoce
- Les cellules circulantes tumorales dans de cancer du sein métastatique
- Des signatures génomiques dans le cancer du sein de stade précoce

1) Stromal TILs: evaluate %TILs in the tumor stroma

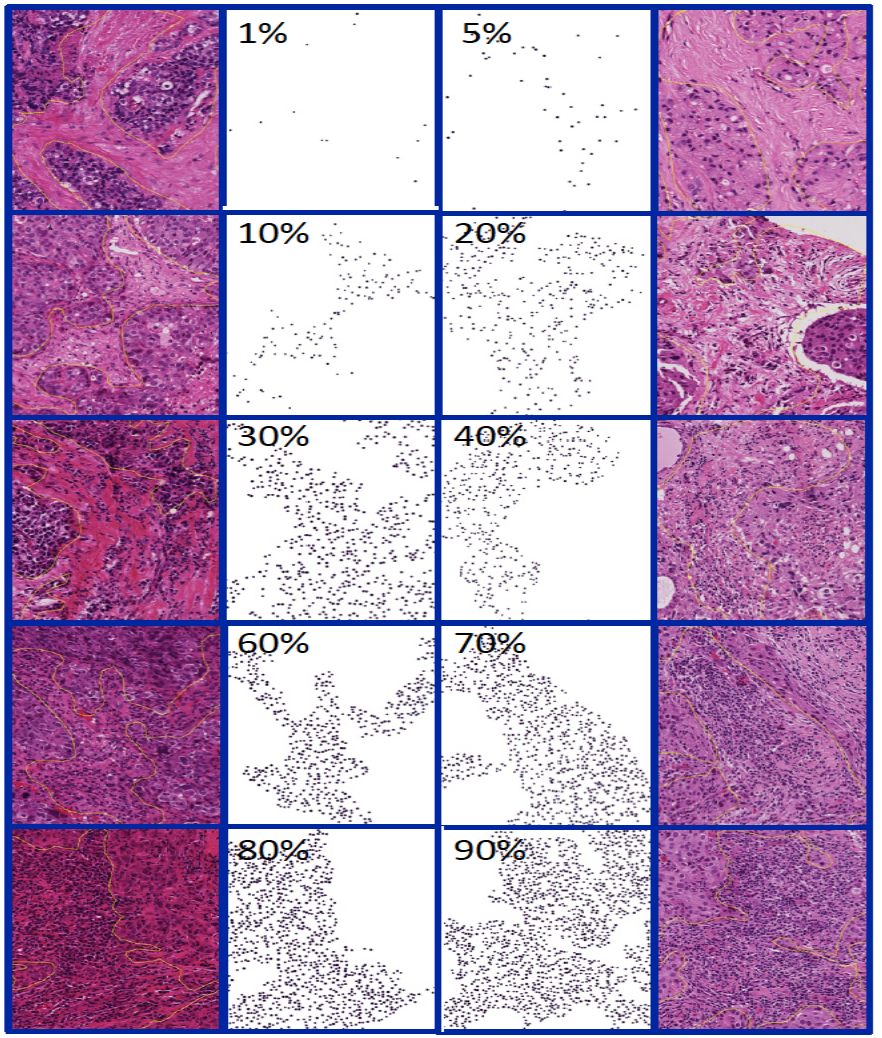
review

Annals of Oncology 00: 1–13, 2014
doi:10.1093/annonc/mdu450

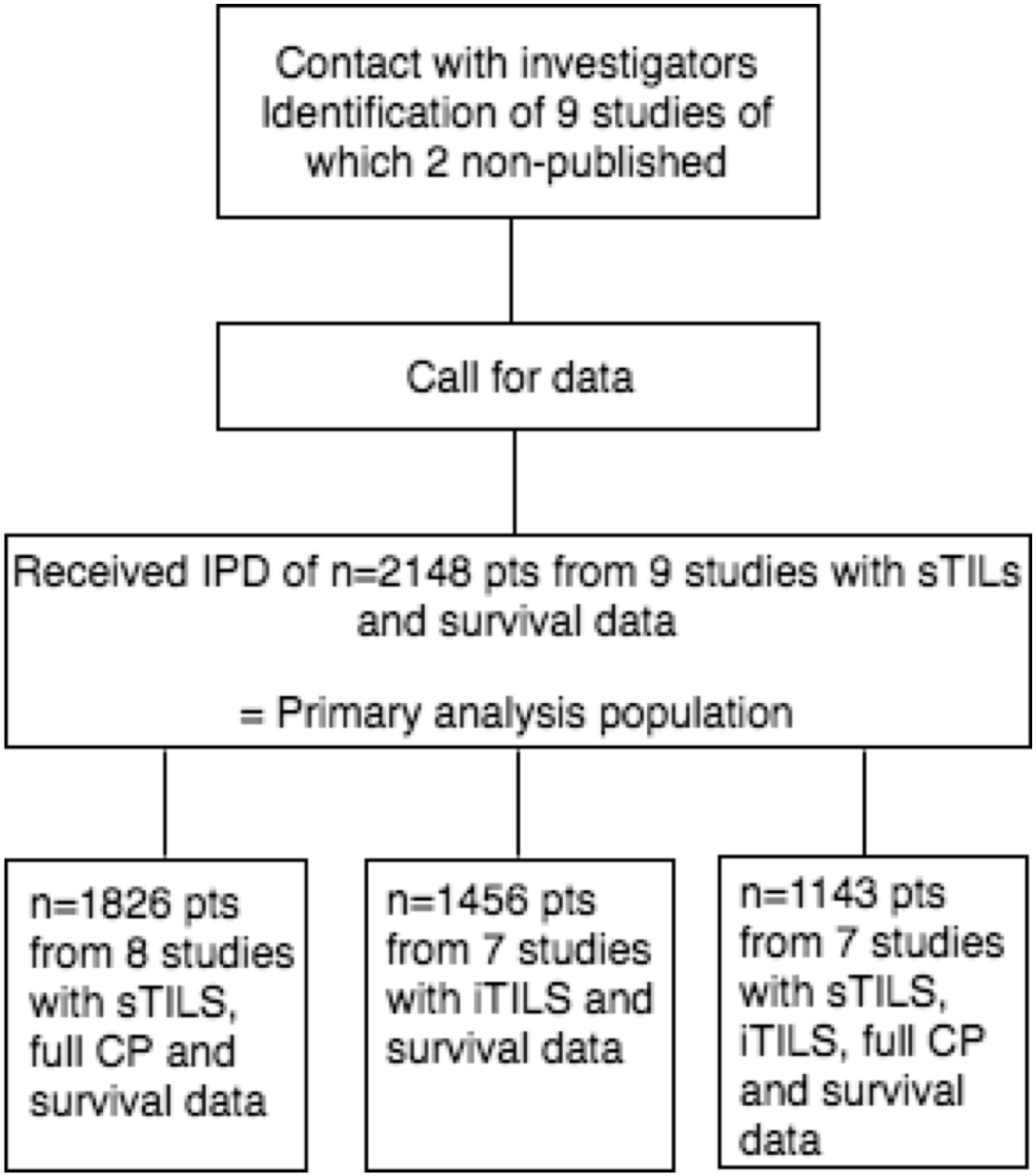
The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014

- Ring studies to obtain reproducible measurements between pathologists !
- Protocol for pooled analysis

Salgado, Denkert et al, 2014



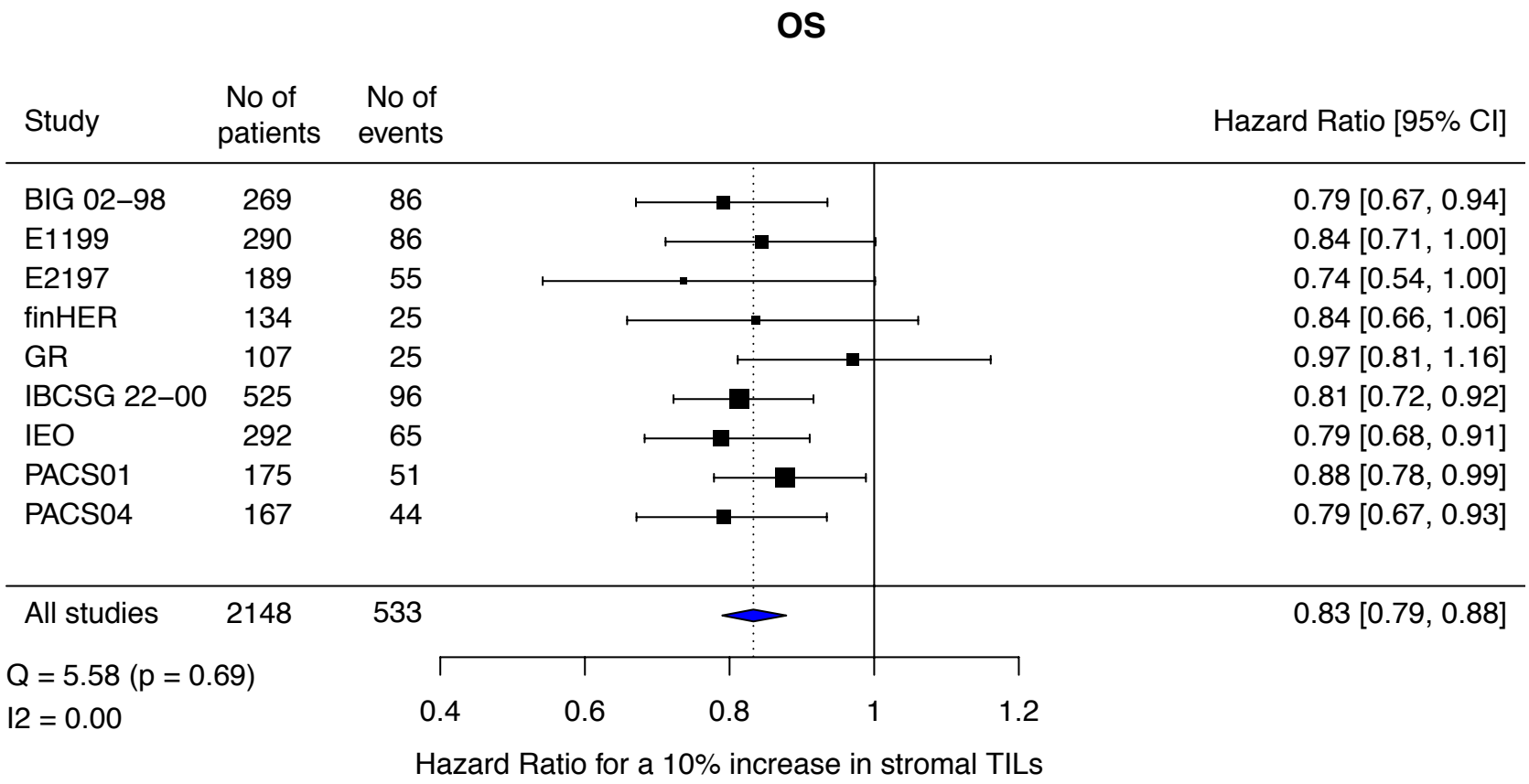
Flow chart



IPD: individual patient data; pts: patients, TILs: tumour infiltrating lymphocytes; sTIL: stromal TILs (primary biomarker); iTILs: intrautmoral TILs; CP: clinicopathological factors age, nodal status, tumour size, tumour grade, treatment (anthracycline or anthracycline plus taxanes)

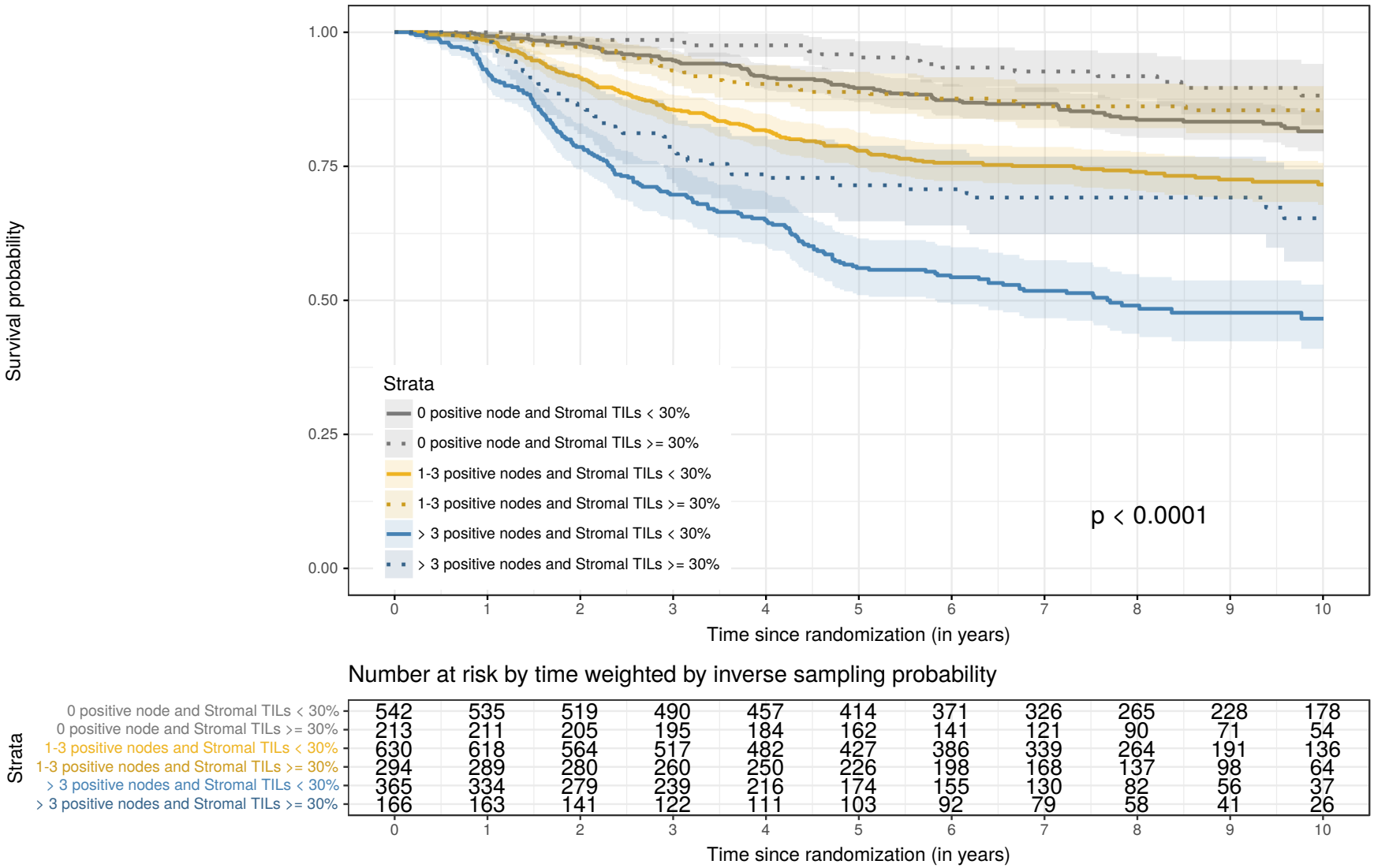
Objectif primaire : évaluer la valeur pronostique de la présence de TILs dans le stroma tumoral dans les cancers du sein triple négatifs (TNBC)

Obtaining high level of clincial validity for a biomarker: Tumour Infiltrating lymphocytes in triple negative breast cancer



Loi et al JCO 2019

Obtaining high level of evidence for a biomarker: TILs example



Loi et al JCO 2019

Added prognostic value

Likelihood ratio test *for stromal tils and intratumoral TILs with or without adjustment on clinical factors (CP: age, tumor size, number of positive nodes, histological grade and treatment)*

n=1826	IDFS (608 events)		DDFS (482 events)		OS (438 events)	
	χ^2	p	χ^2	p	χ^2	p
Stromal TILs vs NULL	70.69	$< 10^{-6}$	89.13	$< 10^{-6}$	70.38	$< 10^{-6}$
CP vs NULL	138.78	$< 10^{-6}$	179.58	$< 10^{-6}$	157.65	$< 10^{-6}$
Stromal TILs+CP vs NULL	187.69	$< 10^{-6}$	235.36	$< 10^{-6}$	206.12	$< 10^{-6}$
Stromal TILs+CP vs Stromal TILs	117.00	$< 10^{-6}$	146.23	$< 10^{-6}$	135.74	$< 10^{-6}$
Stromal TILs+CP vs CP	48.91	$< 10^{-6}$	55.78	$< 10^{-6}$	48.47	$< 10^{-6}$

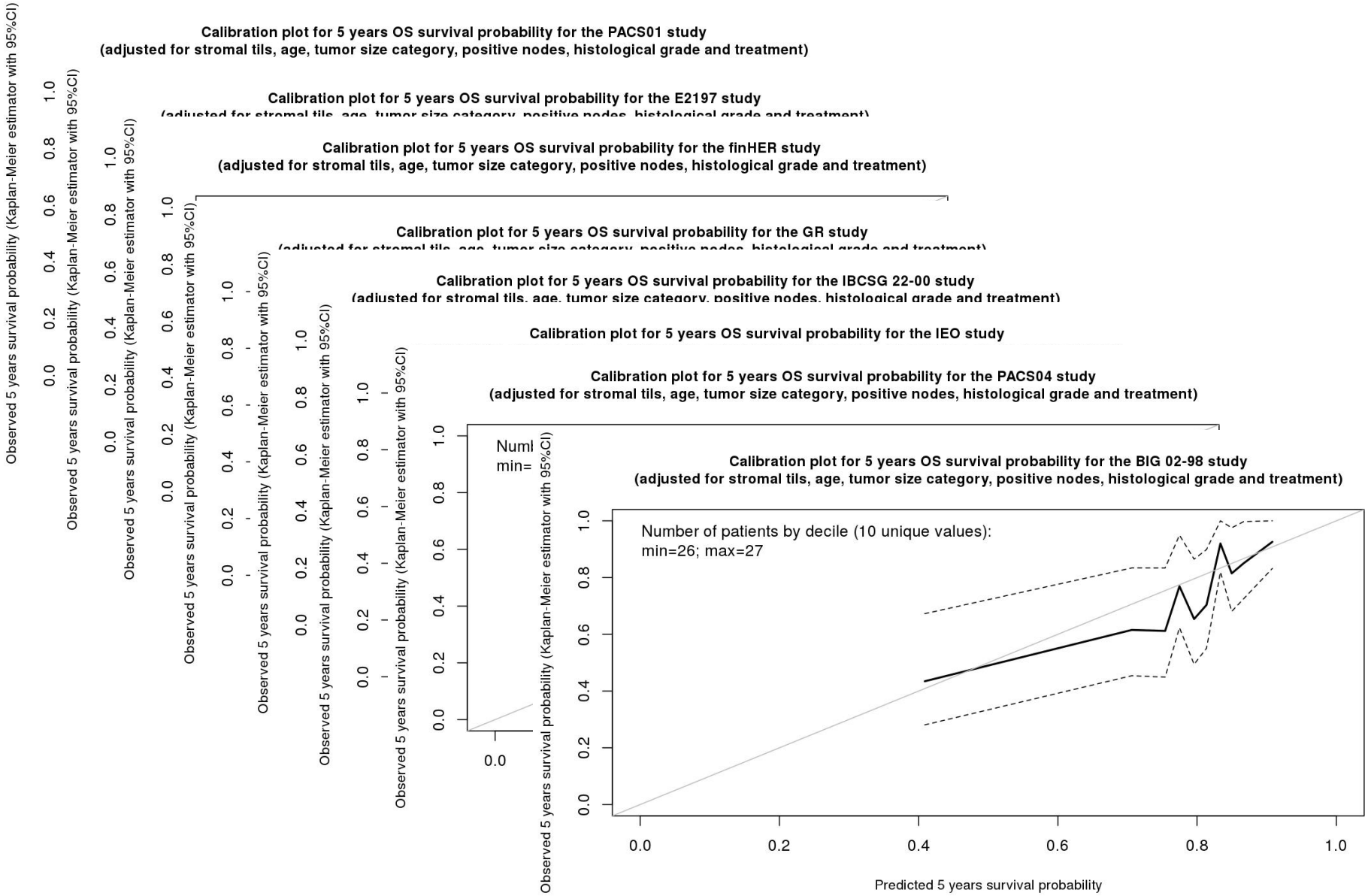
Loi et al JCO 2019

5-year AUC in leave-one study out crossvalidation

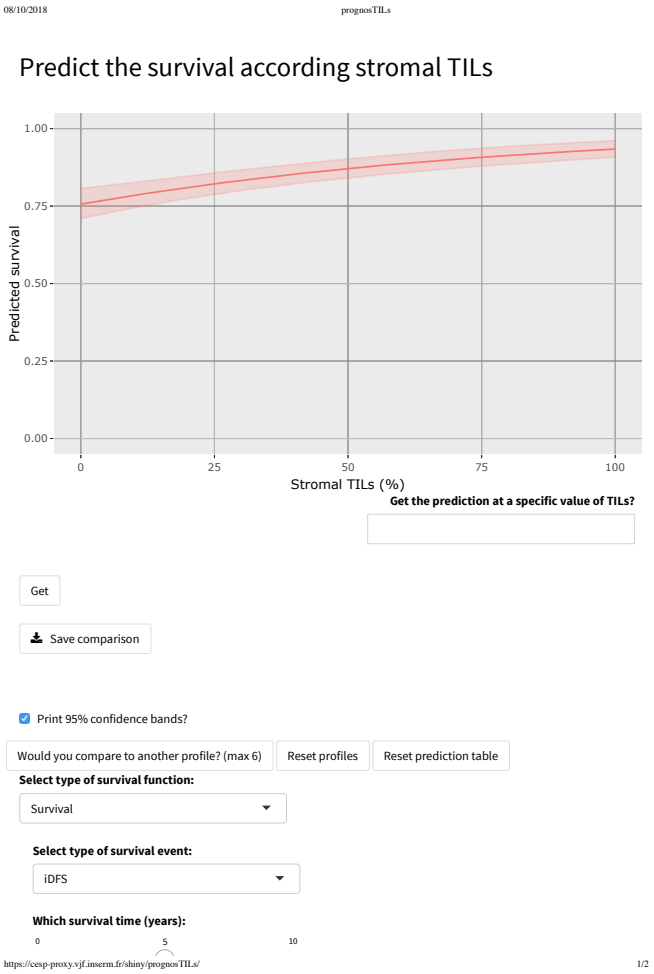
(CP: age, tumor size, number of positive nodes, histological grade and treatment) using leave one study out cross-validation

Score components	IDFS (414 events)	DDFS (333 events)	OS (300 events)
Stromal TILs	0.597 [0.541; 0.659]	0.604 [0.525; 0.672]	0.586 [0.556; 0.671]
Intratumoral TILs	0.597 [0.524; 0.659]	0.601 [0.540; 0.668]	0.580 [0.534; 0.627]
Stromal TILs+Intratumoral TILs	0.607 [0.560; 0.657]	0.614 [0.557; 0.667]	0.593 [0.567; 0.664]
CP	0.649 [0.547; 0.713]	0.672 [0.549; 0.759]	0.681 [0.563; 0.808]
Stromal TILs+CP	0.681 [0.559; 0.756]	0.701 [0.573; 0.793]	0.694 [0.601; 0.769]
Intratumoral TILs+CP	0.673 [0.571; 0.714]	0.692 [0.577; 0.780]	0.689 [0.580; 0.781]
Stromal TILs+Intratumoral TILs+CP	0.684 [0.566; 0.752]	0.700 [0.573; 0.794]	0.693 [0.603; 0.766]

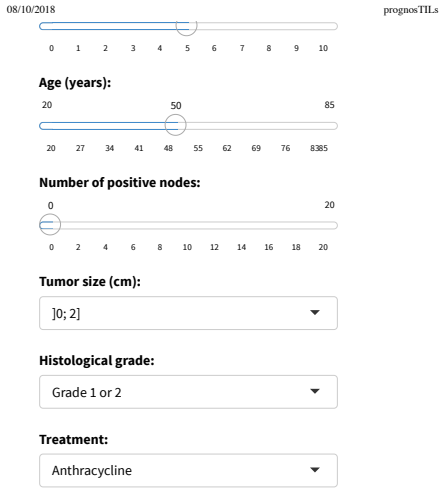
Calibration in leave-one-study out crossvalidation



Obtaining high level of evidence for a biomarker: TILs example



https://www.tilsinbreastcancer.org/prognosis-tool/



2) Cellules tumorales circulantes

Goals:

- Analysis in homogeneous fashion (both endpoints and biomarker data)
- Resolve conflicting results between studies (heterogeneity)
- Increase statistical power (published and unpublished)
- Adjust for clinicopathological factors
- Added value to established clinicopathological factors
- Subgroups

Bidard et al Lancet Oncol 2014

Studies included

CONSORT

Letter of intent

#2,400 potentially eligible pts in 18 centers

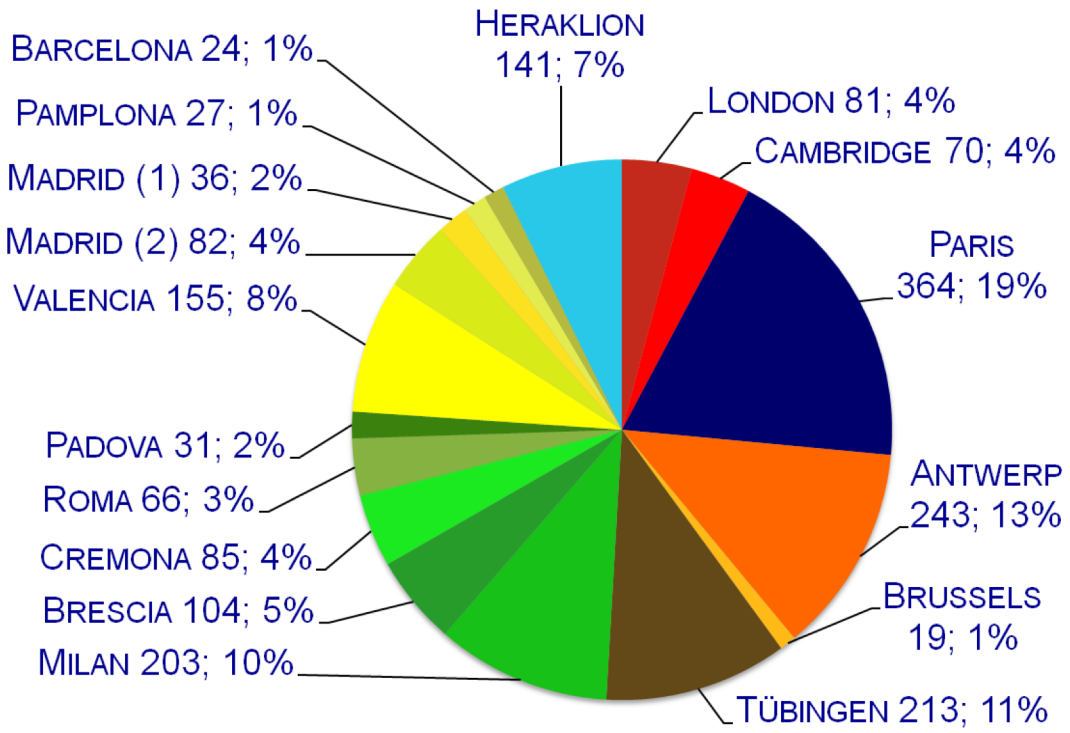
Call for data → **1 center off study**

2,174 pt data received

Data cleaning → **230 ineligible pts**

1,944 individual patient data from 17 centers included

Patients / Centres



CTC at baseline

≥5 CTC / 7.5mL were detected in 47% of the 1,944 patients at baseline

1st quartile	Median	3rd quartile	Maximum
0 CTC	3 CTC	25 CTC	58160 CTC

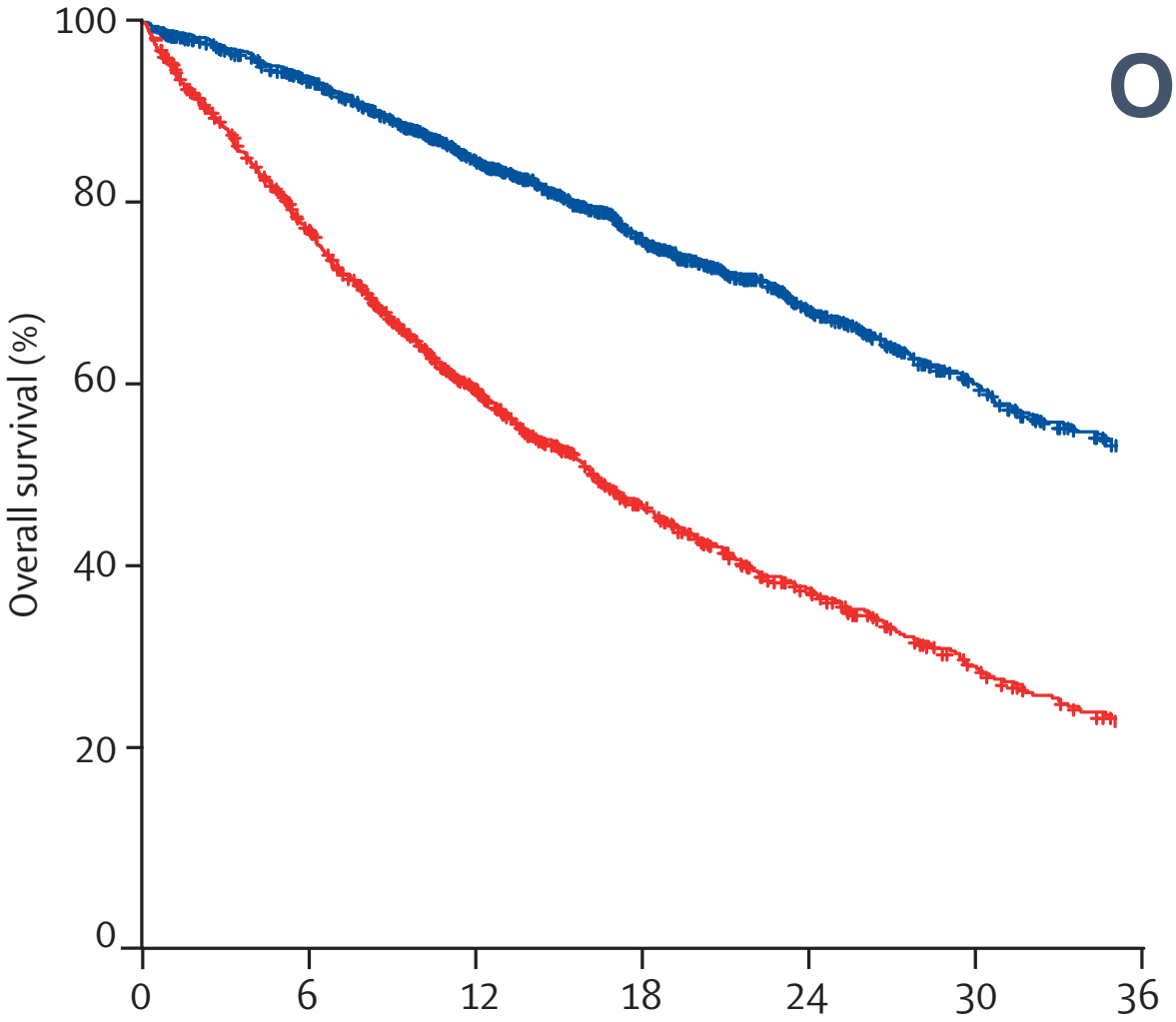
CTC count at baseline was associated with

	First line (N=1,110)	**All patients**
Performance status	p<0.0001	p<0.0001
Liver metastases	p<0.0001	p<0.0001
Bone metastases	p<0.0001	p<0.0001
Elevated CEA	p<0.0001	p<0.0001
Elevated CA15-3	p<0.0001	p<0.0001
Tumor subtype	p=0.71	p<0.0001

≥5 CTC

HR+	**51%**
HER2+	**38%**
T. Neg	**44%**

Overall survival



Number at risk

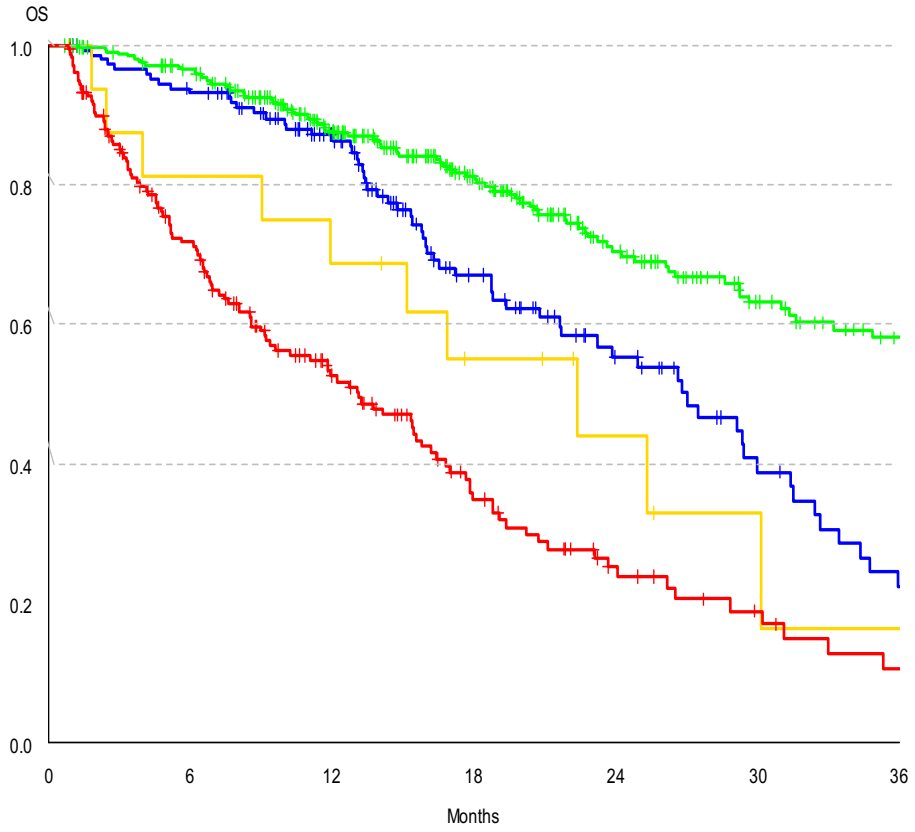
CTC <5	1033	896	701	496	333	230	162
CTC ≥5	911	639	396	237	147	85	53

	Patients	Events	Median overall survival in months (95% CI)
CTC <5	1033	371	37·1 (32·8–41·9)
CTC ≥5	911	558	15·5 (13·5–16·8)

Bidard et al Lancet Oncol 2014

Early CTC changes during treatment

Baseline & week 3-5 (landmark)



Overall Survival

N= 672 patients; p<0.0001

	N Pts	N Events	Median OS months [95%CI]
Stable neg: <5 - <5	327	104	41 [37-53]
Decrease: ≥5 - <5	149	70	27 [22-31]
Increase: <5 - ≥5	17	10	22 [12-NE]
Stable pos: ≥5 - ≥5	179	116	13 [9-16]

Added value to ClinicoPathological model

Jacknife Resampling procedure

	Model 1 average c-index	Model 2	Model 2 average c-index	Average c-index increase model 2–model 1 (95% CI)	Average increase χ^2 (95% CI)	Likelihood ratio test p value
Progression-free survival (N=1196 patients)						
Model 1: CP	0·668	CP+CTC_{BL} (< or ≥5 CTC)	0·684	0·016 (0 to 0·029)	38·4 (21·9 to 60·3)	<0·0001
Model 1: CP	0·668	CP+CTC_{BL} (splines)	0·673	0·005 (–0·001 to 0·010)	18·7 (9·1 to 35·4)	<0·0001
Overall survival (N=1501 patients)						
Model 1: CP	0·714	CP+CTC_{BL} (< or ≥5 CTC)	0·745	0·031 (0·013 to 0·047)	64·9 (41·3 to 93·4)	<0·0001
Model 1: CP	0·714	CP+CTC_{BL} (splines)	0·721	0·007 (0·001 to 0·014)	21·2 (10·2 to 37·3)	<0·0001
Progression-free survival, CTC count at weeks 3–5 (N=436 patients)						
Model 1: CP+CTC_{BL}	0·652	CP+CTC_{BL}+CTC_{3-5} (< or ≥5 CTC)	0·659	0·008 (–0·009 to 0·021)	8·2 (0·78 to 20·4)	0·004
Model 1: CP+CTC_{BL}	0·652	CP+CTC_{BL}+CTC_{3-5} (splines)	0·655	0·004 (–0·009 to 0·017)	7·4 (2·3 to 16·7)	0·02
Overall survival, CTC count at weeks 3–5 (N=568 patients)						
Model 1: CP+CTC_{BL}	0·720	CP+CTC_{BL}+CTC_{3-5} (< or ≥5 CTC)	0·732	0·011 (–0·008 to 0·027)	11·5 (2·6 to 25·1)	0·0007
Model 1: CP+CTC_{BL}	0·721	CP+CTC_{BL}+CTC_{3-5} (splines)	0·725	0·004 (–0·01 to 0·018)	8·2 (3·4 to 23·7)	0·02
Progression-free survival, CTC count at weeks 6–8 (N=279 patients)						
Model 1: CP+CTC_{BL}	0·602	CP+CTC_{BL}+CTC_{6-8} (< or ≥5 CTC)	0·628	0·026 (0 to 0·053)	15·3 (5·2 to 28·3)	<0·0001
Model 1: CP+CTC_{BL}	0·601	CP+CTC_{BL}+CTC_{6-8} (splines)	0·613	0·012 (–0·01 to 0·036)	10·2 (3·7 to 18·6)	0·006
Overall survival, CTC count at weeks 6–8 (N=380 patients)						
Model 1: CP+CTC_{BL}	0·671	CP+CTC_{BL}+CTC_{6-8} (< or ≥ 5 CTC)	0·686	0·016 (–0·015 to 0·041)	14·6 (4·0 to 30·6)	0·0001
Model 1: CP+CTC_{BL}	0·670	CP+CTC_{BL}+CTC_{6-8} (splines)	0·680	0·010 (–0·028 to 0·051)	10·6 (3·4 to 22·1)	0·005
Progression-free Survival, CTC count available both at weeks 3–5 and 6–8 (N=184 patients)						
Model 1: CP+CTC_{BL}	0·560	CP+CTC_{BL}+CTC_{3-5}(< or ≥5 CTC)	0·579	0·019 (–0·018 to 0·055)	5·5 (0·66 to 12·7)	0·02
Model 1: CP+CTC_{BL}	0·562	CP+CTC_{BL}+CTC_{6-8} (< or ≥5 CTC)	0·590	0·029 (–0·019 to 0·065)	9·2 (2·1 to 18·1)	0·002
Overall survival, CTC count available both at weeks 3–5 and 6–8 (N=216 patients)						
Model 1: CP+CTC_{BL}	0·617	CP+CTC_{BL}+CTC_{3-5} (< or ≥5 CTC)	0·634	0·017 (–0·027 to 0·057)	7·2 (0·0 to 30·6)	0·007
Model 1: CP+CTC_{BL}	0·613	CP+CTC_{BL}+CTC_{6-8} (< or ≥5 CTC)	0·633	0·021 (–0·046 to 0·067)	10·1 (2·2 to 20·9)	0·001

CTC=circulating tumour cells. CP=baseline clinicopathological model (appendix pp 3–5). CTC_{BL}=CTC count at baseline. CTC_{3-5}=CTC count at 3–5 weeks. CTC_{6-8}=CTC count at 6–8 weeks.

Table 2: **Assessment of added prognostic information of CTC at baseline and during treatment, by model 1**

3) Gene modules and response to neoadjuvant chemotherapy in breast cancer subtypes: a pooled analysis (JCO 2012)

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial

José Baselga, Ian Bradbury, Holger Eidtmann, Serena Di Cosimo, Evandro de A Veerle Van Dooren, Gursel Aktan, Aron Goldhirsch, Tsai-Wang Chang, Zsolt H Georg Kunz, Joo Hyuk Sohn, Vladimir Semiglazov, Guillermo Lerzo, Marketa P Richard D Gelber, Martine Piccart-Gebhart, on behalf of the NeoALTTO Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 26, 2012 VOL. 366 NO. 4

Neoadjuvant Chemotherapy and Bevacizumab for HER2-Negative Breast Cancer

Gunter von Minckwitz, M.D., Holger Eidtmann, M.D., Mahdi Rezai, M.D., Peter A. Fasching, M.D., Hans Tesch, M.D., Holm Eggemann, M.D., Iris Schrader, M.D., Kornelia Kittel, M.D., Claus Hanusch, M.D., Rolf Kreienberg, M.D., Christine Solbach, M.D., Bernd Gerber, M.D., Christian Jackisch, M.D., Georg Kunz, M.D., Jens-Uwe Blohmer, M.D., Jens Huober, M.D., Maik Hauschild, M.D., Tanja Fehm, M.D., Berit Maria Müller, M.D., Carsten Denkert, M.D., Sibylle Loibl, M.D., Valentina Nekljudova, Ph.D., and Michael Untch, M.D., for the German Breast Group and the Arbeitsgemeinschaft Gynäkologische Onkologie–Breast Study Groups

Prognostic Signatures

Chromosomal Instability

Microenvironment

Oncogenic Pathways

GGI
Gene70
CIN70
Stroma1
Stroma2
Immune1
Immune2
RAS
MAPK
PTEN
AKTmTOR
PIK3CA
IGF1
SRC
MYC
E2F3
BetaCatenin

Gene Modules

$$\text{Module Score}(s) = \frac{\sum_{i \in n} w_i x_i}{\sum_{i \in n} |w_i|}$$

2.5% and 97.5% quantiles of Gene Modules scaled to [-1,1] within a study

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PLoS MEDICINE

Guidelines and Guidance

Key Issues in Conducting a Meta-Analysis of Gene Expression Microarray Datasets

Adaikalavan Ramasamy*, Adrian Mondry, Chris C. Holmes, Douglas G. Altman

Microarray technology measures the mRNA levels of tens of thousands of genes in tissue samples simultaneously in a high-throughput and cost-effective manner. Since its introduction over a decade ago [1], it has found widespread use in the fields of molecular genetics and functional genomics. It has been applied in order to understand underlying biological mechanisms [2], to discover novel subgroups of diseases [3–5], to examine drug response [6,7], to classify patients into disease groups [3], and to predict disease outcomes [8–10]. Some molecular signatures discovered with microarray technology are now being evaluated in prospective randomized clinical trials [11,12].

Despite their great prom
report findings that are no
to the mildest of data pertu
include improper analysis
false positives, and inadequ
The situation is exacerbate
to large numbers of potent
thousands of probes are in
of biological samples.

Generalizability across st
assessed before considerin
For example, the findings
from a particular geograph

Summary Points

- Improvements in microarray technology and its increasing use have led to the generation of many highly complex datasets that often try to address similar biological questions.
- Meta-analysis, a statistical approach that combines results from independent but related studies, is a relatively inexpensive option that has the potential to increase both the statistical power and generalizability of single-study analysis.
- Meta-analysis of microarray datasets, and genomic data in general, is desirable, and is much enhanced when raw data are available.

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PLoS MEDICINE

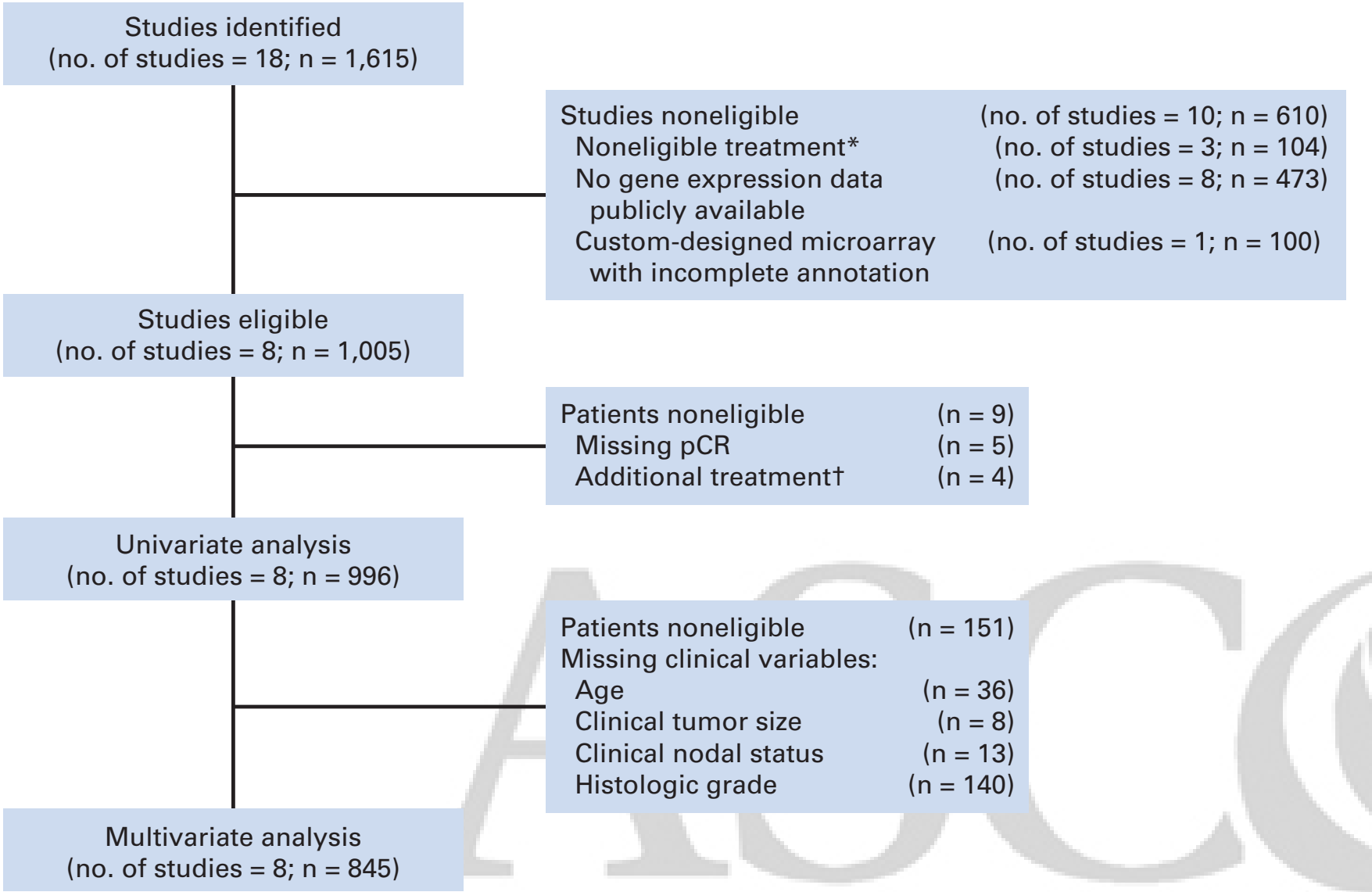
Guidelines and Guidance

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): Explanation and Elaboration

Douglas G. Altman[1]*, Lisa M. McShane[2], Willi Sauerbrei[3], Sheila E. Taube[4]

1 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom, **2** US National Cancer Institute, Bethesda, Maryland, United States of America, **3** Institut fuer Medizinische Biometrie und Medizinische Informatik, Universitaetsklinikum Freiburg, Freiburg, Germany, **4** ST-Consulting, Bethesda, Maryland, United States of America

Flow Chart


Studies identified
(no. of studies = 18; n = 1,615)
Studies noneligible (no. of studies = 10; n = 610)
Noneligible treatment* (no. of studies = 3; n = 104)
No gene expression data publicly available (no. of studies = 8; n = 473)
Custom-designed microarray with incomplete annotation (no. of studies = 1; n = 100)
Studies eligible
(no. of studies = 8; n = 1,005)
Patients noneligible (n = 9)
Missing pCR (n = 5)
Additional treatment† (n = 4)
Univariate analysis
(no. of studies = 8; n = 996)
Patients noneligible (n = 151)
Missing clinical variables:
Age (n = 36)
Clinical tumor size (n = 8)
Clinical nodal status (n = 13)
Histologic grade (n = 140)
Multivariate analysis
(no. of studies = 8; n = 845)

Included studies (all Affymetrix)

Characteristic	All Trials (N = 996)	EORTC 10994 A (n = 102)	EORTC 10994 AT (n = 58)	I-SPY-1 AT (n = 79)	LBJ/INEN/ GEICAM AT (n = 57)	MDACC Trial A (n = 87)	MDACC Trial AT (n = 91)	TOP A (n = 114)	MAQCII/ MDACC AT (n = 265)	MAQCIII A (n = 82)	USO-02103 AT (n = 61)
Age, years											
≤ 50	528	38	30	51	30	52	48	69	127	48	35
> 50	432	28	28	28	27	35	43	45	138	34	26
Unknown	36	36	0	0	0	0	0	0	0	0	
cT											
T0-1	65	2	1	1	1	5	8	16	26	3	2
T2	514	63	33	32	19	37	39	79	149	44	19
T3	255	34	20	38	18	18	19	5	42	21	40
T4	154	0	0	8	19	26	25	14	48	14	0
Unknown	8	3	4	0	0	1	0	0	0	0	0
cN											
N0	336	37	21	25	16	28	31	52	73	33	20
N1	465	55	28	46	25	33	38	57	119	32	32
N2	127	7	5	6	15	22	16	3	38	10	5
N3	55	0	0	2	1	3	6	2	35	2	4
Unknown	13	3	4	0	0	1	0	0	0	5	
ER status*											
Negative	562	65	58	36	21	38	42	114	117	41	30
Positive	434	37	0	43	36	49	49	0	148	41	31
HER2 status†											
Negative	852	74	40	76	57	77	75	81	231	82	59
Positive	144	28	18	3	0	10	16	33	34	0	2
Histologic grade											
1	47	2	0	6	5	5	10	2	13	3	1
2	308	22	16	24	19	31	30	20	102	25	19
3	503	32	37	27	23	36	36	87	150	37	38
Unknown	138	46	5	22	10	15	15	5	0	17	3
pCR											
Yes	233	39	26	14	11	7	19	16	57	24	20
No	763	63	32	65	46	80	72	98	208	58	41
No. of relapses	117	0		16	17	0		23	48		13
No. of patients with follow-up	519	0		79	57	0		102	227		41
GEO		GSE6861		GSE25066	GSE25066	GSE20271		GSE16446	GSE20194 GSE25066	GSE22093	GSE23988 GSE25066
References		Bonnefoi et al[38]		Hatzis et al[41]	Hatzis et al[41]	Tabchy et al[39]		Desmedt et al[37]	Shi et al[40] Hatzis et al[41]	Hatzis et al[41]	Hatzis et al[41] Iwamoto et al[42]

Power calculation?

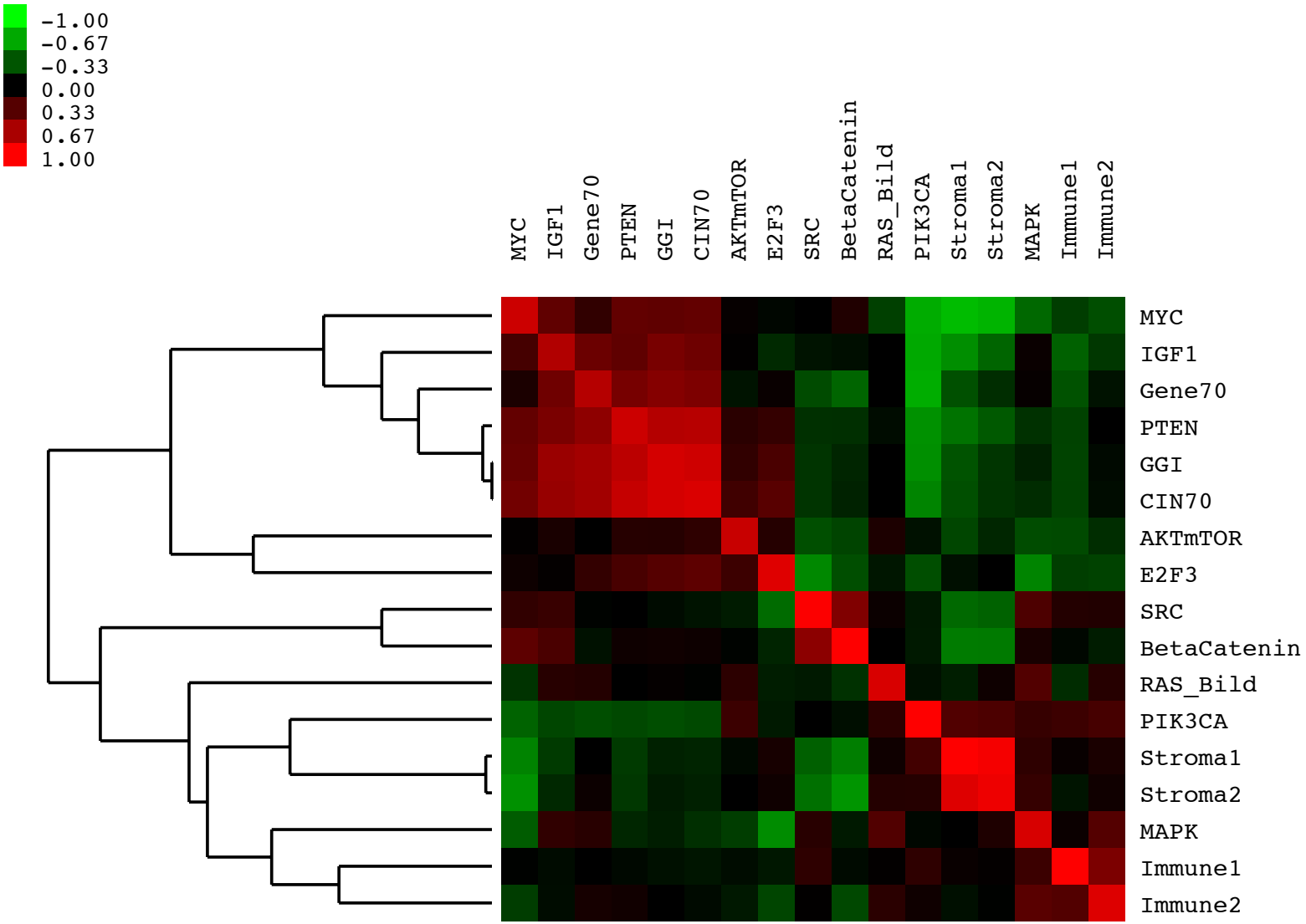
- Scaled gene modules follow a normal distribution N(0,s=0.5).
- A 1-unit increase in scaled module scores would correspond to 2s.
- Overall pCR: 24%, ER-/HER2-: 25%, HER2: 36%, ER+/HER2-: 10%.

- Power for detecting an odds ratio of 2 in pCR for a 1-unit increase in a module score at the α=0.05 with a 2-sided test, would be approximately above 99% for all pts and in the subtypes ER-/HER2-: 89% power, ER+/HER2- 54% and HER2+: 50%.
- odds ratio of 3: power above 99% for all pts and inER-/HER2-: 99%, ER+/HER2-: 91% and HER2+: 88%.

- Assume the clinicopathological model and data set effect would explain 18% of the variation in pCR. For detecting an adjusted odds ratio of 2, the power would be approximately 97% for all patients, 76% for ER-/HER2-, 40% for ER+/HER2- and 37% for HER2+.

Hsieh et al Stat Med 1998

Gene Modules Correlation



Clinicopathological model

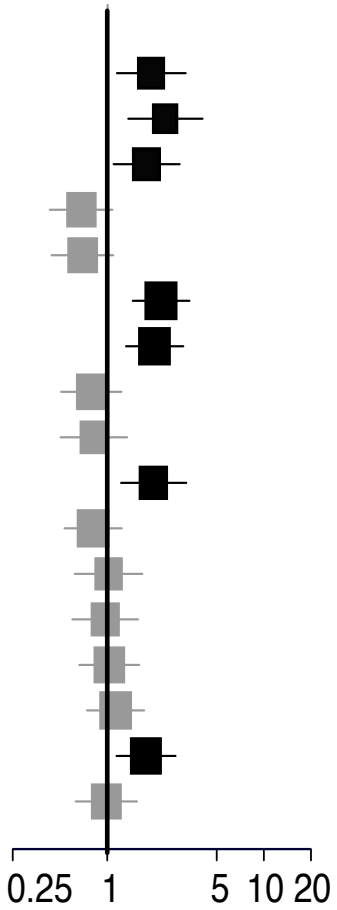
	Patients	pCR	OR	95% CI (low)	95% CI (high)	P
Age						
≤ 50	457	104	1			
> 50	388	85	0.89	0.62	1.28	5.2E-01
cT						
T0-1 & T2	514	124	1			
T3 &T4	331	65	0.59	0.40	0.87	9E-03
Cn						
N0	300	63	1			
N1 & N2 & N3	545	126	0.99	0.68	1.47	9.8E-01
Histological grade						
1 & 2	351	39	1			
3	494	150	2.48	1.60	3.92	6.6E-05
ER status						
Negative	487	159	1			
Positive	358	30	0.24	0.15	0.40	2E-08
HER2 status						
Negative	729	147	1			
Positive	116	42	2.41	1.48	3.92	4E-04
Treatment						
Anthracyclines	293	61	1			
Anthracyclines& taxanes	552	128	1.39	0.73	2.67	3.2E-01
Study						
EORTC10994	103	45	1			
I-SPY-1	57	11	0.62	0.25	1.51	3E-01
LBJ/IN/GEI	47	7	0.59	0.20	1.61	3.2E-01
MAQCIII	60	18	1.39	0.61	3.14	4.3 E-01
MAQCII/ MDACC	265	57	0.56	0.29	1.05	7E-02
MDACC trial	146	18	0.35	0.17	0.68	2E-03
TOP	109	15	0.16	0.07	0.35	4.7E-06
USO-02103	58	18	1.18	0.51	2.74	7E-01

All patients, multivariate

A

ALL
(845 pts, 189 pCR)

	OR	95% CI	P	FDR
GGI	1.7	(1.12,2.6)	1.3E−02	3.7E−02
Gene70	2.02	(1.29,3.2)	2.4E−03	1.3E−02
CIN70	1.61	(1.08,2.42)	2.1E−02	5.1E−02
Stroma1	0.73	(0.49,1.06)	1.0E−01	2.1E−01
Stroma2	0.74	(0.5,1.07)	1.1E−01	2.1E−01
Immune1	1.92	(1.36,2.73)	2.2E−04	3.7E−03
Immune2	1.78	(1.25,2.53)	1.3E−03	1.1E−02
RAS	0.82	(0.57,1.18)	3.0E−01	4.9E−01
MAPK	0.85	(0.56,1.27)	4.2E−01	6.0E−01
PTEN	1.75	(1.18,2.62)	5.8E−03	2.5E−02
AKTmTOR	0.84	(0.59,1.19)	3.2E−01	4.9E−01
PIK3CA	1.01	(0.67,1.53)	9.5E−01	9.5E−01
IGF1	0.97	(0.65,1.45)	8.9E−01	9.5E−01
SRC	1.02	(0.71,1.47)	9.1E−01	9.5E−01
MYC	1.1	(0.78,1.56)	5.8E−01	7.6E−01
E2F3	1.6	(1.12,2.3)	1.1E−02	3.7E−02
BetaCatenin	0.98	(0.68,1.43)	9.4E−01	9.5E−01



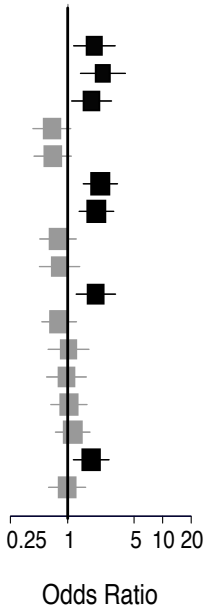
OR: odds ratio, FDR: false discovery rate

A

ALL

(845 pts, 189 pCR)

	OR	95% CI	P	FDR
GGI	1.7	(1.12,2.6)	1.3E−02	3.7E−02
Gene70	2.02	(1.29,3.2)	2.4E−03	1.3E−02
CIN70	1.61	(1.08,2.42)	2.1E−02	5.1E−02
Stroma1	0.73	(0.49,1.06)	1.0E−01	2.1E−01
Stroma2	0.74	(0.5,1.07)	1.1E−01	2.1E−01
Immune1	1.92	(1.36,2.73)	2.2E−04	3.7E−03
Immune2	1.78	(1.25,2.53)	1.3E−03	1.1E−02
RAS	0.82	(0.57,1.18)	3.0E−01	4.9E−01
MAPK	0.85	(0.56,1.27)	4.2E−01	6.0E−01
PTEN	1.75	(1.18,2.62)	5.8E−03	2.5E−02
AKTmTOR	0.84	(0.59,1.19)	3.2E−01	4.9E−01
PIK3CA	1.01	(0.67,1.53)	9.5E−01	9.5E−01
IGF1	0.97	(0.65,1.45)	8.9E−01	9.5E−01
SRC	1.02	(0.71,1.47)	9.1E−01	9.5E−01
MYC	1.1	(0.78,1.56)	5.8E−01	7.6E−01
E2F3	1.6	(1.12,2.3)	1.1E−02	3.7E−02
BetaCatenin	0.98	(0.68,1.43)	9.4E−01	9.5E−01

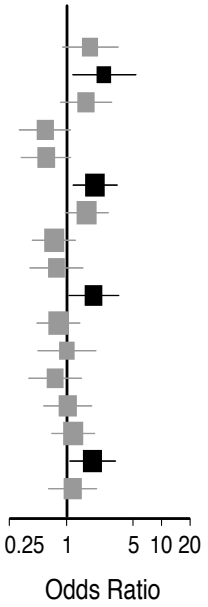


B

ER−/HER2−

(394 pts, 120 pCR)

	OR	95% CI	P	FDR
GGI	1.59	(0.91,2.81)	1.0E−01	2.2E−01
Gene70	2.11	(1.12,4.03)	2.2E−02	1.6E−01
CIN70	1.47	(0.88,2.47)	1.4E−01	2.7E−01
Stroma1	0.65	(0.38,1.08)	9.7E−02	2.2E−01
Stroma2	0.66	(0.4,1.08)	9.9E−02	2.2E−01
Immune1	1.76	(1.13,2.76)	1.3E−02	1.6E−01
Immune2	1.49	(0.96,2.31)	7.4E−02	2.2E−01
RAS	0.77	(0.5,1.19)	2.4E−01	4.1E−01
MAPK	0.81	(0.47,1.38)	4.3E−01	5.7E−01
PTEN	1.71	(1.04,2.85)	3.7E−02	1.6E−01
AKTmTOR	0.84	(0.54,1.3)	4.3E−01	5.7E−01
PIK3CA	1	(0.55,1.8)	9.9E−01	9.9E−01
IGF1	0.79	(0.46,1.34)	3.8E−01	5.7E−01
SRC	1.02	(0.62,1.65)	9.5E−01	9.9E−01
MYC	1.13	(0.73,1.75)	5.7E−01	6.9E−01
E2F3	1.67	(1.06,2.67)	2.9E−02	1.6E−01
BetaCatenin	1.12	(0.69,1.82)	6.4E−01	7.3E−01

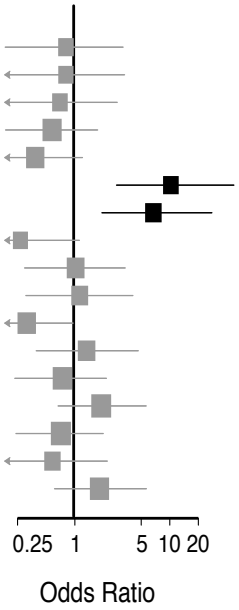


C

HER2+

(116 pts, 42 pCR)

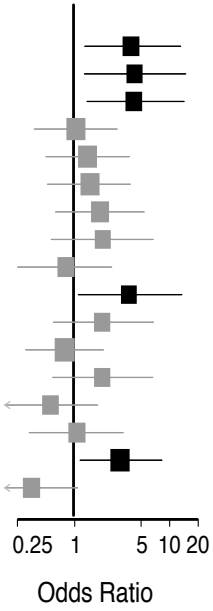
	OR	95% CI	P	FDR
GGI	0.86	(0.25,2.72)	8.0E−01	8.7E−01
Gene70	0.85	(0.24,2.8)	8.0E−01	8.7E−01
CIN70	0.76	(0.22,2.41)	6.4E−01	8.4E−01
Stroma1	0.65	(0.25,1.62)	3.5E−01	7.5E−01
Stroma2	0.46	(0.17,1.19)	1.2E−01	4.0E−01
Immune1	7.13	(2.38,25.51)	1.0E−03	1.8E−02
Immune2	5.01	(1.77,16.35)	4.1E−03	3.5E−02
RAS	0.34	(0.09,1.12)	8.7E−02	3.7E−01
MAPK	1.04	(0.37,2.84)	9.4E−01	9.4E−01
PTEN	1.13	(0.38,3.31)	8.2E−01	8.7E−01
AKTmTOR	0.39	(0.14,0.99)	5.4E−02	3.1E−01
PIK3CA	1.3	(0.47,3.69)	6.2E−01	8.4E−01
IGF1	0.79	(0.3,1.94)	6.2E−01	8.4E−01
SRC	1.74	(0.73,4.33)	2.2E−01	6.1E−01
MYC	0.77	(0.31,1.82)	5.6E−01	8.4E−01
E2F3	0.65	(0.21,1.97)	4.5E−01	8.4E−01
BetaCatenin	1.68	(0.68,4.35)	2.7E−01	6.5E−01



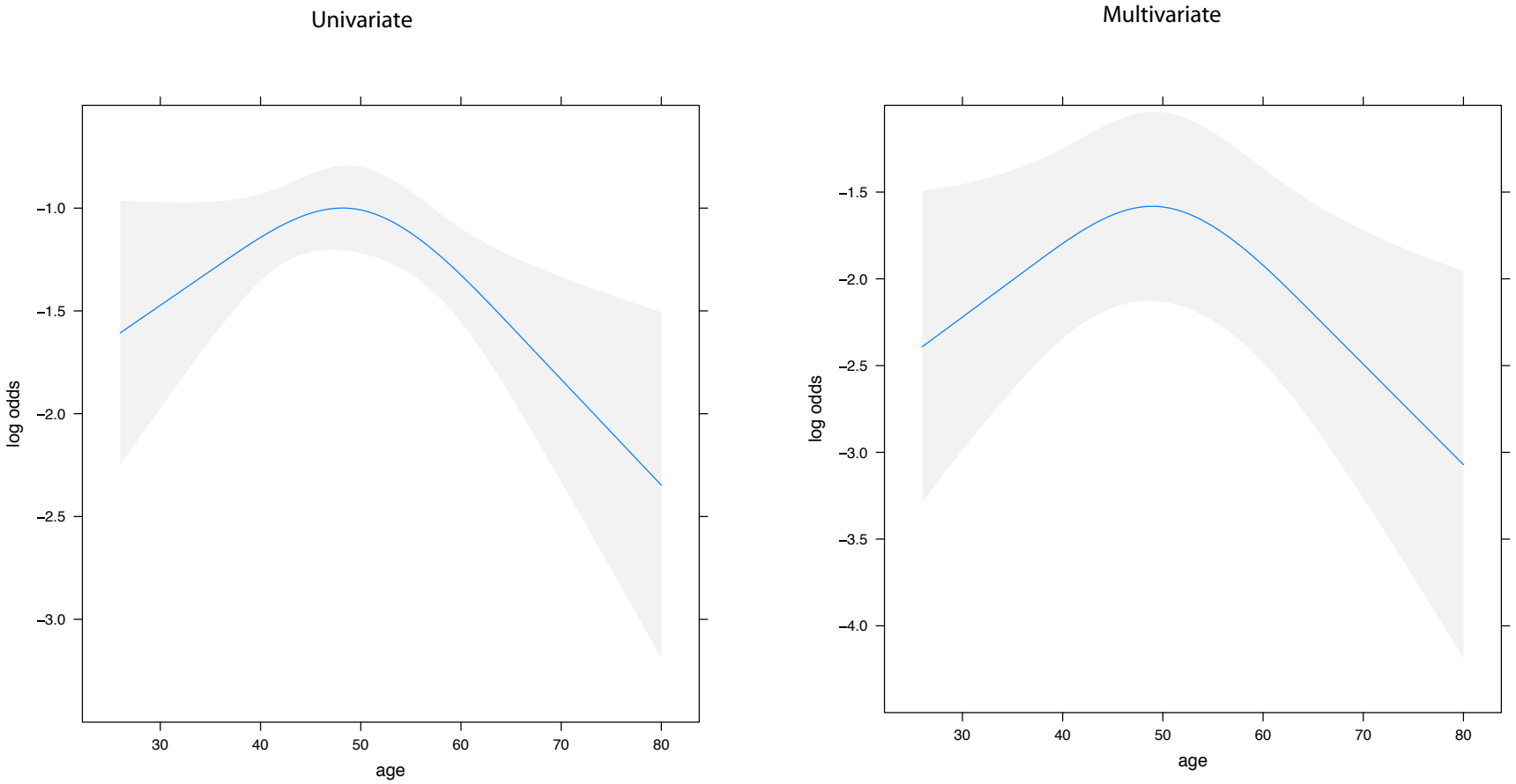
ER+/HER2−

(335 pts, 27 pCR)

	OR	95% CI	P	FDR
GGI	3.19	(1.26,8.72)	1.8E−02	1.0E−01
Gene70	3.43	(1.25,9.66)	1.8E−02	1.0E−01
CIN70	3.38	(1.31,9.35)	1.4E−02	1.0E−01
Stroma1	1.05	(0.45,2.42)	9.1E−01	9.1E−01
Stroma2	1.33	(0.57,3.1)	5.1E−01	6.7E−01
Immune1	1.4	(0.59,3.15)	4.3E−01	6.1E−01
Immune2	1.71	(0.7,4.17)	2.4E−01	4.4E−01
RAS	1.81	(0.64,5)	2.6E−01	4.4E−01
MAPK	0.86	(0.32,2.16)	7.5E−01	8.5E−01
PTEN	3.06	(1.1,8.94)	3.5E−02	1.2E−01
AKTmTOR	1.78	(0.66,5.02)	2.6E−01	4.4E−01
PIK3CA	0.84	(0.38,1.83)	6.6E−01	8.0E−01
IGF1	1.78	(0.65,4.96)	2.6E−01	4.4E−01
SRC	0.63	(0.23,1.63)	3.5E−01	5.4E−01
MYC	1.07	(0.41,2.73)	8.9E−01	9.1E−01
E2F3	2.56	(1.14,5.97)	2.5E−02	1.1E−01
BetaCatenin	0.43	(0.17,1.09)	7.5E−02	2.1E−01

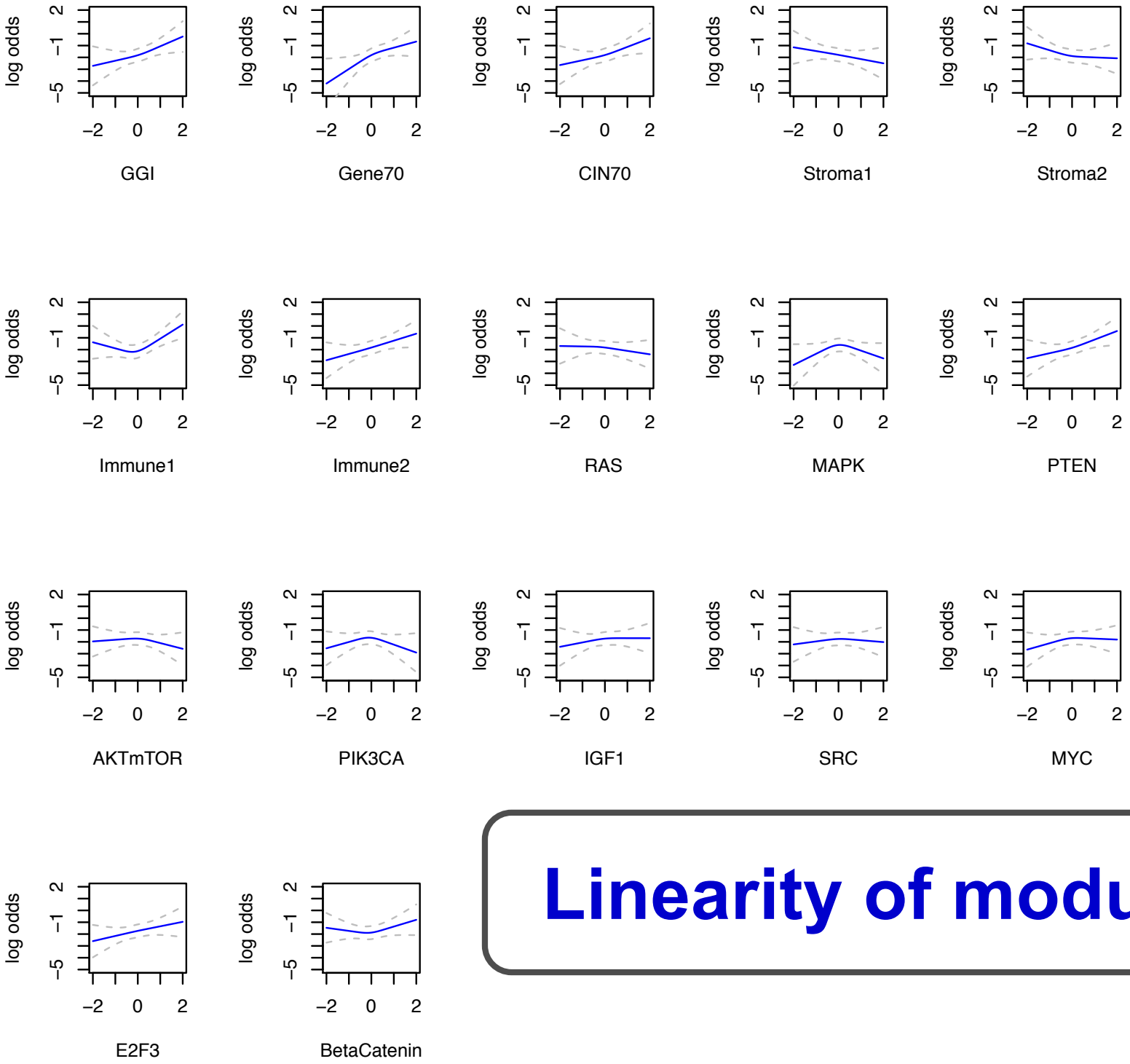


Effect of age (restricted cubic splines)



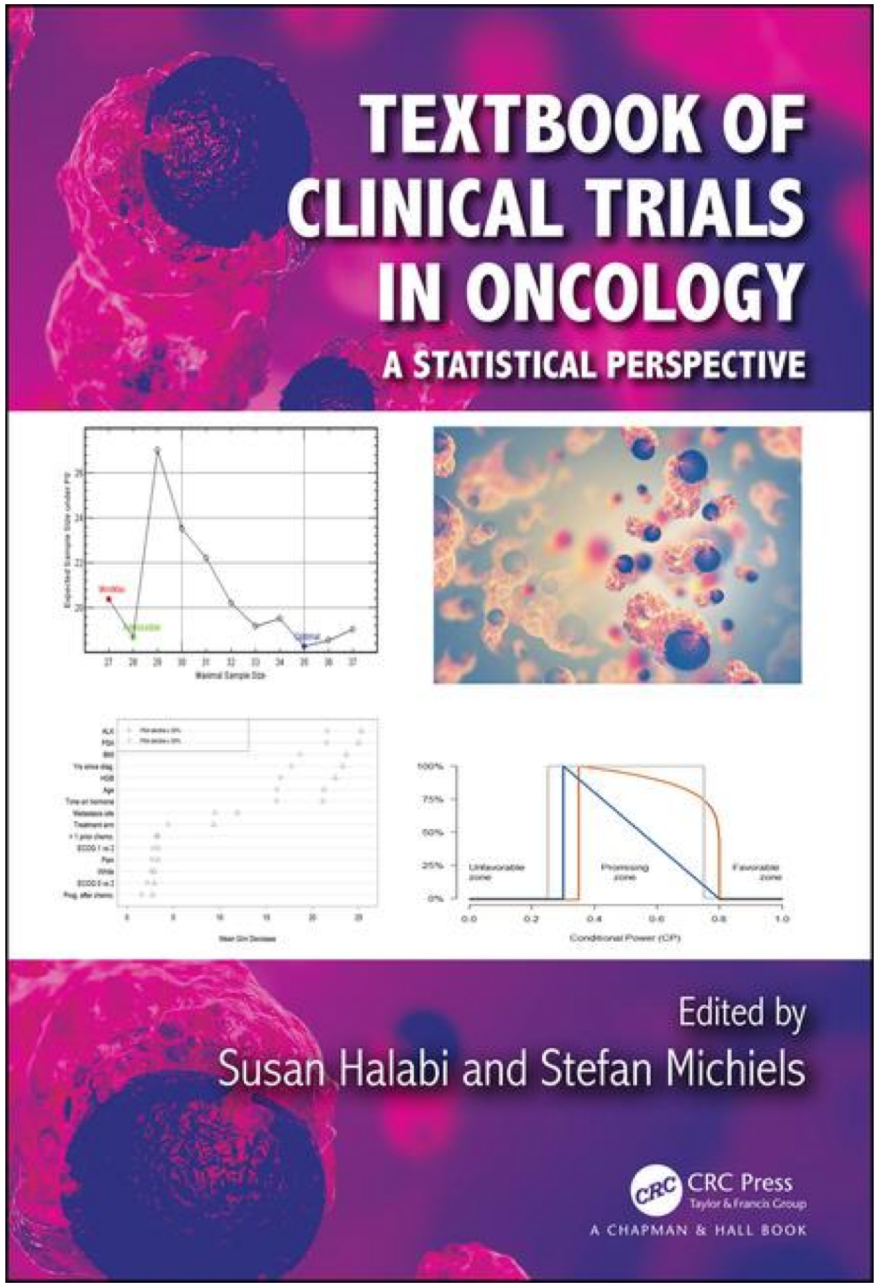
A test for association (likelihood ratio test, 2 df) between the gene module and pCR and a test for non-linearity (1 df) were applied.

Harrell, Regression modelling strategies, Springer, 2011



Linearity of modules?

Thank you for your attention!



https://www.crcpress.com/9781138083776

Published May 2019

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