High-dimensional biomarkers as treatment modifiers in randomized clinical trials

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Disclosure

I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.

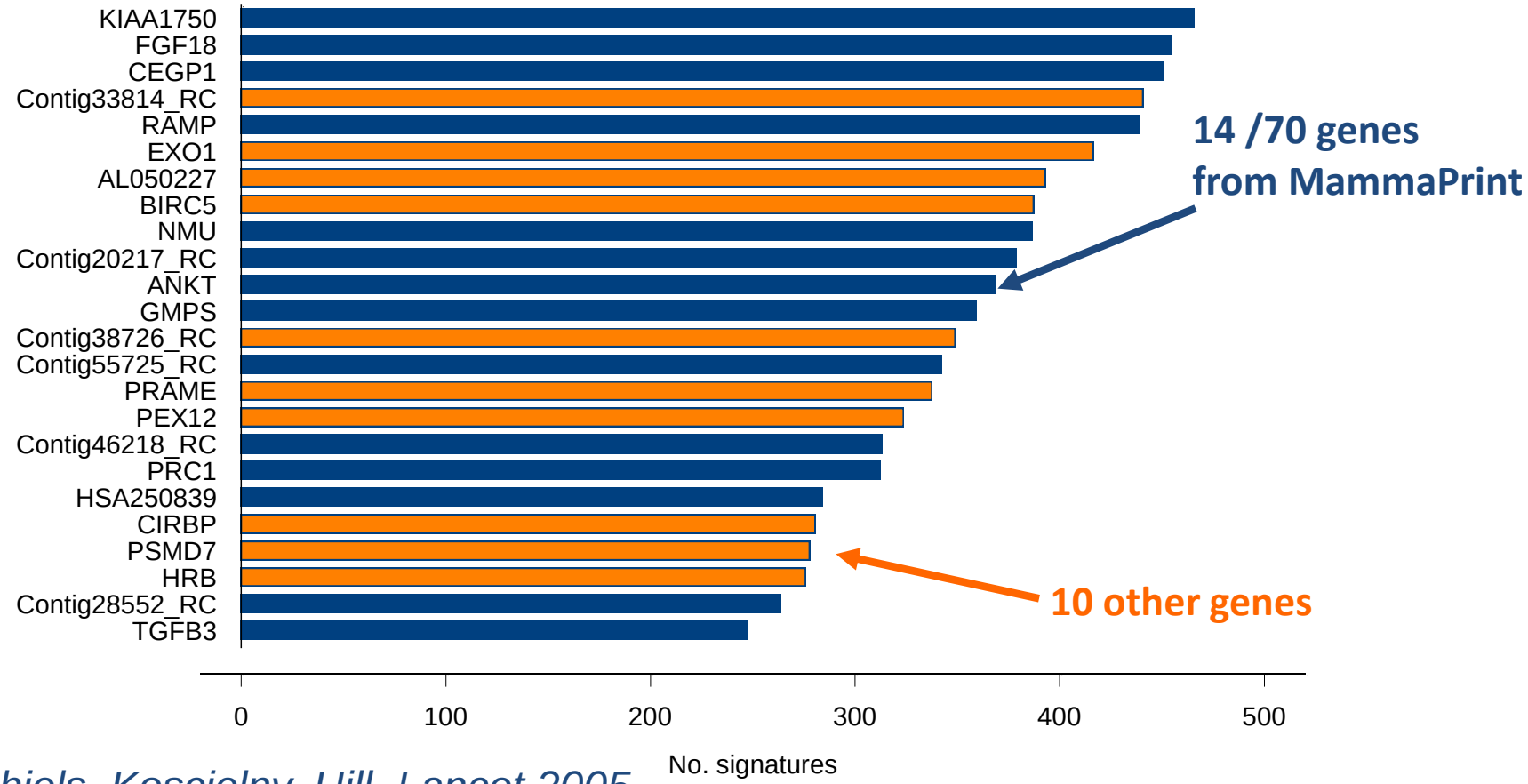
Lessons from early breast cancer: prognostic signatures

Available gene signatures for a price of 400-4175$…

- IHC4: 4 genes
- Oncotype Dx: 16 cancer genes
- PAM50 (ROR): 50 genes
- Mammaprint Dx: 70 genes
- Endopredict: 8 cancer genes
- Mapquant Dx (GGI) : 97 genes
- …

Instability of gene selection in original Mammaprint training data

Genes included in at least 250 out of 500 (50%) signatures for a training set size of 78 patients



Michiels, Koscielny, Hill. Lancet 2005

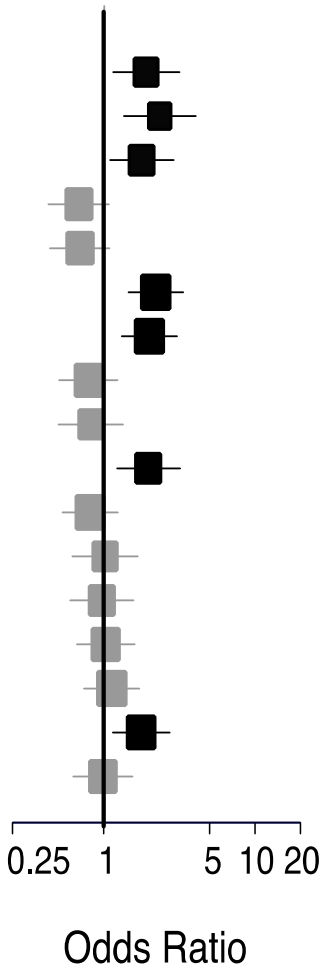
Association of gene modules with pathological complete response after anthracyclines, beyond clinicopathological factors

OR: odds ratio for a 1-unit change in gene module, adjusted for clinicopathological factors

FDR: false discovery rate

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



Ignatiadis et al JCO 2012

Move to treatment-effect modifiers

Past:

- Development of prognostic signatures by a model

$$Outcome \sim biomarker$$

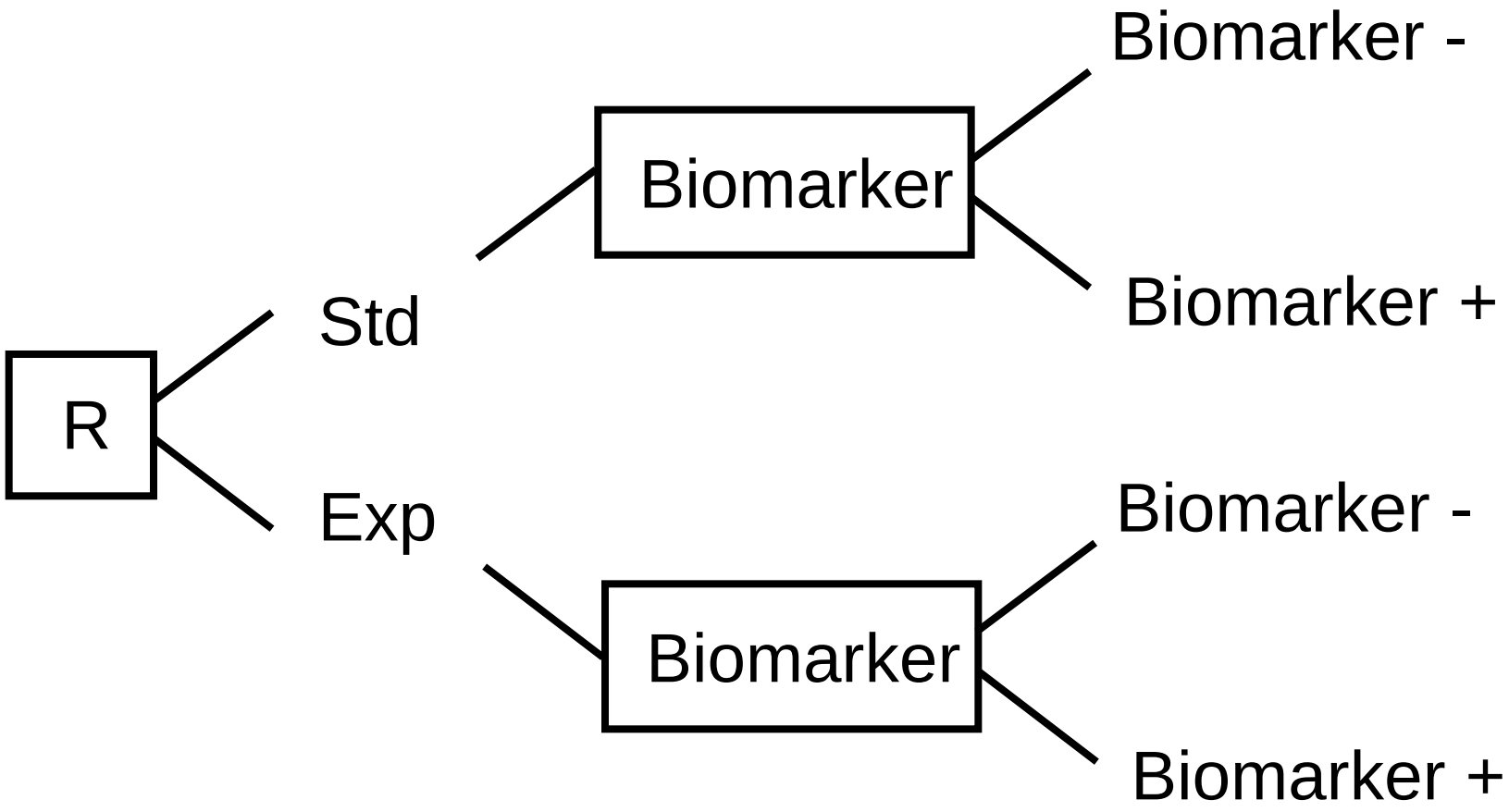
- e.g. 99% of published breast cancer signatures

Future:

- Development of “predictive” or treatment-effect modifying signatures

$$Outcome \sim biomarker + treatment + \mathbf{treatment \times biomarker}$$

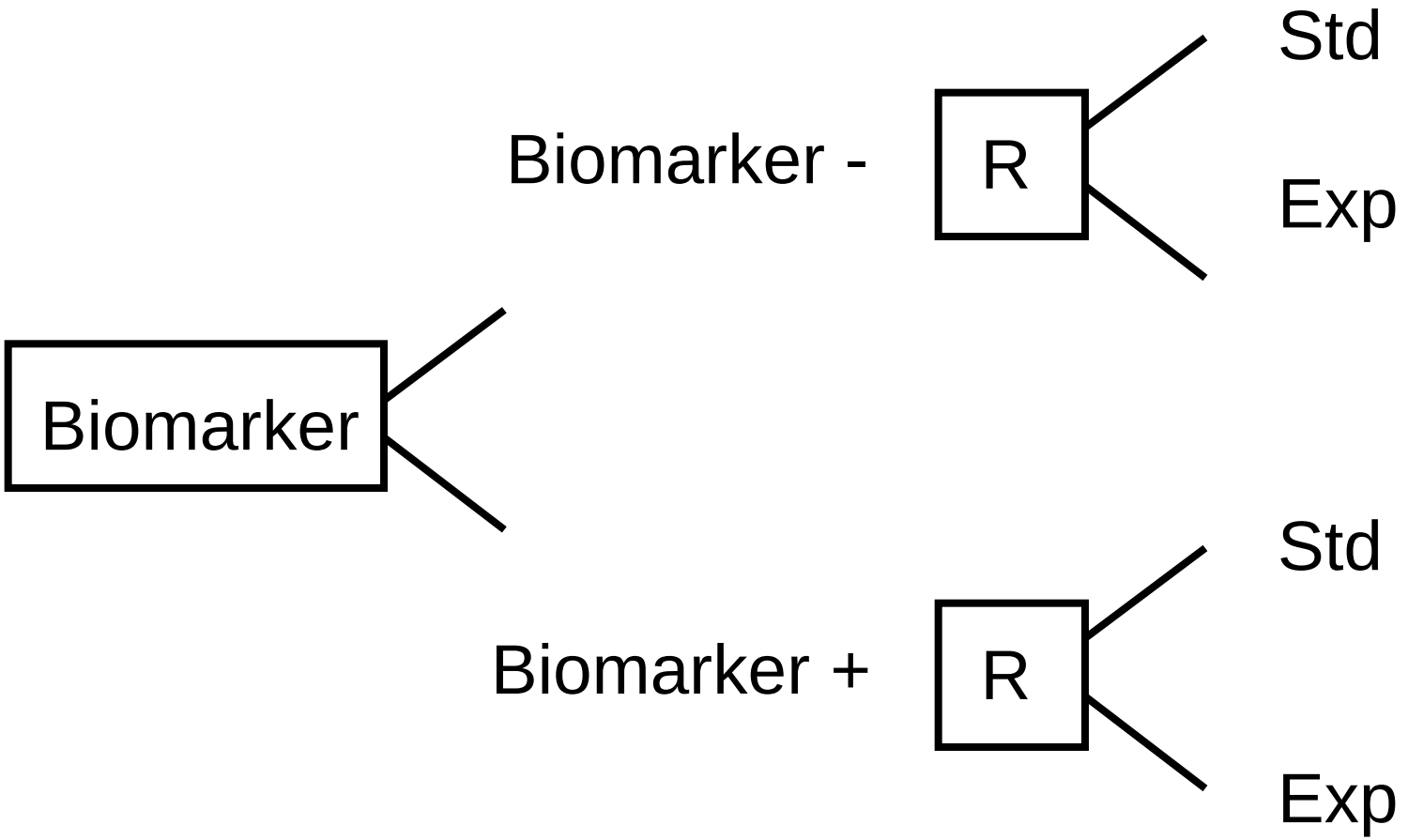
Randomize-all design



R: Randomization; Std: standard arm; Exp: experimental arm

Buyse, Michiels et al, Expert Rev Mol Diag 2011

Interaction (biomarker-stratified) randomized design

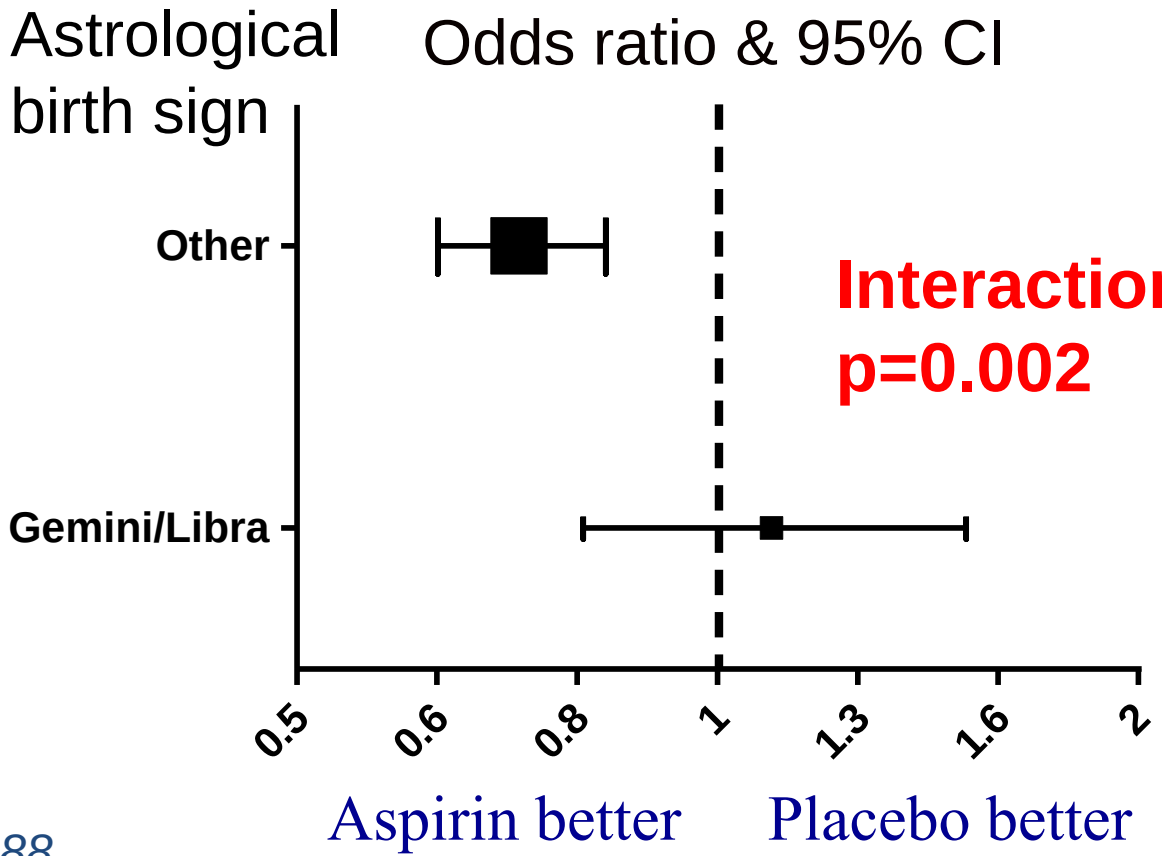


Typically large trials are needed!
AND/OR more sensitive endpoints (such as tumour measurements)

Buyse, Michiels et al, Expert Rev Mol Diag 2011

Most famous subgroup?

ISIS-2: aspirin vs control - effects on vascular death in 17,187 patients with acute myocardial infarction



Interaction p-value p=0.002

Peto et al Lancet 1988

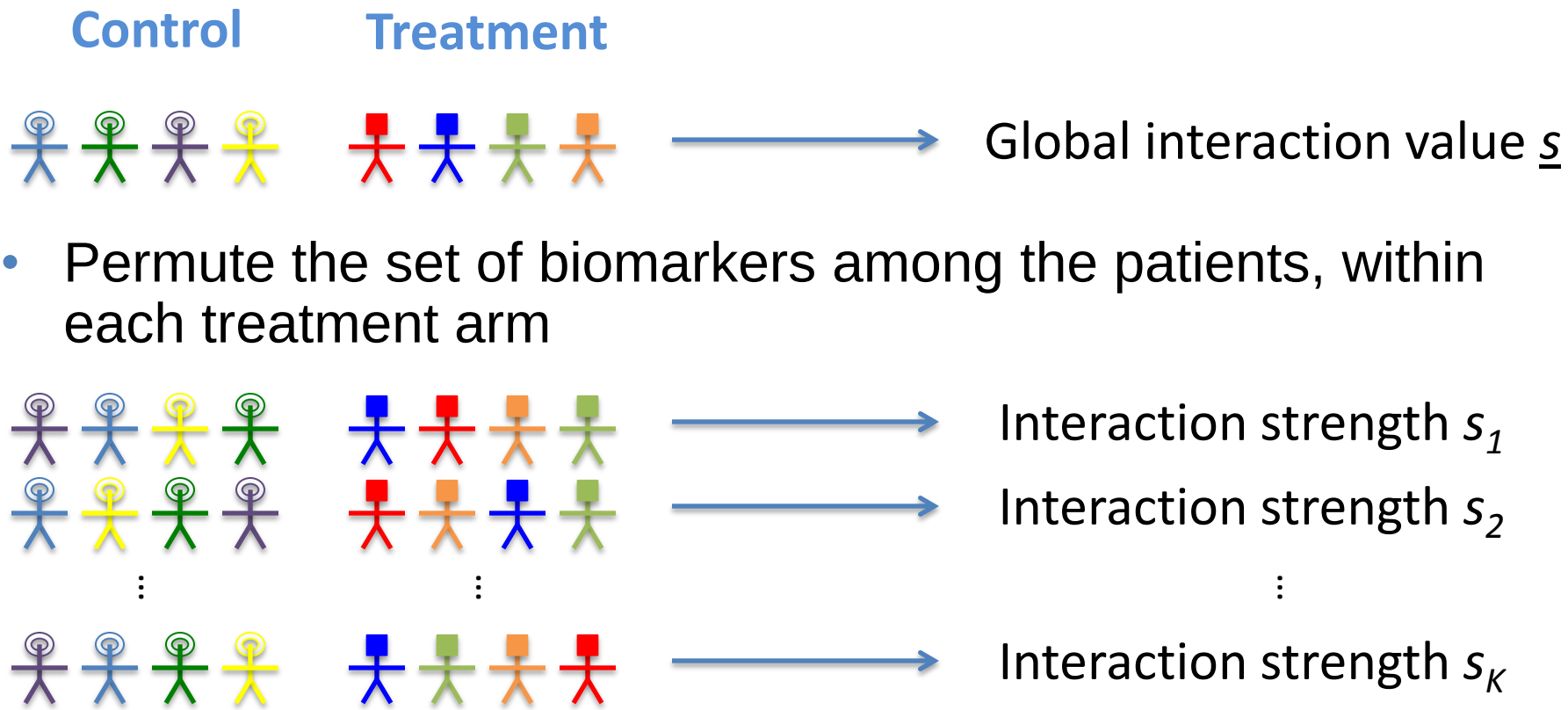
Stepwise strategy for high-dimensional data in a randomized clinical trial (RCT)

- **Step 1:** Perform a global interaction test for control of the global Type I error at a prespecified α level (e.g. 5%)

- **Step 2:** Only when global test is significant, develop classifier in a survival model with interaction effects
  - Use 10-fold crossvalidation to estimate treatment effects in composite biomarker score defined subsets (similar to Matsui CCR 2012)
  - Applying survival model on full RCT data: **indication classifier** for future patients (Simon Stat Med 2012)

Michiels, Rotolo in Matsui, Buyse, Simon 2014

Step I: Global interaction test by permutation

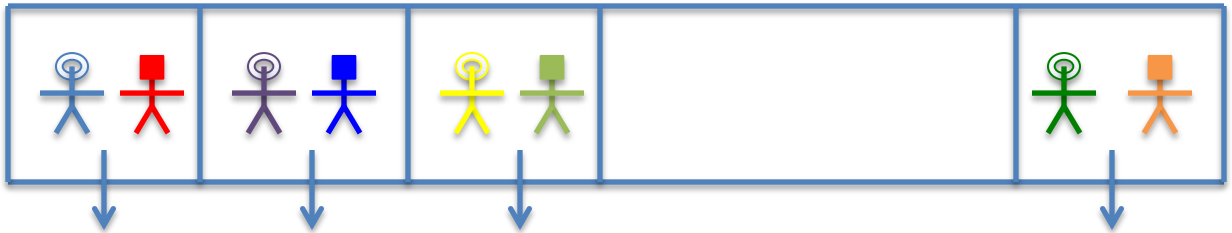


- Permute the set of biomarkers among the patients, within each treatment arm

- p-value = the proportion of *K* permutations in which the test statistic for global interaction exceeds the test statistic s for the original data

Michiels, Potthoff, George Stat Med 2011

Step II: Develop a composite biomarker classifier through 10-fold crossvalidation



Divide the RCT in 10 parts

Part 1 Part 2 Part 3 Part 10

Develop biomarker score (training set, 9/10 parts)

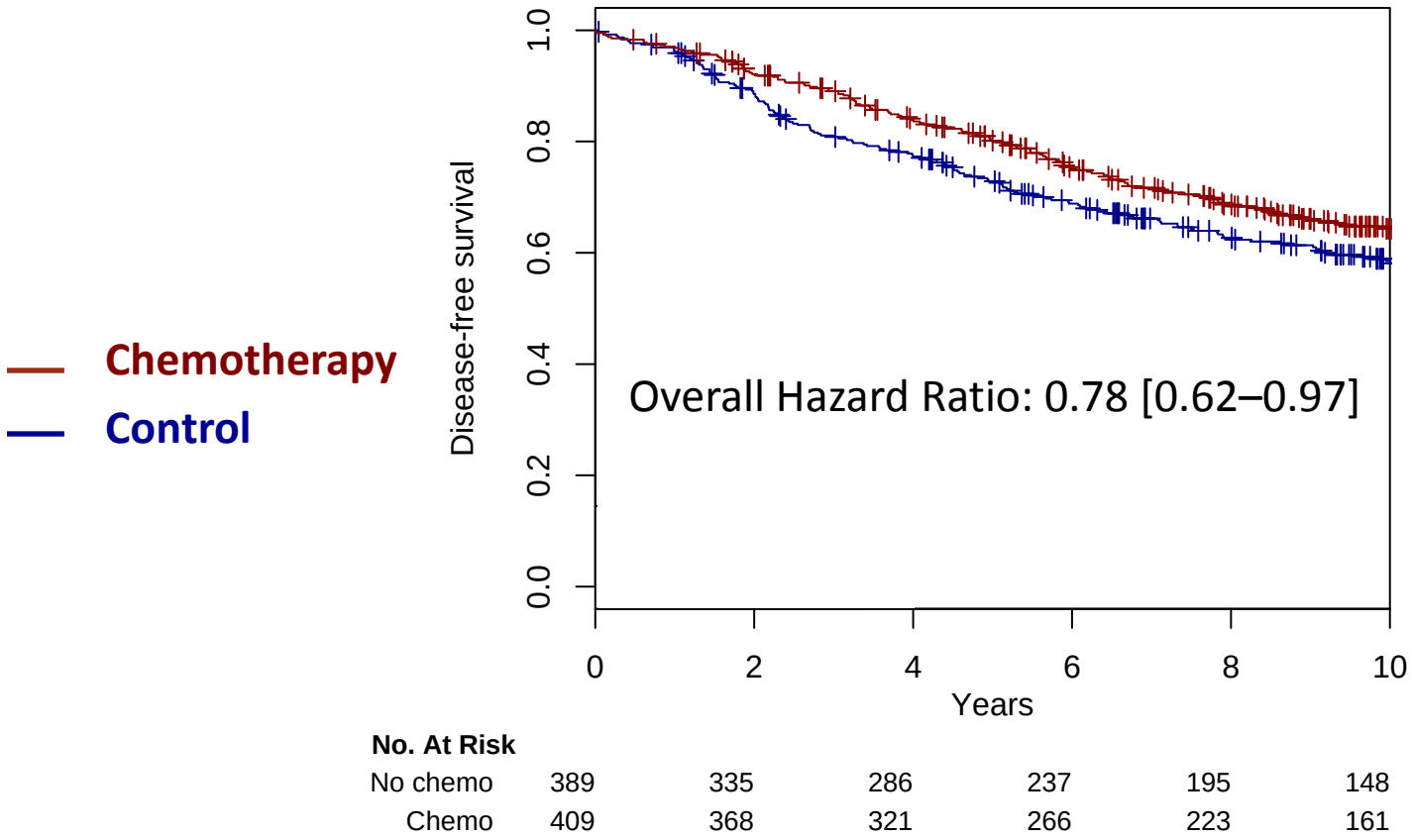
Evaluate biomarker score (validation set, 1/10 parts)

- Repeat this process 10 times
- Estimate treatment effects according to composite biomarkers scores in the 10 validation sets

Michiels, Rotolo in Matsui, Buyse, Simon 2014

French breast RCTs example

- Tissue-array from two French breast cancer RCTs of adjuvant chemotherapy with long term follow-up (798 pts)
- 11 biomarkers (ER,PR, HER2, EGFR, p53, p27…)
- Disease-free survival, 320 events

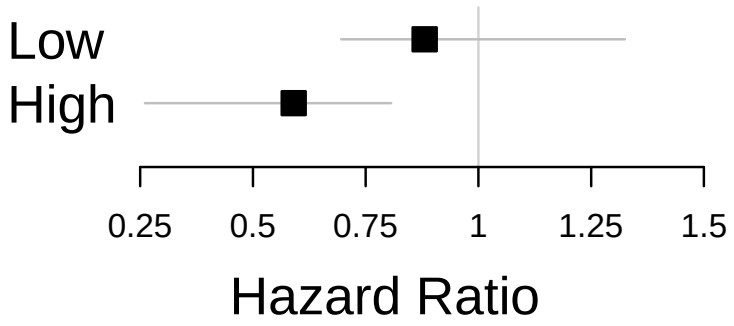


French breast RCTs example

Step I: Global test, 2000 permutations

- Three different proposed global statistics yield p-values = 0.045, 0.009 and 0.013

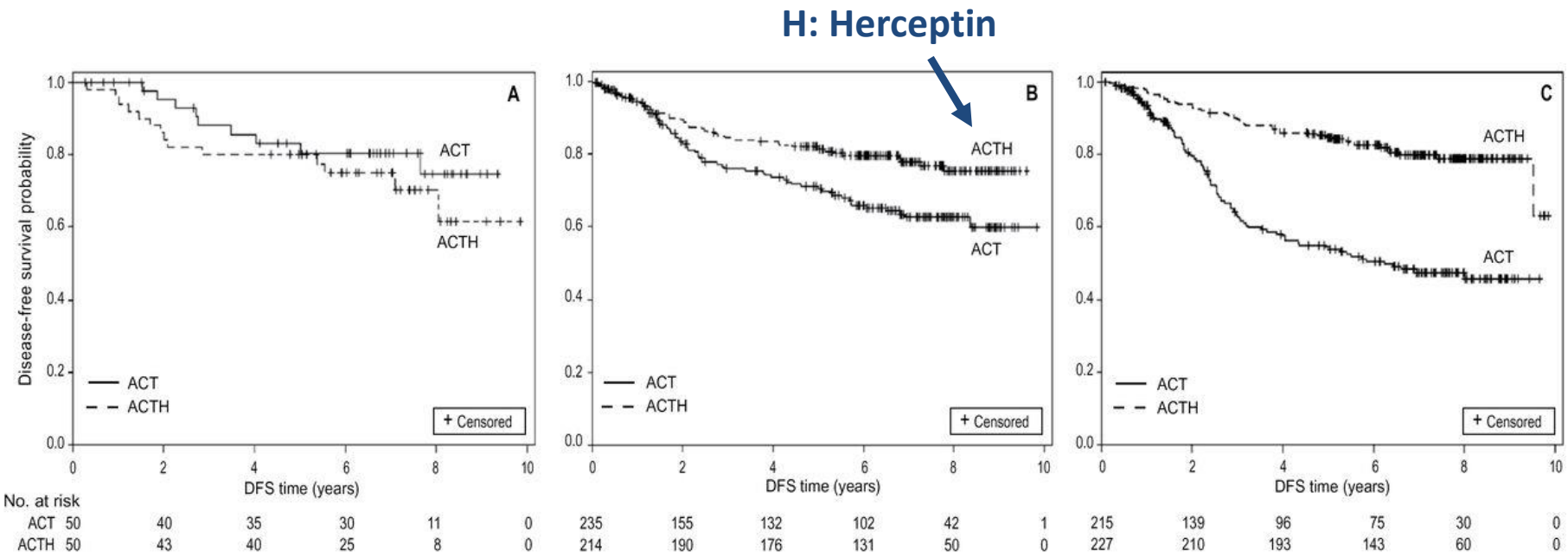
Step II: Crossvalidated treatment effects according to composite biomarker score (cut-off at 0.5)



Michiels, Rotolo in Matsui, Buyse, Simon 2014

Prediction of benefit of adjuvant trastuzumab

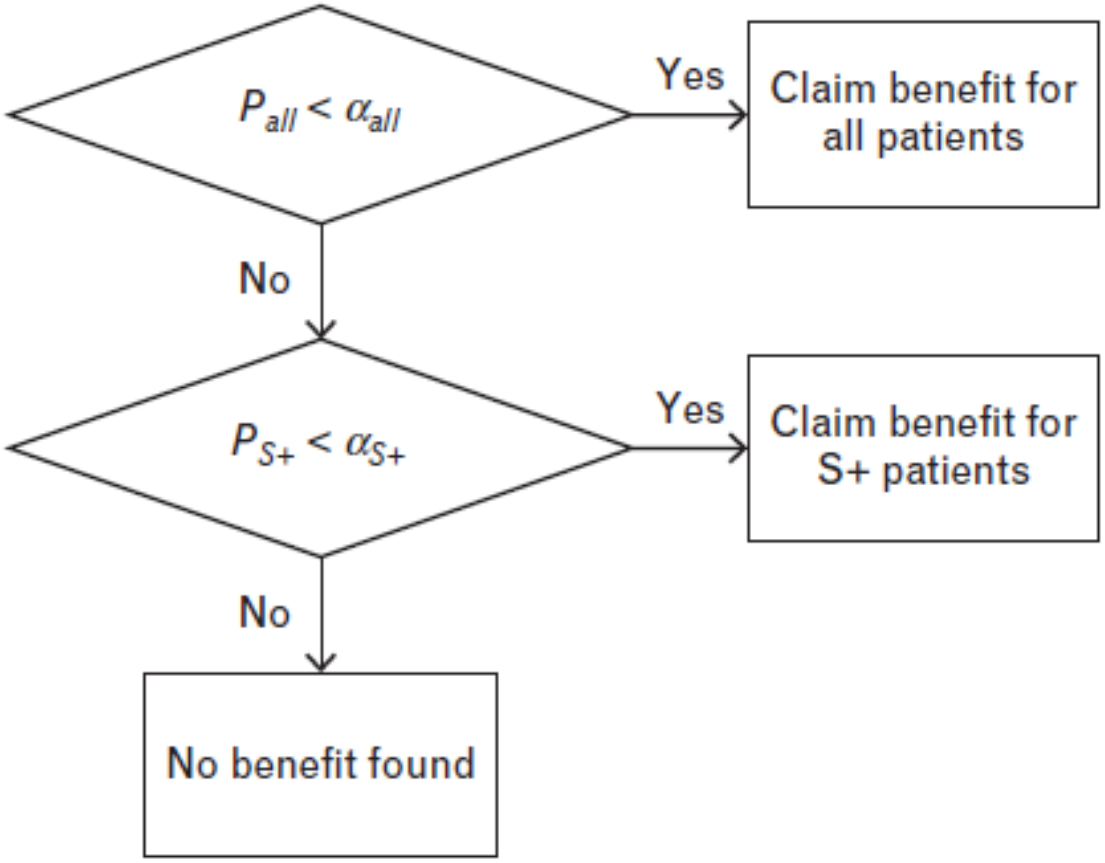
- Training-validation strategy in NSABP B31 trial, 8-gene signature
  Interaction between trastuzumab and signature: p<0.001



HR=1.58 (0.67 -3.69) **HR=0.60 (0.41-0.89)** **HR=0.28 (0.20-0.41)**

Pogue-Geile K L et al. J Natl Cancer Inst 2013

Alternative 1: Prospective subset testing



S+ : signature-positive patients; all: all patients

Buyse, Michiels, Curr Op Onc 2013

Alternative 1: Prospective subset testing

- Simplest approach: split significance level:

  $\alpha = \alpha_{all} + \alpha_{S+}$

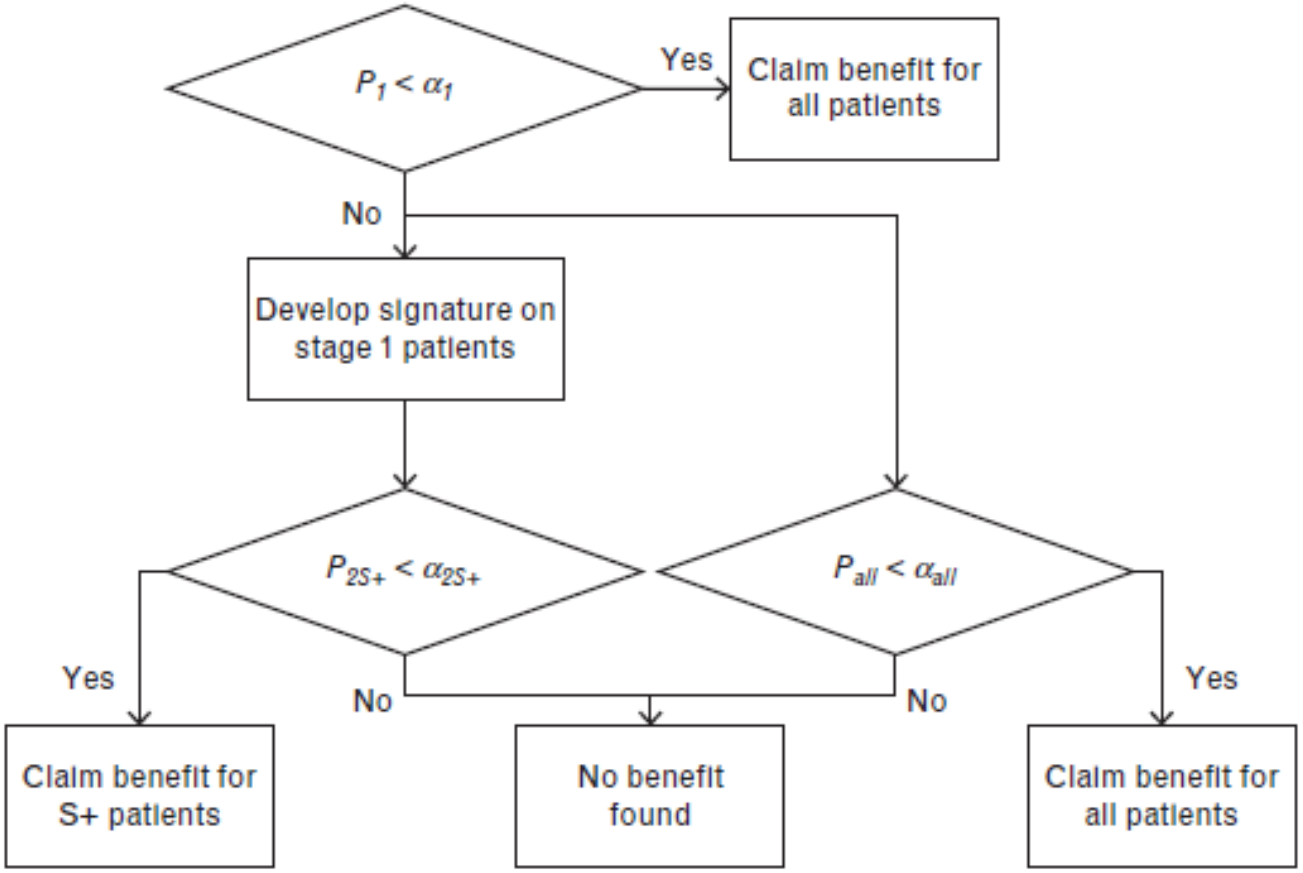
  - the new treatment is compared with the control in the overall population, ignoring the biomarker
  - if $p_{all} \leq \alpha_{all}$ claim effectiveness for all patients
  - if not, the new treatment is compared with the control in biomarker + patients only, and if $p_{S+} \leq \alpha_{S+}$, claim effectiveness for biomarker + patients only

- There are less conservative, yet properly controlled, ways of adjusting α for both (correlated) tests

Wang, Pharm Stat 2007; Jiang, JNCI 2007; Alosh, Stat Med 2009; Wang, Biom J 2009; Spiessens, Contr Clin Trials 2010

Alternative 2: Two-stage adaptive signature design

1: stage 1 patients
2S+: stage 2 signature-patients
all: all patients



- There exists a crossvalidation version (*Freidlin et al CCR 2010*)

Buyse, Michiels 2013; extension from Freidlin, Simon, CCR 2005

Pros and contras

- Prospective subset testing: needs prespecified signature
- Gene signature can be developed on a first stage of the trial but statistical power could be small
- Challenge for two-stage adaptive design: possible heterogeneity of treatment effects before and after the adaptation (changes in patient recruitment or other temporal trends)
- Crossvalidation scheme : need for independent validation trial when all data is repeatedly used to develop the signature?

Conclusion

- Move on from *prognostic* gene signatures (trying to be predictive of treatment benefit) to gene signatures **developed on RCT data as treatment modifier**
- Global interaction test at significance level a by permuting a statistic among the patients within the treatment groups
- **Continuous** gene signature development in RCT by crossvalidation approach
- Strong **challenges in controlling confounding**: handling of specimens, measurement error, tumour heterogeneity, biopsy vs primary vs metastatic specimen

Main references

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