

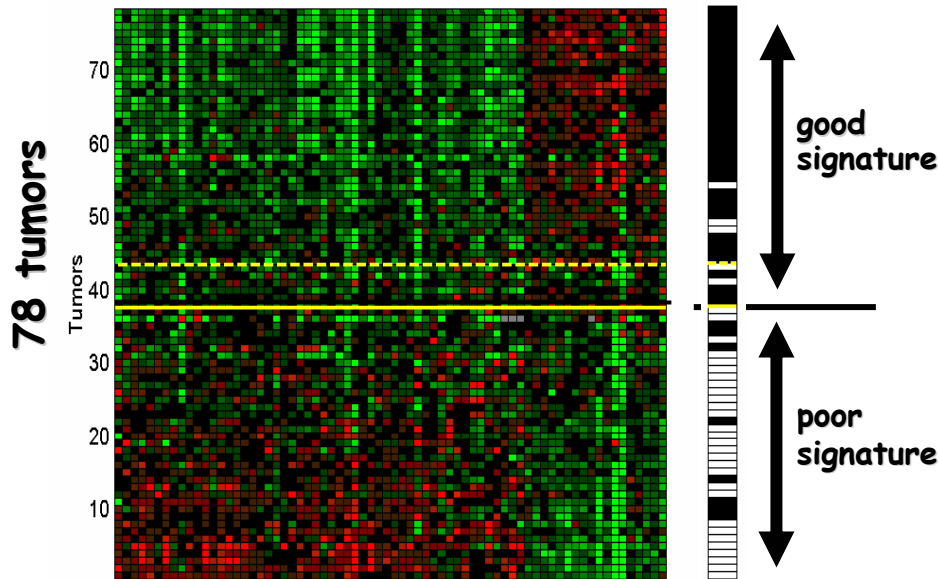


TRANSBIG multi-centre independent validation of the Rotterdam 76-gene prognostic signature for patients with node-negative breast cancer.

Christine Desmedt, Fanny Piette, Fatima Cardoso, Yixin Wang, Sherene Loi, Françoise Lallemand, Jan Klijn, Benjamin Haibe-Kains, Giuseppe Viale, Mauro Delorenzi, Yi Zhang, Mahasti Saghatchian d'Assignies, Jonas Bergh, Rosette Lidereau, Paul Ellis, Adrian Harris, John Foekens, Marc Buyse, Martine J. Piccart, Christos Sotiriou
on behalf of the TRANSBIG Consortium

Amsterdam 70-gene signature

70-gene signature



The « 70 gene prognosis signature »:

- is a powerful prognostic tool
- outperforms clinical /pathological criteria (St Gallen, NIH)
- could reduce « overtreatment »

Van't Veer et al., Nature, 2002

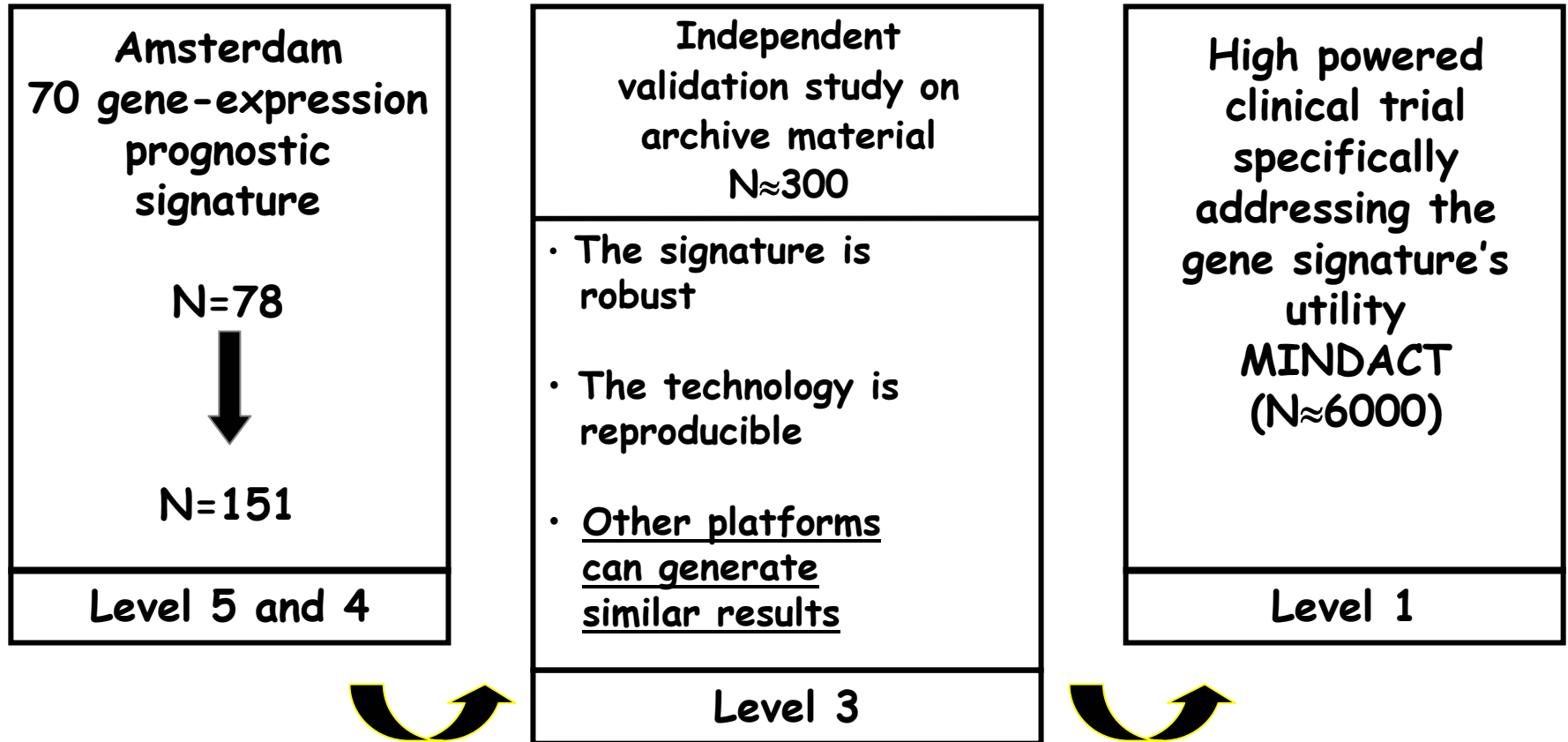
Validation series

n=151 node - patients (+ 144 node + patients)

Van de Vijver, NEJM, 2002



Background TRANSBIG

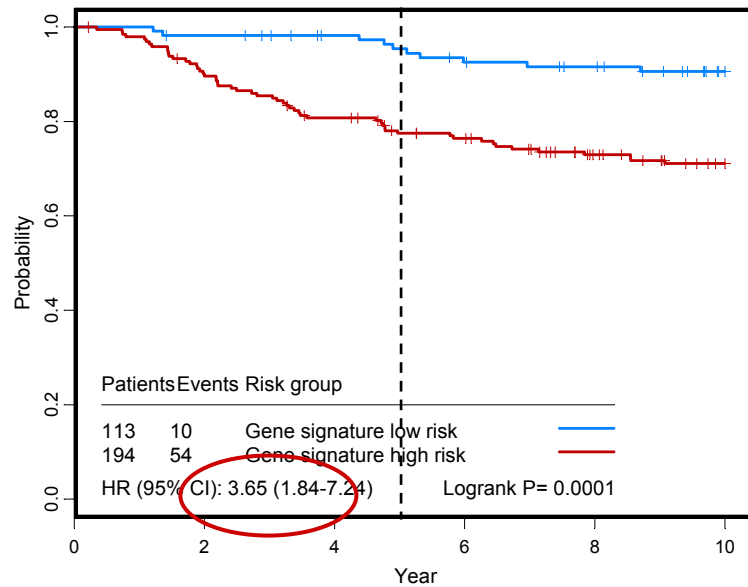


Levels of evidence for biomarkers studies

E.U. GRANT, 6th Framework Programme

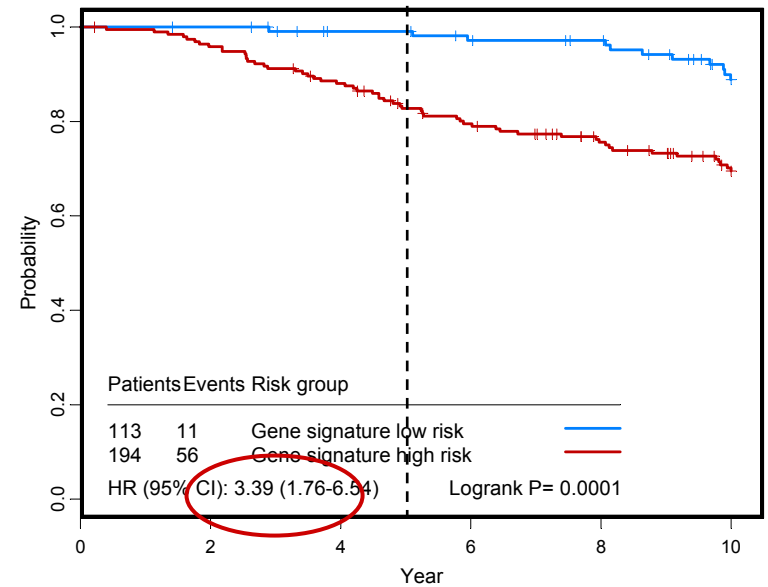
TRANSBIG Validation of the Amsterdam signature

Time to distant metastases



| | | | | | | |
|----------------|-----|-----|----------------|-----|-----|-----|
| Low clin risk | 113 | 110 | 104 | 97 | 93 | 81 |
| High clin risk | 194 | 172 | 153 | 138 | 119 | 105 |
| | | | Number at risk | | | |

Overall Survival



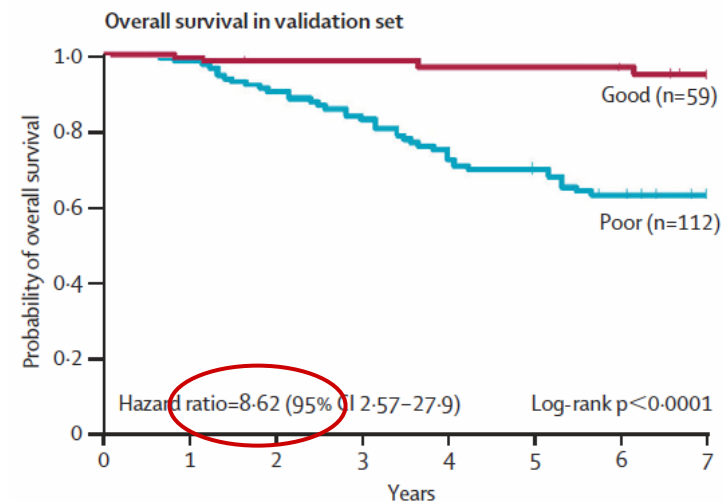
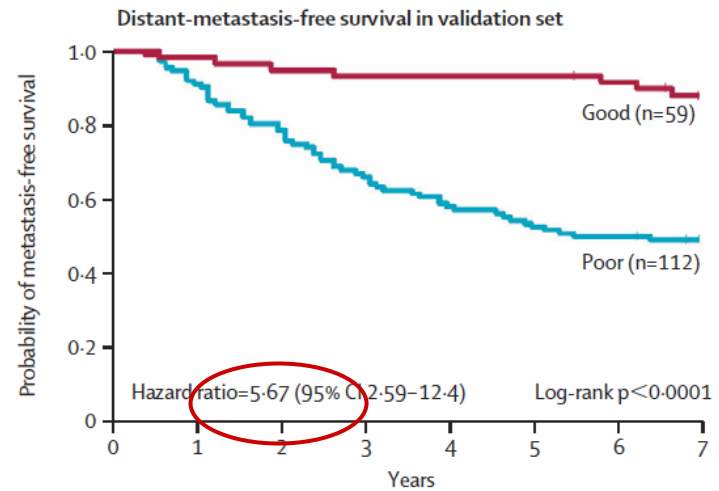
| | | | | | | |
|----------------|-----|-----|----------------|-----|-----|-----|
| Low clin risk | 113 | 112 | 105 | 101 | 98 | 82 |
| High clin risk | 194 | 185 | 168 | 147 | 130 | 110 |
| | | | Number at risk | | | |

Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer

Yixin Wang, Jan G M Klijn, Yi Zhang, Anieta M Sieuwerts, Maxime P Look, Fei Yang, Dmitri Talantov, Mieke Timmermans, Marion E Meijer-van Gelder, Jack Yu, Tim Jatkoe, Els M J J Berns, David Atkins, John A Foekens

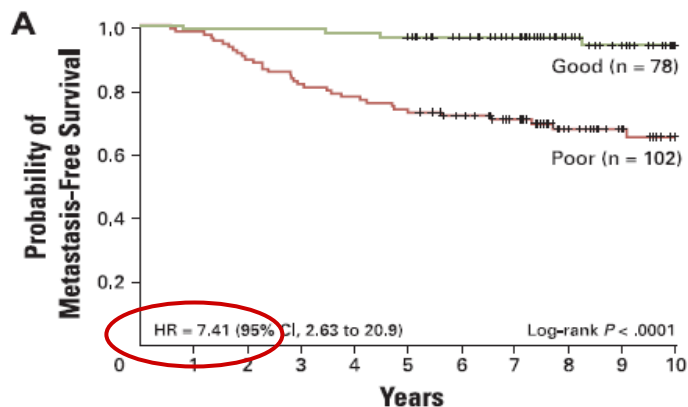
Lancet 2005

**Training set= 115 N- pts
(80 ER+/35 ER-)
Test set= 171 N- pts
(129 ER+/42 ER-)
1 center
No systemic therapy
Median FU:101 months
Clinical endpoint:TDM
Affymetrix Platform**



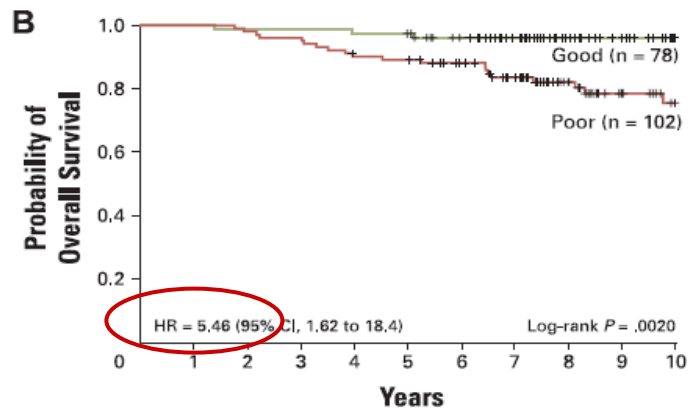
Multicenter Validation of a Gene Expression–Based Prognostic Signature in Lymph Node–Negative Primary Breast Cancer

John A. Foekens, David Atkins, Yi Zhang, Fred C.G.J. Sweep, Nadia Harbeck, Angelo Paradiso, Tanja Cufer, Anieta M. Sieuwerts, Dmitri Talantov, Paul N. Span, Vivianne C.G. Tjan-Heijnen, Alfredo F. Zito, Katja Specht, Heinz Hoefler, Rastko Golouh, Francesco Schittulli, Manfred Schmitt, Louk V.A.M. Beex, Jan G.M. Klijn, and Yixin Wang



Patients at risk:

| | | | | | | | | | | | |
|----------------|-----|-----|----|----|----|----|----|----|----|----|----|
| Good signature | 78 | 77 | 77 | 77 | 76 | 75 | 65 | 56 | 41 | 33 | 21 |
| Poor signature | 102 | 100 | 91 | 83 | 79 | 75 | 66 | 56 | 39 | 28 | 19 |



Patients at risk:

| | | | | | | | | | | | |
|----------------|-----|-----|-----|----|----|----|----|----|----|----|----|
| Good signature | 78 | 78 | 77 | 77 | 76 | 76 | 67 | 56 | 41 | 33 | 21 |
| Poor signature | 102 | 102 | 100 | 99 | 91 | 90 | 79 | 67 | 49 | 32 | 23 |

180 N- pts
4 centers
No systemic therapy
Median FU: 100 months
Clinical endpoint: TDM

Study Objective

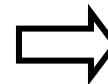
Test the 76-gene signature
using the **SAME** validation **TRANSBIG** series

Similar
performance?



MINDACT

Strikingly different
performance?



- Delay MINDACT
- Further work needed...

RNA



Brussels

Jules Bordet Institute

Gene expression profiling

5 TRANSBIG
Institutions

- UK (Guy's, Oxford) :
1984 => 1996
- France (IGR, CRH) :
1978 => 1998
- Sweden (Karolinska) :
1980 => 1990

Raw
data



Veridex

Low vs High risk signature
classification

Clinical
data

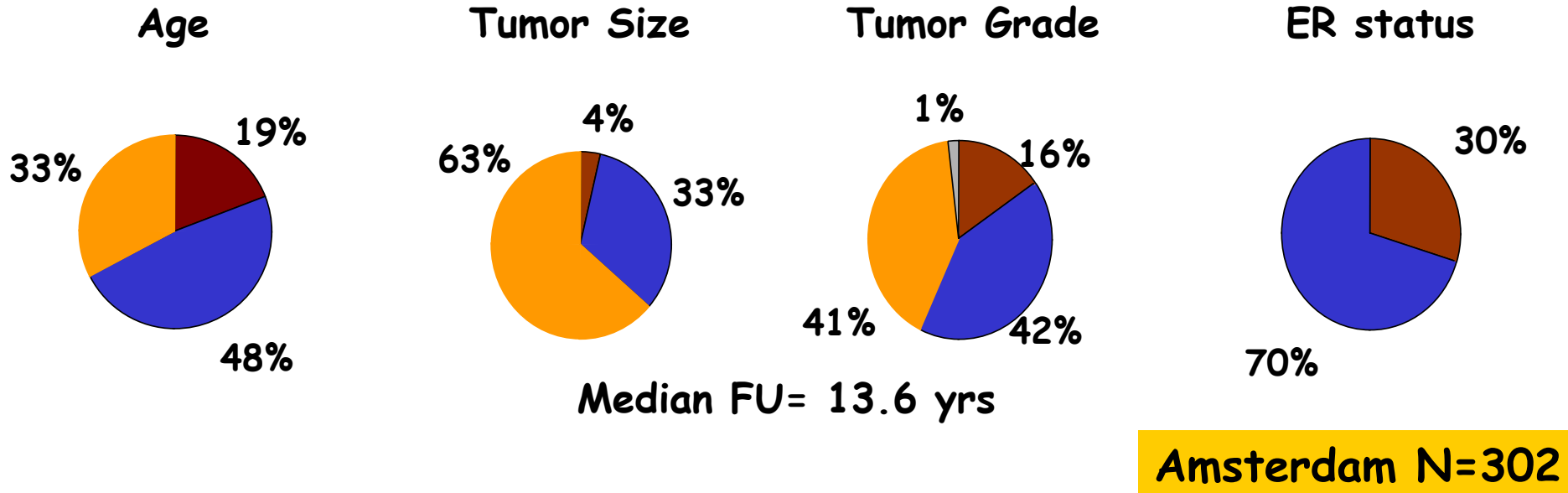
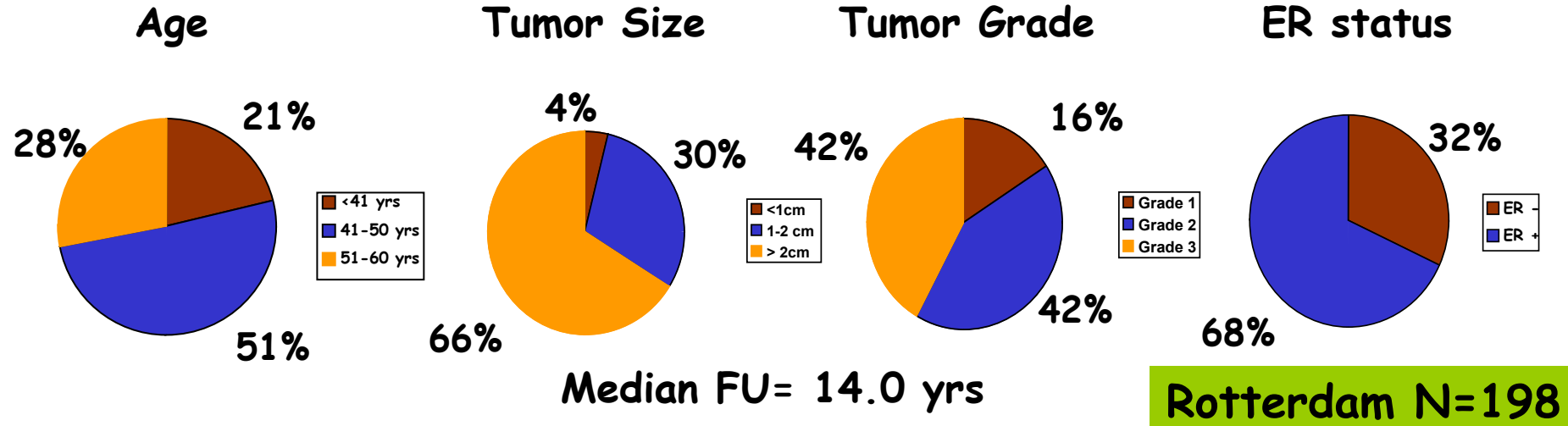


International
Drug
Development
Institute

IDDI

Comparison of clinical vs gene
signature of prognostic risk

Patients Characteristics in the 2 validation series



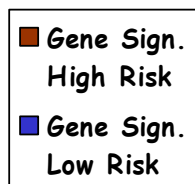
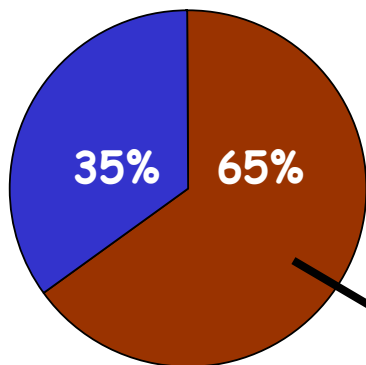
Results

Patient's data

Clinical Risk defined by the Adjuvant! Software
(www.adjuvantonline.com)

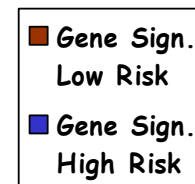
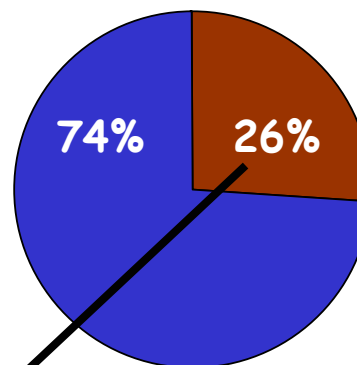
LOW Clinical Risk

N=46



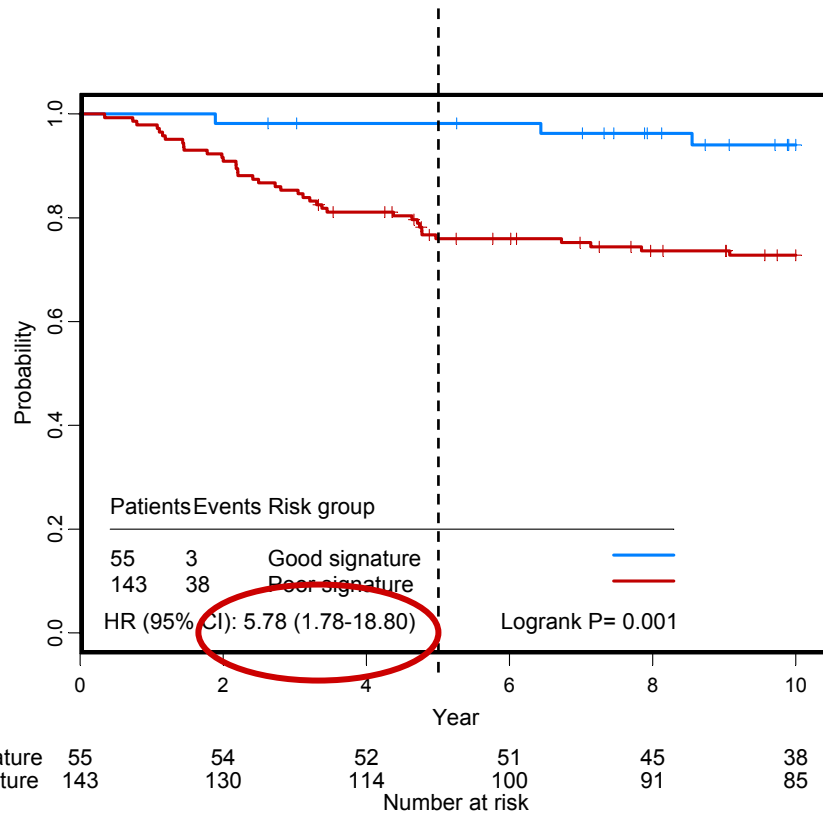
HIGH Clinical Risk

N=152



Discordant cases

Time to Distant Metastases



5-year survival:

low risk group: 0.98 (0.88-1.00)

high risk group: 0.76 (0.68-0.82)

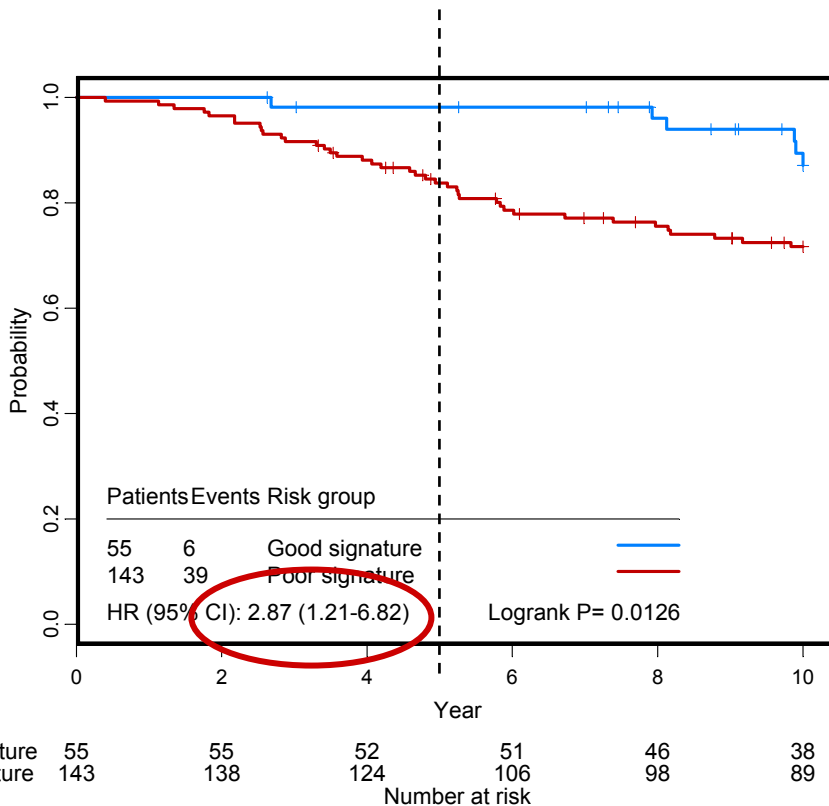
10 year survival:

low risk group: 0.94 (0.83-0.98)

high risk group: 0.73 (0.65-0.79)

HR and logrank p-value were obtained after stratification for the centre

Overall Survival



5-year survival:

low risk group: 0.98 (0.88-1.00)

high risk group: 0.84 (0.77-0.89)

10 year survival:

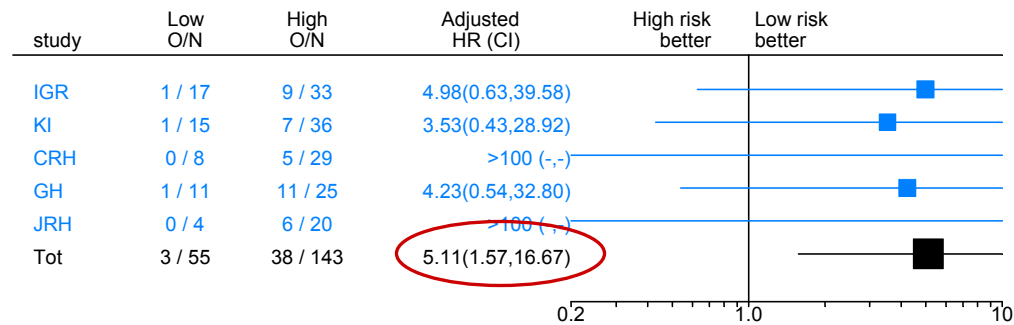
low risk group: 0.87 (0.73-0.94)

high risk group: 0.72 (0.63-0.78)

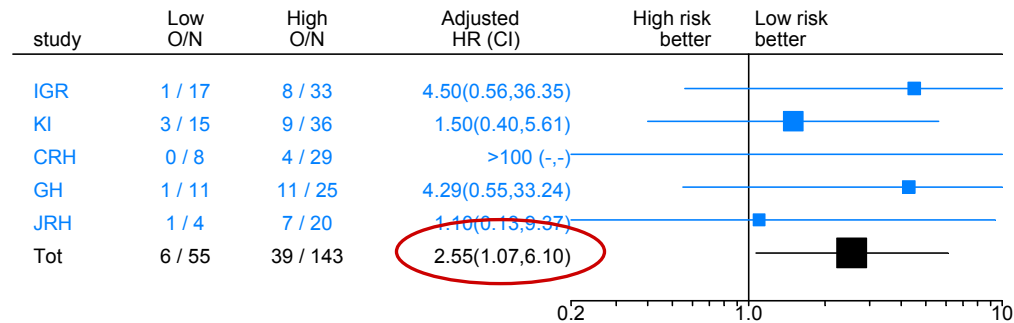
HR and logrank p-value were obtained after stratification for the centre

76-gene signature adjusted for Clinical Risk (Adjuvant!)

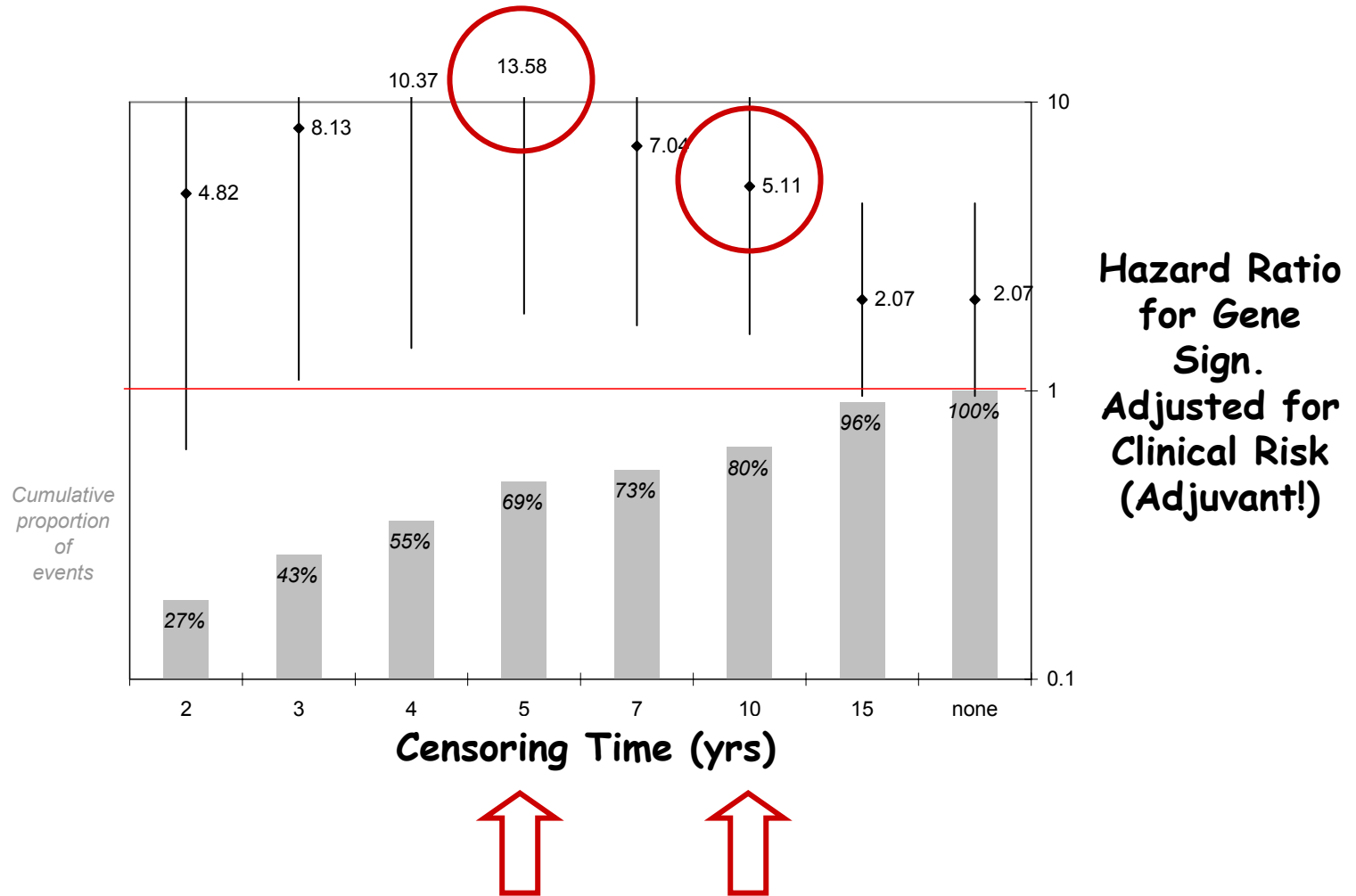
Time to Distant Metastases



Overall Survival

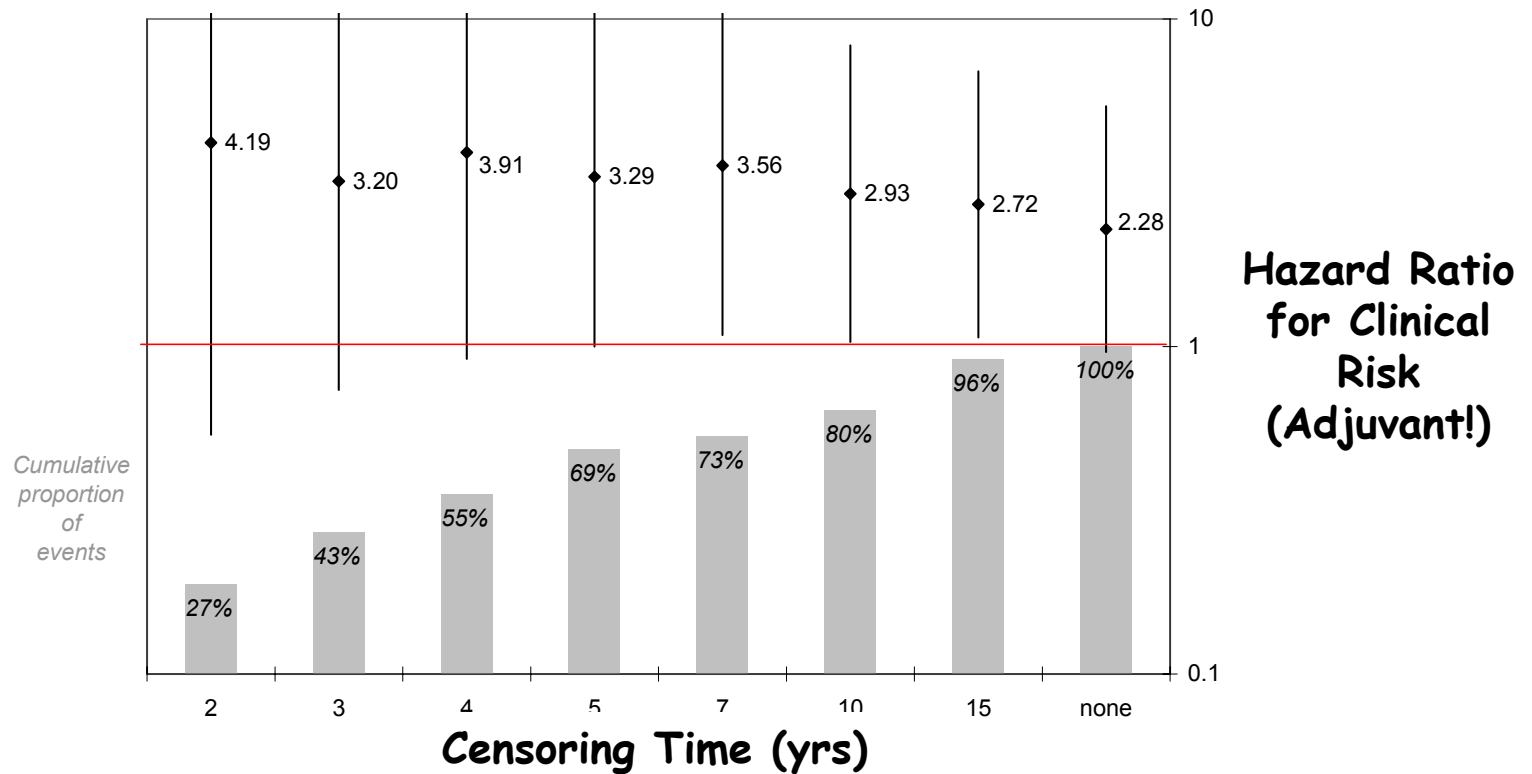


Time-dependency of the signature



Similar phenomenon was seen with the Amsterdam signature!

Clinical Risk (Adjuvant!) over time



Conclusions

1. We have independently validated the Rotterdam 76-gene signature using the TRANSBIG validation series.
2. The performances of the Rotterdam and Amsterdam signatures are similar.
3. We observed a strong time dependency of both signatures, which was not seen for the clinical risk.

Conclusions

4. This independent multi-center study adds to the growing evidence that gene expression signatures are of clinical relevance, especially to identify patients at high risk of early distant metastases.
5. This two-year intensive “validation” work reinforces the belief that the time is right to launch a prospective trial (MINDACT) that will validate the added value of these signatures for adjuvant treatment tailoring.

Acknowledgements



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Fatima Cardoso - TransBig coordinator



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Sherene Loi
Giuseppe Viale



Yixin Wang
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F. Lallemand
B. Haibe-Kains

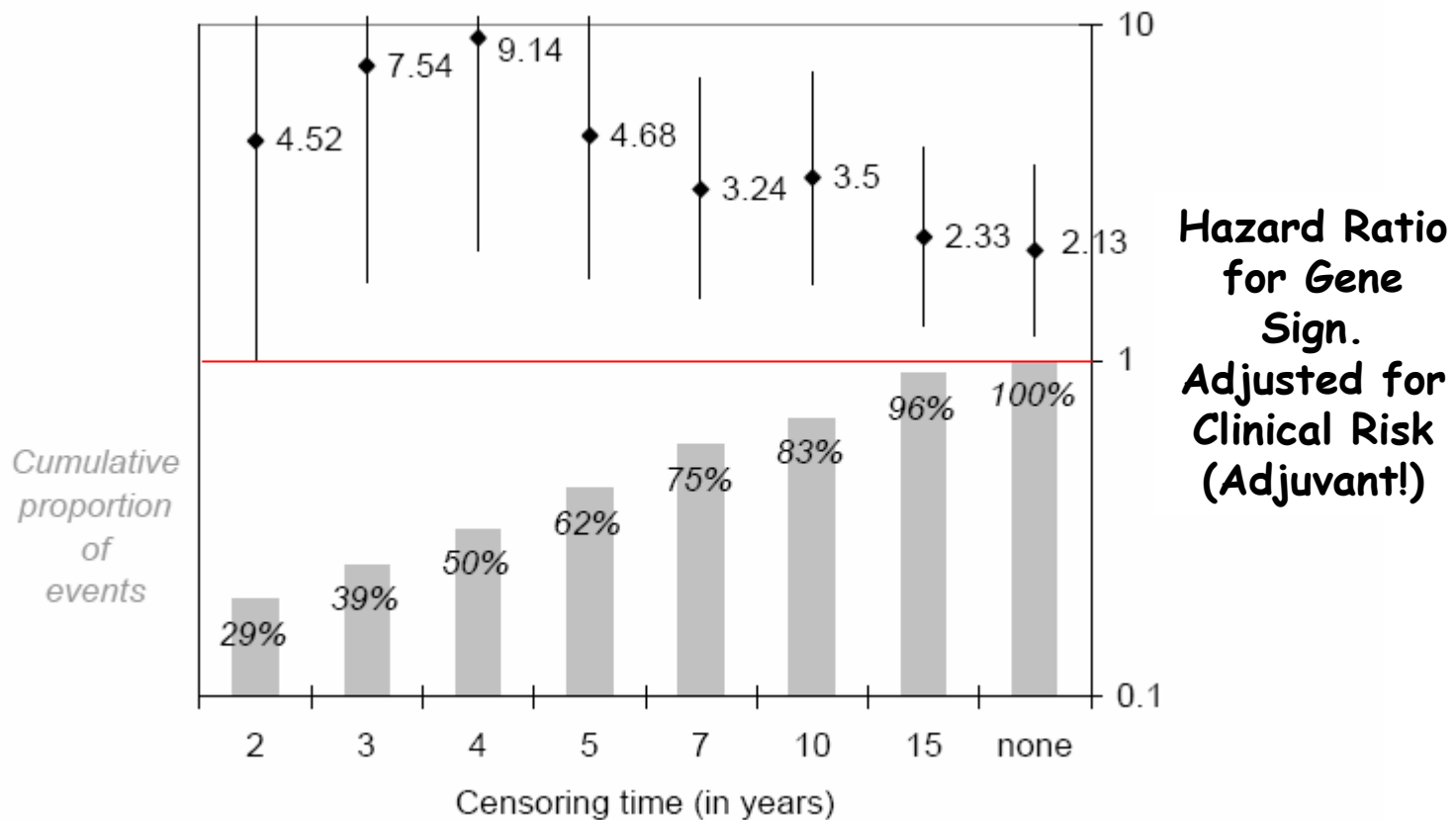
Jonas Bergh
Rosette Lidereau
Paul Ellis
Adrian Harris

On behalf on the TransBig Consortium

Backup

Time-dependency of the signature

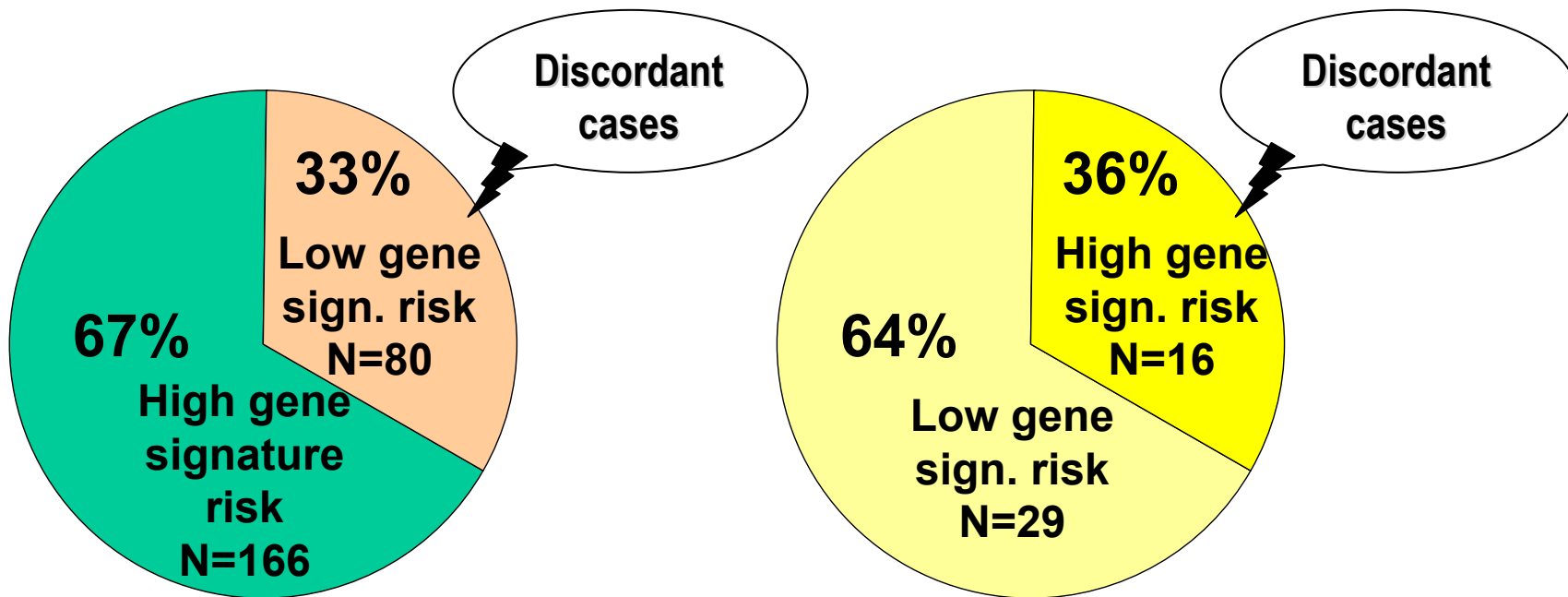
AMSTERDAM SIGNATURE



CONCORDANCE BETWEEN CLINICAL AND GENE SIGNATURE RISK CLASSIFICATIONS

Amsterdam Signature

Threshold for low clinical risk defined as predicted 10-year O.S. > 90%



High clinical risk N=246

Low clinical risk N=45

| Discordant cases with other clinical risk classifications | |
|---|-----------------|
| St-Gallen = 35% | St-Gallen = 43% |
| NPI = 36% | NPI = 54% |