Gene expression profiling of breast cancer: past and future

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Outline

- Prognosis/prediction of response
- IMPAKT meeting (Brussels 2012) guideline session
- Future directions

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Example of a clinical case

A 61-year-old postmenopausal woman with left breast cancer

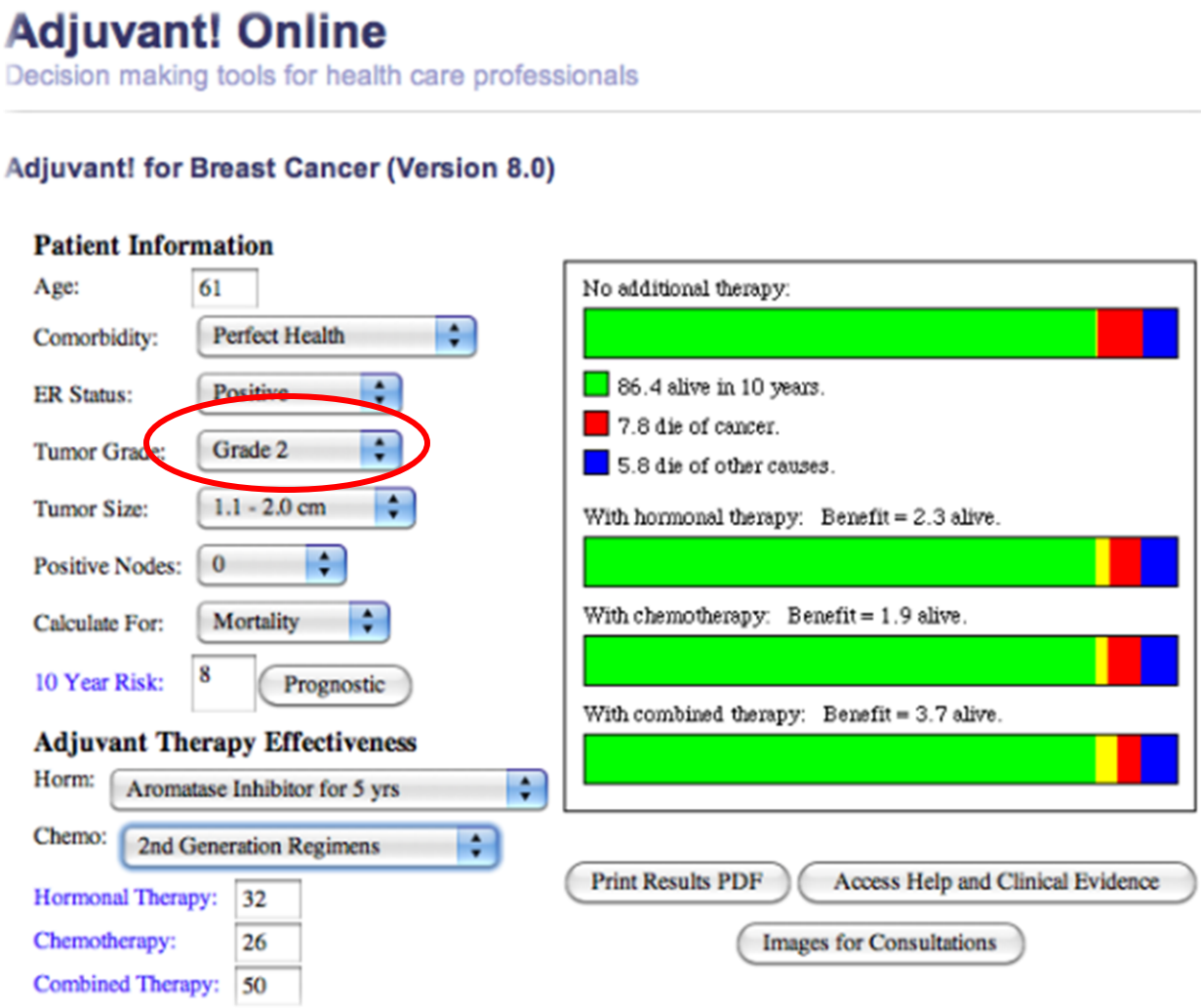
Surgery:

Breast Conserving Surgery *and* Sentinel Node Biopsy

Pathology:

-Infiltrating ductal carcinoma
-Histological **grade 2**
-no vascular or lymphatic channel invasion
-tumor size **1.9 cm** with clear surgical margins
-**ER 85%** cells positive, **PR 65%** cells positive
-**Ki-67 15%**
-**HER2 negative**
-lymphadenectomy: **all axillary nodes negative**

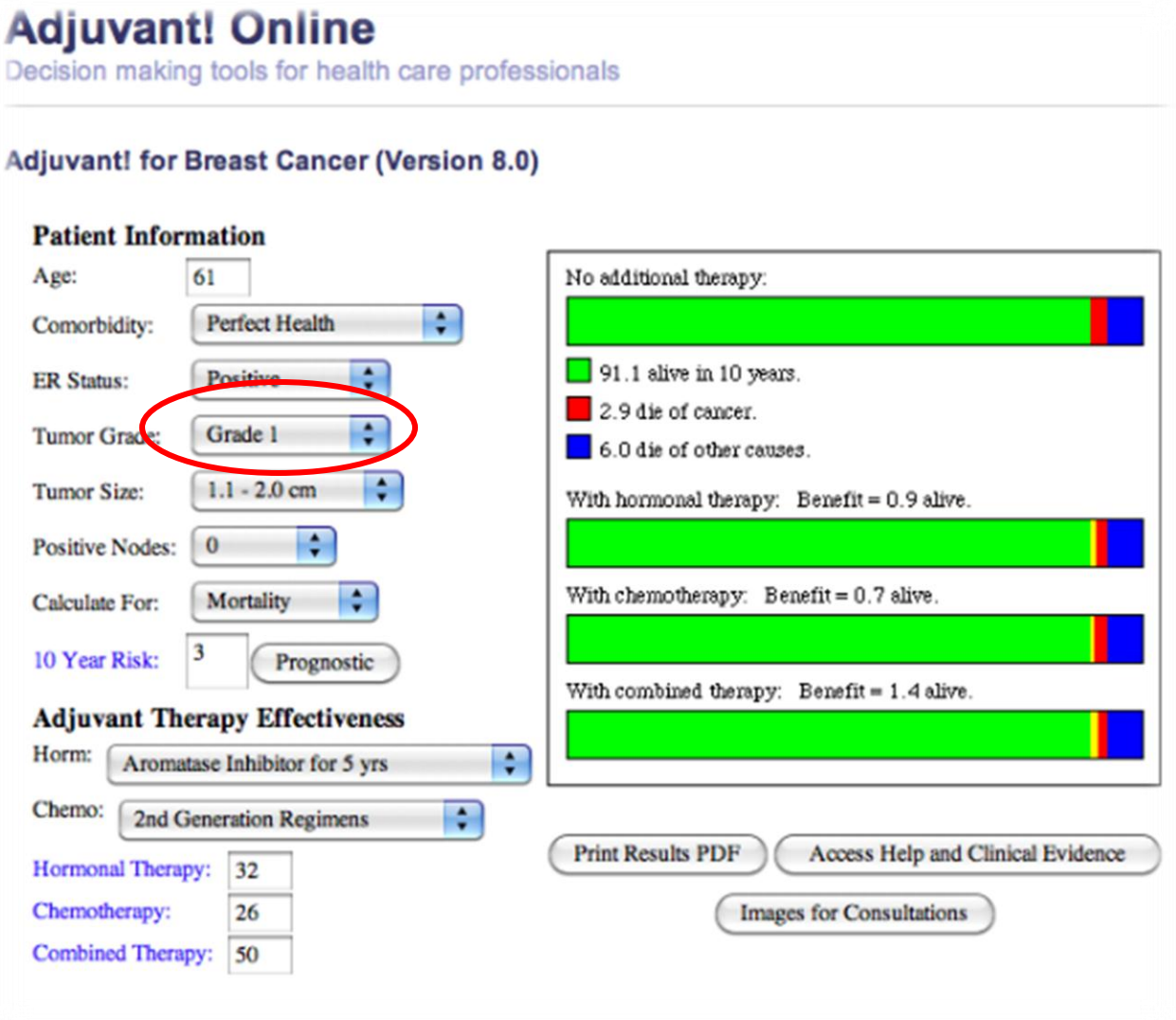
Adjuvant! Online



?

Ki67 15%

Adjuvant! Online

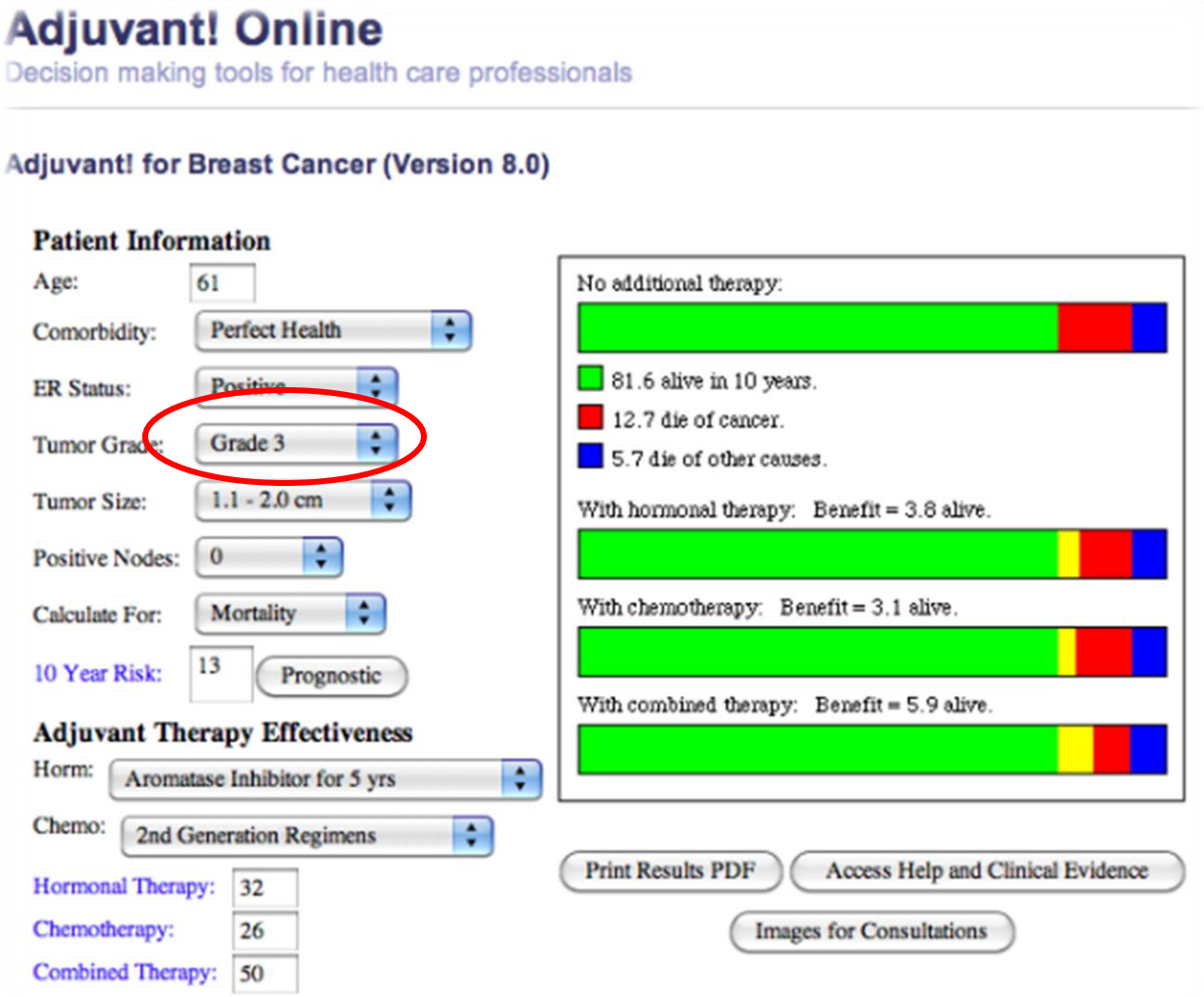


Next day… same pathologist regrade and Ki67:

-GRADE 1

-Ki67 10%

Adjuvant! Online



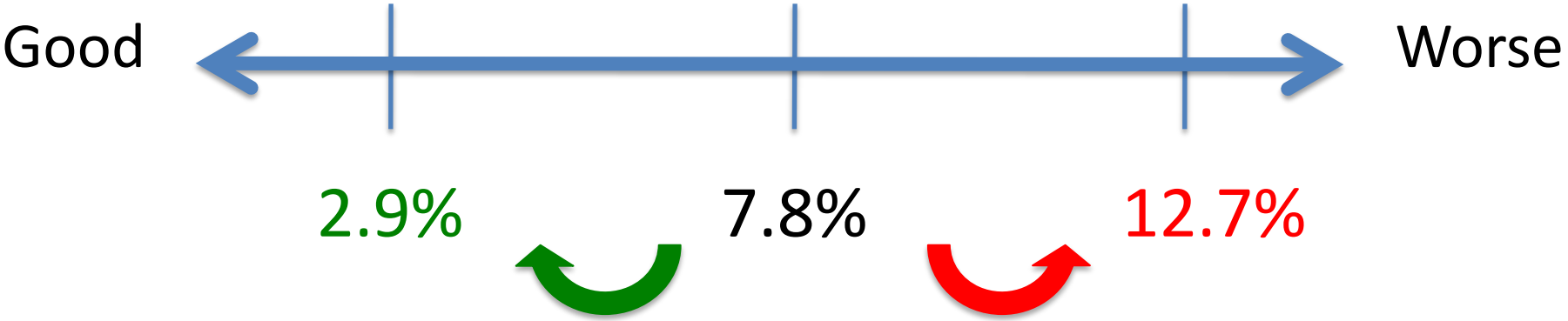
Another center

-Ki67 20%

-GRADE 3

Prognosis - 10 years survival Adjuvant! Online

Same patient -> 2 ≠ days ->2 ≠ pathologists…

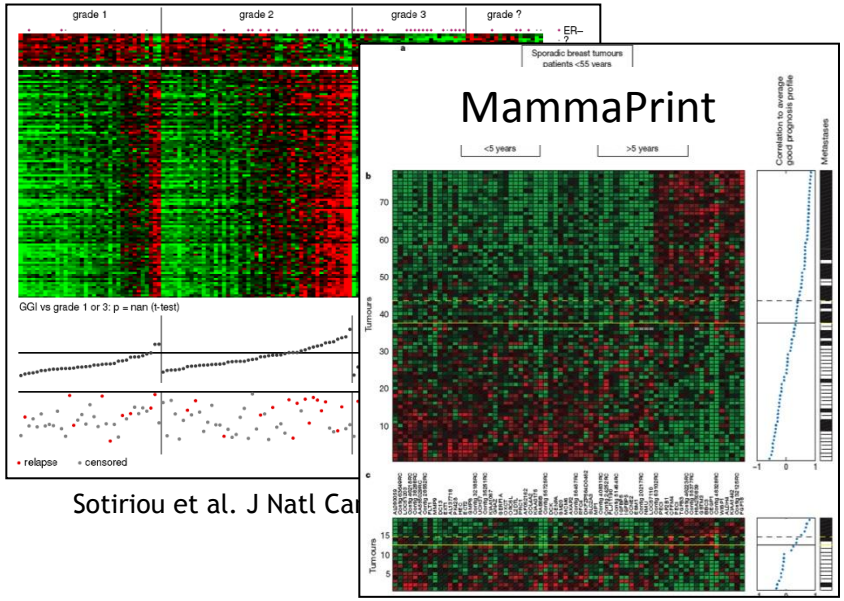


≠ grading (Ki67%)

Chemotherapy question?

Gene prognostic signatures:

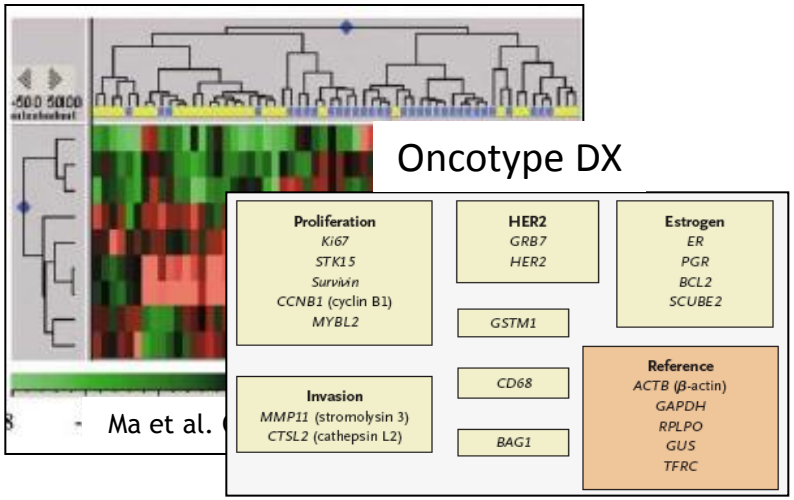
Genomic Grade Index (GGI)



Sotiriou et al. J Natl Ca

Van't Veer et al. Nature,2002

H/I + MGI



Ma et al.

Paik et al. NEJM, 2004

Population: Untreated
Tissue: Fresh/Frozen

Population: Tamoxifen-treated
Tissue: FFPE

Add additional information to current clinico-pathological parameters for treatment decision making for ***some*** patients

Recurrence score
Independent validation (TransATAC)

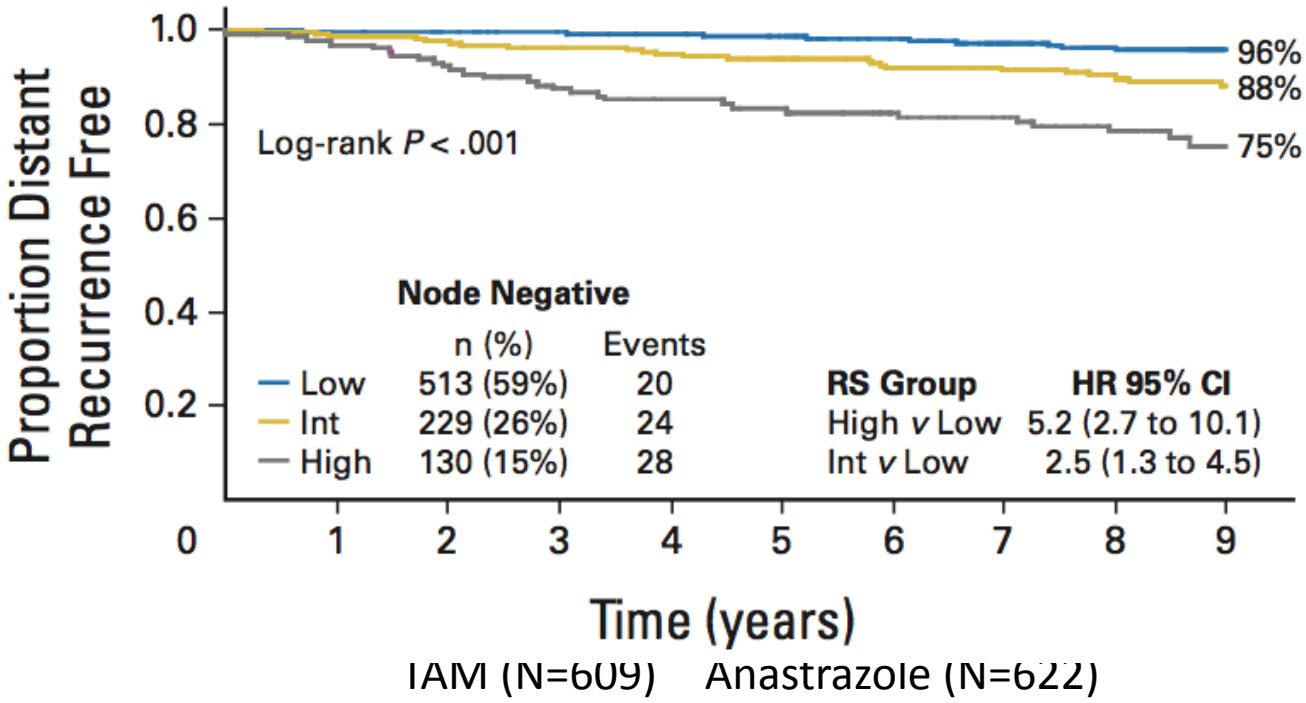
Postmenopausal
ER+, No chemo

R

TAM

Anastrazole

Anastrazole+ TAM



96%!

Dowsett M, et al. J Clin Oncol. 2010;28(11):1829-1834.

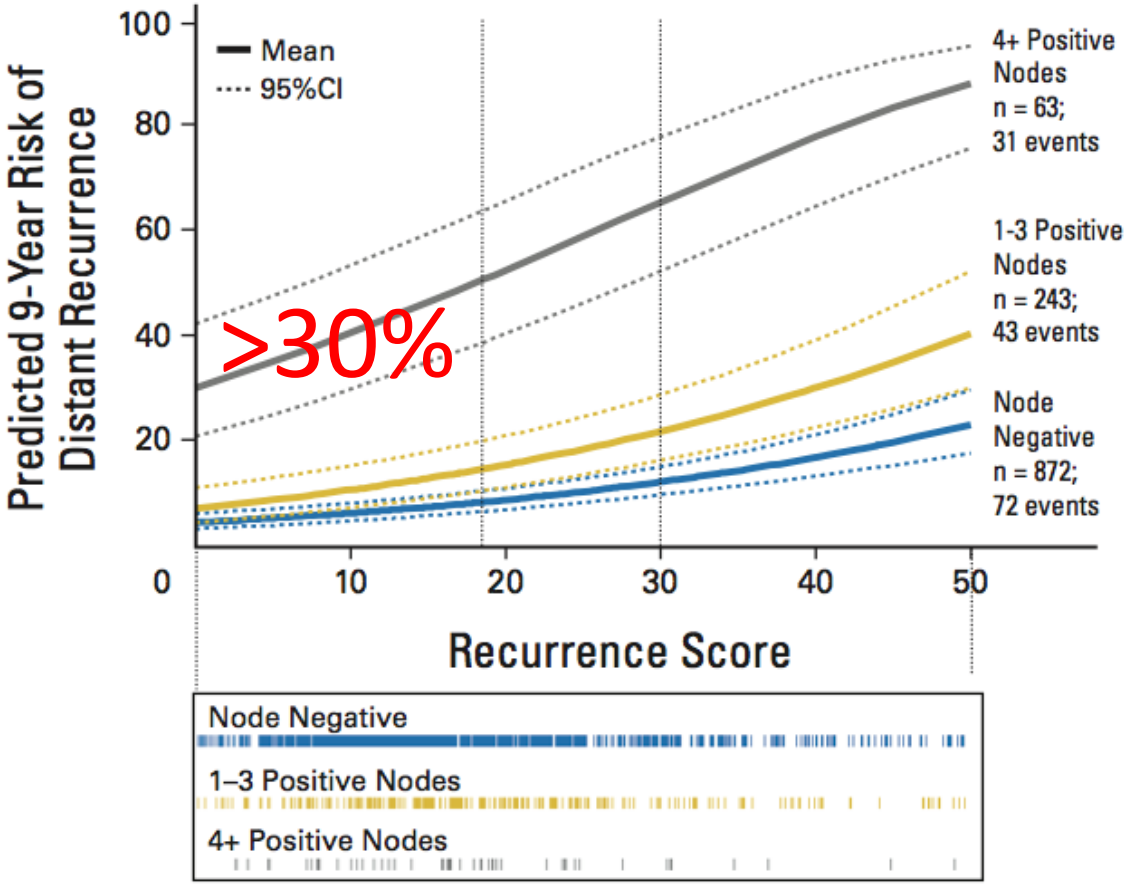
Key messages

- ✓ Proliferation = driving force of 1st generation gene expression prognostic signatures
- ✓ Informative for ER+/HER2- BC
- ✓ Stage (T,N) still matters

Sotiriou C, et al. Nat Rev Cancer. 2007;7(7):545-553.
Sotiriou C, et al. N Engl J Med. 2009;360(8):790-800.

Stage (T,N) still matters
Prognostic signatures don't help!

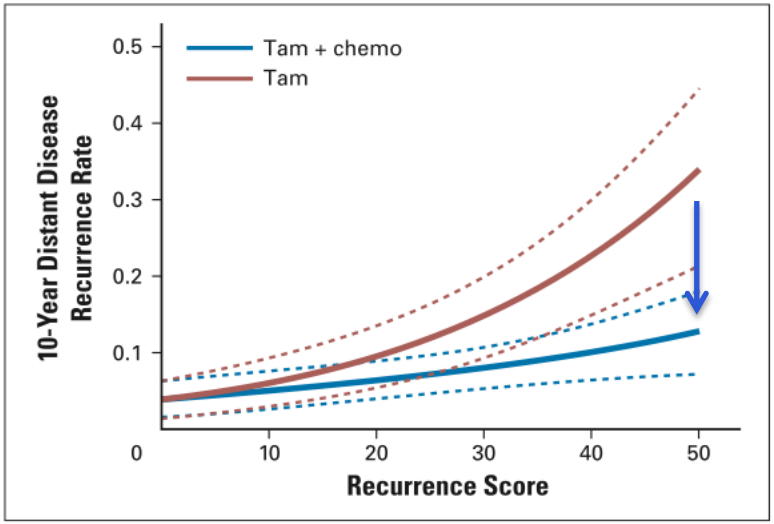
Trans ATAC



Dowsett M, et al. J Clin Oncol. 2010;28(11):1829-1834.

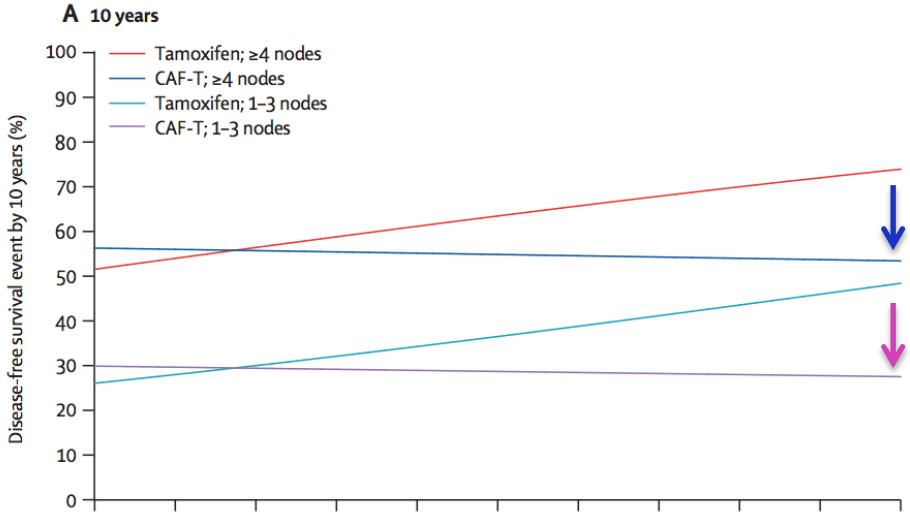
High proliferative breast cancers benefit from chemotherapy…

CMF regimen
N-



Paik et al, JCO 2006

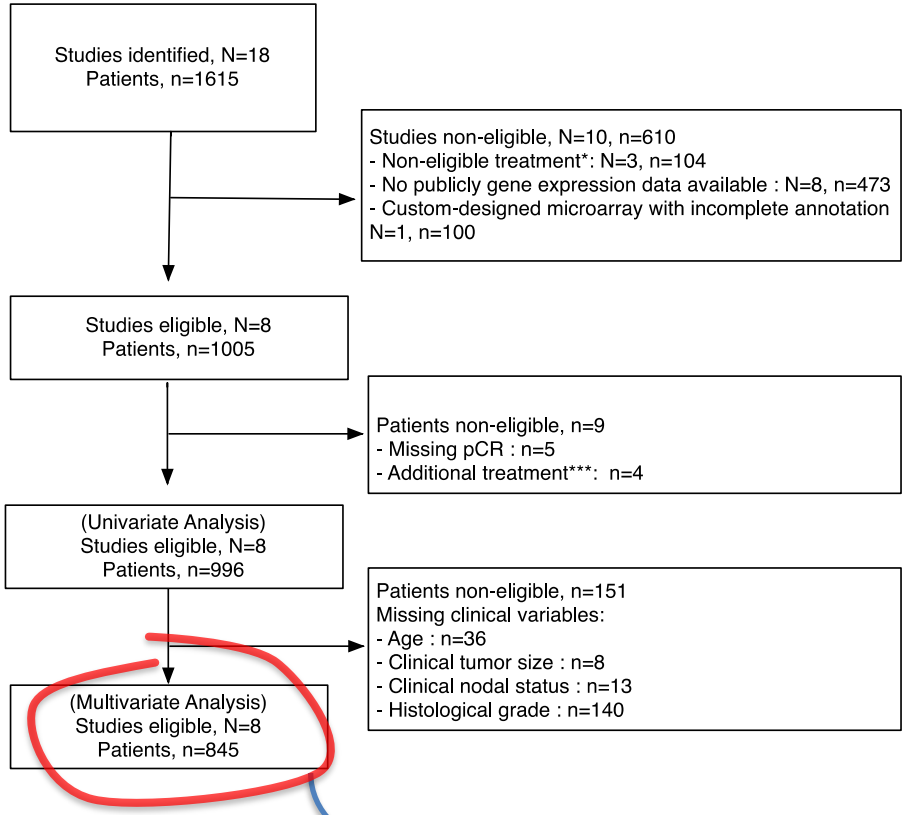
CAF regimen
N+



Albain et al, Lancet Oncology 2009

Ki67, PAM50 and other proliferation-based signatures…

Tumor microenvironment matters…



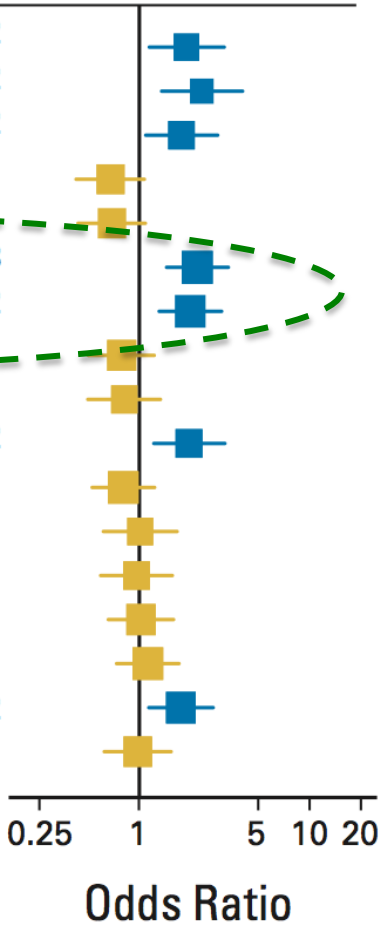
Several molecular processes and molecular pathways

? Response to chemotherapy

Ignatiadis M, et al. *J Clin Oncol*. 2012 Apr 16.

High immune signal = better chemo response (N= 845 pts)

	OR	95% CI	*P*	FDR
GGI	1.70	1.12 to 2.6	1.3E-02	3.7E-02
Gene70	2.02	1.29 to 3.2	2.4E-03	1.3E-02
CIN70	1.61	1.08 to 2.42	2.1E-02	5.1E-02
Stroma1	0.73	0.49 to 1.06	1.0E-01	2.1E-01
Stroma2	0.74	0.5 to 1.07	1.1E-01	2.1E-01
Immune1	1.92	1.36 to 2.73	2.2E-04	3.7E-03
Immune2	1.78	1.25 to 2.53	1.3E-03	1.1E-02
RAS	0.82	0.57 to 1.18	3.0E-01	4.9E-01
MAPK	0.85	0.56 to 1.27	4.2E-01	6.0E-01
PTEN	1.75	1.18 to 2.62	5.8E-03	2.5E-02
AKTmTOR	0.84	0.59 to 1.19	3.2E-01	4.9E-01
PIK3CA	1.01	0.67 to 1.53	9.5E-01	9.5E-01
IGF1	0.97	0.65 to 1.45	8.9E-01	9.5E-01
SRC	1.02	0.71 to 1.47	9.1E-01	9.5E-01
MYC	1.10	0.78 to 1.56	5.8E-01	7.6E-01
E2F3	1.60	1.12 to 2.3	1.1E-02	3.7E-02
BetaCatenin	0.98	0.68 to 1.43	9.4E-01	9.5E-01

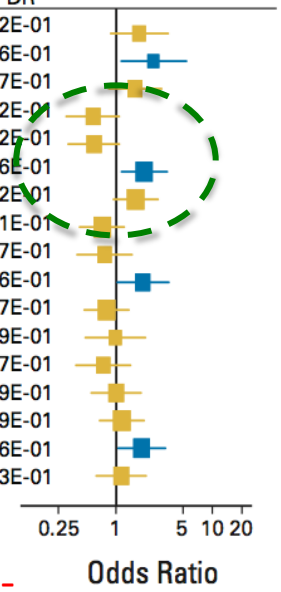


Ignatiadis M, et al. *J Clin Oncol*. 2012 Apr 16.

Different processes/pathways are associated with pCR in different BC subtypes

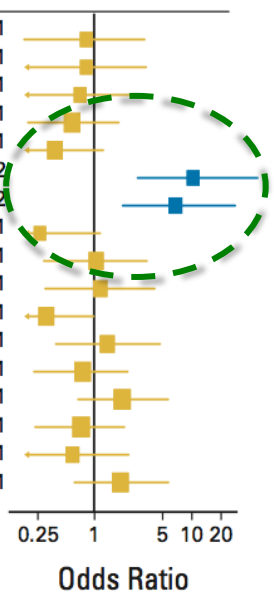
ER-/HER2-

	OR	95% CI	*P*	FDR
GGI	1.59	0.91 to 2.81	1.0E-01	2.2E-01
Gene70	2.11	1.12 to 4.03	2.2E-02	1.6E-01
CIN70	1.47	0.88 to 2.47	1.4E-01	2.7E-01
Stroma1	0.65	0.38 to 1.08	9.7E-02	2.2E-01
Stroma2	0.66	0.4 to 1.08	9.9E-02	2.2E-01
Immune1	1.76	1.13 to 2.76	1.3E-02	1.6E-01
Immune2	1.49	0.96 to 2.31	7.4E-02	2.2E-01
RAS	0.77	0.5 to 1.19	2.4E-01	4.1E-01
MAPK	0.81	0.47 to 1.38	4.3E-01	5.7E-01
PTEN	1.71	1.04 to 2.85	3.7E-02	1.6E-01
AKTmTOR	0.84	0.54 to 1.3	4.3E-01	5.7E-01
PIK3CA	1.00	0.55 to 1.8	9.9E-01	9.9E-01
IGF1	0.79	0.46 to 1.34	3.8E-01	5.7E-01
SRC	1.02	0.62 to 1.65	9.5E-01	9.9E-01
MYC	1.13	0.73 to 1.75	5.7E-01	6.9E-01
E2F3	1.67	1.06 to 2.67	2.9E-02	1.6E-01
BetaCatenin	1.12	0.69 to 1.82	6.4E-01	7.3E-01



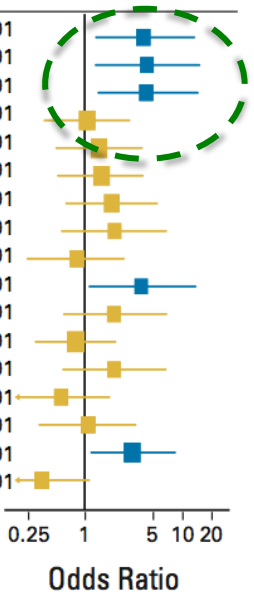
HER2+

	OR	95% CI	*P*	FDR
GGI	0.86	0.25 to 2.72	8.0E-01	8.7E-01
Gene70	0.85	0.24 to 2.8	8.0E-01	8.7E-01
CIN70	0.76	0.22 to 2.41	6.4E-01	8.4E-01
Stroma1	0.65	0.25 to 1.62	3.5E-01	7.5E-01
Stroma2	0.46	0.17 to 1.19	1.2E-01	4.0E-01
Immune1	7.13	2.38 to 25.51	1.0E-03	1.8E-02
Immune2	5.01	1.77 to 16.35	4.1E-03	3.5E-02
RAS	0.34	0.09 to 1.12	8.7E-02	3.7E-01
MAPK	1.04	0.37 to 2.84	9.4E-01	9.4E-01
PTEN	1.13	0.38 to 3.31	8.2E-01	8.7E-01
AKTmTOR	0.39	0.14 to 0.99	5.4E-02	3.1E-01
PIK3CA	1.30	0.47 to 3.69	6.2E-01	8.4E-01
IGF1	0.79	0.3 to 1.94	6.2E-01	8.4E-01
SRC	1.74	0.73 to 4.33	2.2E-01	6.1E-01
MYC	0.77	0.31 to 1.82	5.6E-01	8.4E-01
E2F3	0.65	0.21 to 1.97	4.5E-01	8.4E-01
BetaCatenin	1.68	0.68 to 4.35	2.7E-01	6.5E-01



ER+/HER2-

	OR	95% CI	*P*	FDR
GGI	3.19	1.26 to 8.72	1.8E-02	1.0E-01
Gene70	3.43	1.25 to 9.66	1.8E-02	1.0E-01
CIN70	3.38	1.31 to 9.35	1.4E-02	1.0E-01
Stroma1	1.05	0.45 to 2.42	9.1E-01	9.1E-01
Stroma2	1.33	0.57 to 3.1	5.1E-01	6.7E-01
Immune1	1.40	0.59 to 3.15	4.3E-01	6.1E-01
Immune2	1.71	0.7 to 4.17	2.4E-01	4.4E-01
RAS	1.81	0.64 to 5	2.6E-01	4.4E-01
MAPK	0.86	0.32 to 2.16	7.5E-01	8.5E-01
PTEN	3.06	1.1 to 8.94	3.5E-02	1.2E-01
AKTmTOR	1.78	0.66 to 5.02	2.6E-01	4.4E-01
PIK3CA	0.84	0.38 to 1.83	6.6E-01	8.0E-01
IGF1	1.78	0.65 to 4.96	2.6E-01	4.4E-01
SRC	0.63	0.23 to 1.63	3.5E-01	5.4E-01
MYC	1.07	0.41 to 2.73	8.9E-01	9.1E-01
E2F3	2.56	1.14 to 5.97	2.5E-02	1.1E-01
BetaCatenin	0.43	0.17 to 1.09	7.5E-02	2.1E-01



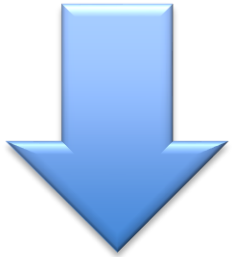
Ignatiadis M, et al. *J Clin Oncol*. 2012 Apr 16.

Outline

- Prognosis/prediction of response
- IMPAKT meeting (Brussels 2012) guideline session
- Future directions

Clinical utility?

6 ≠ gene prognostic signatures including PAM50 ROR score ?



Guidelines session in Brussels

IMPAKT BREAST CANCER CONFERENCE

IMProving cAre and Knowledge through Translational research

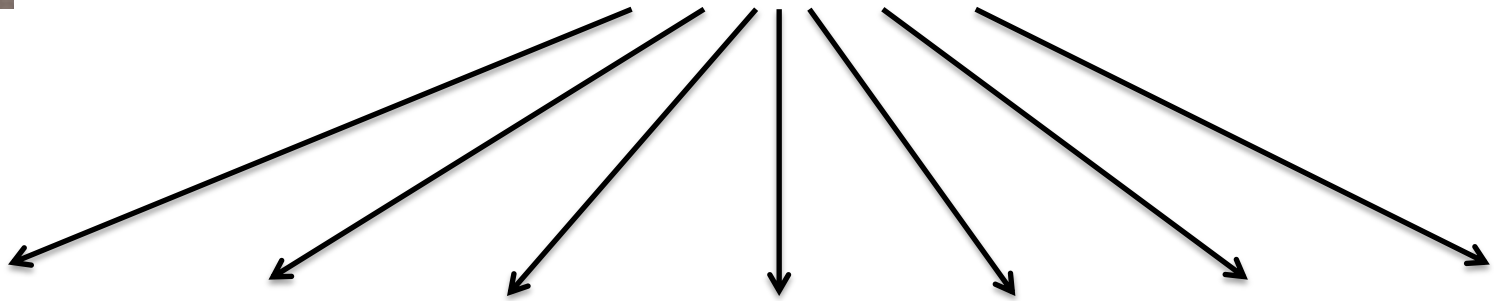
IMPAKT BREAST CANCER CONFERENCE
IMProving cAre and Knowledge through Translational research

Evaluation Process

Medical Oncology

Eligible articles for all 6 signatures were evaluated
(Q/C was performed by another reviewer)

Medical Oncology



Medical Oncology
Conference chair

Laboratory

Gynecology /Surgery

Statistics

Medical Oncology
Task Force chair

Medical Oncology

Surgery

Pathology

Medical Oncology
Conference chair

Evaluation Methods

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

Steven M. Teutsch, MD, MPH[1], Linda A. Bradley, PhD[2], Glenn E. Palomaki, BS[3], James E. Haddow, MD[3], Margaret Piper, PhD[4], Ned Calonge, MD, MPH[5], W. David Dotson, PhD[2,6], Michael P. Douglas, MS[2,6], and Alfred O. Berg, MD, MPH[7], Chair, on behalf of the EGAPP Working Group

Analytical validity

A test's ability to accurately and reliably ***measure*** genotype of interest

Clinical validity

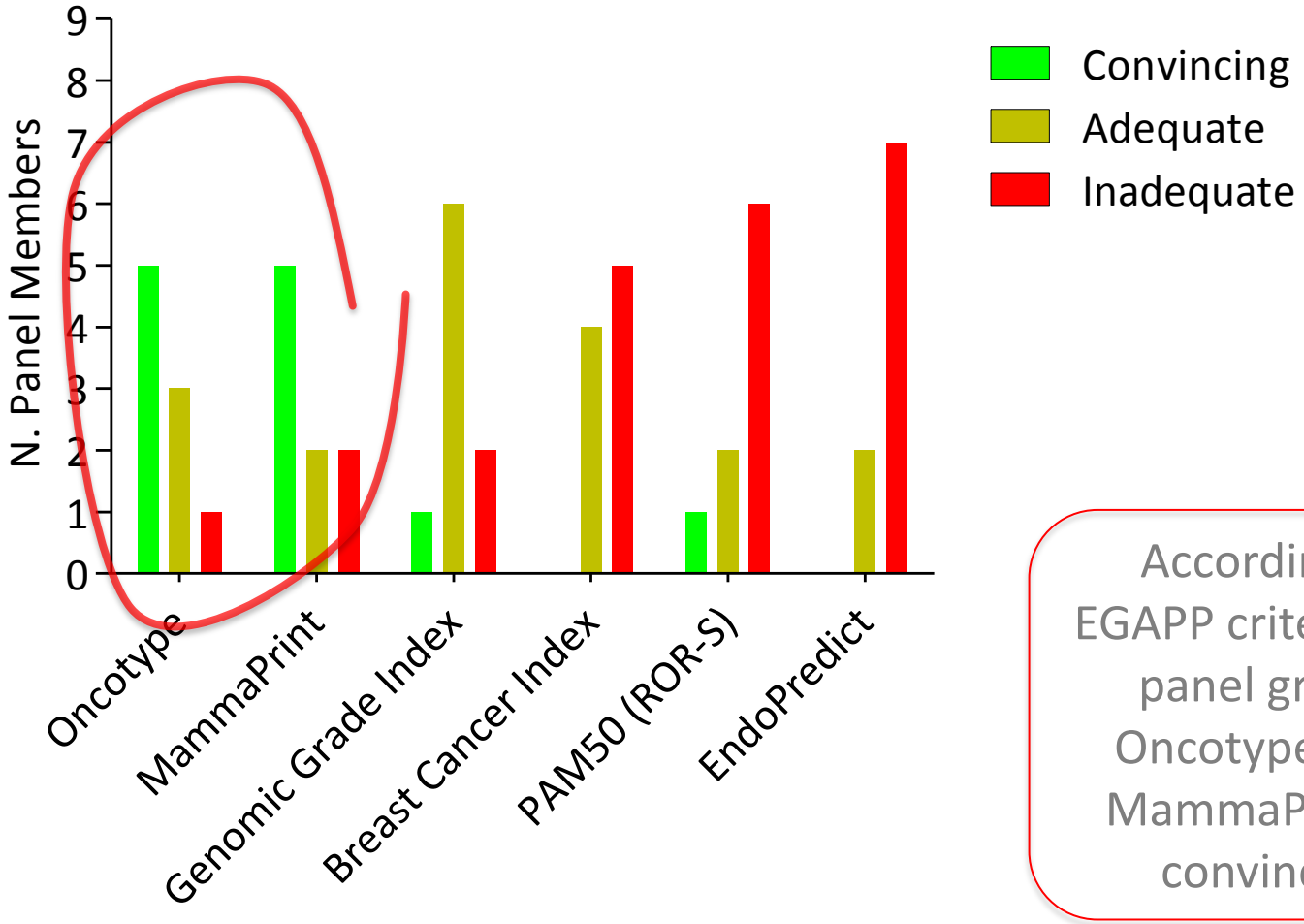
A test's ability to accurately and reliably identify or predict a ***relevant breast cancer survival endpoint***

Clinical utility

The evidence that using a test to guide management in patients with early stage breast cancer will ***significantly improve health-related outcomes***

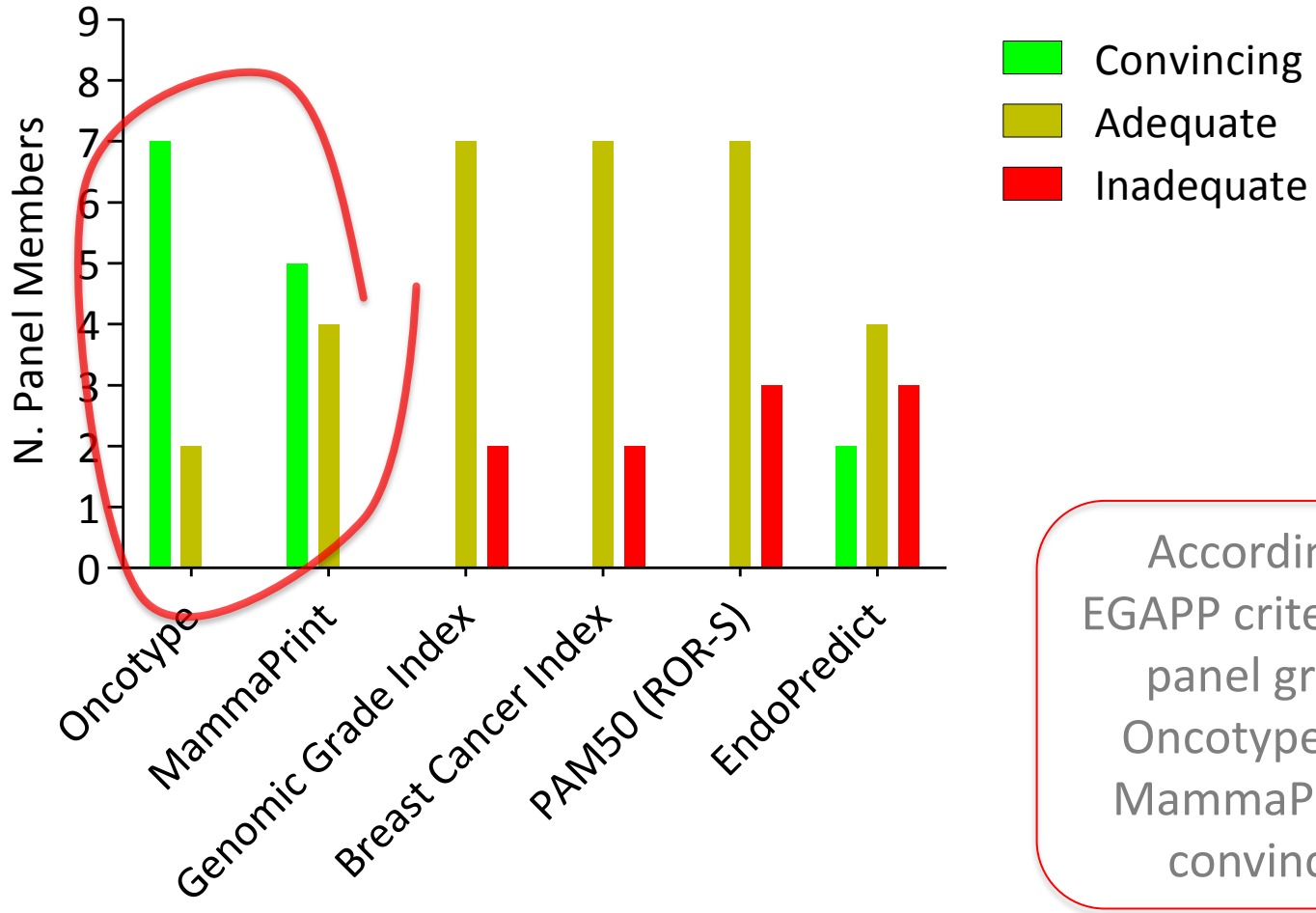
Genetics IN Medicine • Volume 11, Number 1, January 2009

Analytical Validity



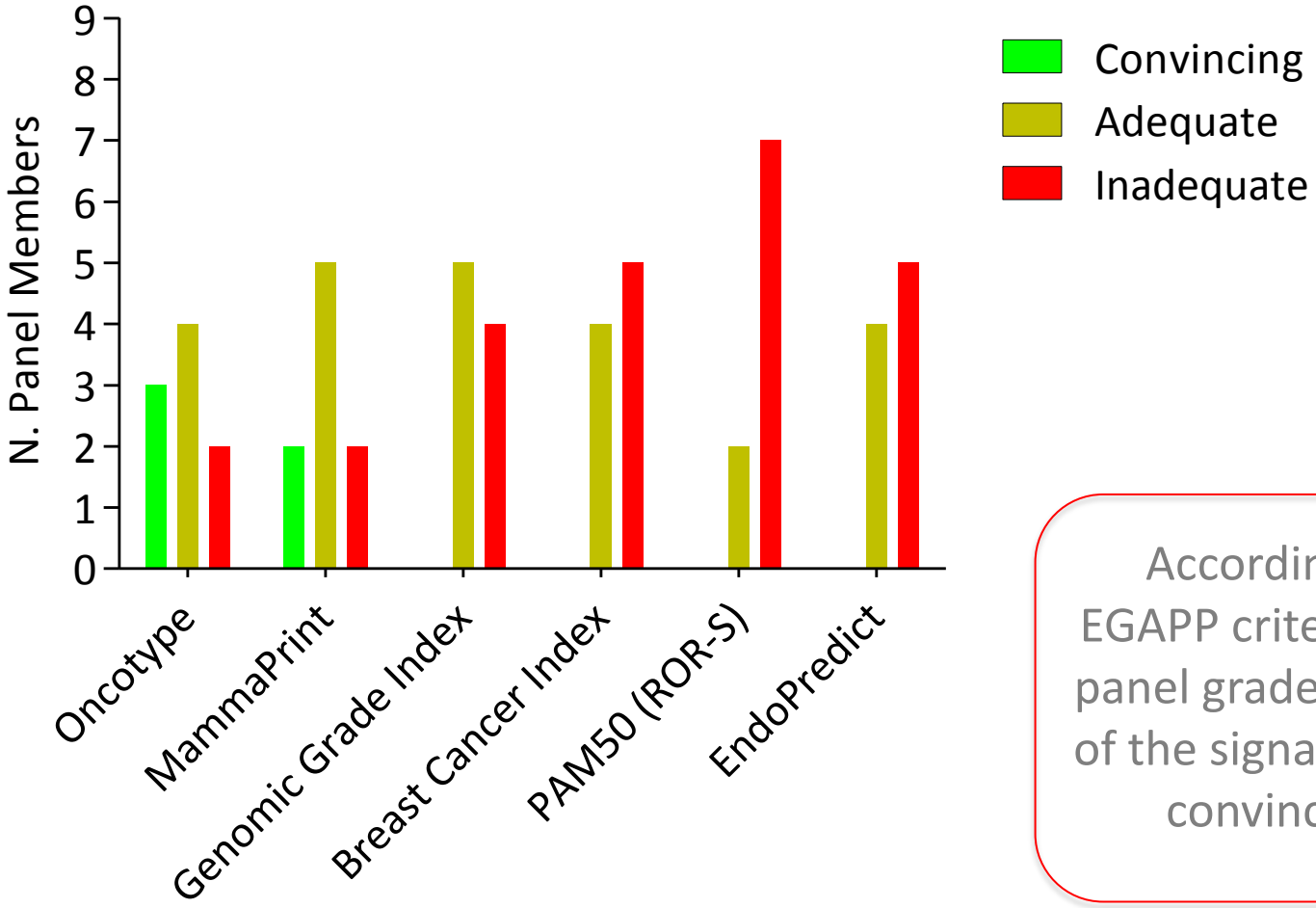
According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

Clinical Validity



According to EGAPP criteria, the panel grades Oncotype Dx & MammaPrint as convincing

Clinical *Utility*



According to EGAPP criteria, the panel grades **NONE** of the signatures as convincing

Take home messages from the past…

- ✓ Level I evidence ***is still awaited*** (MINDACT, TAILORx, RxPONDER)

- ✓ May consider to use the genomic tests in:
  - ER+/HER2-/N-
  - Relatively high absolute risk with low comorbidity
  - Absolute benefit of chemotherapy (>1%)
  - ***Patient's preference!***

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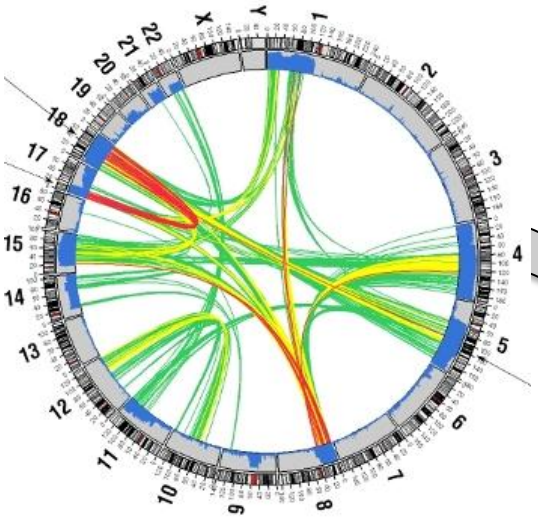
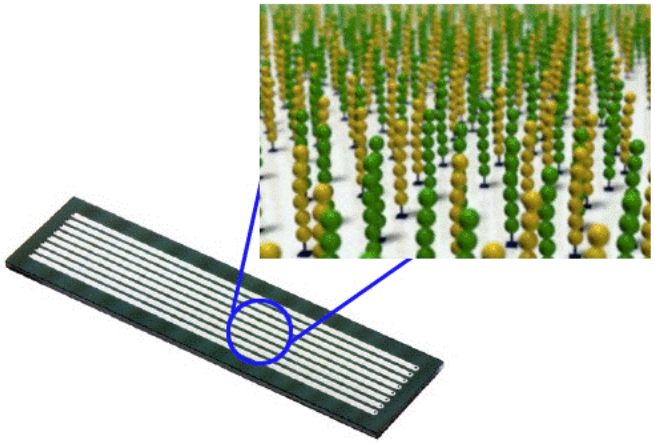
Integration of genomic data with transcriptional data



Genomic data



RNA-seq data

Define and target the right phenotype

ARTICLE

doi:10.1038/nature10983

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Christina Curtis[1,2]†*, Sohrab P. Shah[3,4]*, Suet-Feung Chin[1,2]*, Gulisa Turashvili[3,4]*, Oscar M. Rueda[1,2], Mark J. Dunning[2], Doug Speed[2,5]†, Andy G. Lynch[1,2], Shamith Samarajiwa[1,2], Yinyin Yuan[1,2], Stefan Gräf[1,2], Gavin Ha[3], Gholamreza Haffari[3], Ali Bashashati[3], Roslin Russell[2], Steven McKinney[3,4], METABRIC Group†, Anita Langerød[6], Andrew Green[7], Elena Provenzano[8], Gordon Wishart[8], Sarah Pinder[9], Peter Watson[3,4,10], Florian Markowetz[1,2], Leigh Murphy[10], Ian Ellis[7], Arnie Purushotham[9,11], Anne-Lise Børresen-Dale[6,12], James D. Brenton[2,13], Simon Tavaré[1,2,5,14], Carlos Caldas[1,2,8,13] & Samuel Aparicio[3,4]

Illumina HT-12
(gene expression)

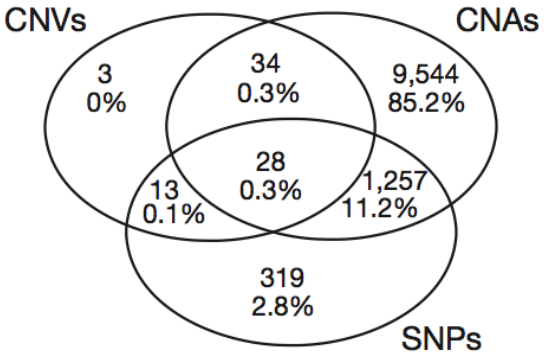
Affymetrix SNP 6.0
(CNA, CNV, SNPs)

Integration of genomic and transcriptomic analysis of breast cancer

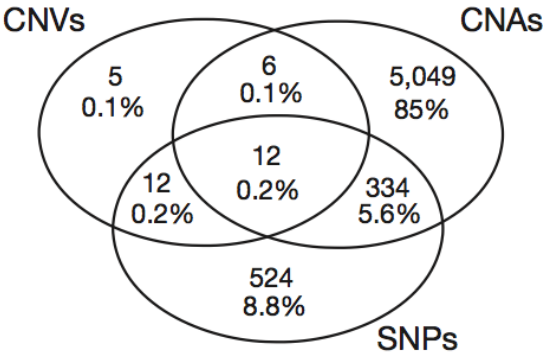
- Refine BC classification
- Define putative drivers

(1) Somatic and germline variants influence breast tumor expression architecture (39% 11,198/28609 probes)

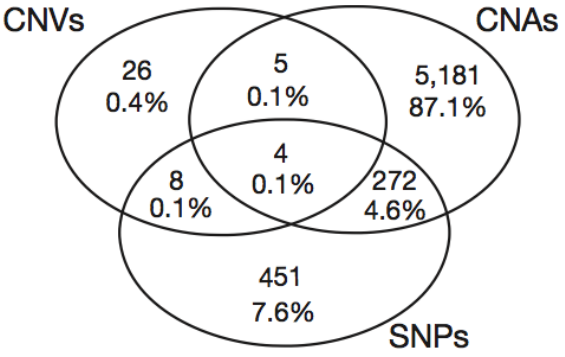
Genome-wide
11,198 genes



Cis 5942 genes

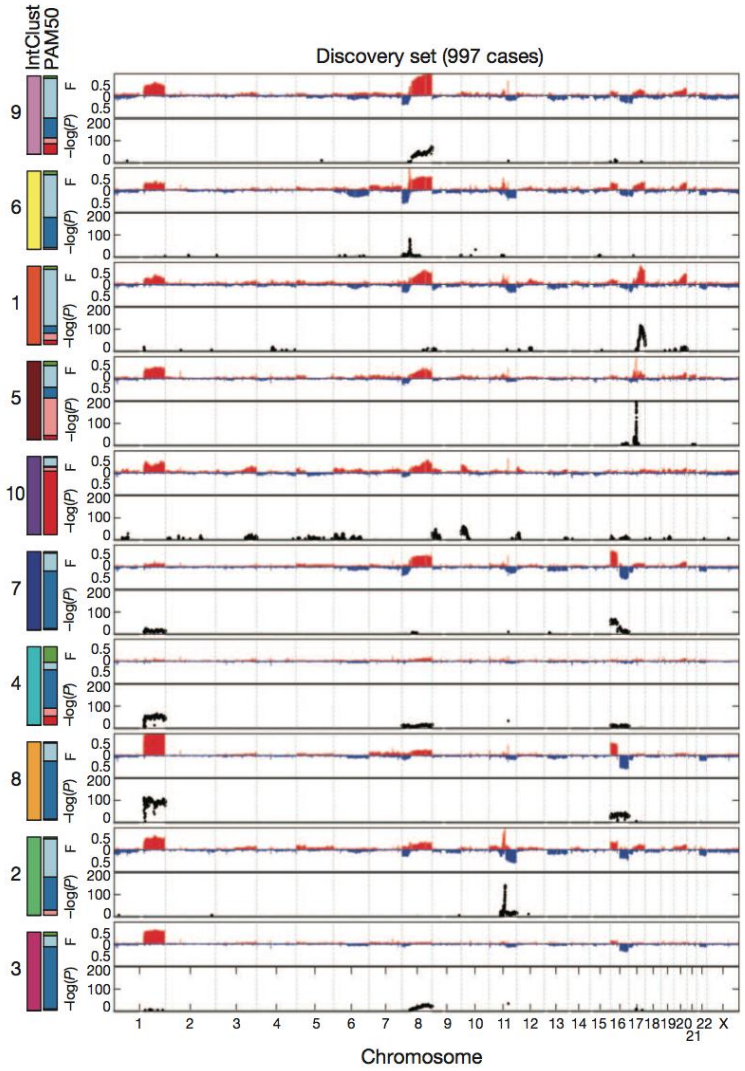


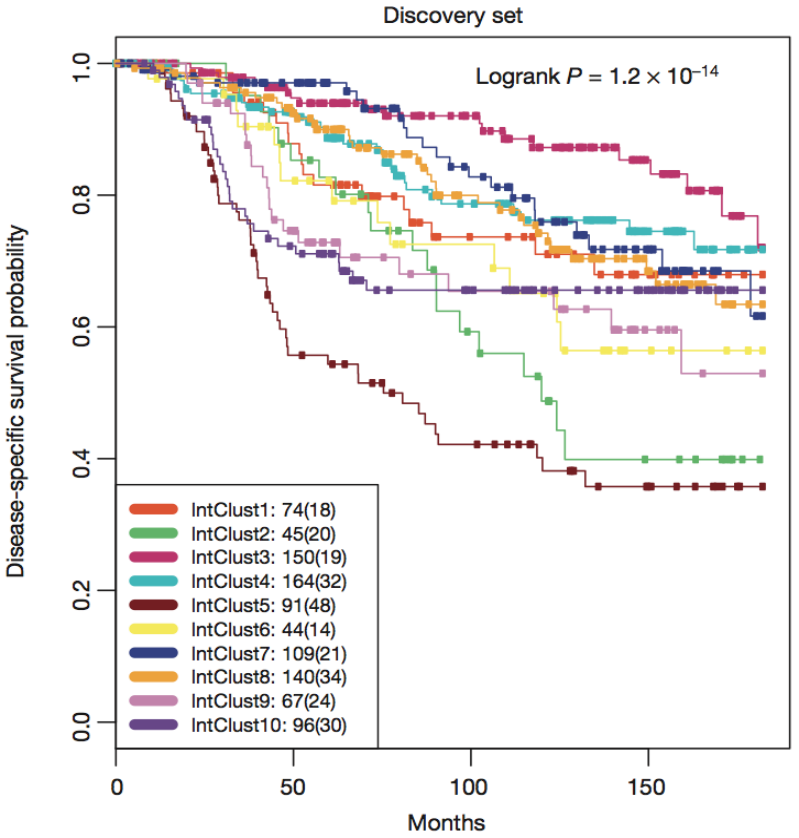
Trans 5947 genes

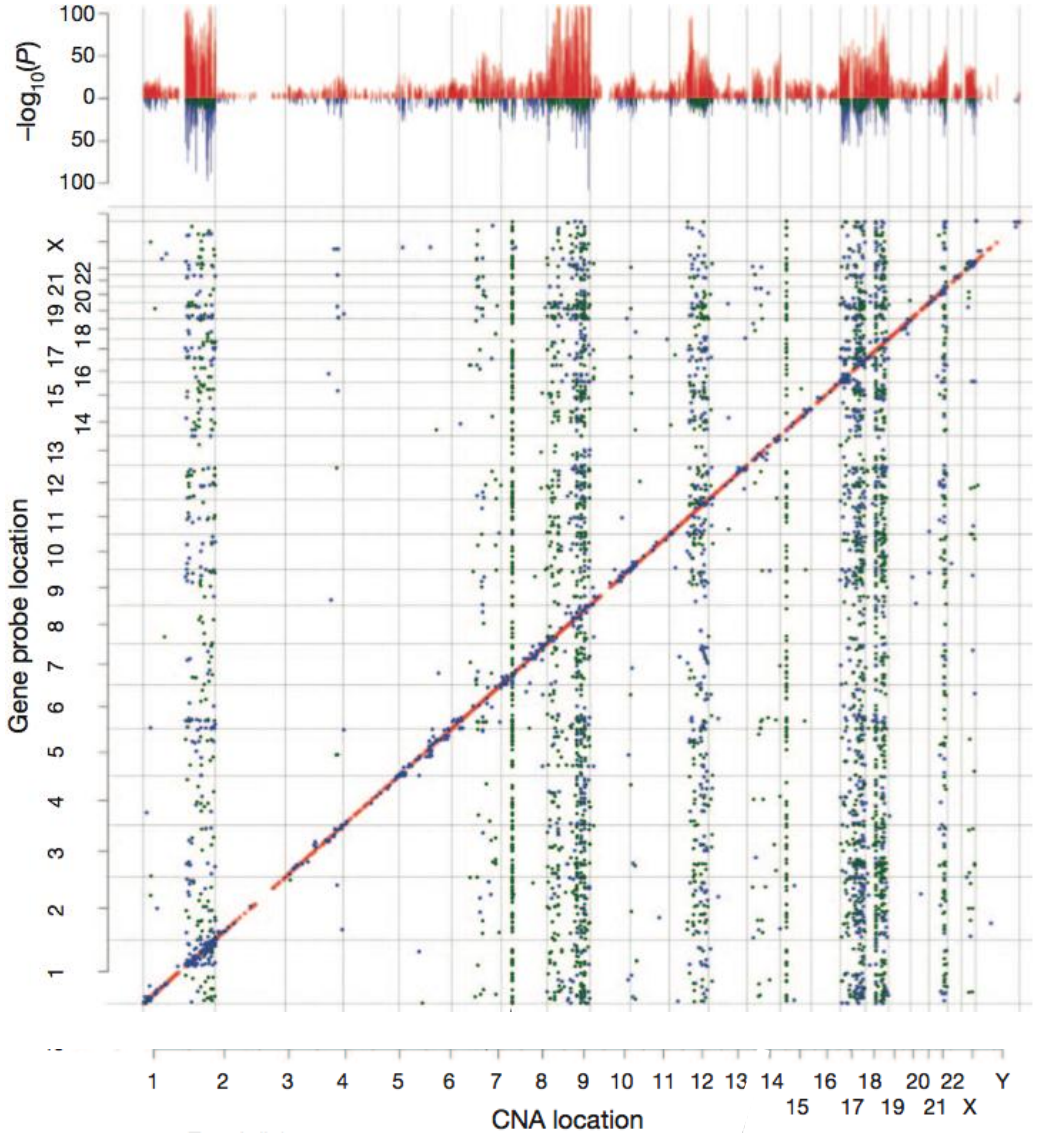


- ***Cis*** = a variant at a locus has an impact on its own expression
- ***Trans*** = a variant at a locus is associated with genes at other sites in the genome

(2) Integrative clustering reveals 10 novel ***IntClust*** molecular subgroups beyond the intrinsic subtypes







(3) ***Trans***-acting associations reveal distinct modules

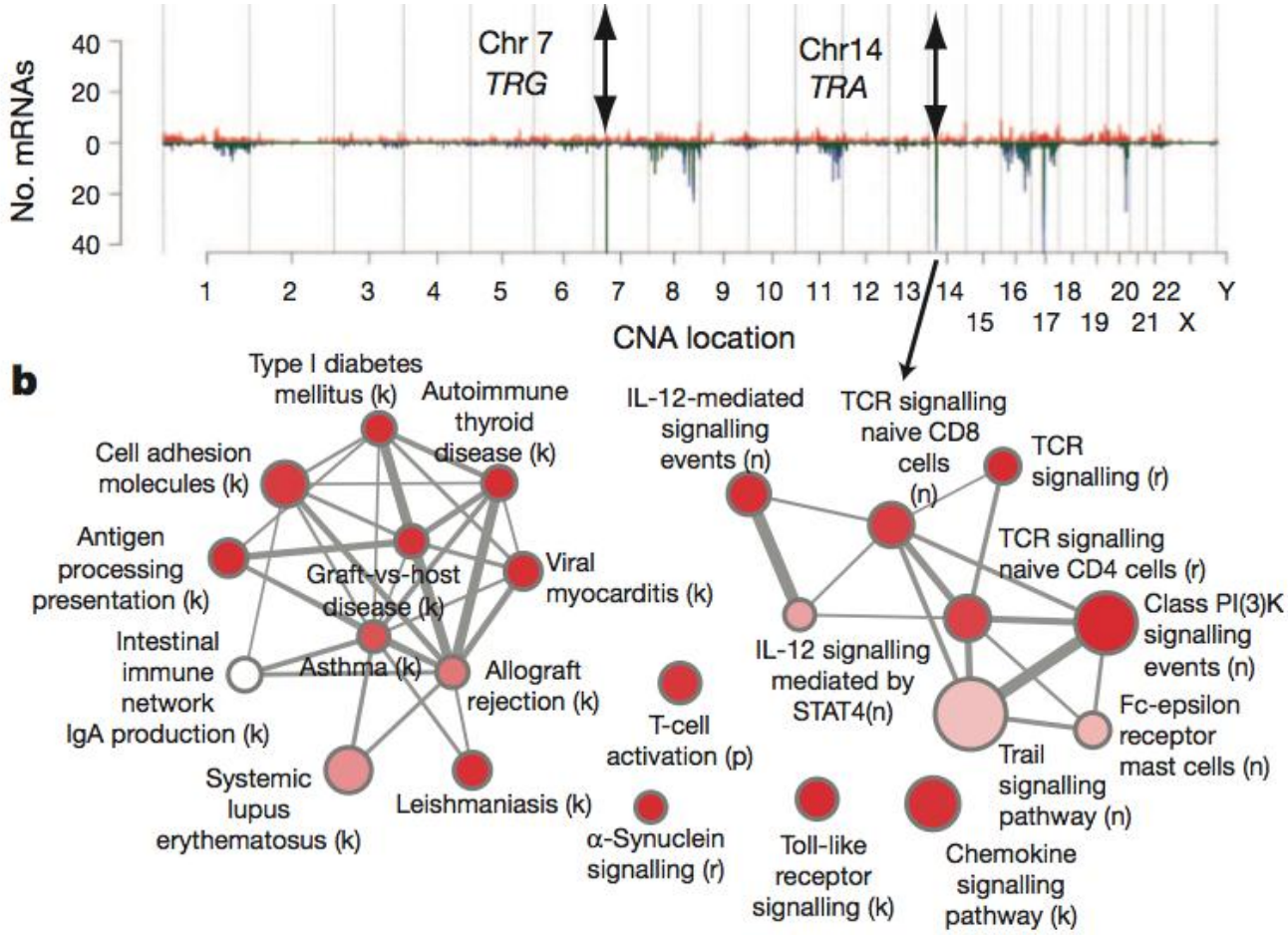
↓

Strong "off-diagonal" patterns!

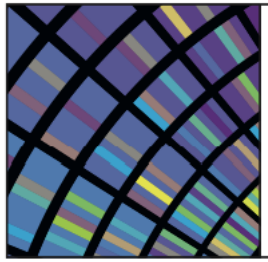
Cis + - Trans + -

These ***trans*** aberrations can be grouped into pathway modules

(induction of adaptive immune response)



The **ENCODE** project provides information on the human genome far beyond that contained within the DNA sequence — it describes ***the functional genomic elements that orchestrate the development and function of a human.***



ENCODE
Encyclopedia of DNA Elements
nature.com/encode

ARTICLE

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Landscape of transcription in human cells

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"Here we report evidence that ***three-quarters of the human genome is capable of being transcribed***, as well as observations about the range and levels of expression, localization, processing fates, regulatory regions and modifications of almost all currently annotated and thousands of previously un-annotated RNAs. ***These observations, taken together, prompt a redefinition of the concept of a gene***"

The ***huge challenge*** is how to make sense out of all this…

"You're the first patient ever to make sense of that chart. I'd say you're dyslexic."