MammaPrint

The current situation and future developments

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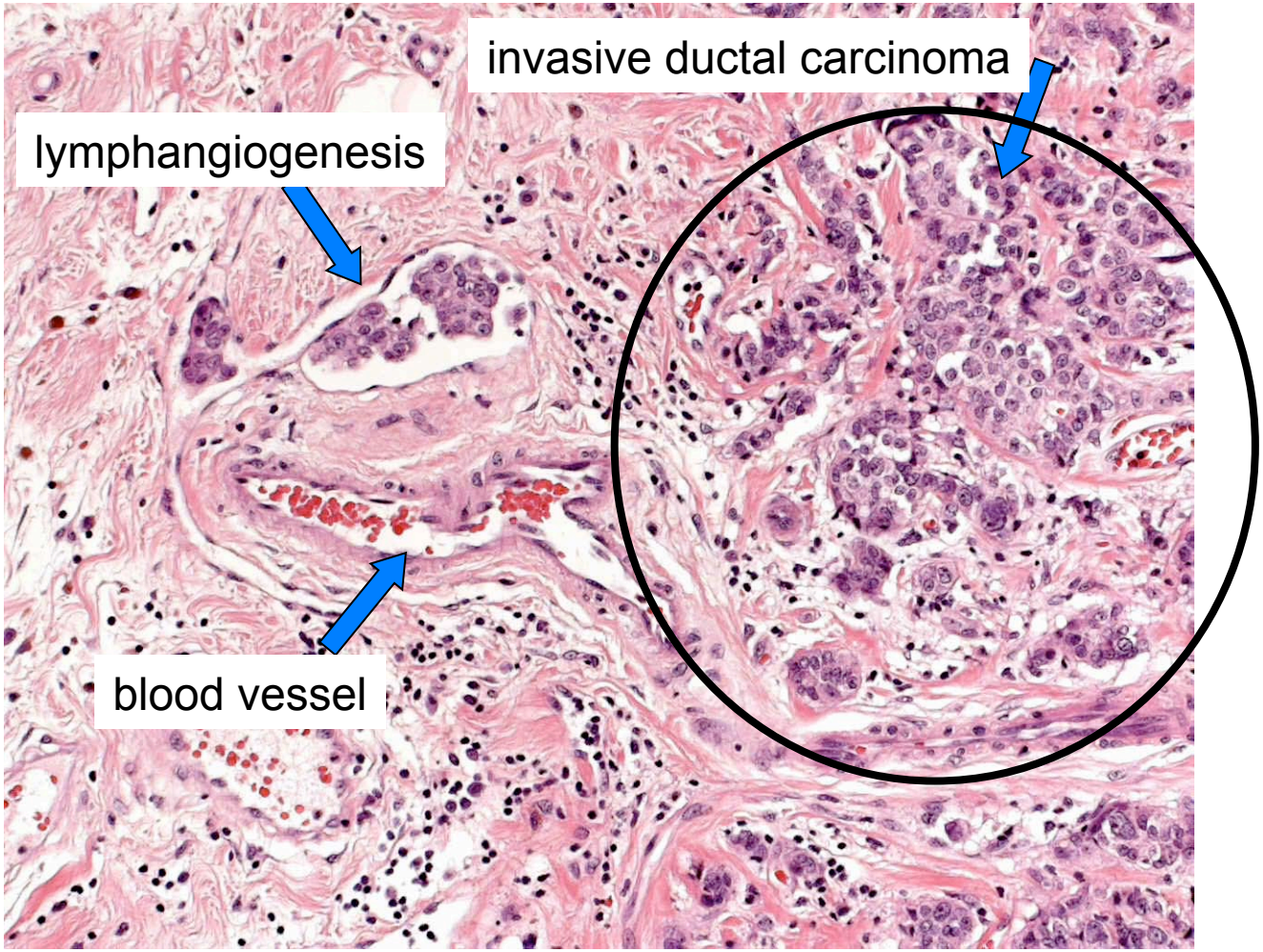
NCCN / JCCNB Seminar - Tokyo
October 18, 2009

株式会社DNAチップ研究所 -
MammaPrint（マンマプリント）-

mammaprint™

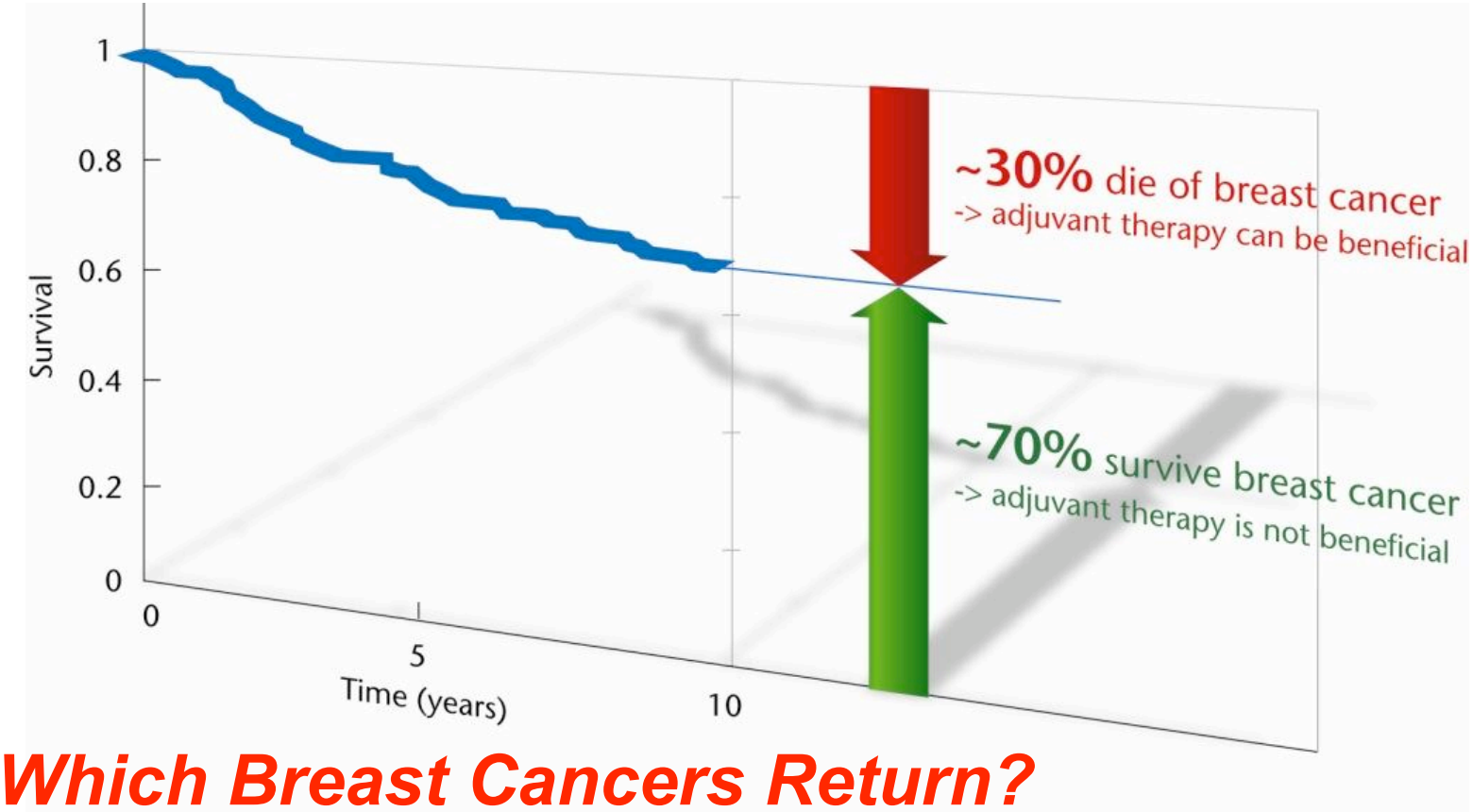
decoding breast cancer.

Breast Cancer
Invasive Ductal Carcinoma



Breast Cancer - Survival

Kaplan-Meier Survival Curves



Which Breast Cancers Return?

Breast Cancer Treatment Options

+/-

Surgery

Local Radiotherapy

(Neo-)Adjuvant systemic therapy

1. Chemotherapy
2. Endocrine therapy
3. Targeted therapy

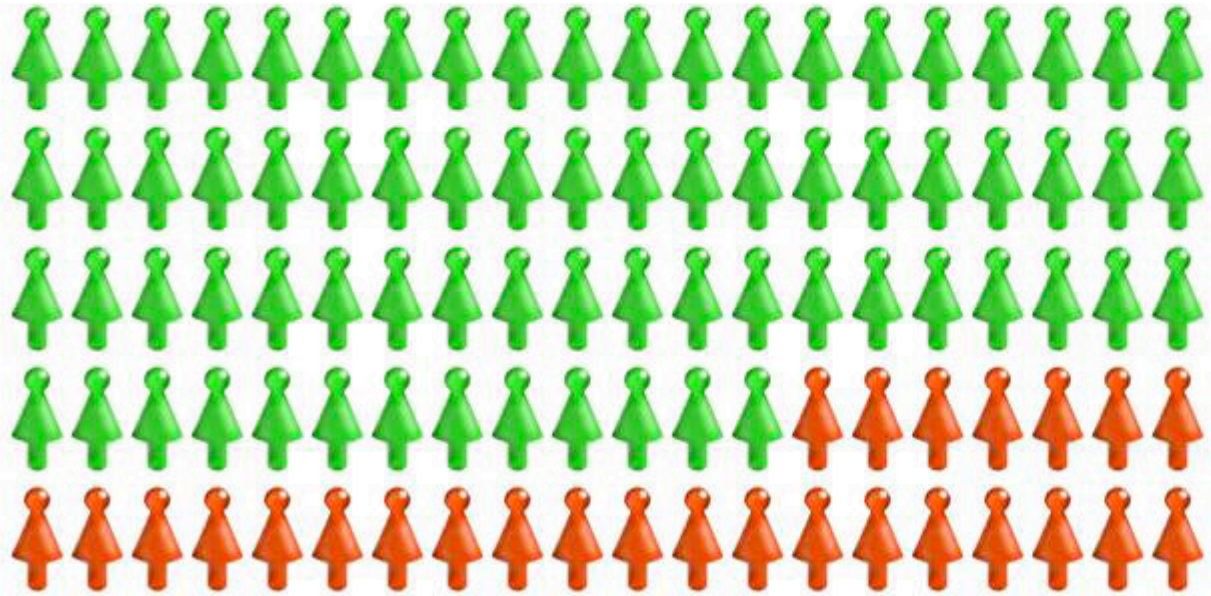
After surgery and Radiotherapy:
1) Who to treat, 2) How to treat - what drugs

Need and benefit of adjuvant treatment

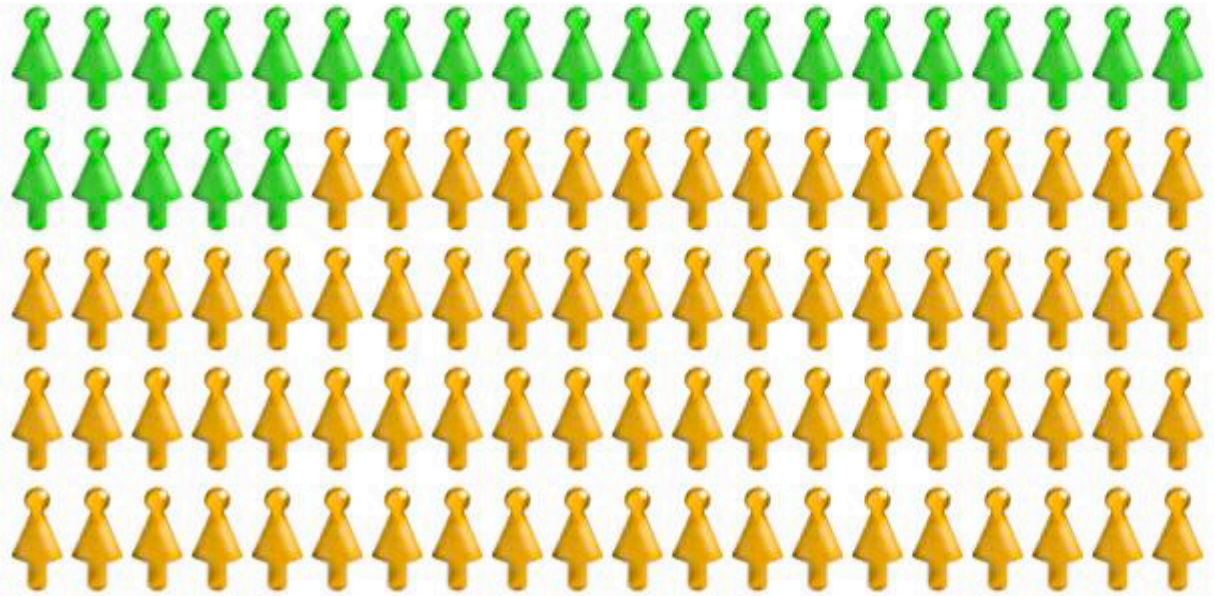
- Risk of recurrence and death → Prognosis
- Likelihood of benefit from therapy
  based on overall biology
  and/or expression of target → Prediction

Of 100 women with breast cancer (stage 1/2)

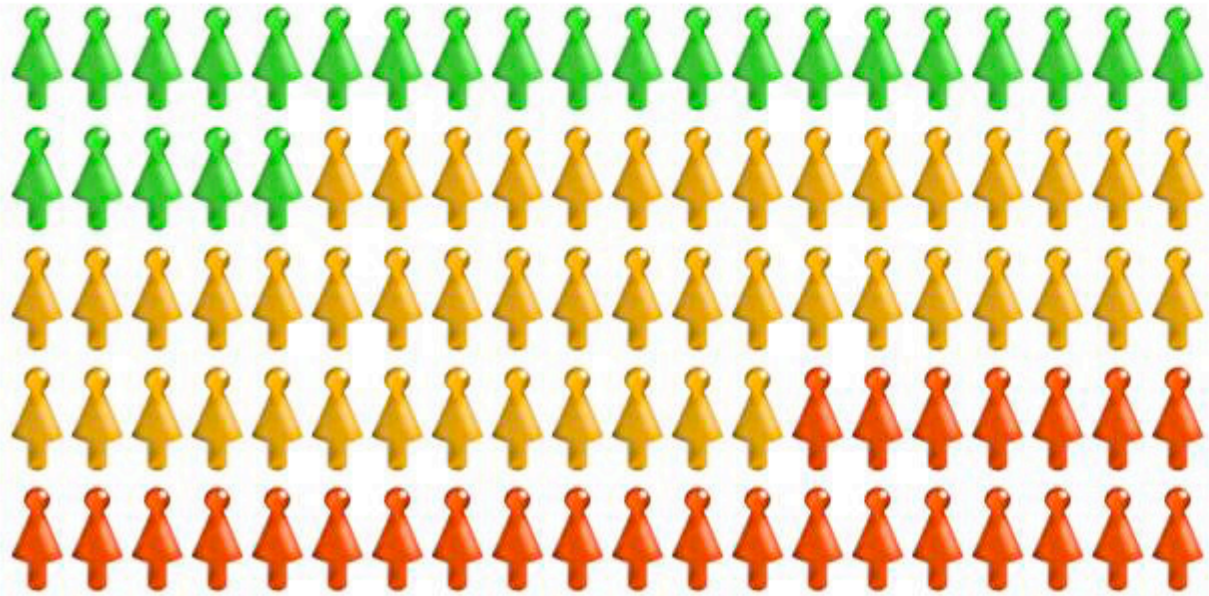
……~25% will develop a recurrence



…….75% of all patients is treated with chemotherapy



So, overall 50% of patients receive toxic chemotherapy
of which they do not benefit,
but may suffer the toxic side-effects



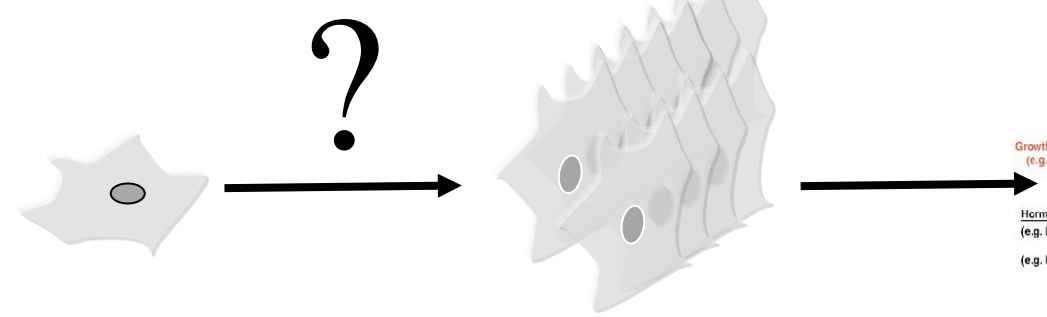
Can we do better?

The Microscope, 350 years

Van Leeuwenhoek microscope,
17th century
(Hospital of Netherlands Cancer Institute
is named Antoni van Leeuwenhoek Hospital)

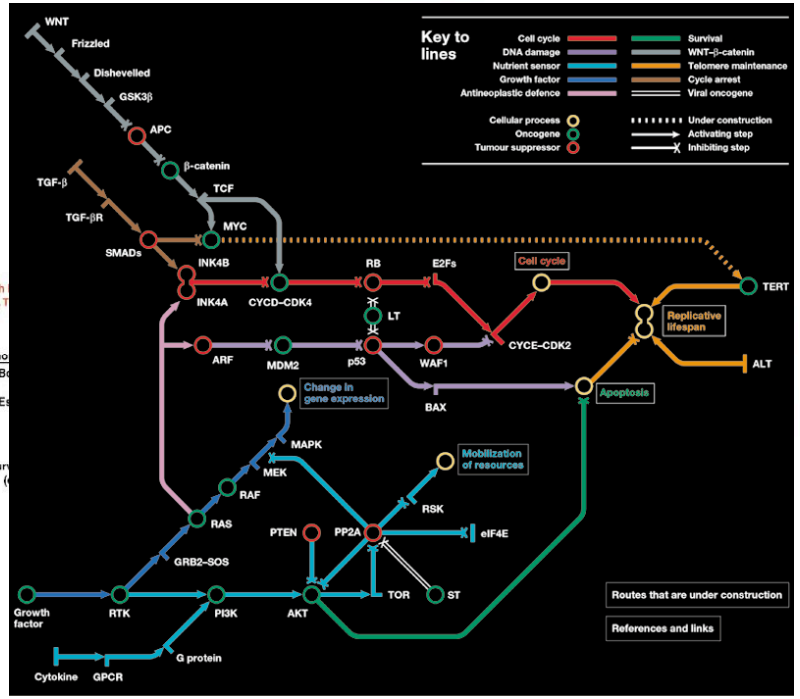
Digital microscope,
21th century

30 years of progress in cancer research



Normal cell

Cancer



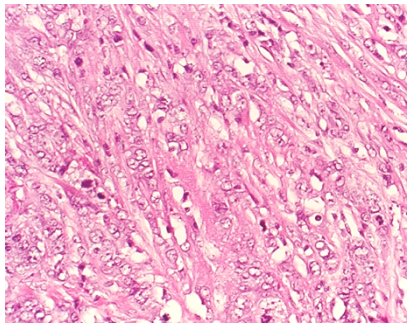
1979

2009

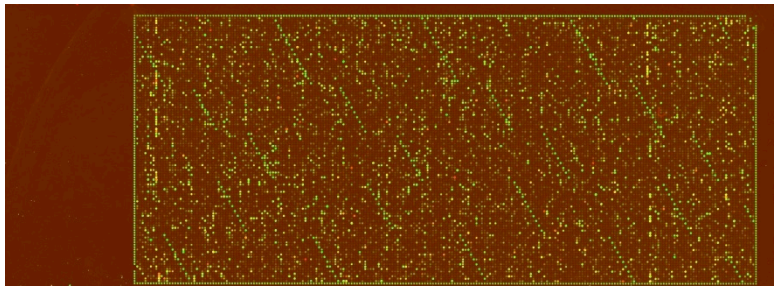
New diagnostics of cancer:

from micro-scope to micro-array to micro-xxx

Micro-scope

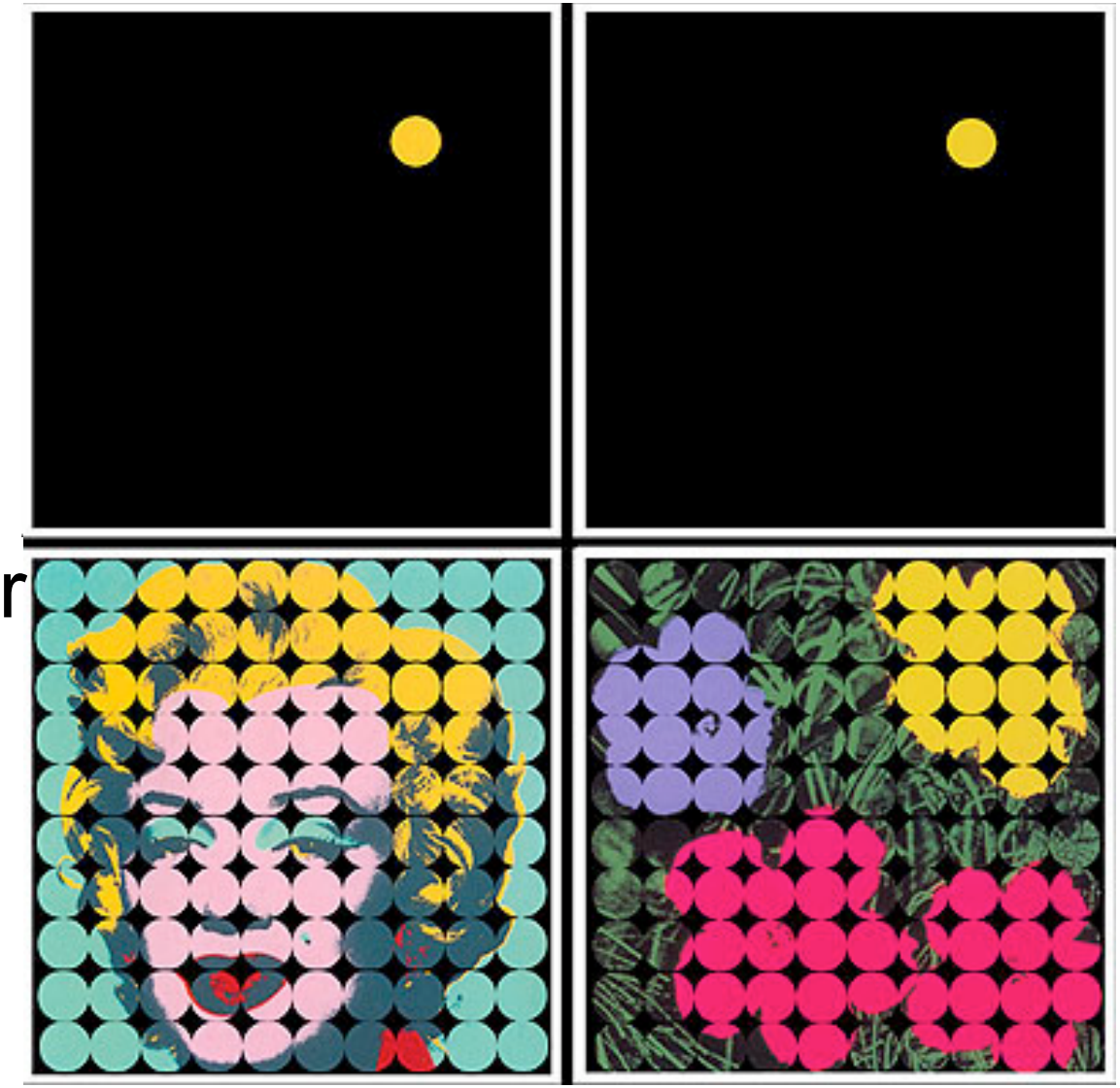


Micro-array



Comprehensive set shows the picture

Breast Cancer



RNA Gene Expression Profiling

70 gene MammaPrint signature; Recurrence Score

H/ITM (HOXB13/IL17BR); Genomic Grade; 76 gene Rotterdam signature

DNA microarray technology:

- Allows us to determine the activity of thousands of genes in a single experiment

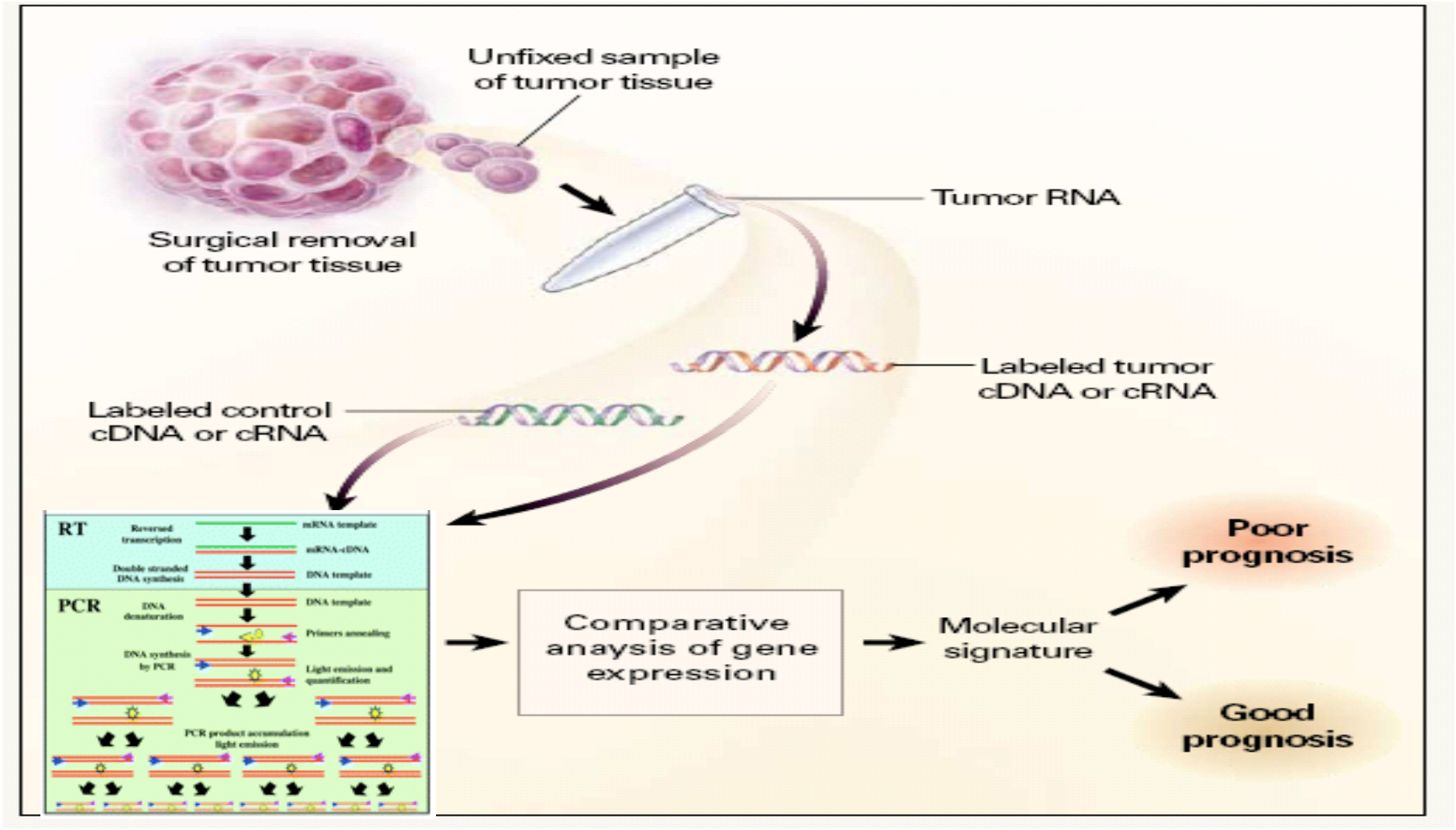
gene expression signature

expression profiling

DNA microarray technology

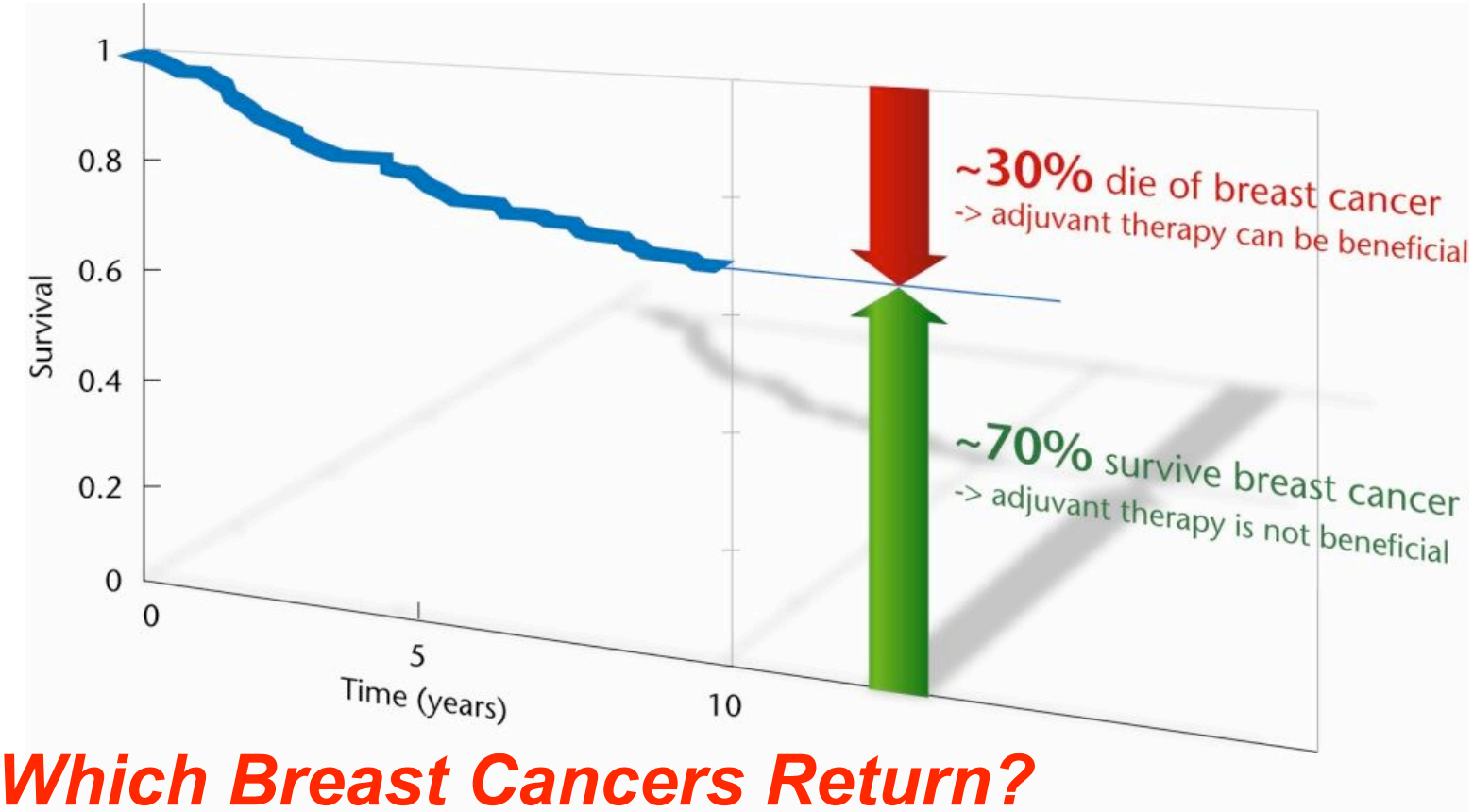
- Provides patterns that allow you to recognize
  different etiological origin,
  different classes of outcome of disease
  (prognosis, treatment response)

Multi Gene Expression Profiles in Clinical Practice



Breast Cancer - Survival

Kaplan-Meier Survival Curves



Which Breast Cancers Return?

Current Clinical Management

lymph node negative breast cancer

adjuvant treatment selection criteria

- (US or EU) consensus criteria: > 80%

As only 25-30% of these patients develop distant metastases, some 40-60% of patients are over-treated with adjuvant (chemo)therapy, some may be undertreated

Clinicopathological Risk Assessment
Adjuvant! Online

Patient Information

Age: 50

Comorbidity: Average for Age

ER Status: Positive

Tumor Grade: Grade 3

Tumor Size: 2.1 - 3.0 cm

Positive Nodes: 0

Calculate For: Mortality

10 Year Risk: 24 Prognostic

Adjuvant Therapy Effectiveness

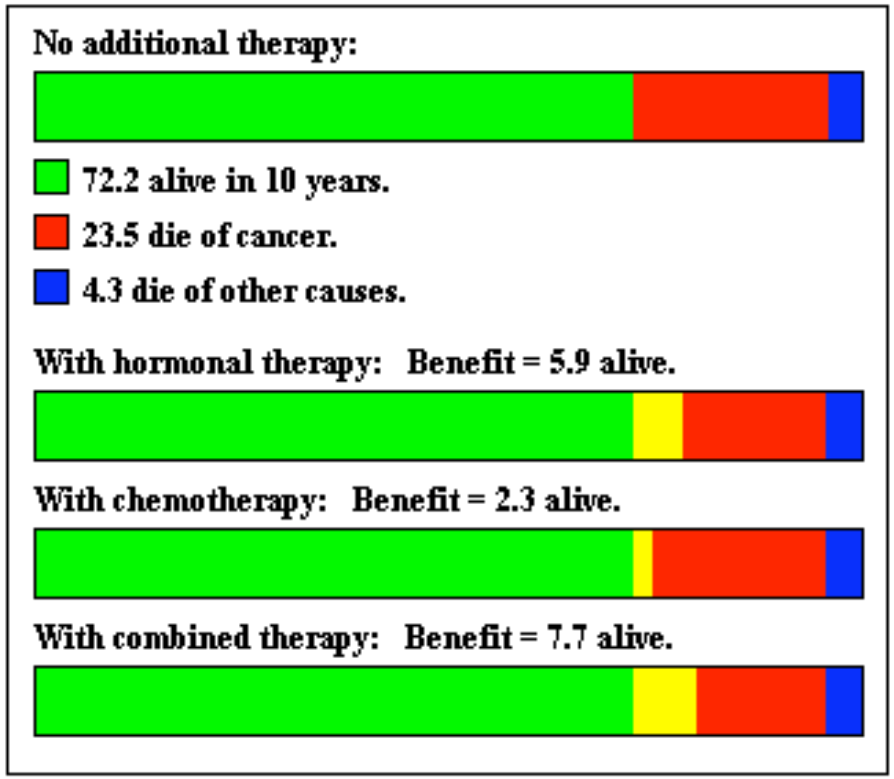
Horm: Overview 98 (Tamoxifen)

Chemo: Overview 98 (CMF-Like)

Hormonal Therapy: 28

Chemotherapy: 11

Combined Therapy: 36



Print

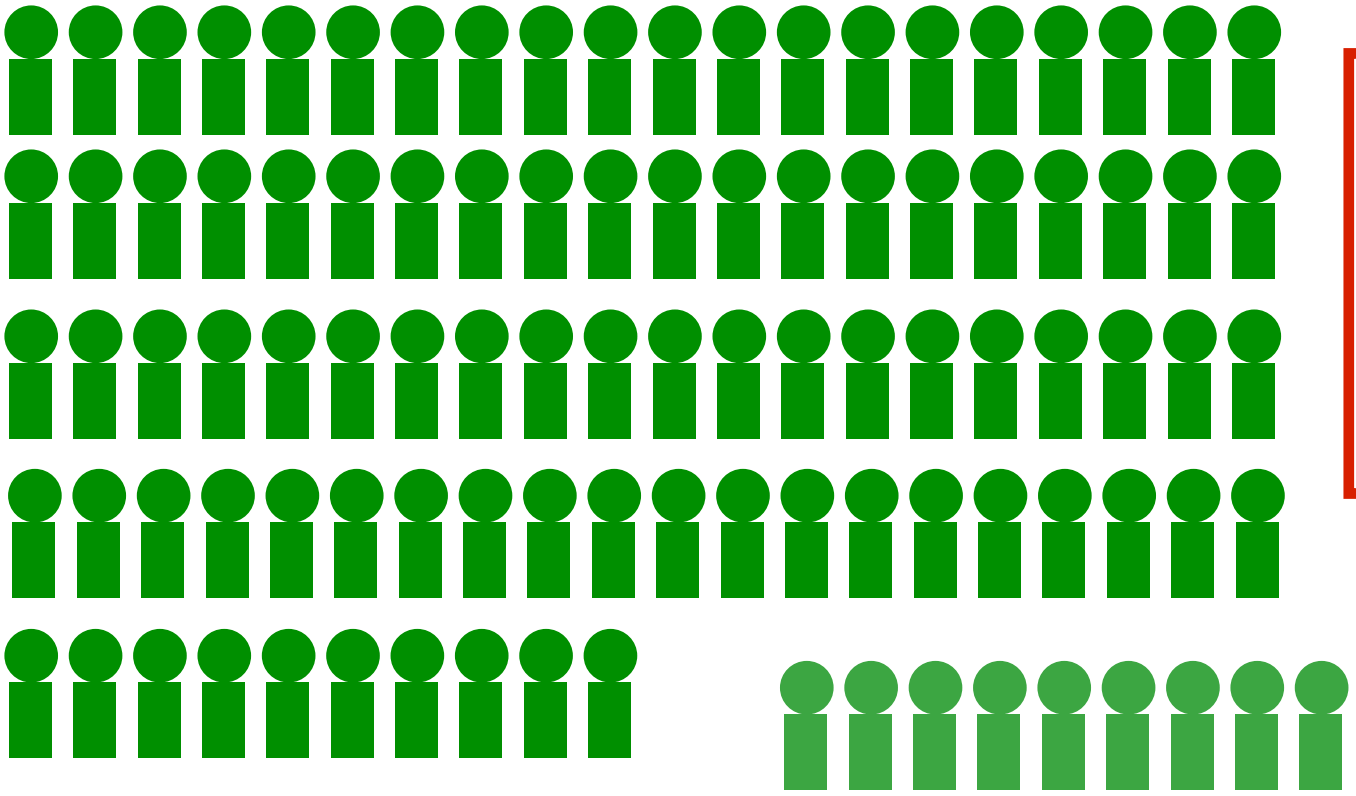
Help

www.**adjuvantonline.com/** - キャッシュ - 類似ページ

The Problem For Using Chemotherapy

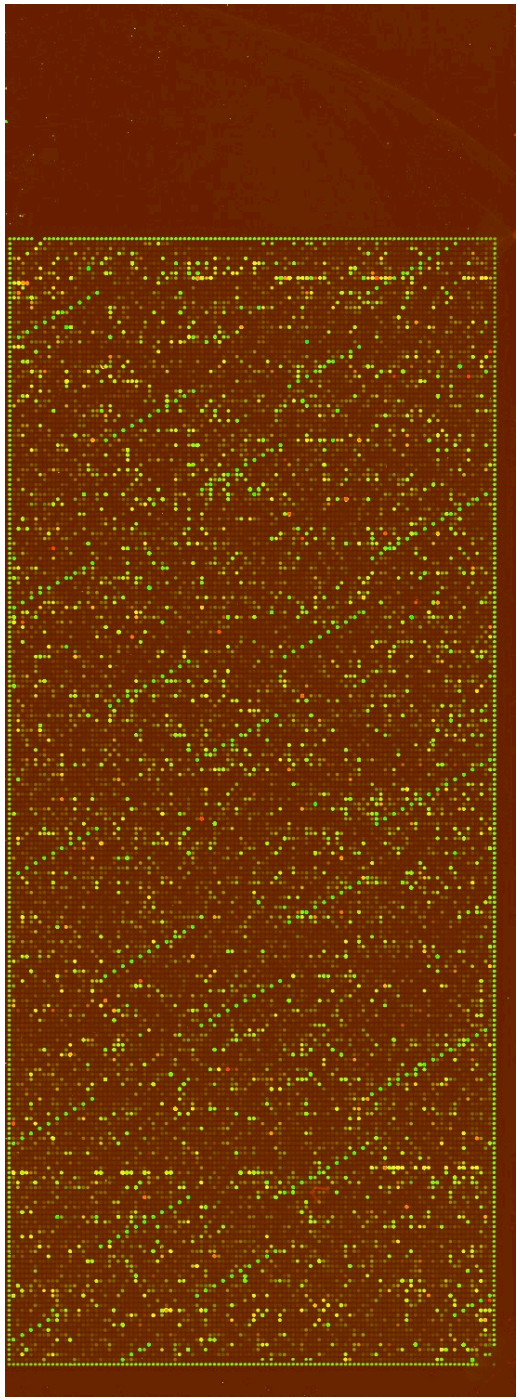
(Most Common Presentation Of Breast Cancer
Today: T1 N0 ER+ Grade 2)

Need To Treat 100 Women



And Only One Benefits!

Courtesy Peter Ravdin



Breast Cancer retrospective series n=78 with known outcome

Scanned image of 25K human oligonucleotide microarray

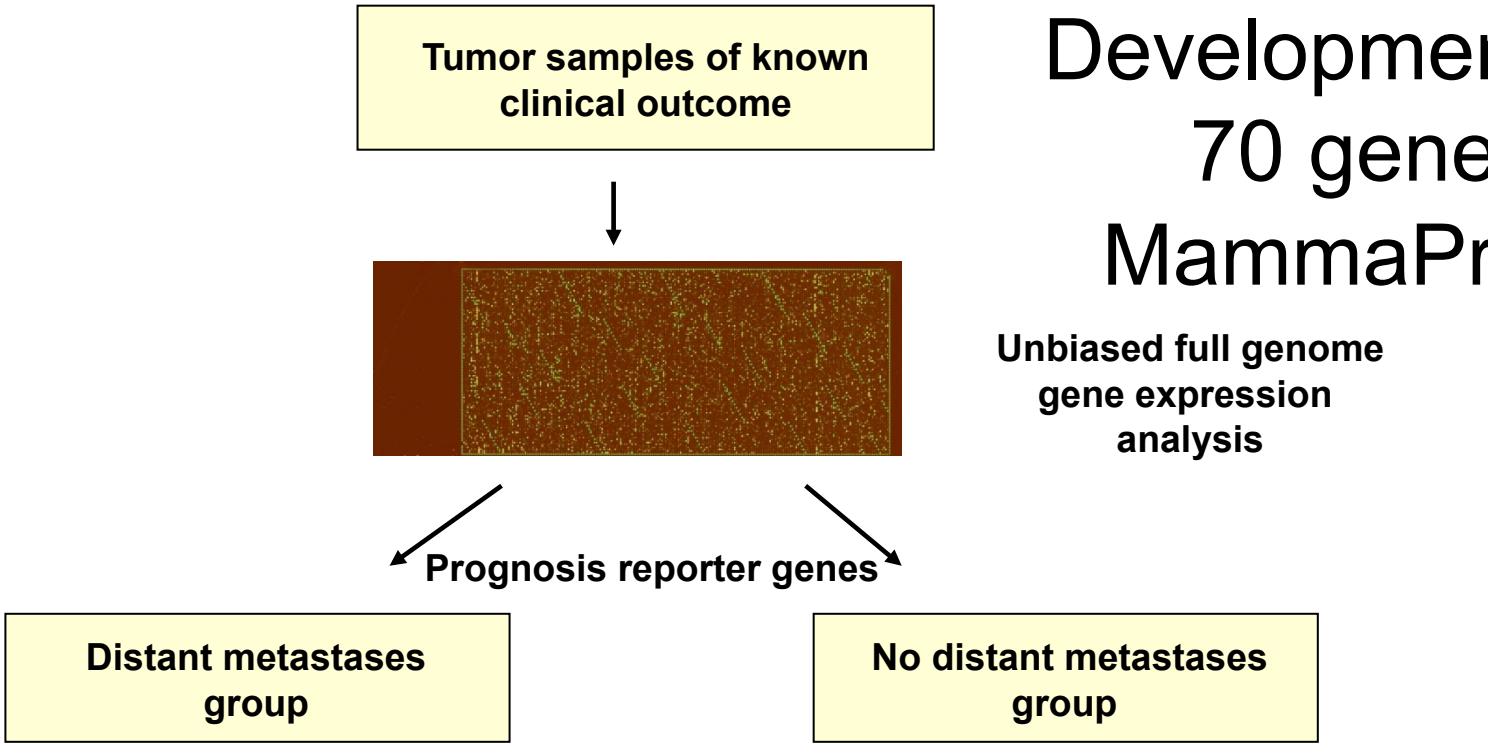
Hybridized with mixture of ‘red’-labeled cRNA of a tumor sample and ‘green’-labeled reference cRNA

Determine:

- fluorescence intensities
- recognize patterns related to clinical parameter over a series of tumors

Nature, 2002

Development of 70 gene MammaPrint



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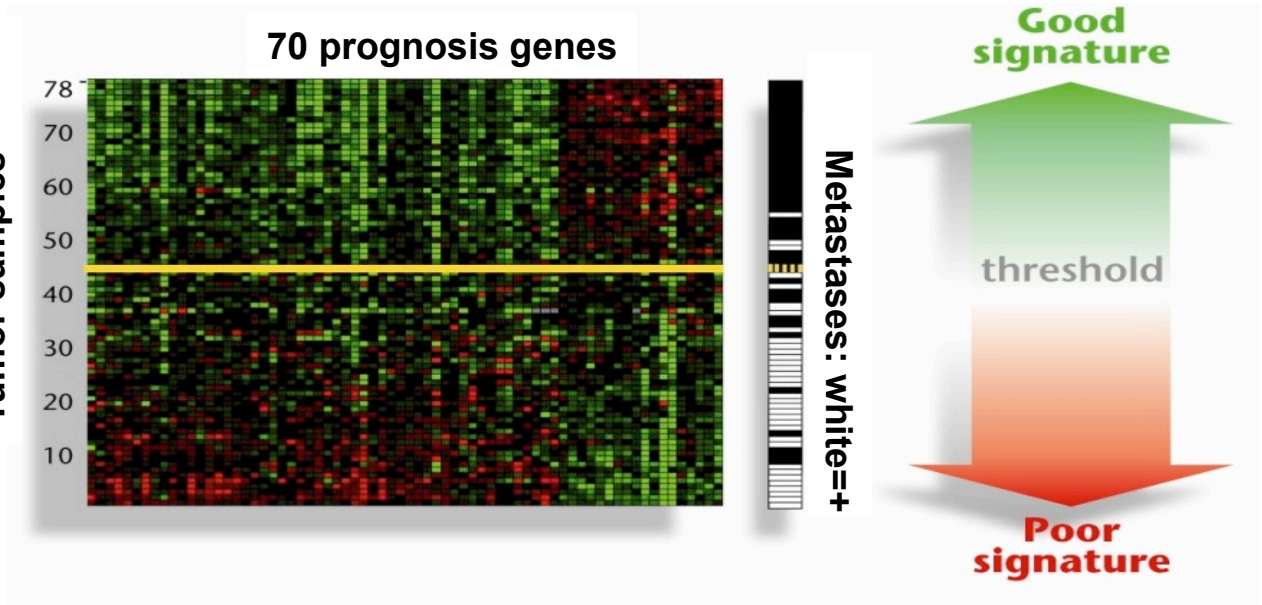
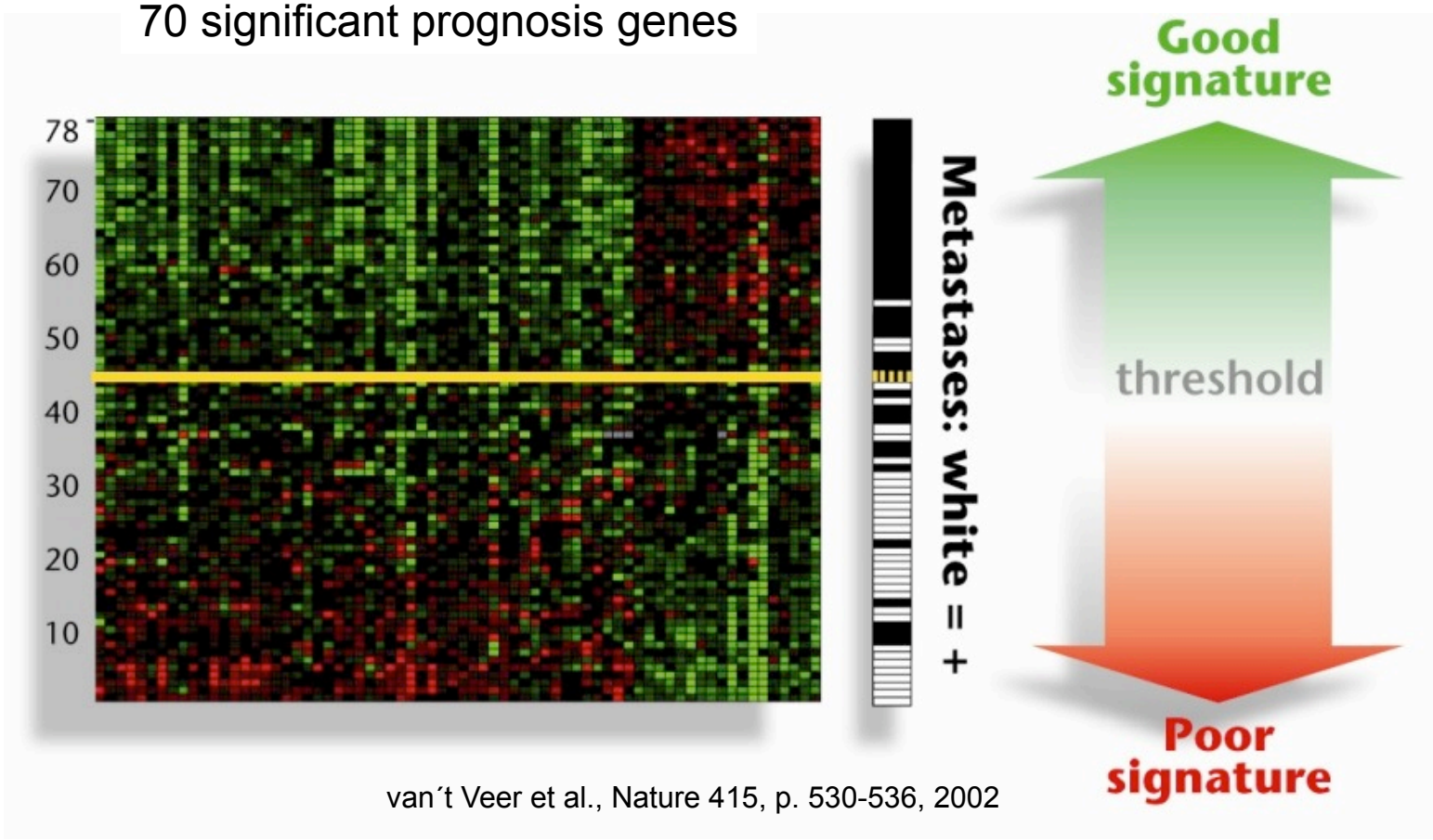


Nature, 2002

70 Gene MammaPrint Signature

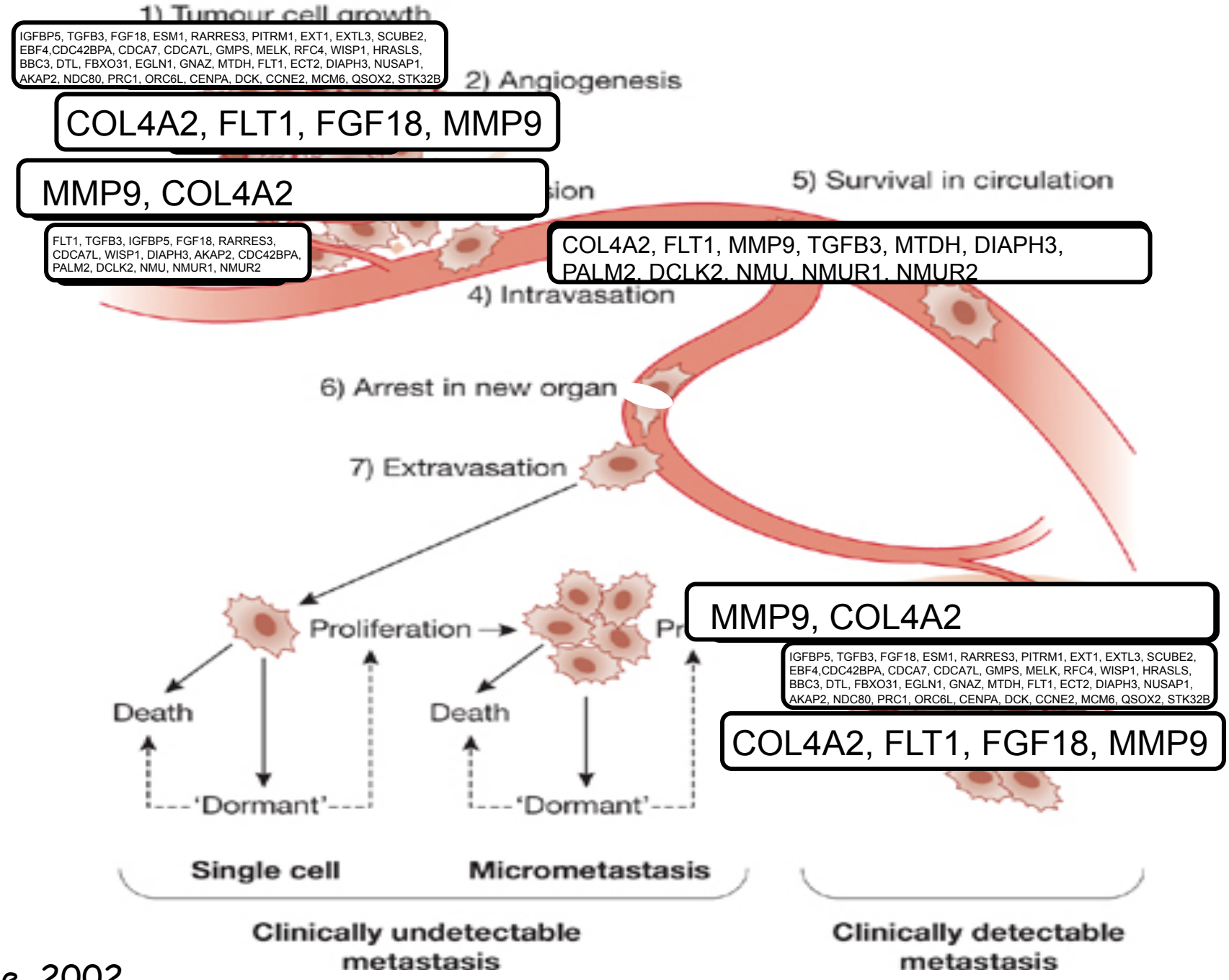
Supervised analysis on n=78 tumors, >96% adjuvantly untreated



threshold set with 10% false negatives

91 % sensitivity, 73% specificity

Nature, 2002

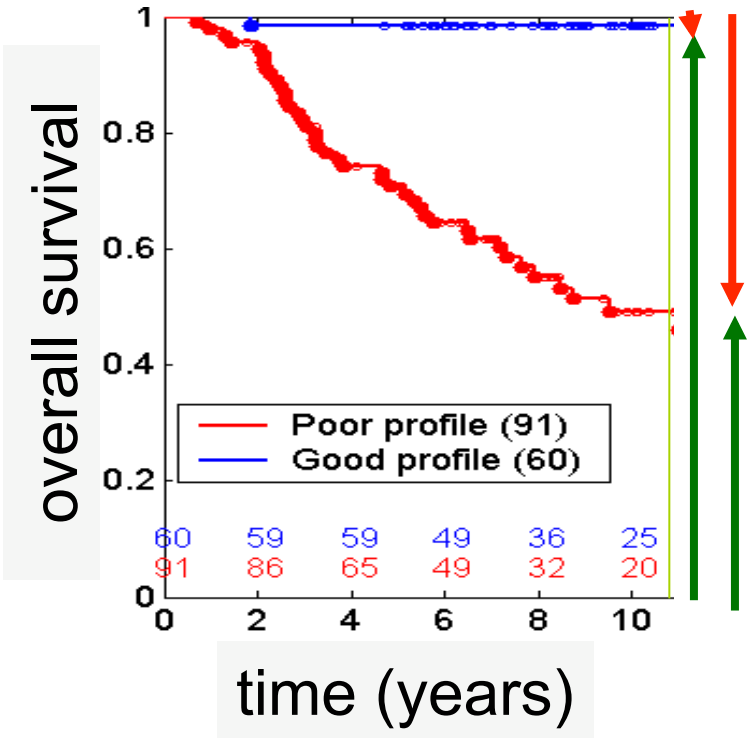

1) Tumour cell growth
IGFBP5, TGFB3, FGF18, ESM1, RARRES3, PITRM1, EXT1, EXTL3, SCUBE2, EBF4,CDC42BPA, CDCA7, CDCA7L, GMPS, MELK, RFC4, WISP1, HRASLS, BBC3, DTL, FBXO31, EGLN1, GNAZ, MTDH, FLT1, ECT2, DIAPH3, NUSAP1, AKAP2, NDC80, PRC1, ORC6L, CENPA, DCK, CCNE2, MCM6, QSOX2, STK32B
2) Angiogenesis
COL4A2, FLT1, FGF18, MMP9
MMP9, COL4A2
FLT1, TGFB3, IGFBP5, FGF18, RARRES3, CDCA7L, WISP1, DIAPH3, AKAP2, CDC42BPA, PALM2, DCLK2, NMU, NMUR1, NMUR2
5) Survival in circulation
COL4A2, FLT1, MMP9, TGFB3, MTDH, DIAPH3, PALM2, DCLK2, NMU, NMUR1, NMUR2
4) Intravasation
6) Arrest in new organ
7) Extravasation
Proliferation
Death
'Dormant'
Death
'Dormant'
MMP9, COL4A2
IGFBP5, TGFB3, FGF18, ESM1, RARRES3, PITRM1, EXT1, EXTL3, SCUBE2, EBF4,CDC42BPA, CDCA7, CDCA7L, GMPS, MELK, RFC4, WISP1, HRASLS, BBC3, DTL, FBXO31, EGLN1, GNAZ, MTDH, FLT1, ECT2, DIAPH3, NUSAP1, AKAP2, NDC80, PRC1, ORC6L, CENPA, DCK, CCNE2, MCM6, QSOX2, STK32B
COL4A2, FLT1, FGF18, MMP9
Single cell
Micrometastasis
Clinically undetectable metastasis
Clinically detectable metastasis

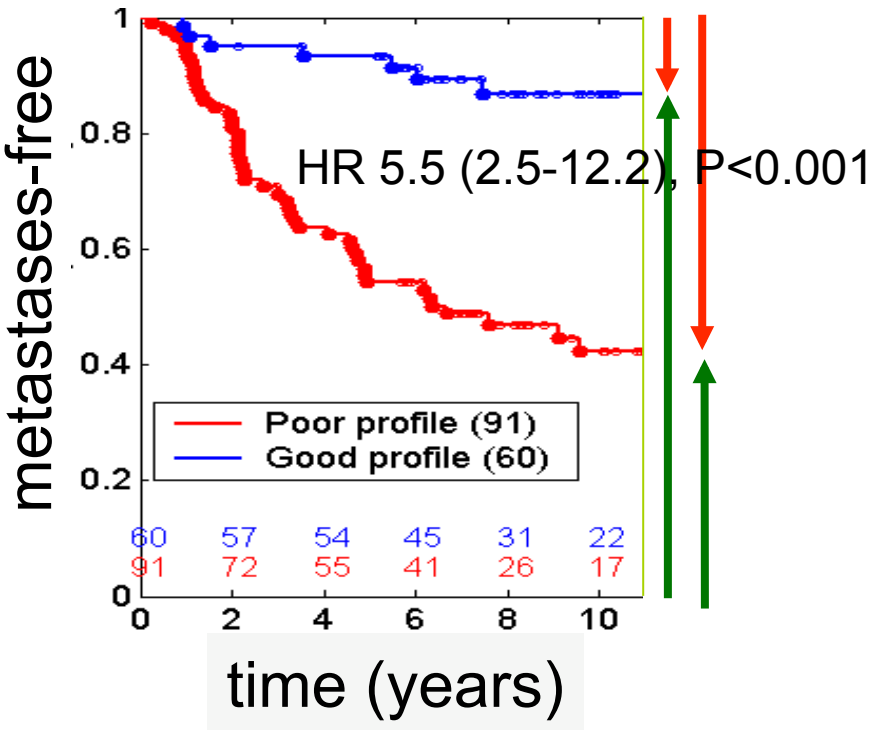
Nature, 2002

Breast Cancer – MammaPrint signature

Confirmation on Retrospective Consecutive series

n= 151; Distinguishes in 40% good profile, 60% poor profile





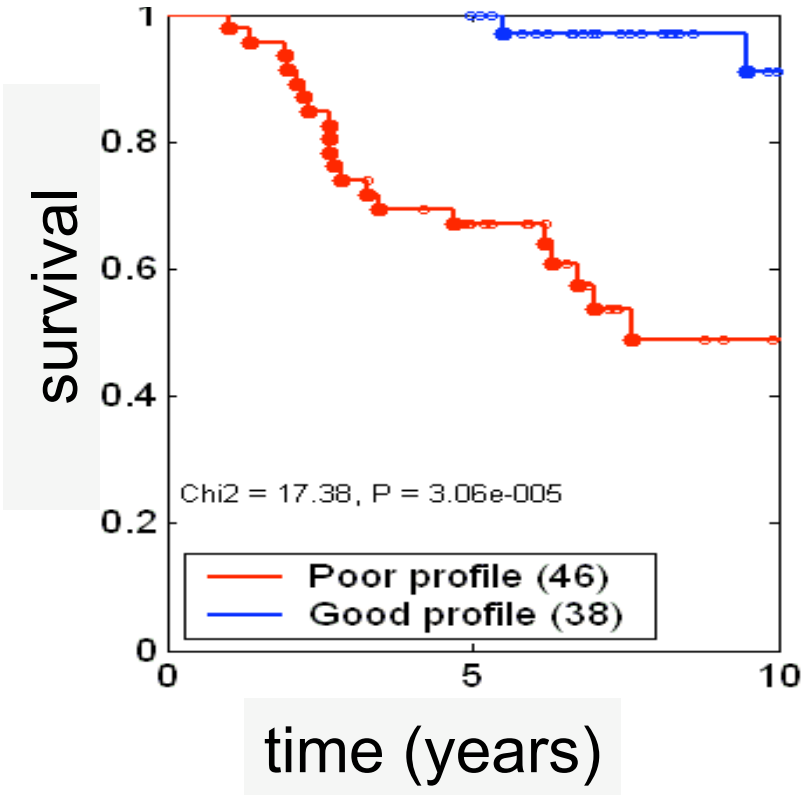
151 patients, <53, LN0
~95% adjuvantly untreated
10 year survival curve

NEJM, 2002

Improved Clinical Management

MammaPrint and tumor diameter (LN0, <53)

Small tumors, < 15mm



lymph node negative and positive patients

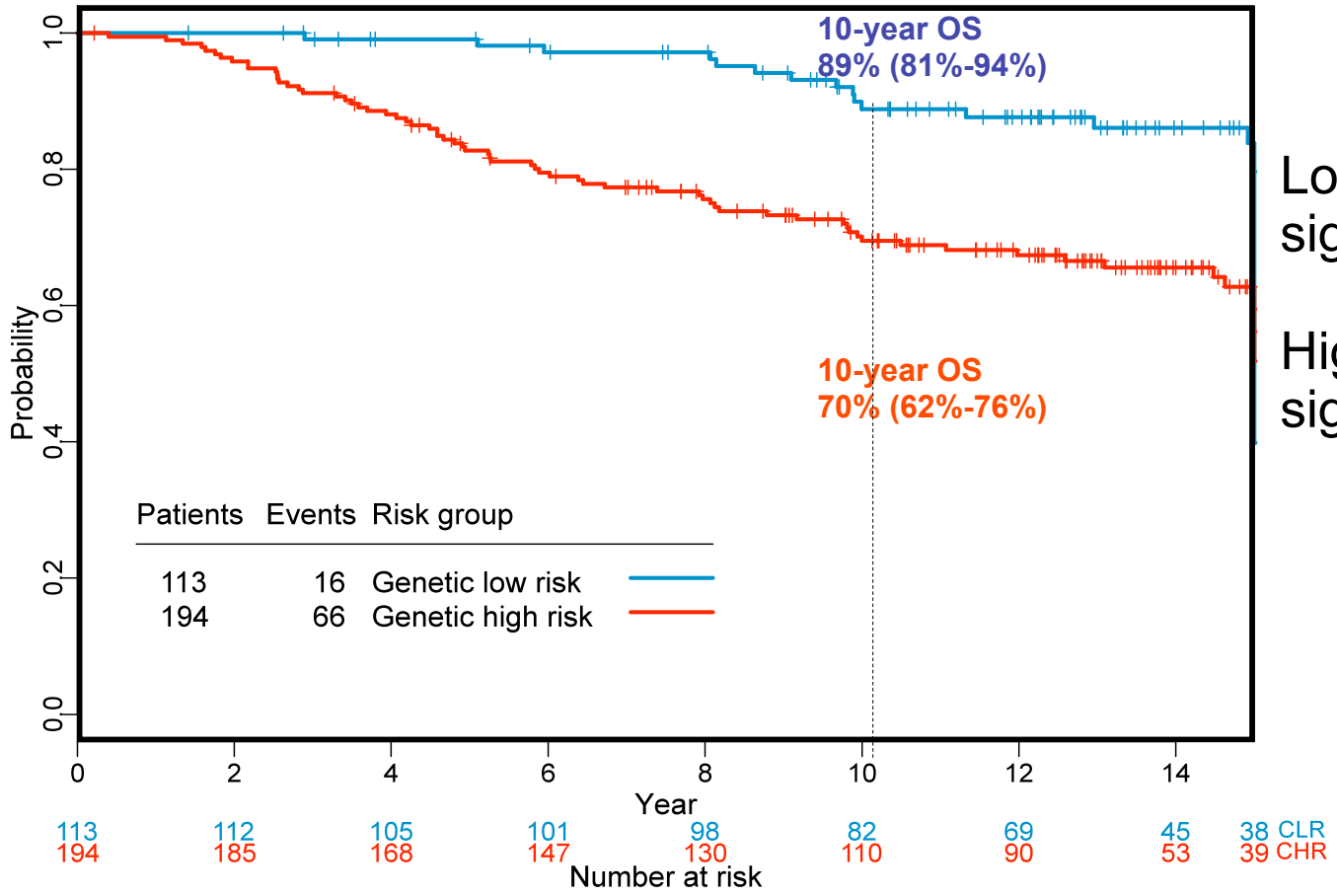
NEJM, 2002

Profiling:
40 % in good profile
60 % in poor profile

Small Tumors generally considered low risk, more than half may be at (MammaPrint) high risk.
UNDERTREATMENT!

International Validation 70-gene signature

TransBIG - 5 European Hospitals, 302 pts, adjuvantly untreated



Low risk signature

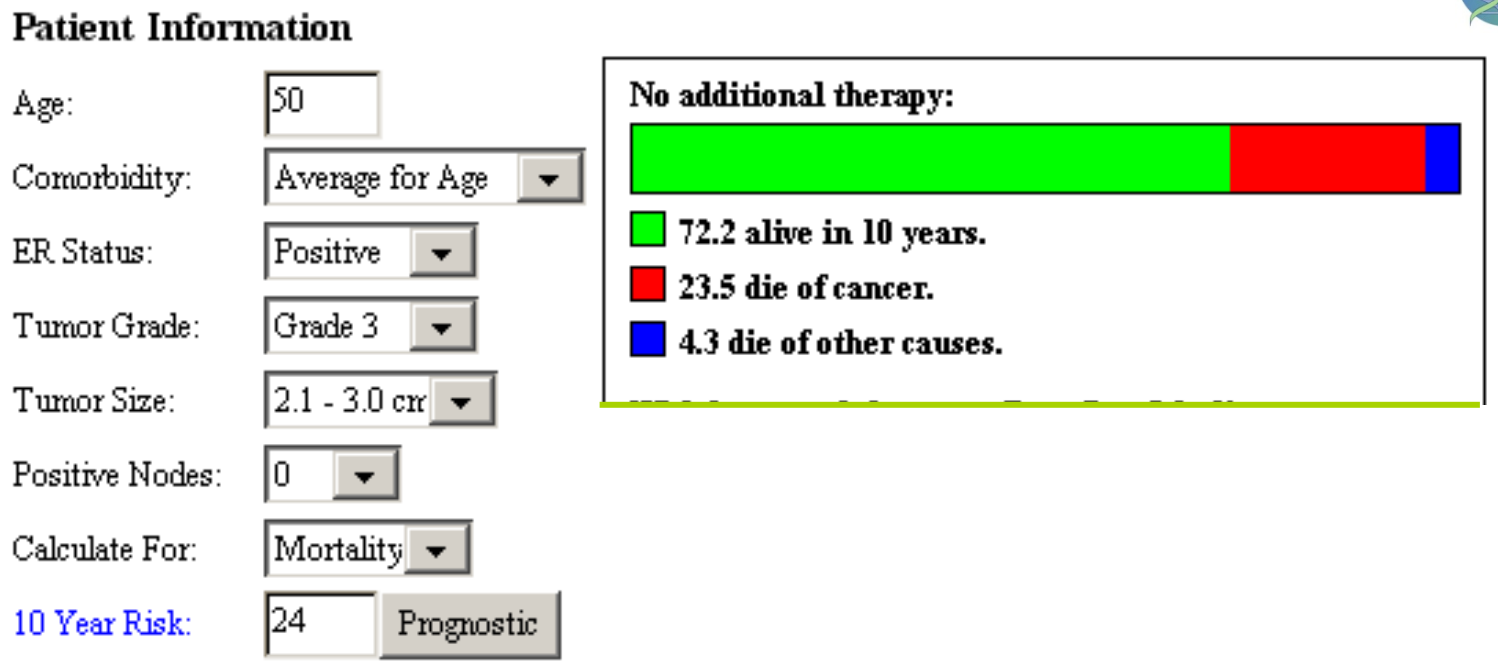
High risk signature

HR 2.87 (1.66-4.96) (P<0.001) multivariate

Overall survival by gene signature risk

Buyse, JNCI, 2006

ADJUVANT! ONLINE FOR BREAST CANCER



"Clinical low risk" defined as predicted 10-year survival probability

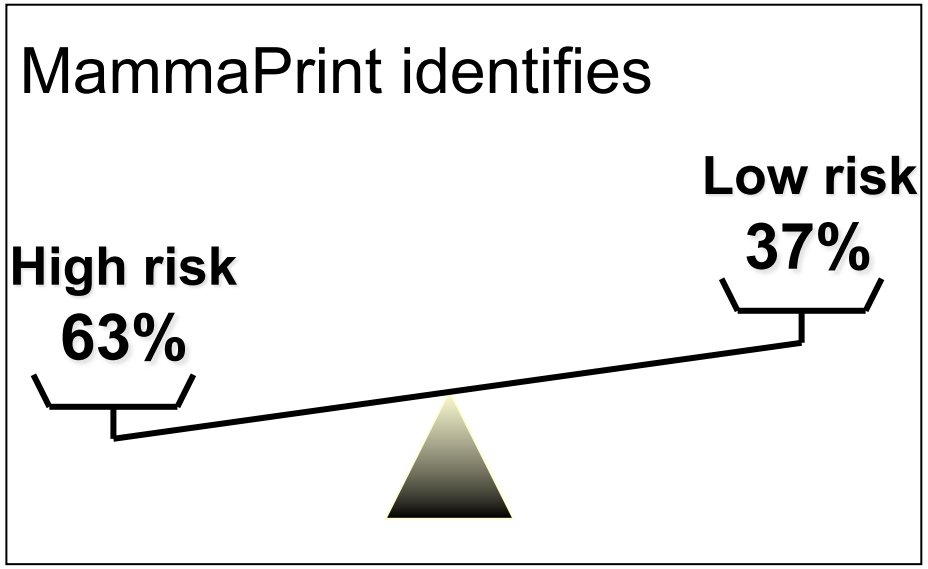
≥ 88% for ER+ patients

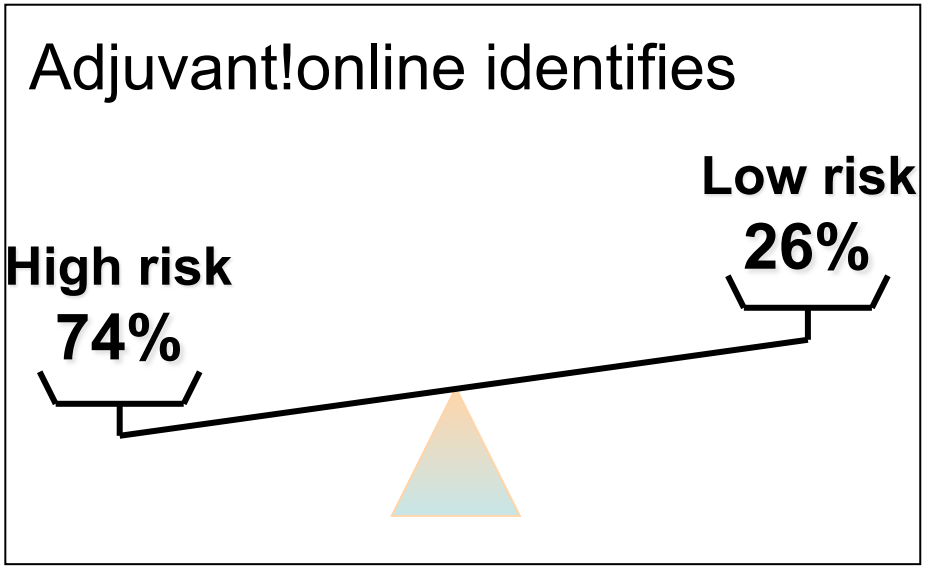
≥ 92% for ER- patients

Buyse, JNCI, 2006

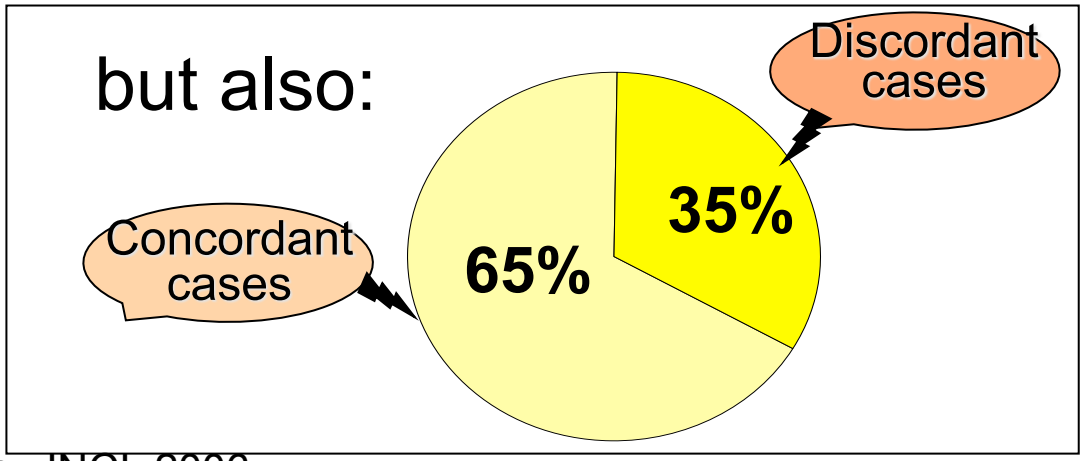
Risk assessment 302 patients

TransBIG - 5 European Hospitals





more high risk!



Adjuvant! "Clinical low risk" defined as 10-year survival probability

- ≥ 88% for ER+ patients
- ≥ 92% for ER- patients

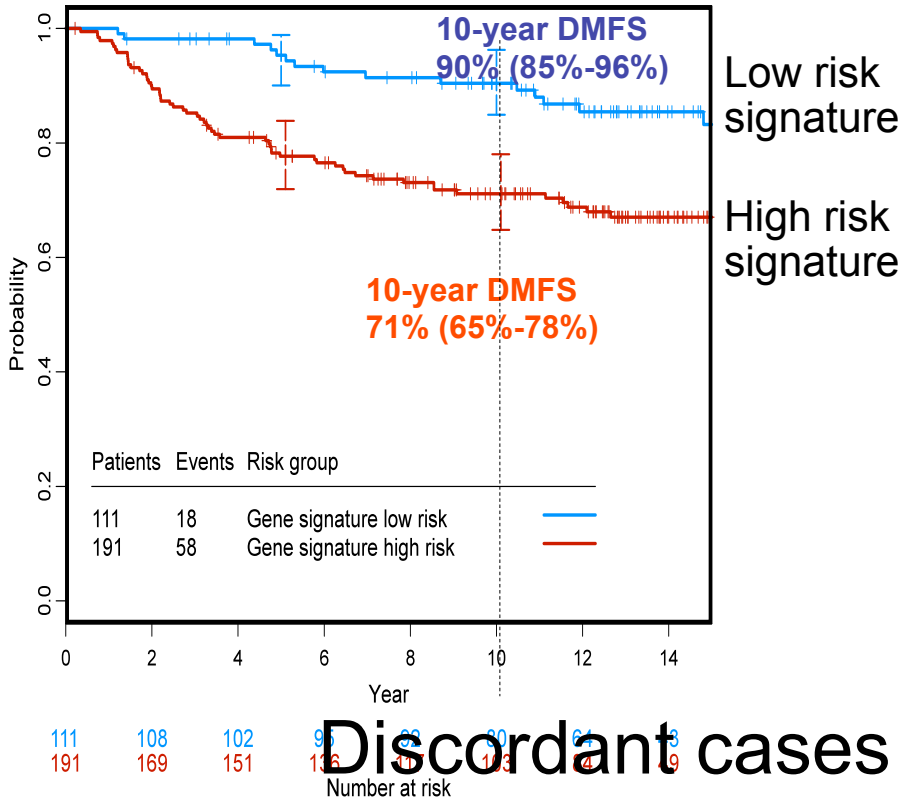
Buyse, JNCI, 2006

Metastasis-free survival

70 genes vs Adjuvant!

TransBIG - 5 European Hospitals

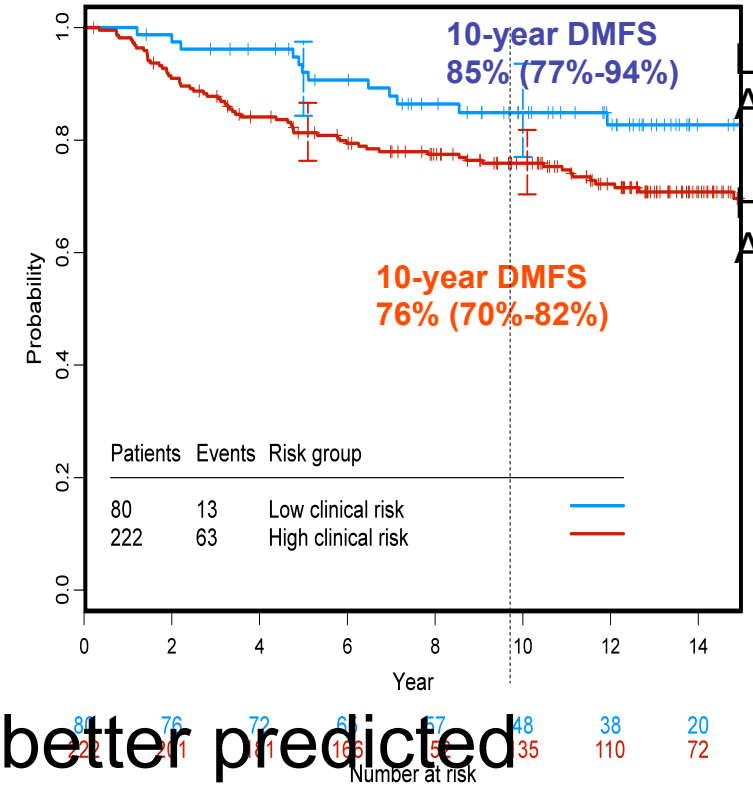
70 gene signature



Low risk signature

High risk signature

Adjuvant!



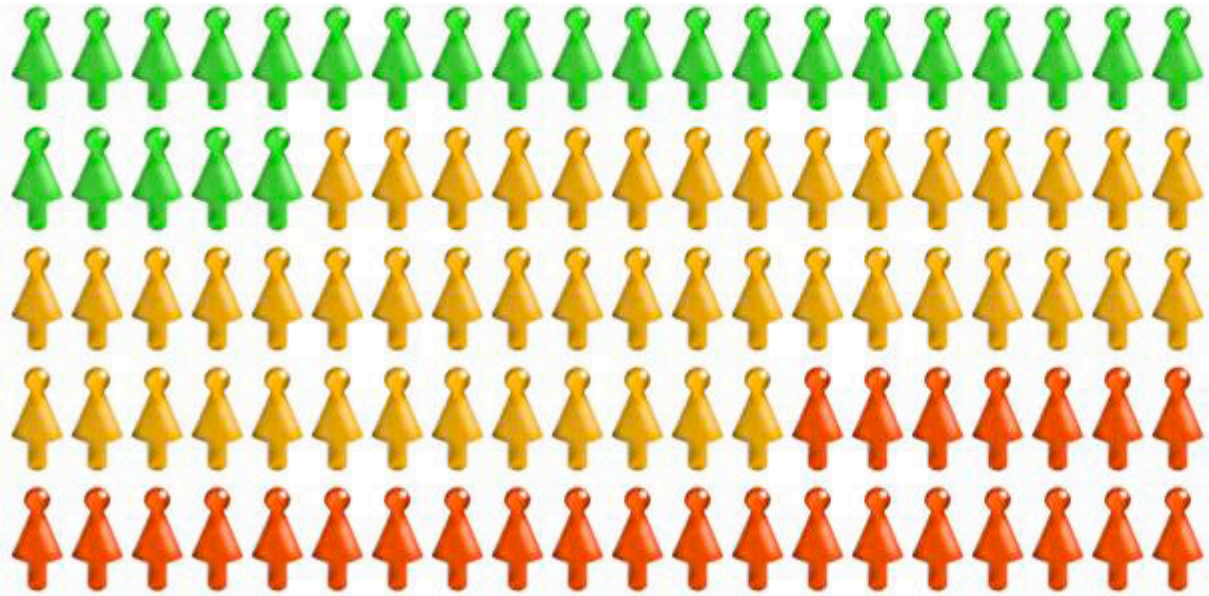
Low risk Adjuvant!

High risk Adjuvant!

Discordant cases better predicted by 70 gene prognosis signature

Buyse, JNCI, 2006

75% of patients receive toxic chemotherapy



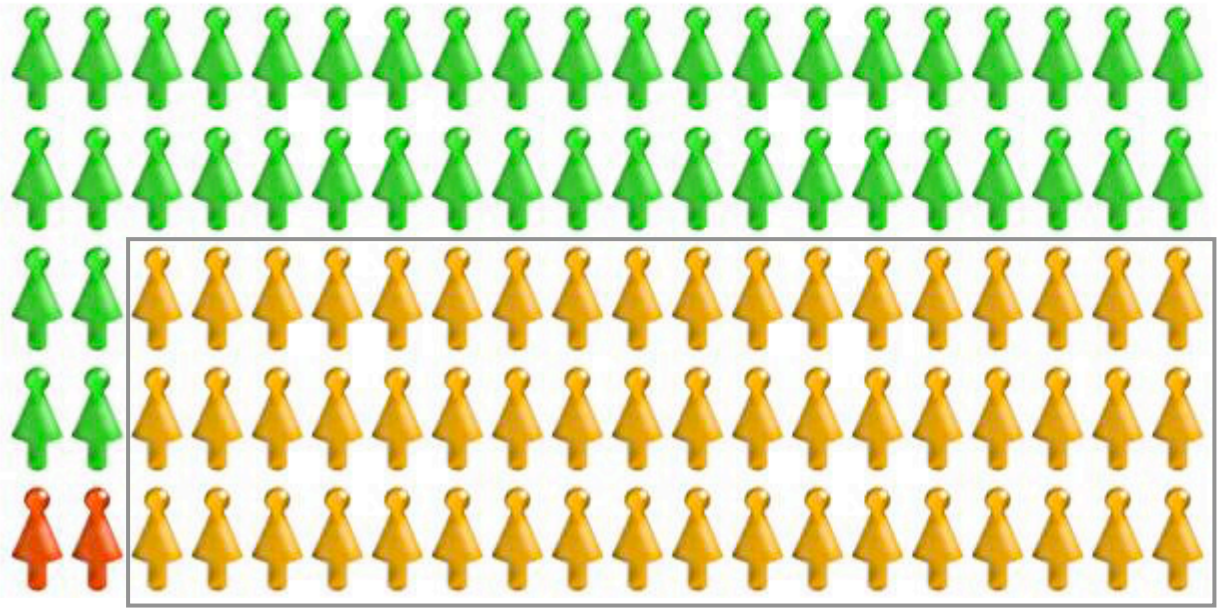
Current clinicopathological risk assessment

Current diagnostics:

50% of patients receive toxic chemotherapy of which they do not benefit,
but may suffer the toxic side-effects
Some patients who need chemotherapy may not be selected

MammaPrint risk assessment

MammaPrint:



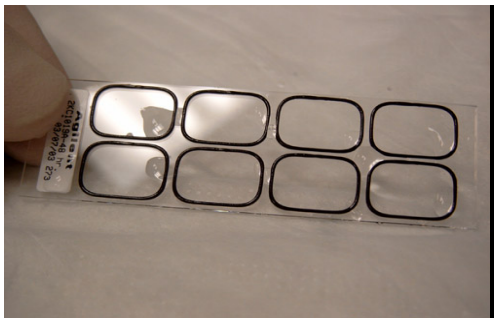
Improving assignment: less over- and under-treatment

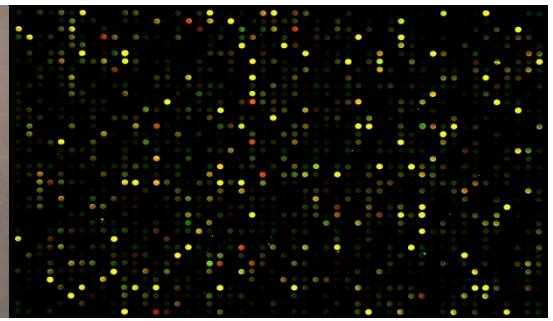
MammaPrint from Research to Diagnostics

Current Achievements:

- Retrospective validation - Completed
- Prospective Technology assessment - Cost-effectiveness

- Diagnostic test - International CE marked
- Laboratory - CLIA registered
- Diagnostic test - ISO17025 certified
- Diagnostic test - CAP accredited
- Diagnostic test and clinical use - FDA approved, IVDMIA feb07
- Treatment Recommendations - Dutch Guidelines 08
- Treatment Recommendations - StGallen 09 International Guidelines





Reproducibility
Test Result >98%
Success rate >95%

Glas et al,
BMC Genomics 2006

Clinical Utility MammaPrint

Use of 70-gene signature to predict prognosis of patients with node-negative breast cancer: a prospective community-based feasibility study (RASTER)

Jolien M Bueno-de-Mesquita, Wim H van Harten, Valesca P Retel, Laura J van 't Veer, Frits S A M van Dam, Kim Karsenberg, Kirsten F L Douma, Harm van Tinteren, Johannes L Peterse†, Jelle Wesseling, Tin S Wu, Douwe Atsma, Emiel J T Rutgers, Guido Brink, Arno N Floore, Annuska M Glas, Rudi M H Roumen, Frank E Bellot, Cees van Krimpen, Sjoerd Rodenhuis, Marc J van de Vijver, Sabine C Linn

Prospective trial implementing MammaPrint, 2003-2006
PIs Sabine Linn, Marc van de Vijver
Sponsor: Dutch Health Insurance Council

Bueno et al, Lancet Oncol, 2007, Knauer et al, SABCS 2008 #1084

Discordant cases MammaPrint signature versus Guidelines The Netherlands and Adjuvant-on-line

	70–gene prognosis signature, n (%) (n=427)		Discordant findings, n (%), 95% CI, kappa
	Good (n=219)	Poor (n=208)	
Clinical risk (Dutch CBO guidelines)			
Low (n=243)	167 (39)	76 (18)*	128 (30), 26–34, 0·398
High (n=184)	52 (12)*	132 (31)	..
Clinical risk (Adjuvant! Online)			
Low (n=133)	96 (22)	37 (9)*	160 (37), 32–42, 0·258
High (n=294)	123 (29)*	171 (40)	..

~30 % discordant cases led in
~20% to adapted treatment advise

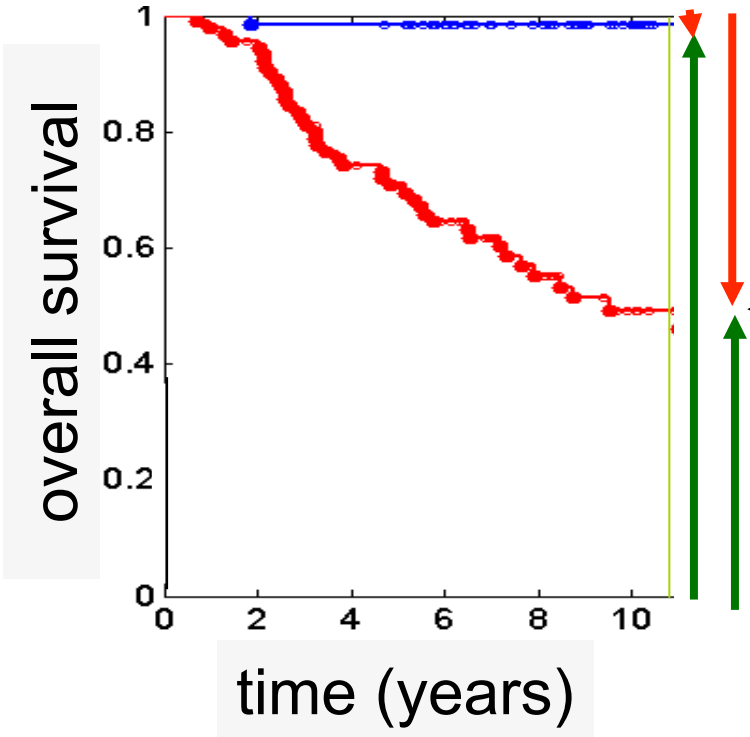
Bueno et al, Lancet Oncol, 2007, Knauer et al, SABCS 2008 #1084

Clinical Utility of MammaPrint

1. Risk Assessment
   - Assign patients to risk categories with high specificity (low risk vs high risk for recurrence)
   - Low risk sufficiently low to forego chemotherapy

Adjuvant treatment decided by risk

MammaPrint stratification in low and high risk of relapse



Low risk:
no chemotherapy, ERpos endocrine th

High risk:
chemotherapy and endocrine therapy

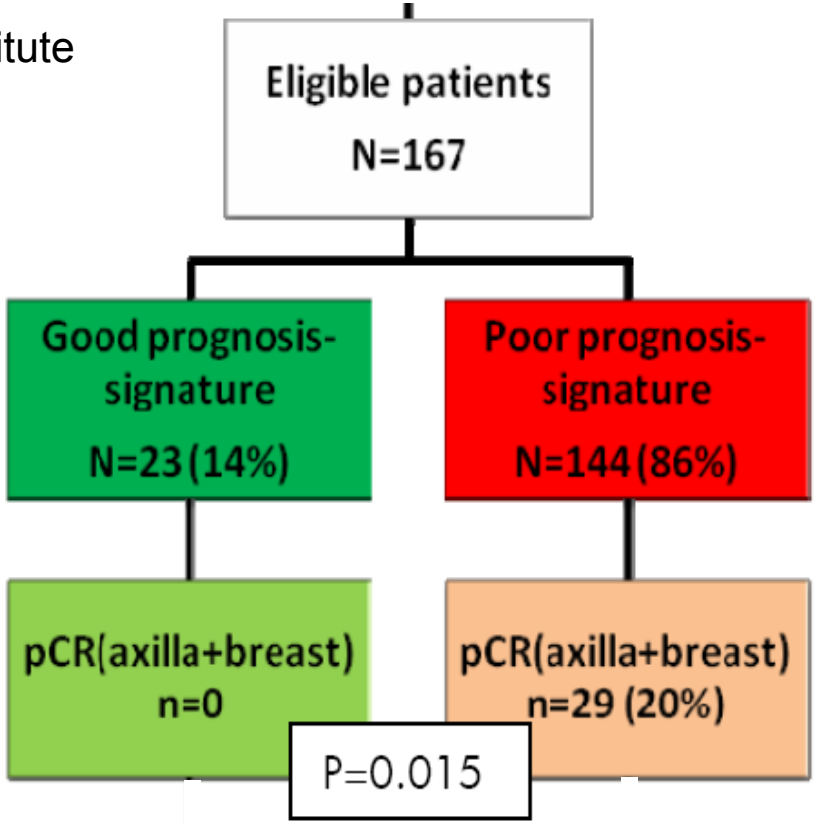
Do high risk patients benefit from chemo?

Clinical Utility and Clinical Benefit MammaPrint

1. Risk Assessment
   - Assign patients to risk categories with high specificity (low risk vs high risk for recurrence)
   - Low risk sufficiently low to forego chemotherapy
2. Chemo Benefit "the chemotherapy choice"
   - High risk should identify patients with early relapse (relevant for chemotherapy benefit)
   - High risk should show clinical benefit for chemotherapy

Response to neo-adjuvant Chemotherapy and MammaPrint

- Netherlands Cancer Institute
- 2 clinical trials
- T-stage >3 cm
  and/or LNplus (SNB/FNA)
- ultrasound guided
  14 gauge biopsies
- MRI imaging
- Pathology



- Antracycline-like
- Antracyclin-Taxane
- Taxane

pCR:
pathological
complete remission

MammaPrint low risk signature -> no benefit of chemotherapy
MammaPrint high risk signature -> benefit of chemotherapy

Straver et al, BCRT 2009, presented at AACR2009

Neo-adjuvant Standard Chemotherapy and MammaPrint Clinical Benefit

- MammaPrint High Risk Signature patients show significantly higher chemosensitivity
- All pCR are found in the High Risk Signature group

High Risk Signature Patients show Clinical Benefit of Chemotherapy

Low Risk Signature Patients do not show Clinical Benefit of Chemotherapy

Straver et al, BCRT 2009

Adjuvant Standard Chemotherapy and MammaPrint Clinical Benefit

Meta-analysis 70 gene signature in Lymph node negative and 1-3 positive node patients

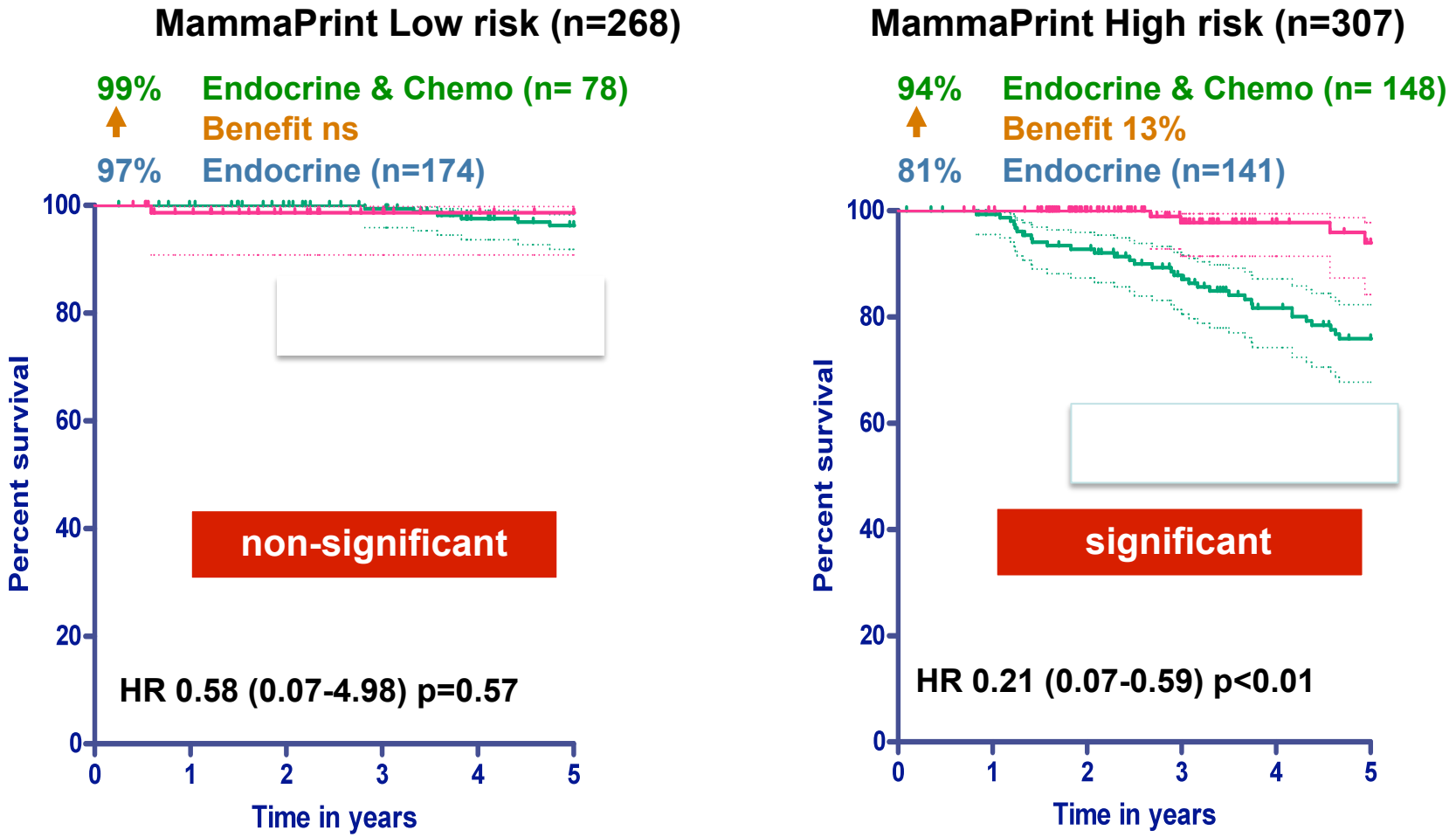
- adjuvant endocrine therapy (tam)

OR

- endocrine (tam) plus chemotherapy

Knauer et al, abstracts StGallen, ASCO and submitted, Albain et al 2009

Breast Cancer Specific Survival (5 yrs)
Endocrine vs Endocrine-Chemo
within MammaPrint low and high risk (n=772)



Interaction term for differential effect p=0.45

Knauer et al, abstracts StGallen, ASCO and submitted, Albain et al 2009

MammaPrint Low risk - Cox multivariate analysis: BCSS at 5 years for ET vs. ET + CT

MammaPrint low risk	**HR (95% CI)**	**p-value**
Age at diagnosis (by year)	1.00 (0.88-1.15)	0.95
Tumorsize (by cm)	0.98 (0.89-1.10)	0.77
No. of positive nodes (0-3)	1.09 (0.37-3.16)	0.88
Grade	0.57 (0.12-2.82)	0.49
ER-positive status	∞ (0-∞)	0.99
PR-positive status	0.09 (0.01-0.90)	0.04
HER2-positive status	∞ (0-∞)	0.99
Adjuvant therapy: ET vs. ET+CT	∞ (0-∞)	0.98

Knauer et al, abstracts StGallen, ASCO and submitted 2009

MammaPrint High risk - Cox multivariate analysis: BCSS at 5 years for ET vs. ET + CT

MammaPrint high risk	**HR (95% CI)**	**p-value**
Age at diagnosis (by year)	0.96 (0.91-1.02)	0.17
Tumorsize (by cm)	1.05 (1.01-1.09)	0.02
No. of positive nodes (0-3)	1.39 (0.95-2.03)	0.09
Grade	1.03 (0.48-2.19)	0.94
ER-positive status	0.48 (0.18-1.34)	0.16
PR-positive status	0.31 (0.09-1.03)	0.06
HER2-positive status	0.72 (0.25-2.10)	0.55
Adjuvant therapy: ET vs. ET+CT	0.21 (0.06-0.80)	0.02

Knauer et al, abstracts StGallen, ASCO and submitted 2009

Adjuvant Standard Chemotherapy and MammaPrint Clinical Benefit

- MammaPrint High Risk signature patients show significant chemo-sensitivity

  (number needed to treat 30)

- MammaPrint Low Risk Signature group does not show significant chemo benefit

  (number needed to treat 333)

MammaPrint High Risk Signature Patients show substantial Clinical Benefit of Adjuvant Chemotherapy

(Cave: not a randomized trial!)

Knauer et al, abstracts StGallen, ASCO and submitted, Albain et al 2009

MammaPrint
current clinical implementation

- FDA approved (only prognostic IVDMIA for breast cancer)
- Dutch CBO guidelines for treatment of breast cancer (2008)
- StGallen International guidelines for treatment of breast cancer (published July 2009)

St Gallen International Expert Consensus 2009

Table 3. Chemoendocrine therapy in patients with ER-positive, HER2-negative disease

Clinicopathological Features			
	Relative Indications for Chemoendocrine therapy	**Factors Not Useful for Decision**	**Relative Indications for Endocrine Therapy Alone**
ER, PgR	Lower ER and PgR level		Higher ER and PgR level
Histological Grade	Grade 3	Grade 2	Grade 1
Proliferation	High[a]	Intermediate[a]	Low[a]
Nodes	Node positive (4 or more involved nodes)	Node positive (1-3 involved nodes)	Node negative
Peritumoral Vascular Invasion (PVI)	Presence of extensive PVI		Absence of extensive PVI
pT-size	> 5cm	2.1 – 5 cm	≤ 2cm
Patient Preference	Use all available treatments		Avoid side effects
Multi-gene Assays			
Gene Signature[b]	High score	Intermediate score	Low score

21 recurrence score

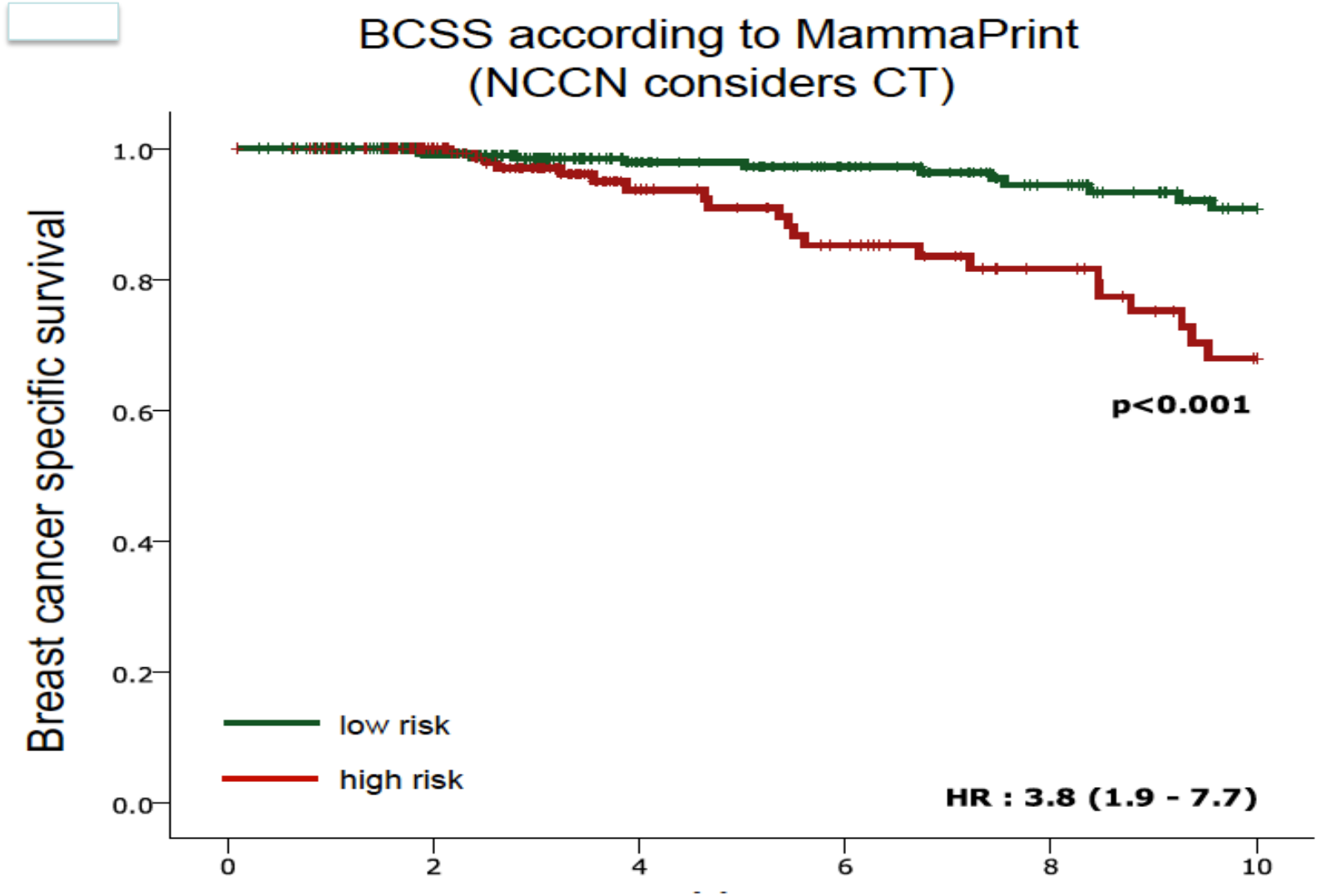
70 gene signature

NCCN 2008
‘consider multi-gene assay’

- Consider 21-gene recurrence score for
  - hormone receptor pos, her2 neg
  - pT1,pT2,pT3 and pN0 or pN1min,
    that are 0.6-1 cm and moderately /poorly differentiated or unfavorable characteristics
  - or > 1cm

NCCN 2008

MammaPrint prediction
in ‘NCCN considers multi-gene assay’

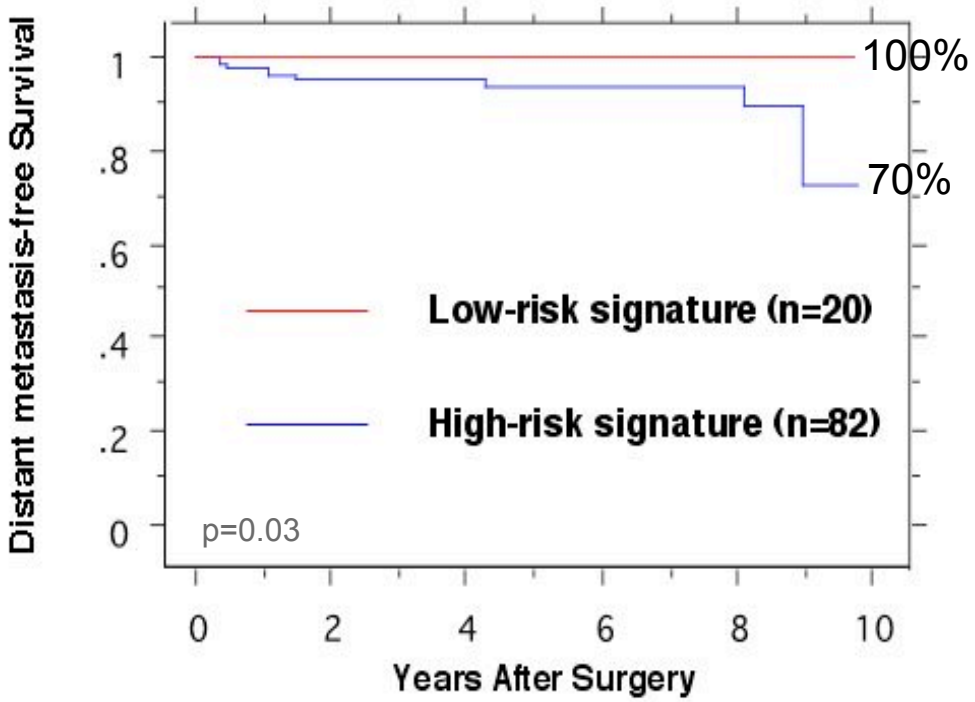


MammaPrint additions: 2009 and future developments 2010

- MammaPrint all ages (FDA expected Oct 09)
- Mammaprint validated for 1-3 positive lymph nodes
- MammaPrint tested in Japanese patients (Prof Kato, Osaka)
- estrogen receptor, progesterone receptor, her2 (TargetPrint) (2009)
- molecular subtypes (luminal, her2, basal)
- drug targets (62 gene research panel)

MammaPrint in Japanese Patients

Osaka Medical Center for Cancer and Cardiovascular Diseases
Pof Kikuya Kato
N=102, treated, 1998-2001



Makoto Ishitobi, Teodora Goranova, Yoshifumi Komoike, Kazuyoshi Motomura, Hiroki Koyama, Annuska Glas, Ellen van Lienen, Hideo Inaji Laura van't Veer and Kikuya Kato

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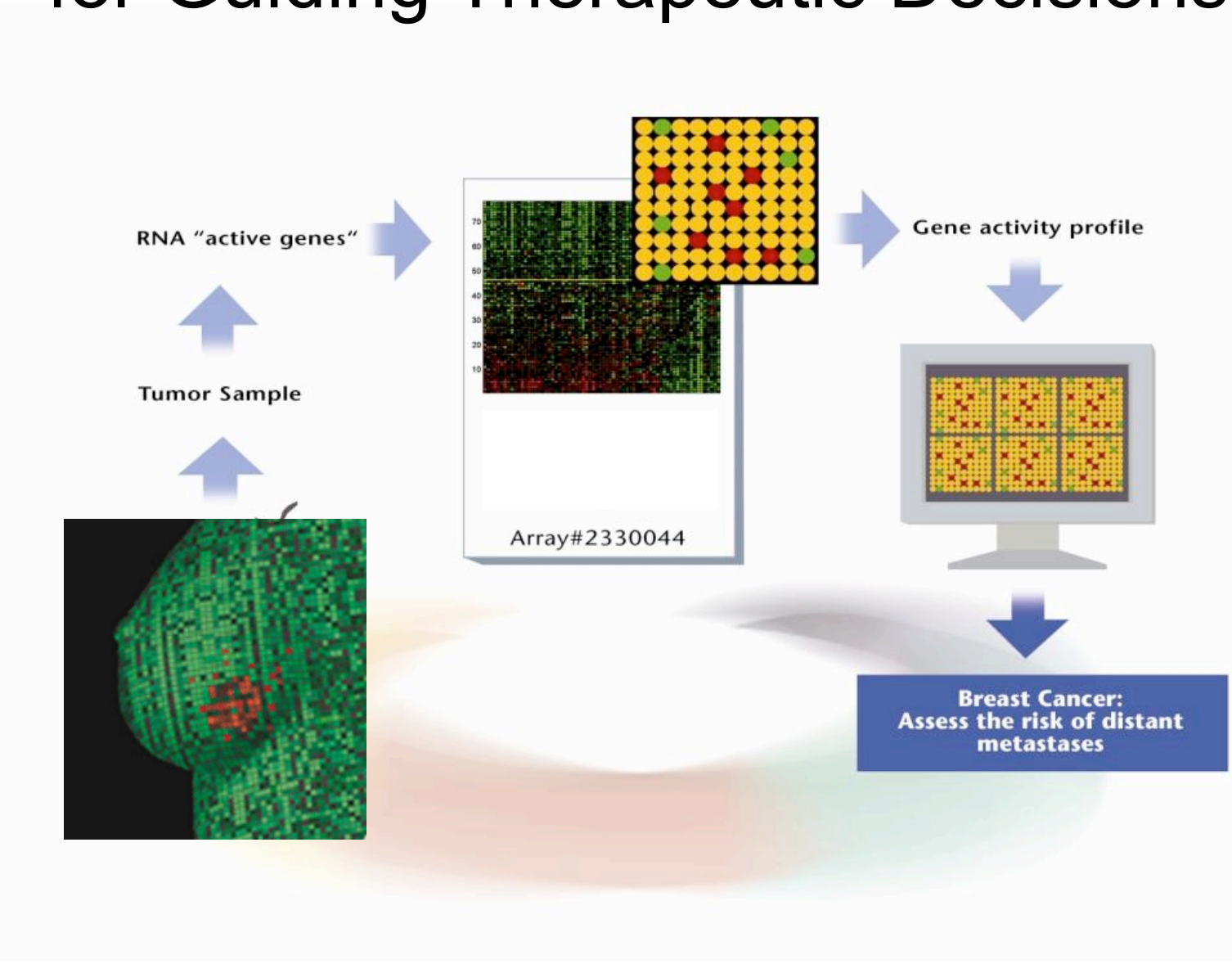
MammaPrint
for Guiding Therapeutic Decisions



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decoding cancer.