

Current Status and Future Development of Tools for Prognosis and Prediction - USA

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HUNTSMAN
CANCER INSTITUTE

AT THE UNIVERSITY
OF UTAH 

Outline

- Introductory thoughts
- Prognostic factors and predictive factors
- Computer-generated prognosis
- Gene expression profiles – current status in USA
- Future needs and wants

Assessment of Recurrence Risk: Prognostic Factors & Predictive Factors

- Tumor Size
- Lymph node status
- Tumor Type/Grade
- Lymphatic/Vascular invasion
- Hormone receptor status
- HER2 status
- Gene expression profiling

Breast Survival

Effects of Tumor & Nodes on Survival

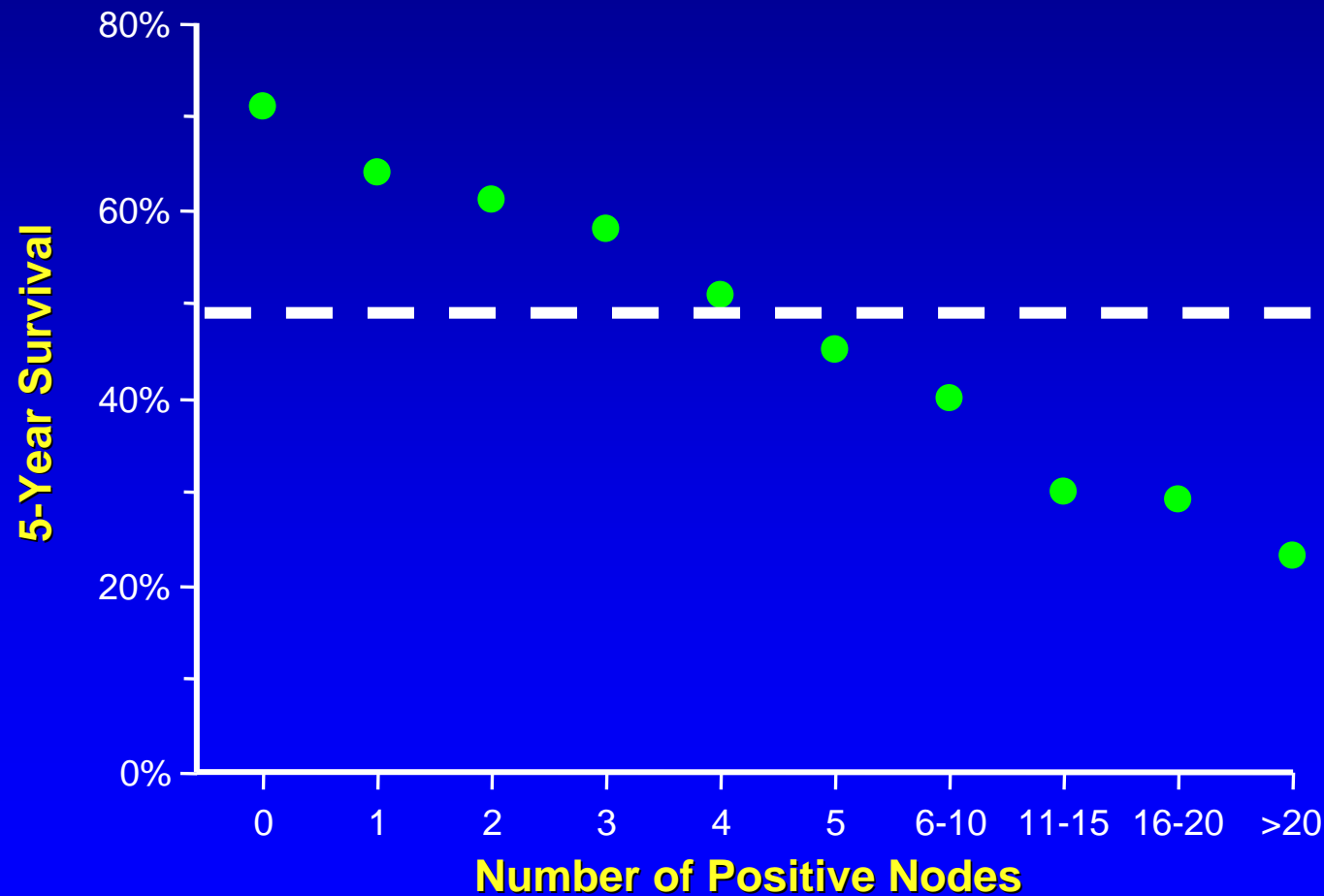
Patients Surviving 5 Years

<i>Tumor Size (cm)</i>	<i>Negative Nodes</i>	<i>1 to 3 Positive Nodes</i>	<i>4 or More Positive Nodes</i>
<0.5	99.2%	95.3%	59.0%
0.5-0.9	98.3%	94.0%	54.2%
1.0-1.9	95.8%	86.6%	67.2%
2.0-2.9	92.3%	83.4%	63.4%
3.0-3.9	86.2%	79.0%	56.9%
4.0-4.9	84.6%	69.8%	52.6%
≥ 5.0	82.2%	73.0%	45.5%

Harris JR, Hellman S. Natural history of breast cancer. In: Hellman S, Lippman ME, Morrow M, Harris JR, eds. *Diseases of the Breast*. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:375391.

BREAST CANCER

5-year survival as function of the number of positive axillary lymph nodes



Breast Cancer v. Other Cancer types

- Well established prognostic features
- Adjuvant therapy clearly advantageous based on numerous trials with long followup
- Application of targeted therapy widely used
- New approaches tested with clinical trials

Prognostic v. Predictive

- Prognostic factors: Correlate with or determine outcome
 - May select patients most likely to recur without adjuvant therapy
- Predictive factors: Reflect the tumor or host response to a specific intervention
 - May help to select the best therapy for a given clinical situation

Not always either/or!!!

Current Targets for Therapy

- Currently include ER, PR, & HER2
- Assays may vary, and accuracy can be lacking: “Who is right when results differ?”
- *Always* important to verify where the test is being done and review its track record
- Assays may and will change with time.

IHC Testing for HER2 Expression

IHC (HercepTest[®]) Scoring


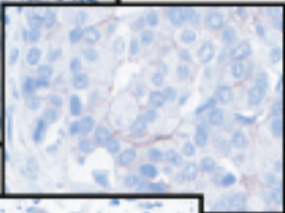
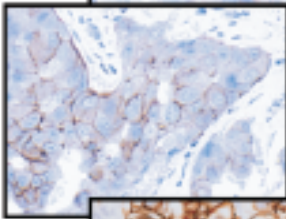
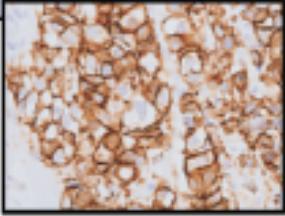
<u>Staining pattern</u>	<u>Score</u>	<u>Interpretation</u>	
No staining	0	Negative	
Faint incomplete staining of cell membrane in >10% of tumor cells	1+	Trace Negative	
Weak to moderate complete staining of cell membrane in >10% of tumor cells	2+	Weak Positive	
Strong complete staining of cell membrane in >10% of tumor cells	3+	Strong Positive	

Figure 4 Scoring method used in the HercepTest IHC assay. Figure courtesy of Kenneth Bloom, MD.

FISH determination of HER2 gene amplification

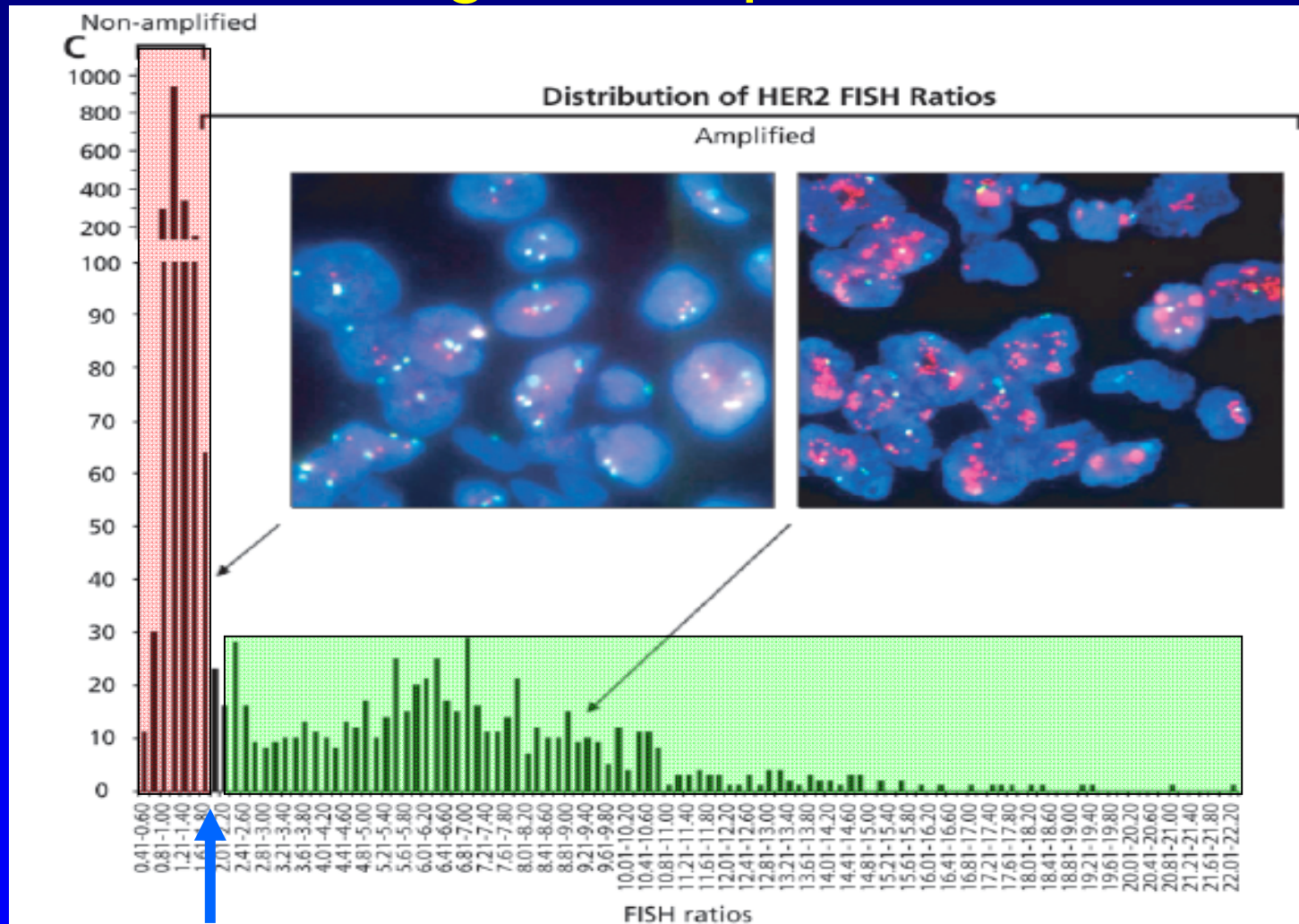


Figure 6 Distribution of *HER2* gene/chromosome 17 ratios in 2,502 breast cancer tumor samples analyzed using the PathVysion FISH method.

Assays may and will change

Hormone Receptors:

RIA → IHC → Gene expression (?)

HER2 Status

IHC → FISH → Gene expression (?)

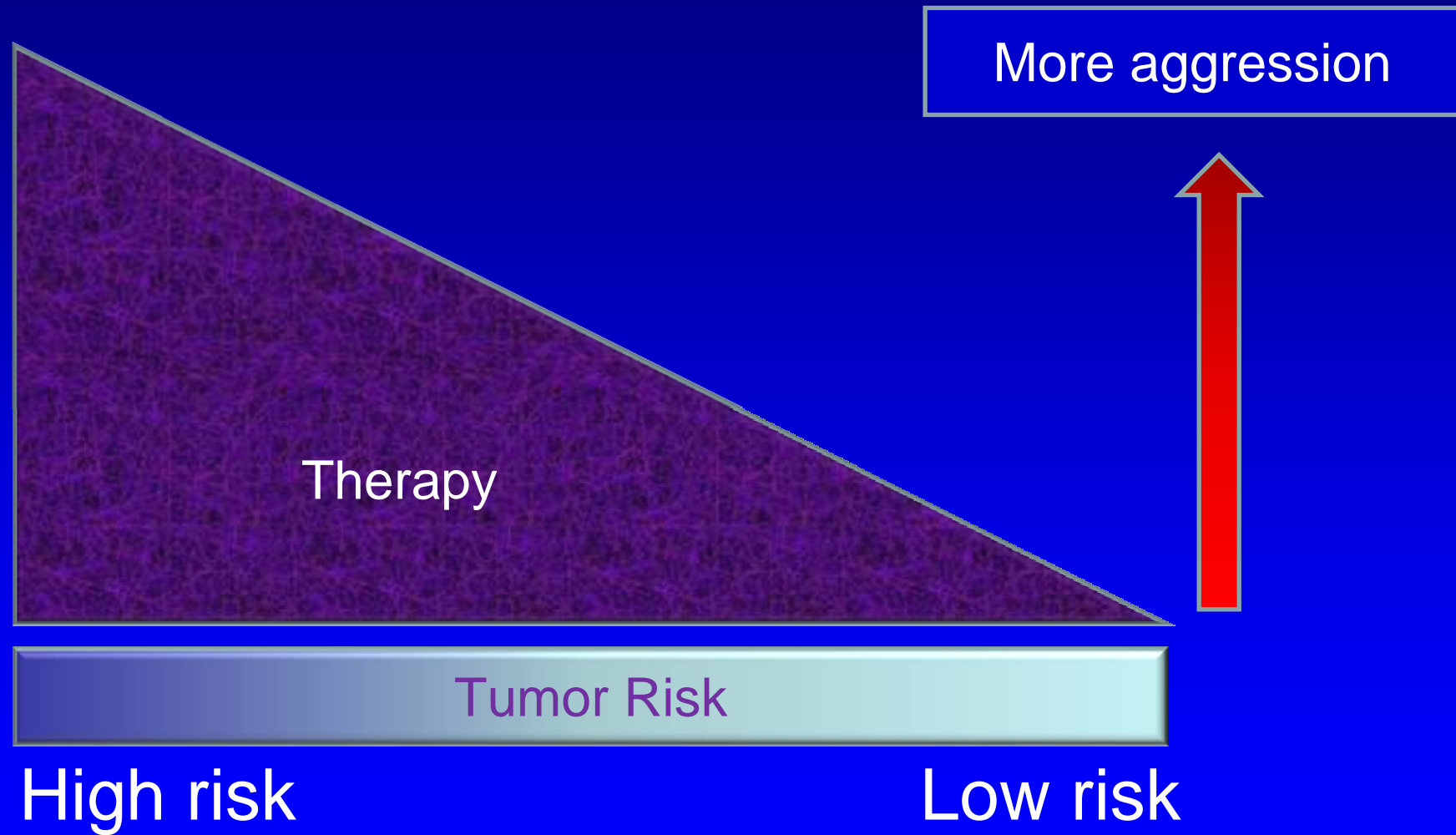
Reasons for change: convenience, expense, accuracy, reproducibility, safety

Cost of one year of Trastuzumab to Huntsman Cancer Institute

- 440 mg vial: ~ \$2987
(¥269,362)

Cost of 17 doses: ~ \$50,787
(¥4,578,860)

Risk Drives Decisions



Reasons for Accurate Prognosis

- Adjuvant chemotherapy has toxicities, and those who don't need it could avoid unnecessary treatment
- Adjuvant chemotherapy is expensive, *both monetarily and emotionally*
- If needed, we would like to provide the most refined and directed therapy possible

Computer models assist in defining benefit

- Absolute benefit is different than relative benefit
- Do physicians overestimate or underestimate the effect of adjuvant therapy?
- Do patients really understand the magnitude of benefit – is the “juice worth the squeeze?”

Caveats

- Cannot include all known or unknown prognostic factors
- 10 year relapse or survival is only one measure of outcome
- Guidelines and estimates *only*

For a more detailed review, see
JNCCN 1:189-196, 2003 (April)
Loprinzi and Ravdin

Adjuvant!

<http://www.adjuvantonline.com>

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:


Chemo:

Hormonal Therapy:

Chemotherapy:


Combined Therapy:

No additional therapy:




■ 84.1 alive in 10 years.
■ 7.7 die of cancer.
■ 8.2 die of other causes.


With hormonal therapy: Benefit = 2.0 alive.



With chemotherapy: Benefit = 0.6 alive.



With combined therapy: Benefit = 2.5 alive.



What do you think?

- 45 year-old premenopausal woman
 - Grade 3 infiltrating ductal carcinoma
 - 2.5 cm primary
 - 2 positive nodes
 - ER negative
 - HER2 positive
- What is her risk of relapse at 10 years?

Her Risk of Systemic Relapse at 10 years is ...

1. 20%
2. 40%
3. 60%
4. 80%

Patient Information

Age:

Comorbidity:

ER Status:

Tumor Grade:

Tumor Size:

Positive Nodes:

Calculate For:

10 Year Risk:

Adjuvant Therapy Effectiveness

Horm:


Chemo:

Hormonal Therapy:

Chemotherapy:


Combined Therapy:

No additional therapy:




37.3 alive and without cancer in 10 years.
61.7 relapse.
1.0 die of other causes.


With hormonal therapy: Benefit = 0.0 without relapse.



With chemotherapy: Benefit = 26.0 without relapse.



With combined therapy: Benefit = 26.0 without relapse.



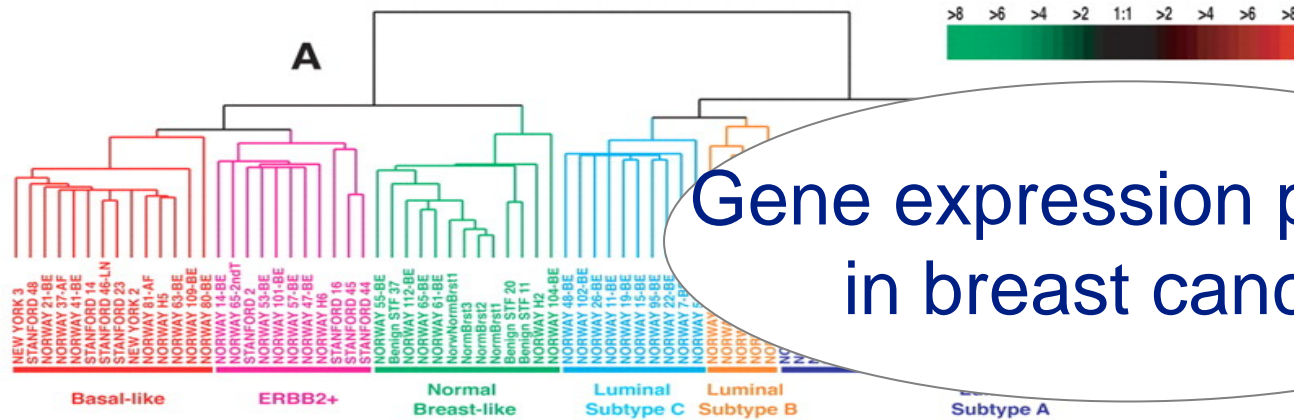
Adjuvant! Online – A few issues

- Commonly used in United States
- Not always easy to explain
- May give a false impression of precision
- Cannot not account for tumor-specific factors

A good start, but we need more

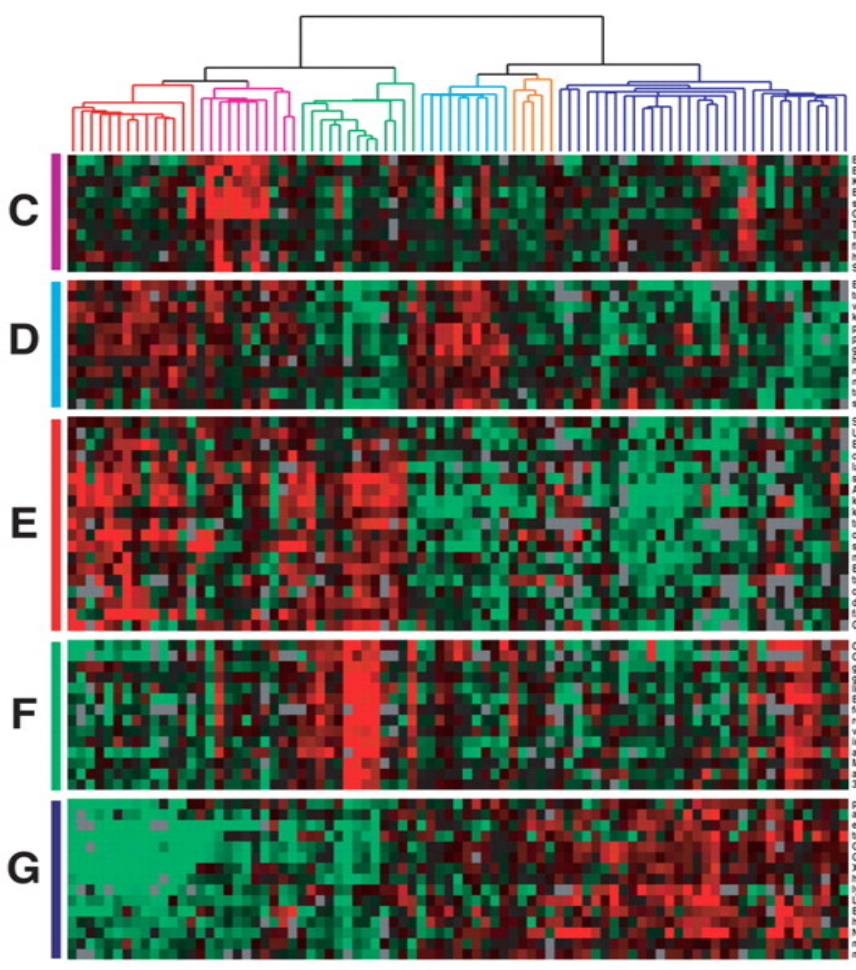
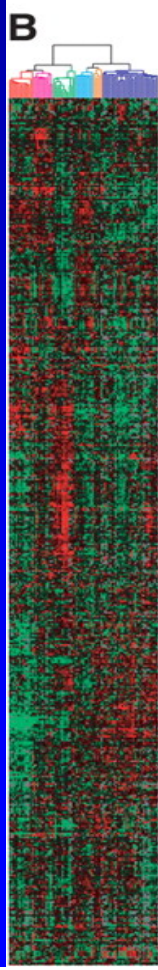
Gene Expression Profiles

- Most current treatments are based on what the cancer looks like under the microscope
- Appearances can be deceiving!!
- New technology using DNA microarrays enables investigators to look at gene expression and *potentially* better classify tumors



Gene expression patterns in breast cancers

PNAS 98:10869,2001



- ERBB2 AA480116
- ESTs T57034
- KIAA130 NS4470
- ERBB2 AA443351
- steroidogenic acute regulatory protein related AA504615
- GRB7 H5702
- TGFB1-induced anti-apoptotic factor 1 AA446222
- TNF receptor-associated factor 4 AA598626
- flotillin 2 R72913
- hypothetical protein FLJ10700 W81165
- SWVSNF related, subfamily e, member 1 W51779
- EST AA010188
- transformin receptor p80, CD71 N21329
- v-myb oncogene homolog-like 2 AA456878
- kinesin-like 5 mitotic kinesin-like protein 1 AA452513
- putative integral membrane transporter AA602214
- putative integral membrane transporter AA033947
- gamma-glutamyl hydrolase conjugase AA455800
- hypothetical protein FLJ10511 AA115275
- nuclease sensitive element binding protein 1 AA599175
- nucleolar protein p40 T74979
- tryptophan 5-monooxygenase activation protein AA609598
- squalene epoxidase R01118
- SRY sex-determining region Y-box 9 AA400464
- UDP-N-acetyl-alpha-D-galactosamine H13688
- ESTs W93120
- cadherin 3, P-cadherin placental AA425217
- laminin, gamma 2 nicotin AA677534
- small inducible cytokine subfamily D R66139
- ATDC AA055485
- keratin 17 AA026642
- keratin 5 W72110
- tropomyosin I, skeletal, fast AA181334
- chitinase 3-like 2 AA668621
- secretory phospholipase inhibitor antileukoprotease AA026264
- nuclear factor I B W87528
- ESTs A0304356
- transforming growth factor, beta 2 N48082
- calpain-like protease AA457238
- dystrophin muscular dystrophy
- fatty acid binding protein 7, brain W72051
- GRD1 oncogene, alpha W42723
- CD36 antigen collagen type I receptor N39161
- CD36 antigen collagen type I receptor R09416
- glutathione peroxidase 3 plasma AA664180
- glycerol-3-phosphate dehydrogenase 1 AA192547
- lipoprotein lipase AA633635
- ESTs T82068
- four and a half LIM domains 1 AA455925
- retinol-binding protein 4, interstitial T72076
- vascular adhesion protein 1 AA036974
- integrin, alpha 7 AA055979
- alcohol dehydrogenase 2 class I, beta N93428
- MY047 protein T62031
- aquaporin 7 H27752
- 36 kDa protein AA088748
- putative G protein-coupled receptor H50224
- acyl-Coenzyme A dehydrogenase H95792
- estrogen receptor 1 AA291749
- intestinal factor 3 intestinal N74131
- GATA-binding protein 3 H72474
- GATA-binding protein 3 R31441
- X-box binding protein 1 W90128
- hepatocyte nuclear factor 3, alpha T74639
- lymphoid nuclear protein related to AF4 H99588
- LIM-1 protein, estrogen regulated H29315
- ESTs AA029948
- hypothetical protein FLJ11280 NS4608
- N-acetyltransferase 1 arylamine R91802
- myosin VI AA626890
- myosin VI AA030004

D

E

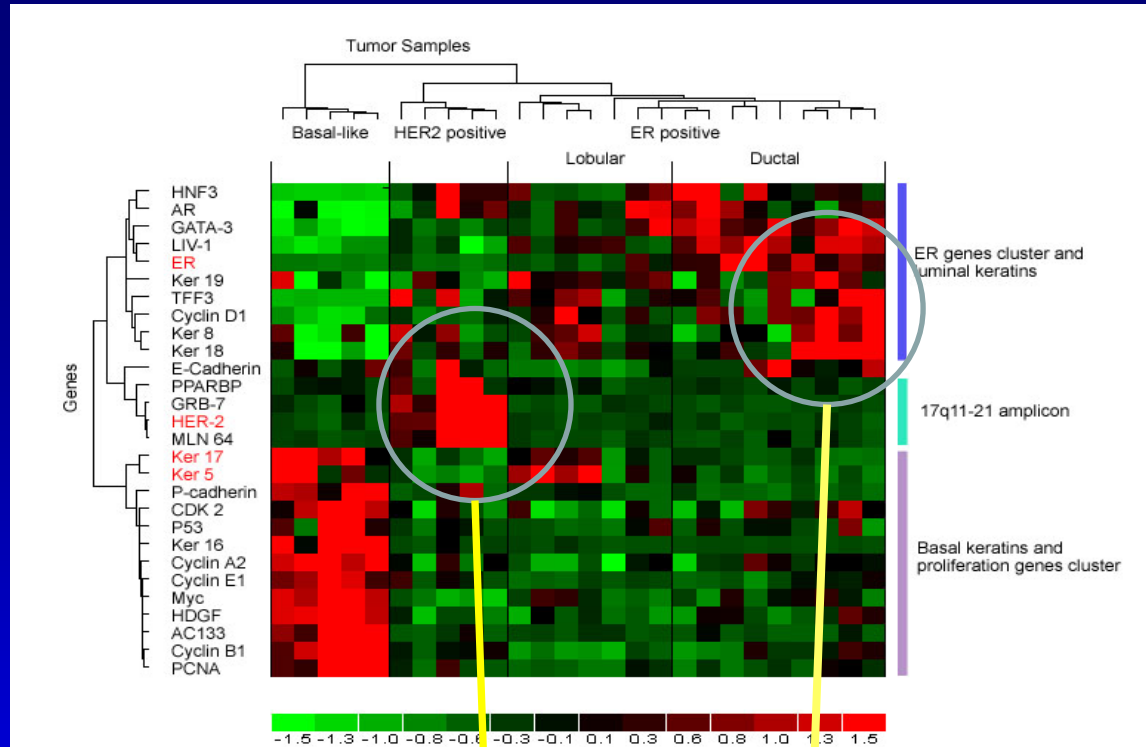
F

G

“ How does truth in a blue and pink world compare to truth in a red and green world?”

- Anon, re: gene expression profiling

RNA Expression Profiling

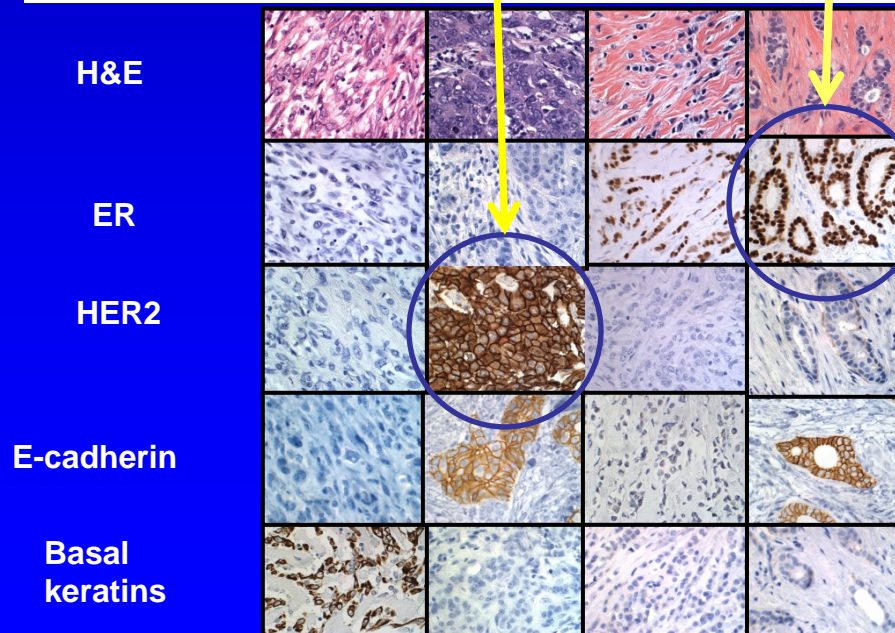


Red = relative increase in RNA

Green = relative decrease in RNA

Black = no change

Protein Expression (IHC)

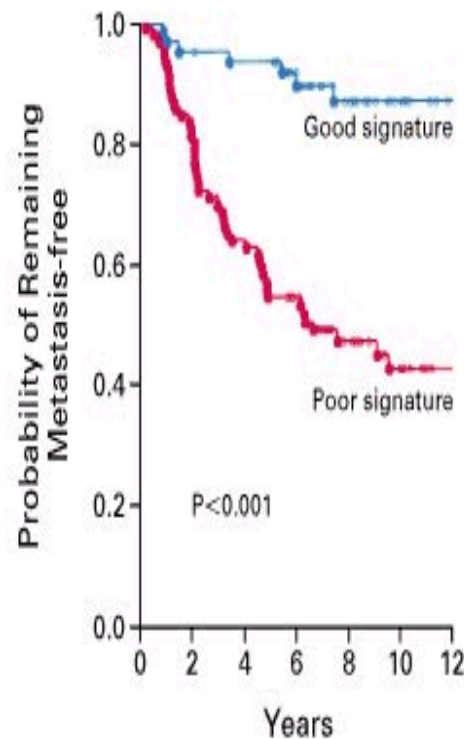


Brown = antigen present

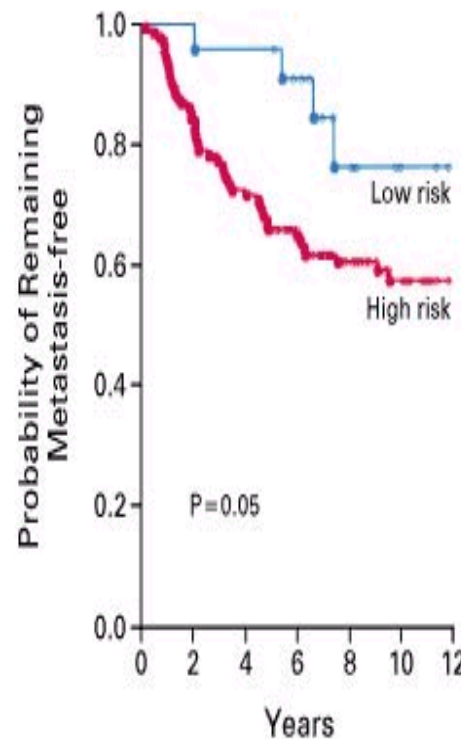
*Image courtesy of Susan Lester, MD, PhD
DFCI / BWH*

Comparison of Risk Stratification Strategies LN Negative Patients

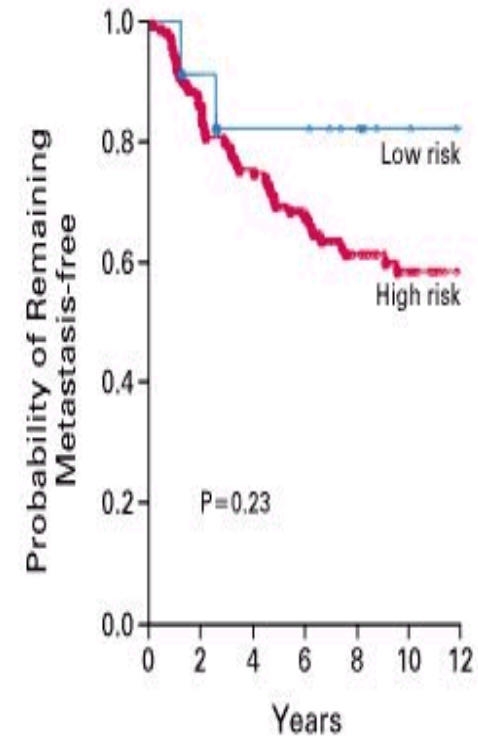
A Gene-Expression Profiling



B St. Gallen Criteria



C NIH Consensus Criteria



van de Vijver, et al. NEJM 2002

Gene Expression Profiles

“Biology is Destiny”

“Biology is King”

Gene Expression Profiling

- *Oncotype DX* – 21 gene assay
- MammaPrint – 70 gene assay
- Technical differences
- Current data based on strong retrospective analyses
- Other techniques and assays *sure to follow*

Oncotype DX Report

RESULTS

Recurrence Score = **16**

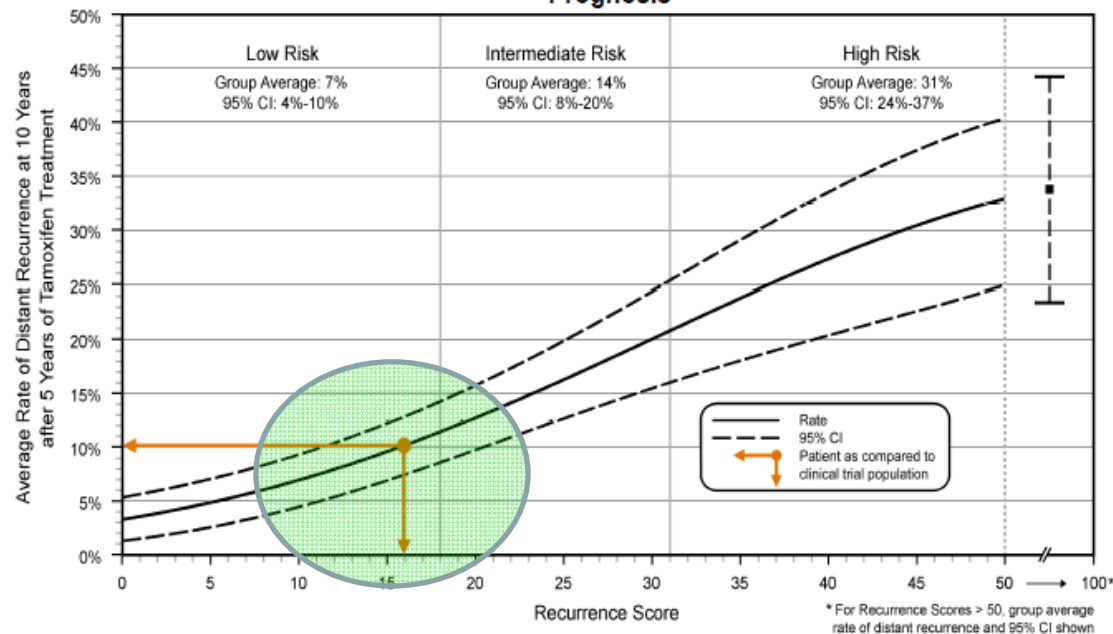
Test Results should be interpreted using the Clinical Experience information contained in this report which is derived from clinical studies involving patient populations with specific clinical features as noted in each section of the Clinical Experience. It is unknown whether the findings summarized in the Clinical Experience are applicable to patients with features different from those described.

CLINICAL EXPERIENCE: PROGNOSIS FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The Clinical Validation study included female patients with Stage I or II, **Node Negative**, ER-Positive breast cancer treated with 5 years of tamoxifen. Those patients who had a Recurrence Score of 16 had an Average Rate of Distant Recurrence of **10% (95% CI: 7%-13%)**

The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

Recurrence Score vs Distant Recurrence in **NODE NEGATIVE**, ER-Positive Breast Cancer Prognosis



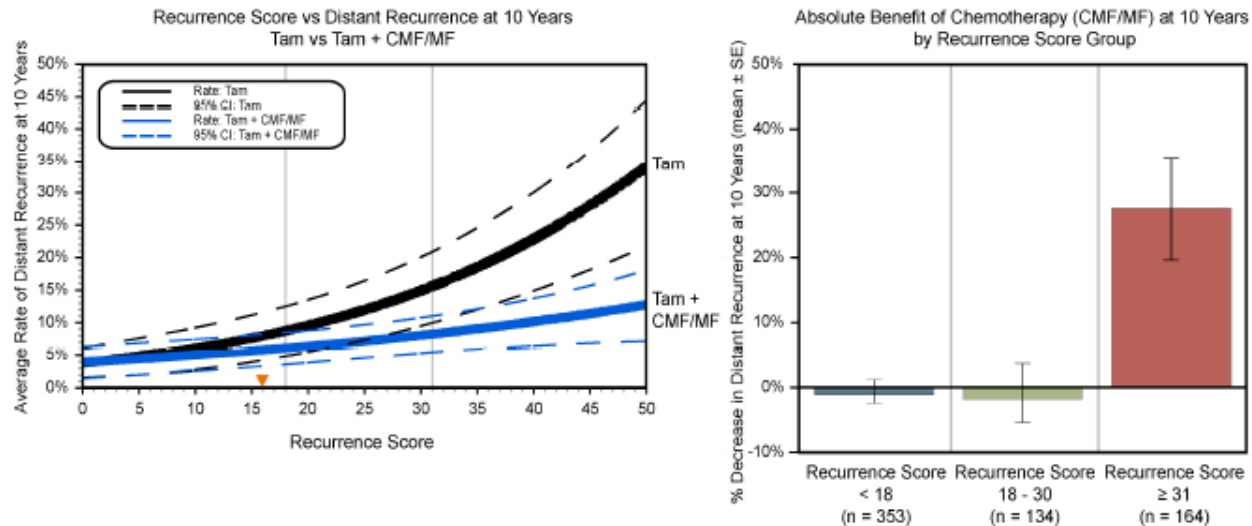
Node Negative

Oncotype DX Report

CLINICAL EXPERIENCE: CHEMOTHERAPY BENEFIT FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

The following results are from a clinical study involving 651 patients from the NSABP B-20 Study. The study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer. Patients were randomized to either tamoxifen alone or tamoxifen plus CMF or MF chemotherapy. For patients in the pre-specified group with Recurrence Scores ≥ 31 , the group average 10-year rates (95% CI) of distant recurrence were 40% (25%, 54%) for Tam alone and 12% (6%, 18%) for Tam + CMF/MF. *J Clin Oncol.* 2006; 24(23): 3726-34.

NODE NEGATIVE, ER-Positive Breast Cancer Chemotherapy Benefit



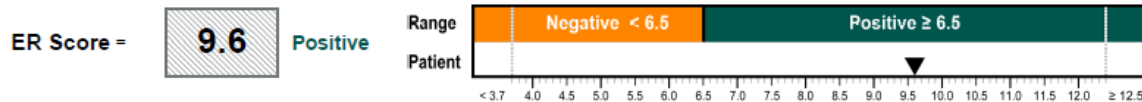
Node Negative

Oncotype DX Report

QUANTITATIVE SINGLE GENE REPORT

The Oncotype DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.¹

The ER, PR, and HER2 Scores are also included in the calculation of the Recurrence Score.

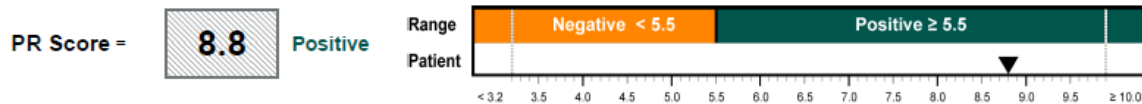


The ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) and 607 samples using the SP1 antibody (immunohistochemistry). The standard deviation for the ER Score is less than 0.5 units.²

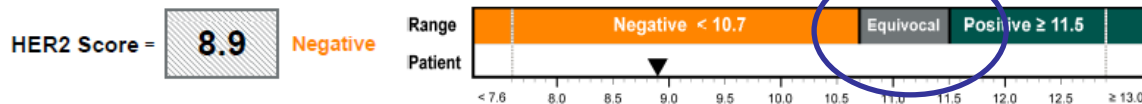
Clinical Experience:

For ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.³

Please note: The Average Rate of Distant Recurrence reported on Page 1 based on the Recurrence Score was determined in patients who received 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.



The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR636 antibody (immunohistochemistry) and another study of 607 samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.²



The HER2 positive cut-off of ≥ 11.5 units, equivocal range from 10.7 to 11.4 units, and negative cut-off of < 10.7 units were validated from concordance studies of 755 samples using the HercepTest™ assay (immunohistochemistry) and another study of 568 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.5 units.⁴

Sample MammaPrint Report

Results

Pathology findings, H&E staining

Sample contains an average of 45% tumor, see *picture*

The sample is classified as:

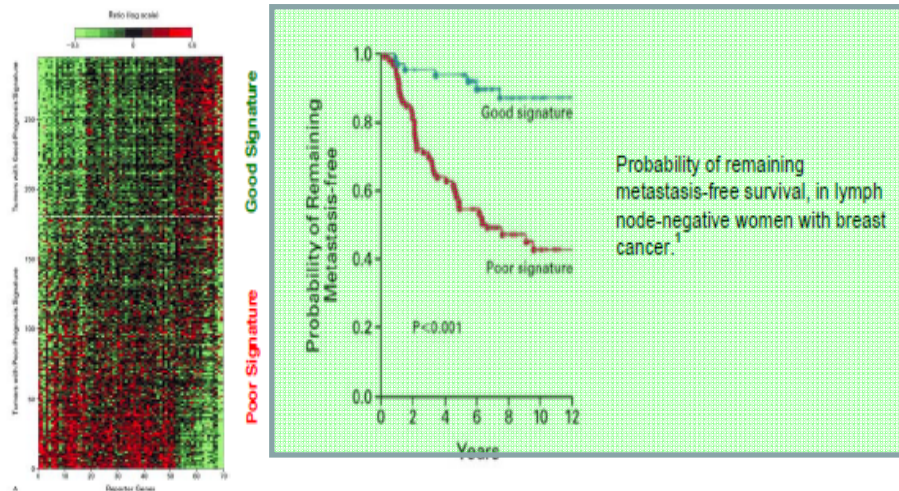
LOW RISK

Analysis Description

The breast cancer tissue sample submitted was analyzed by MammaPrint®, a gene expression analysis of 70 prognostic genes that has been validated to correlate with high or low outcome risk for distant metastasis in women with breast cancer.

Interpretation

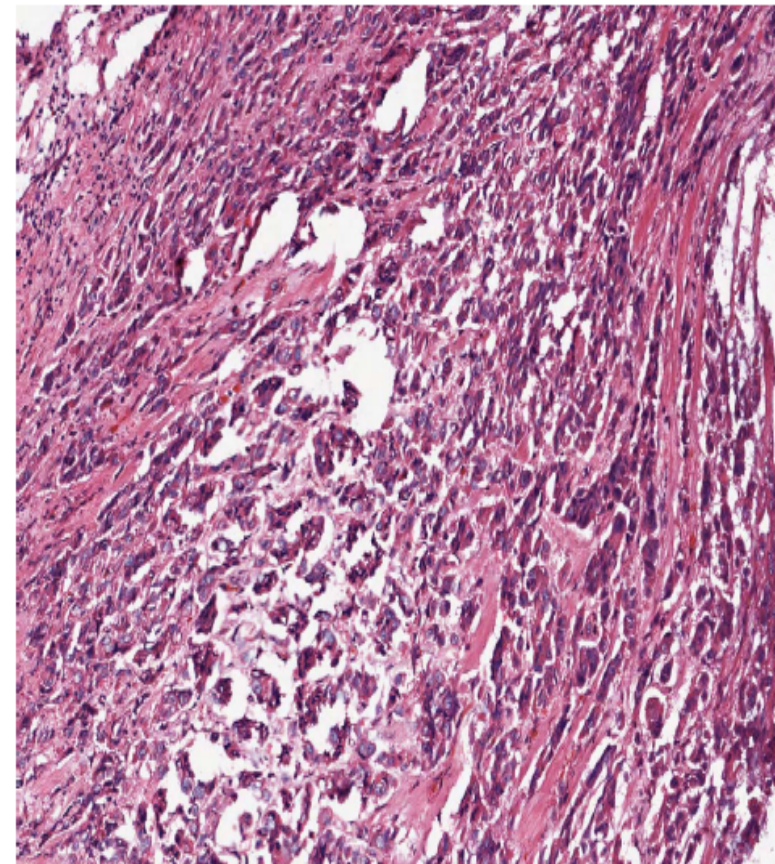
In the reference group as published¹, lymph node-negative patients classified as Low Risk had a 13% chance to develop distant metastases at 10 years, without adjuvant treatment. The patients classified as High Risk had a 56% chance to develop distant metastases at 10 years, without adjuvant treatment. MammaPrint® has been independently validated and shown to provide independent prognostic information to clinicopathological risk assessment for patients with lymph node-negative breast cancer.²



International validation in European patients² showed that patients with a "Good signature" had a probability of 90% of metastasis free survival at 10 years. Patients with a "Poor signature" had a probability of 70% metastasis free survival at 10 years.

H&E Staining

Patient ID



Gene Expression Profiles

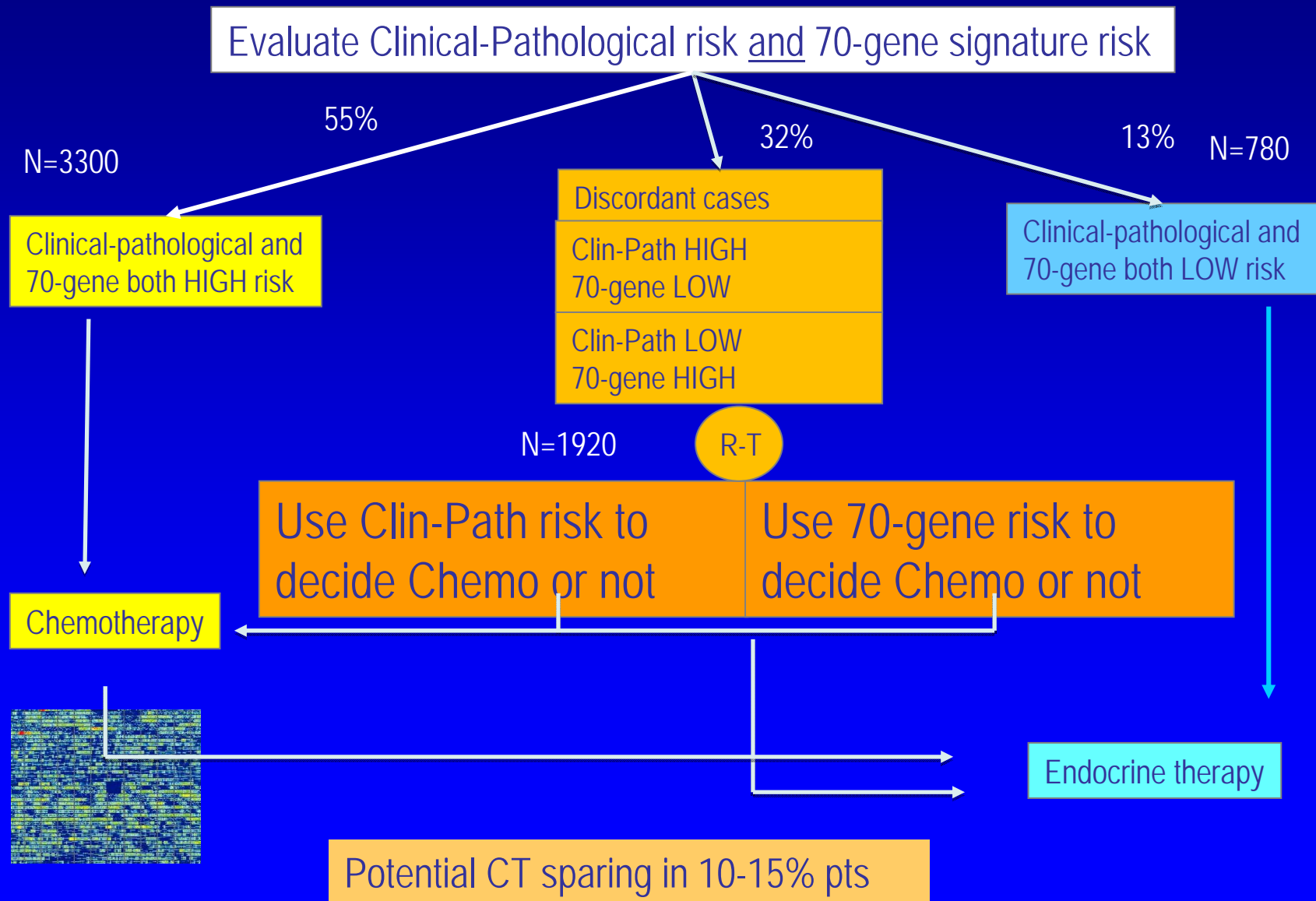
- Gene expression profiles may potentially provide better prognostic information
- Studies show promise, but require confirmation and improved nomenclature
- At the moment, the assays are helpful in a minority of patients

A good start, but we need more

More data will be coming, due to the strength of randomized, prospective trials.

EORTC 10041 BIG 3-04 trial MINDACT TRIAL DESIGN

6,000 Node - & 1-3 N+ women



TAILORx Schema

Node N-, ER+ Breast Cancer

Register
Specimen
banking

Oncotype DX[®] Assay

RS \leq 10
Hormone
Therapy
Registry

RS 11-25
Randomize
Hormone Rx
vs
Chemotherapy
+ Hormone Rx

RS >25
Chemotherapy
+
Hormone Rx

Primary study group

Current Usage of Prognostic and Predictive Factors in USA

- Clinical and pathologic parameters remain important
- Hormone receptor and HER2 status mandatory
- Gene expression profiles:
 - ER positive, node negative *when a chemotherapy choice may be affected*
 - No consensus on use in ER+, Node +, patients

Prognostic vs. Predictive

Hippocrates, *On the Prognostics, Book I*

- **PROGNOSTIC:** “It appears to me a most excellent thing for the physician to cultivate Prognosis; for by foreseeing and foretelling...he will be the more readily believed to be acquainted with the circumstances of the sick.”
- **PREDICTIVE:** “It is impossible to make all the sick people well; this, indeed, would have been better than to be able to foretell what is going to happen.”

The Ideal Prognostic and Predictive Test

- Accurate
- Verifiable
- Reproducible
- Timely
- Acceptable cost
- Convenient

The Ideal Prognostic and Predictive Test

- Adaptable
 - Able to incorporate new information as it becomes available
 - Able to assist in defining *type* of therapy to be given
 - Able to subclassify tumors
 - Able to quantitate new targets
 - Able to incorporate pharmacogenomics

Breast Cancer Complexity


What We Wish ...



What We Have ...



Courtesy of
Antonio Wolff, MD

An abstract painting of autumn leaves in shades of orange, red, and brown, with a blue border. The text "Confusion and Chaos" is overlaid in yellow.

Confusion and Chaos

Coherence
&
Serenity



Thank you!



Wasatch Mountains - Utah