SOCIEDAD DE MASTOLOGIA
6 DE MAYO 2010

ONCOTYPE DX

Dr. Francisco Domínguez

Departamento de Cirugía Oncológica
Facultad de Medicina
Pontificia Universidad Católica de Chile

Conceptos generales

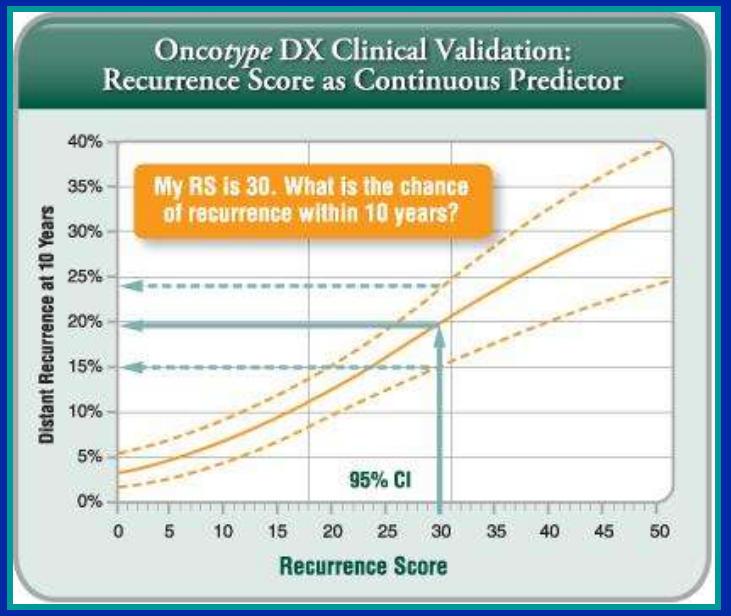
- Diagnóstico y decisiones terapeúticas basados en criterios patológicos e inmunohistoquímicos

- Necesidad de un enfoque más racional, cuantitativo e individualizado

- Uso de QT en pacientes N0, RE+:
  - Beneficio escaso
  - Asume un beneficio igual en todas las pacientes
  - Algunas pacientes son subtratadas
  - Muchas pacientes son sobretratadas

Conceptos generales

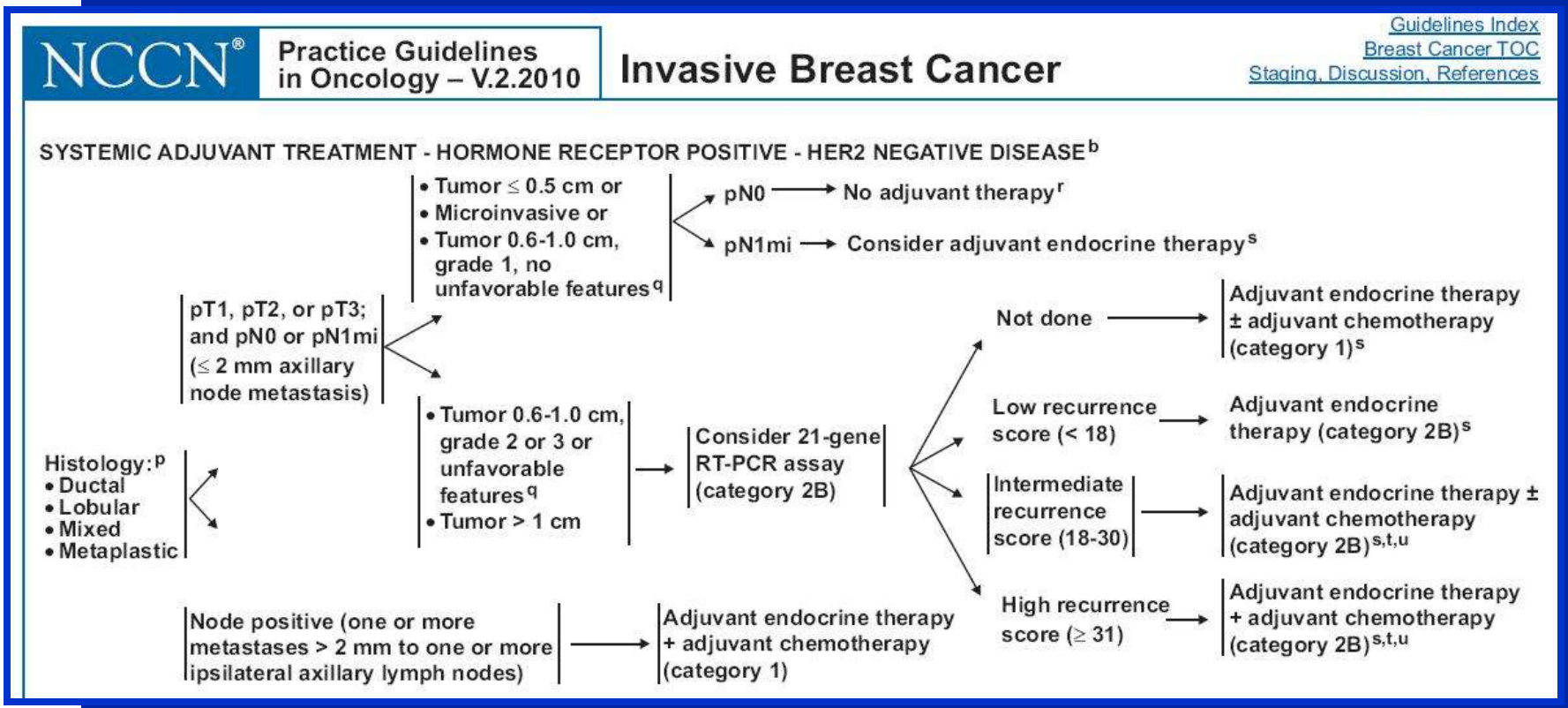
- Estudio de 21 genes que predice en forma personalizada el riesgo de recurrencia y el beneficio de la quimioterapia para pacientes N0 y RE positivo
- Laboratorio Genomic Health, CA, US
- Realizado en 90.000 pacientes
- Estudios en 4.000 pacientes
- Cubierto por Medicare y 90% seguros de salud privados
- US$ 3.978



Conceptos generales

Recomendacion NCCN Oncotype Dx:

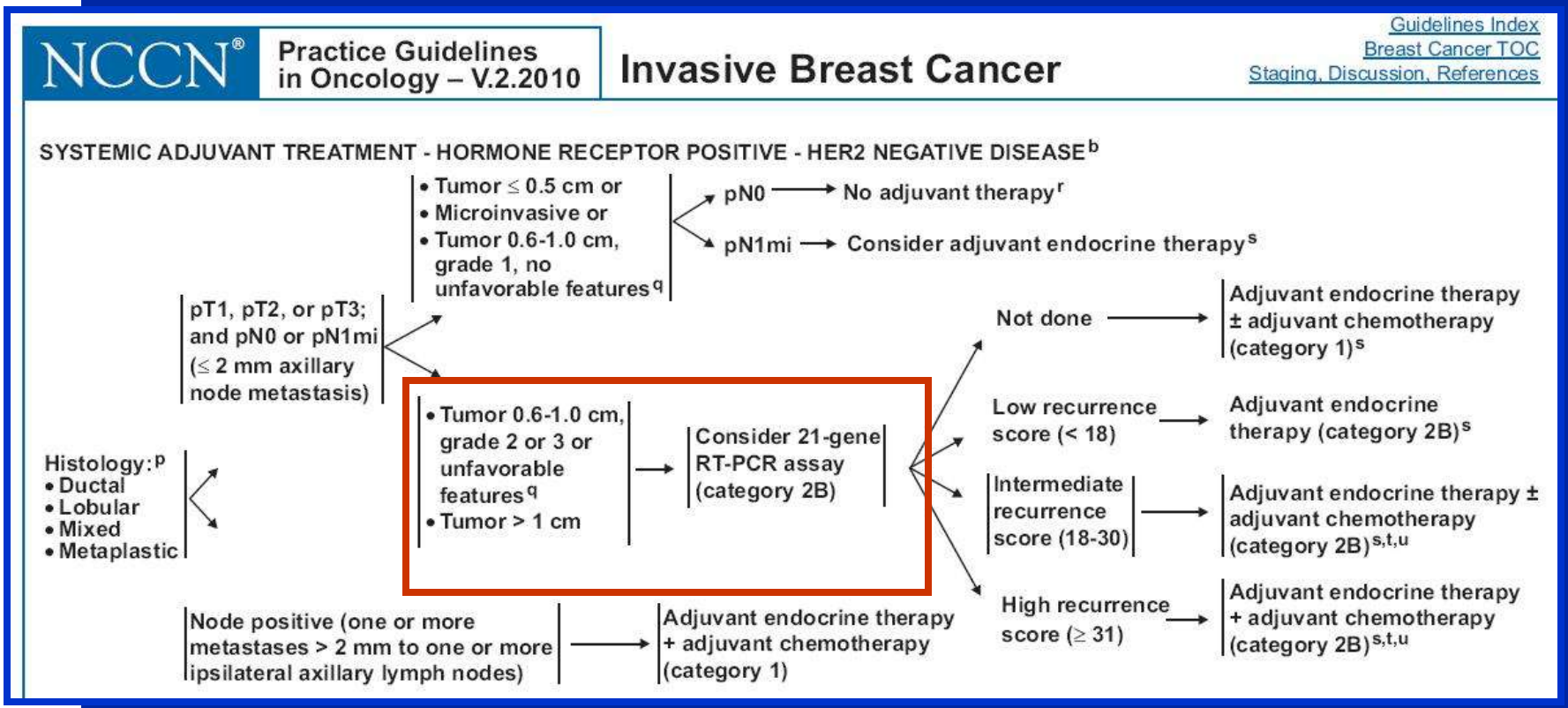
- **Tumores 0.6 a 1.0 cms con caracteristicas desfavorables**
- **Tumores > 1 cms, N0, RE+, HER 2 neg**



Conceptos generales

Recomendacion NCCN Oncotype Dx:

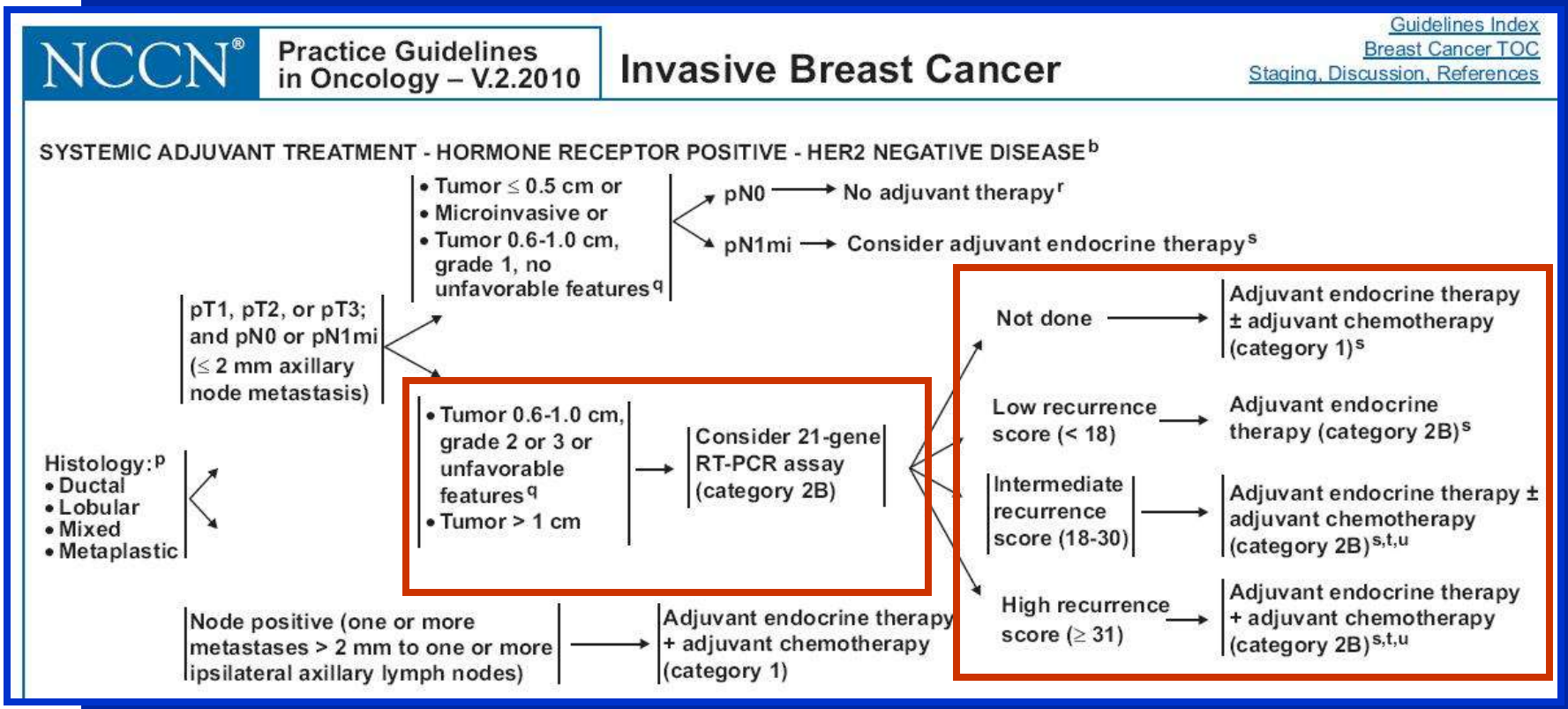
- **Tumores 0.6 a 1.0 cms con caracteristicas desfavorables**
- **Tumores > 1 cms, N0, RE+, HER 2 neg**



Conceptos generales

Recomendacion NCCN Oncotype Dx:

- **Tumores 0.6 a 1.0 cms con caracteristicas desfavorables**
- **Tumores > 1 cms, N0, RE+, HER 2 neg**



Conceptos generales

Recomendacion ASCO Oncotype Dx:

- Predecir riesgo de recurrencia en pacientes tratados con tamoxifeno
- Predecir mejor respuesta a Tamoxifeno y evitar uso QT
- Identificar pacientes con mayor beneficio de la QT

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

Multiparameter gene expression analysis for breast cancer (Note: This topic is new to the guideline)	In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the "Rotterdam Signature," and the Breast Cancer Gene Expression Ratio are under investigation.

DESARROLLO ONCOTYPE DX

2001 Desarrollo método RT-PCR de blocks parafina

↓

2002 Selección de genes candidatos (250 genes)

↓

2002 Estudio relación genes y recurrencia
(N = 447, incluye 233 de NSABP B-20)

↓

2003 Selección de 21 genes

↓

2003 Estudios de validación NSABP B-14 y Kaiser Permanente

GENES EN ESTUDIO

16 GENES RELACIONADOS CON CÁNCER + 5 GENES DE REFERENCIA

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RECURRENCE SCORE =

+ 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Validación Clínica ONCOTYPE DX: Impacto en Decisiones Clínicas

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

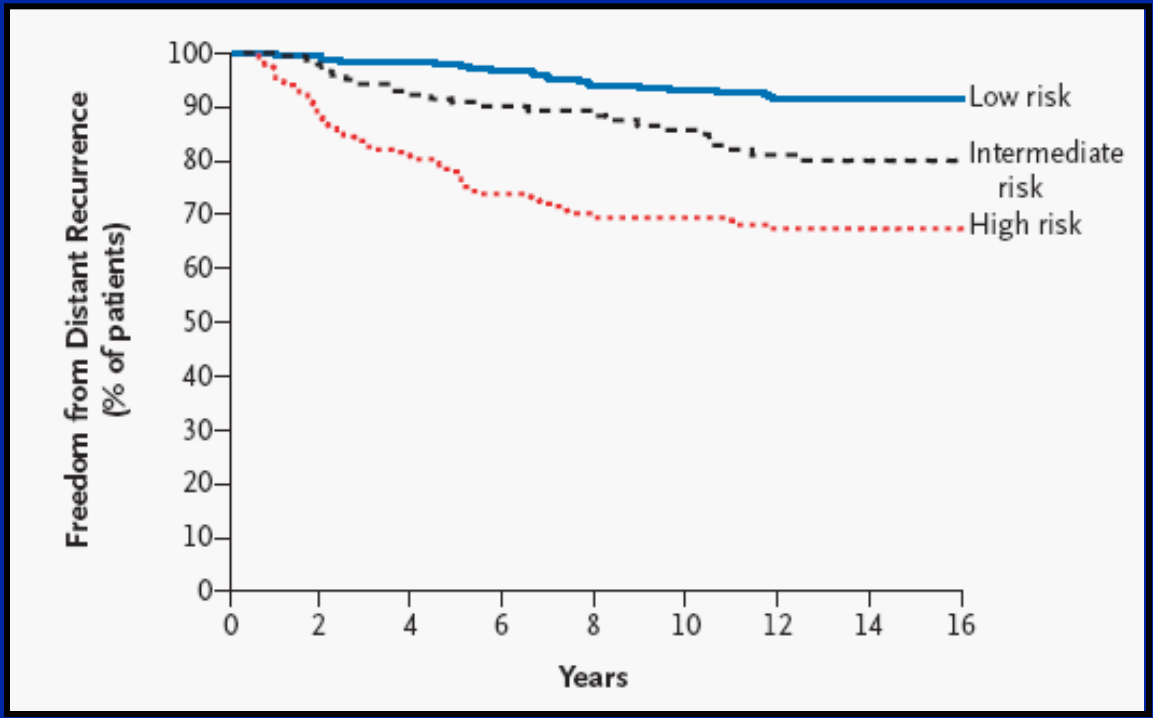
A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

N ENGL J MED 351;27 WWW.NEJM.ORG DECEMBER 30, 2004

Validación Clínica ONCOTYPE DX: Recurrencia a distancia según RS

Category	RS (0 -100)
Low risk	RS <18
Int risk	RS 18 - 30
High risk	RS ≥ 31



Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Validación Clínica ONCOTYPE DX: Recurrencia a distancia según RS

Risk Group	% of Patients	10-yr Rate of Recurrence	95% CI
Low (RS <18)	51%	**6.8%**	4.0%, 9.6%
Intermediate (RS 18-30)	22%	14.3%	8.3%, 20.3%
High (RS ≥31)	27%	**30.5%**	23.6%, 37.4%

Test for the 10-year Distant Recurrence comparison between the low-and high-risk groups: *P* <0.001

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Validación Clínica ONCOTYPE DX: Recurrencia a distancia según RS

Multivariate Cox Models: Age, Size + RS

Variable	Hazard Ratio	95% CI	*P* value
Age < 50	0.71	(0.48, 1.05)	0.084
Size > 2.0 cm	1.26	(0.86, 1.85)	0.231
Recurrence Score	3.21	(2.23, 4.61)	<0.001

Age at surgery used as a binary factor: 0 = <50 yr, 1 = ≥50 yr.
Clinical tumor size (CTS) used as a binary factor: 0 = ≤2 cm, 1 = >2 cm.
Recurrence Score used as a continuous variable, with HR relative to an increment of 50 RS units.

Paik et al. *N Engl J Med.* 2004;351:2817-2826.

Validación Clínica ONCOTYPE DX: Impacto en Decisiones Clínicas

Breast Cancer RESEARCH IMPACT FACTOR 5.05

Breast Cancer Research Vol 8 No 3 Habel *et al.*

Research article

Open Access

A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients

Laurel A Habel[1], Steven Shak[2], Marlena K Jacobs[1], Angela Capra[1], Claire Alexander[2], Mylan Pho[2], Joffre Baker[2], Michael Walker[2], Drew Watson[2], James Hackett[2], Noelle T Blick[1], Deborah Greenberg[3], Louis Fehrenbacher[4], Bryan Langholz[5] and Charles P Quesenberry[1]

[1]Division of Research, Kaiser Permanente, Oakland, California, USA
[2]Genomic Health, Inc., Redwood City, California, USA
[3]Permanente Medical Group Regional Laboratory, Kaiser Permanente, Berkeley, California, USA
[4]Oncology, Kaiser Permanente, Vallejo, California, USA
[5]USC Keck School of Medicine, Los Angeles, California, USA

Corresponding author: Laurel A Habel, laurel.habel@kp.org

Received: 31 Jan 2006 Revisions requested: 16 Feb 2006 Revisions received: 21 Apr 2006 Accepted: 25 Apr 2006 Published: 31 May 2006

Breast Cancer Research 2006, **8**:R25 (doi:10.1186/bcr1412)
This article is online at: http://breast-cancer-research.com/content/8/3/R25
© 2006 Habel *et al.*; licensee BioMed Central Ltd.
This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Validación Clínica ONCOTYPE DX: Estudio Kaiser Permanente

Mortalidad a 10 años pacientes RE+, Tam+

Risk Classifier	10-yr Absolute Risk Kaiser	10-yr Absolute Risk NSABP B14
Recurrence Score		
Low (<18)	2.8%	3.1%
Intermediate (18-30)	10.7%	12.2%
High (≥31)	15.5%	27.0%

[1]Based on methods by Langholz and Borgan, *Biometrics* 1997;53:767-774.

Habel et al. *Breast Cancer Res*. May 2006.

Validación Clínica ONCOTYPE DX: Impacto en Decisiones Clínicas

Prospective multi-center study of the impact of the 21-gene Recurrence Score (RS) assay on medical oncologist (MO) and patient (pt) adjuvant breast cancer (BC) treatment selection

Shelly S. Lo[1], John Norton[1], Patricia B. Mumby[1], Jeffrey Smerage[2], Joseph Kash[3], Helen K. Chew[4], Daniel Hayes[2], Andrew Epstein[5], Kathy S. Albain[1]

[1]Loyola University, Maywood IL, [2]University of Michigan, Ann Arbor MI, [3]Edward Hospital, Naperville IL, [4]UC Davis, Sacramento CA, [5]Mount Sinai Medical Center, New York NY

ASCO 2007, Abstract #577

Validación Clínica ONCOTYPE DX: Impacto en Decisiones Clínicas

Recomendaciones de tratamiento se modifican 31.5% de los casos

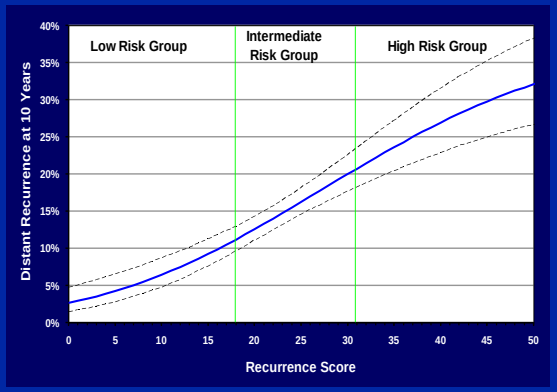
MO Pre to Post-RS Assay Treatment Recommendation	Number of Cases(%)
CHT to HT	20 (22.5)
HT to CHT	3 (3.4)
CHT or HT to Equipoise	5 (5.6)
Treatment plan did not change	61 (68.5)
Total	89 (100)

- **Cambio recomendación de tratamiento en 28 casos (31.5%) posterior a RS Assay.**
- **Cambio más frecuente: QT a Hormonoterapia en 22.5%**

ASCO 2007, Abstract #577

Randomizados en curso:

Trial Assigning IndividuaLized Options for Treatment (Rx) TAILORx



Node-Neg, ER-Pos Breast Cancer

Register
Specimen banking

Oncotype DX® Assay

RS ≤10
Hormone Therapy

RS 11-25
Randomize
Hormone
vs
Chemotherapy + Hormone

RS >25
Chemotherapy + Hormone

Primary study group

SOCIEDAD DE MASTOLOGIA
6 DE MAYO 2010

ONCOTYPE DX