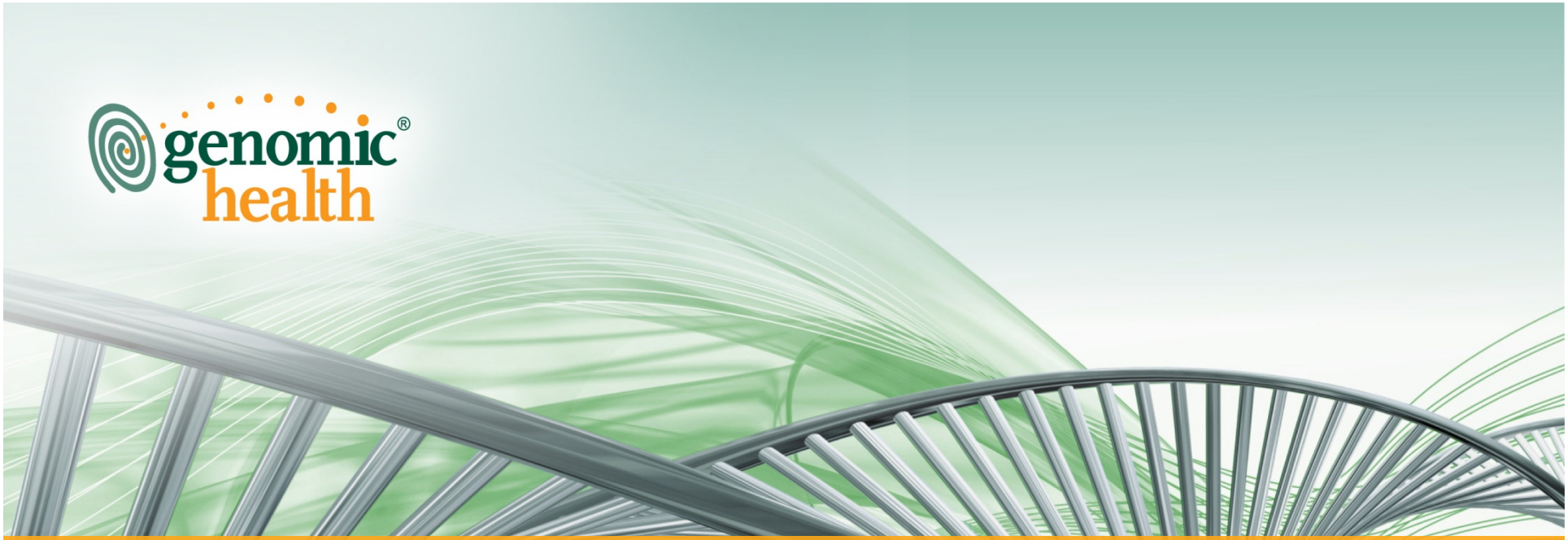


Personalized Medicine Applications in Oncology

11th Annual Population Health Colloquium

Stan Skrzypczak, MS, MBA
Sr. Director, Marketing
Genomic Health, Inc.
March 15, 2011

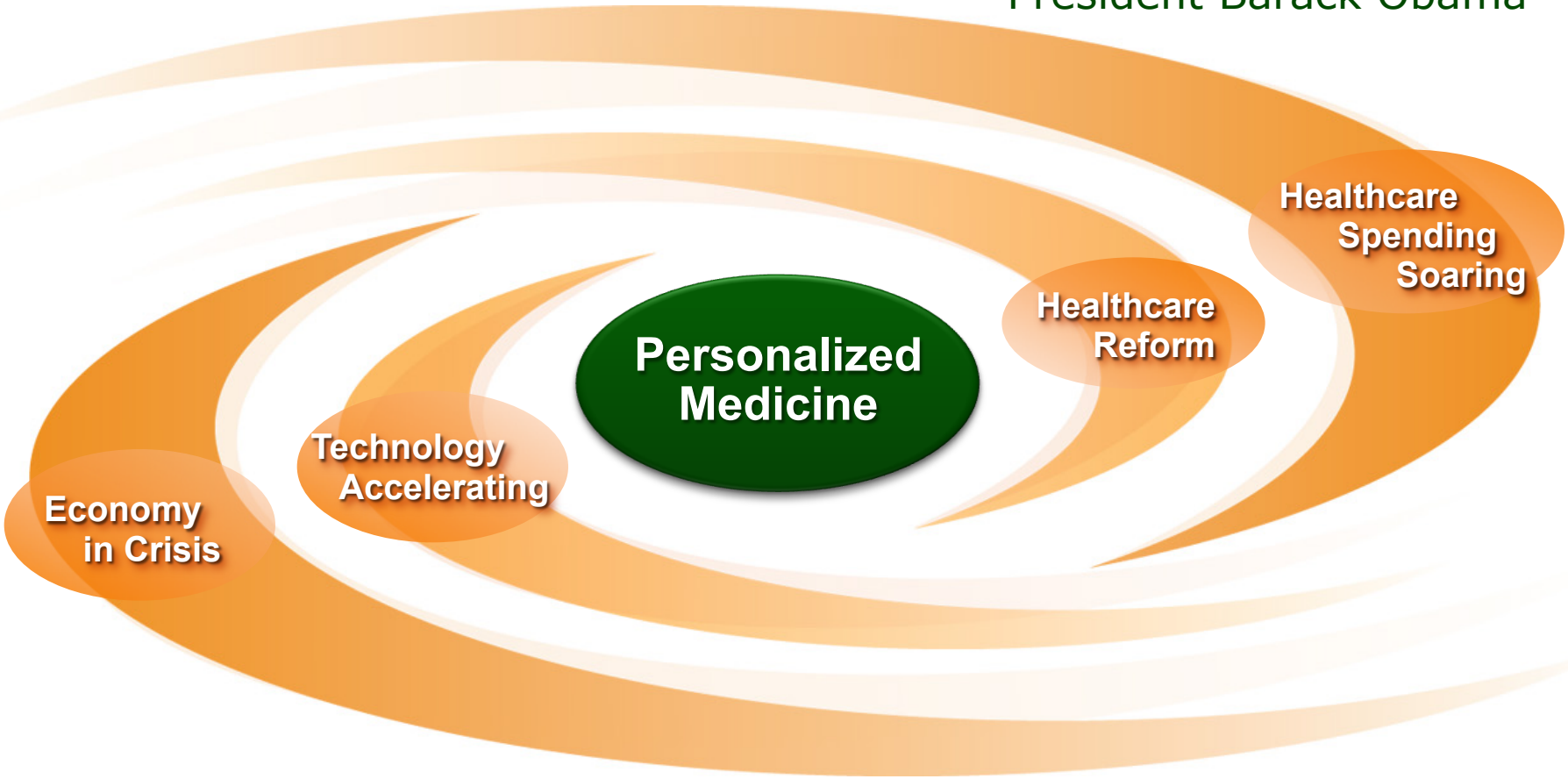
Agenda

- Personalized medicine in oncology healthcare
- Clinical relevance of personalized medicine
- Innovation and adoption in our oncology healthcare system
  - Onco*type* DX® assay as a case study

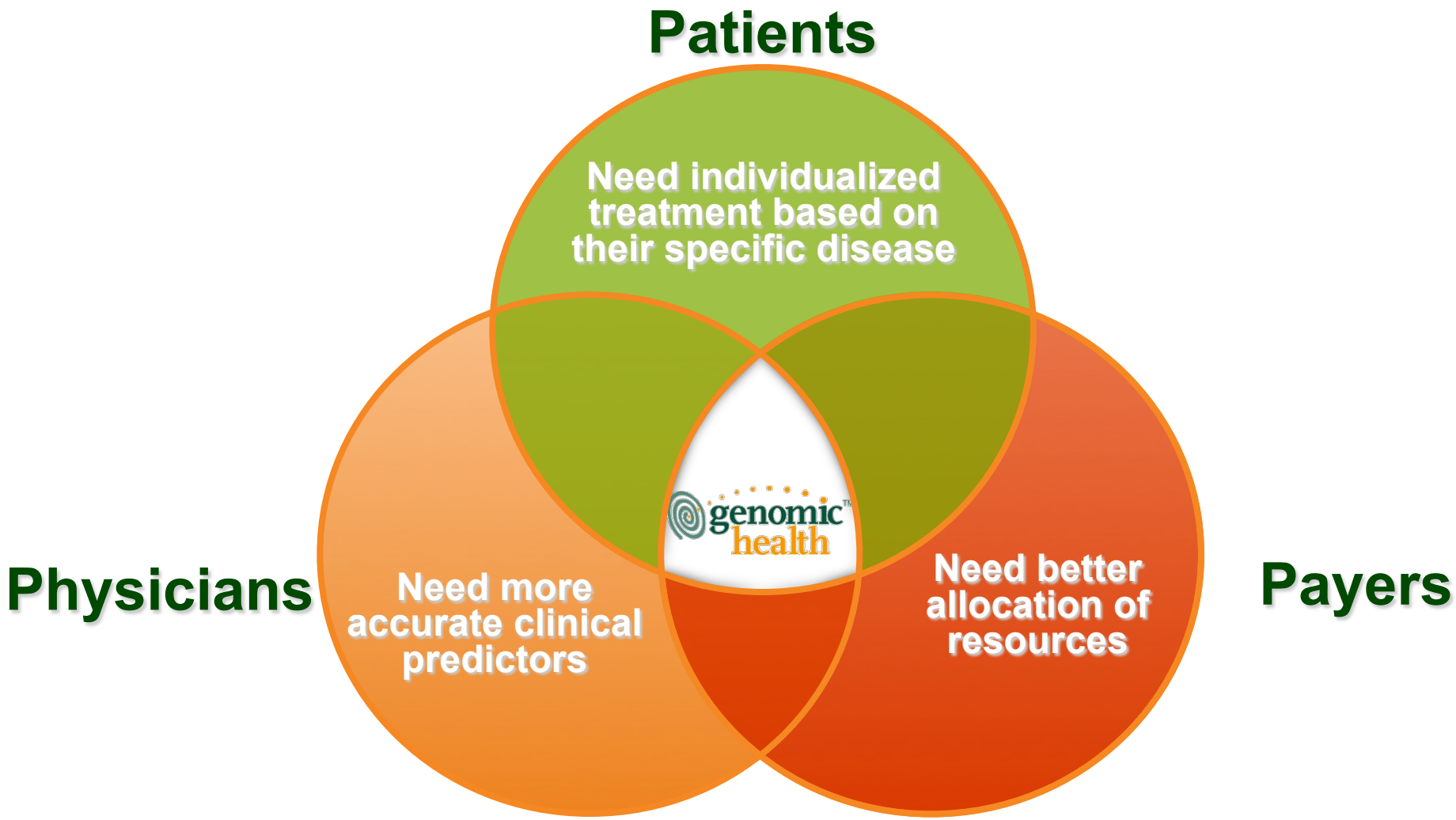
Personalized Medicine embraces all components of a complex situation analysis

"We spend far more on treating illnesses that could have been managed for far less."

– President Barack Obama



All stakeholders are in need of better solutions to healthcare issues



Personalized Medicine: Basic Tenets

Personalized Medicine

- Can improve healthcare delivery
- Can improve healthcare outcomes
- Helps manage healthcare costs and spending

Personalized Medicine: Challenges to broad adoption

- Physician and payer education
  - use and interpretation of new diagnostic tests that individualize treatment
- Diagnostic reimbursement
  - traditionally cost-based rather than value-based
- New individualized diagnostics based on new technologies and innovative test concepts
- Legacy regulatory frameworks
  - must evolve to accommodate new diagnostic technologies and tests

Definitions: Genetics and genetic testing

- Genetics: study of **single genes** and their effects
  - **Single gene point mutations** lead to high likelihood of a certain disease (eg, BRCA-1 & BRCA-2, HNPCC)
- **Genetic testing** identifies heritable single gene mutations within a patient's genome
  - Diagnosis for genetic disease
    - eg, mutation in RET oncogene confirms medullary thyroid cancer as manifestation of MEN2
  - Identify/screen for future health risks
  - Prediction of drug responses
  - Assessment of risks to future children

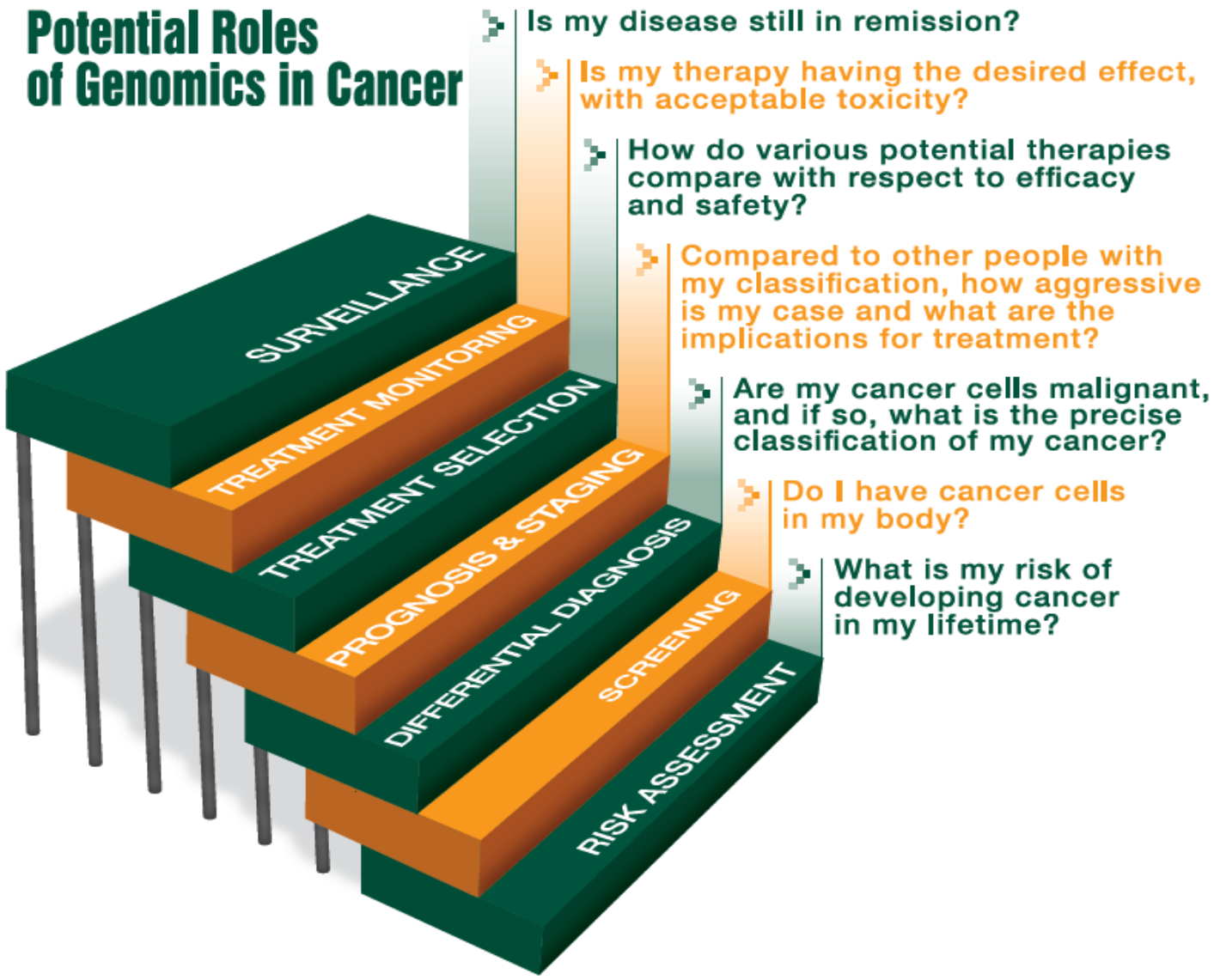
Guttmacher & Collins. NEJM. 2002;347(19):1513.
Burke. NEJM. 2003;347(23):1867.

Genomics vs. genetics

- Genomics: study of **all** genes in the genome, including their interactions with environmental factors
  - Studies of gene expressions and their correlation to clinical outcomes in common diseases
- Genomic-based clinical diagnostics in oncology:
  - Prognosis
    - How aggressive is the tumor biology?
    - What is the likelihood of tumor recurrence?
  - Prediction of treatment benefit
    - What is the likely benefit from treatment?

Simon. JCO. 2005;23(29):7332.

Clinical relevance of Personalized Medicine: Different goals for different diagnostics



Assessing genomic assays: Accuracy and clinical relevance

- **Analytical performance:** Is the quantification of the analyte (s) of interest reliable and reproducible?
- **Clinical validity:** How well does the test relate to the clinical outcome of interest?
- **Clinical utility:** Does the information provided make a contribution to and improve current optimal management of the patient's disease?
- **Economic value:** Assessment of cost savings and/or cost-effectiveness
- Measures are interrelated
  - Analytic performance must be evaluated in context of the clinical use
  - Clinical validity must be assessed in context of analytic performance

Ramsey et al, AJMC, 2006
Sparano, et al., JCO, 2010
Marchioni et al, Ann Intern Med, 2008

Level of evidence in tumor marker studies: Revised criteria

Proper study design determines strength of results

Level of evidence	Study design	Validation studies available
I	Prospective	None required
I	Prospective using archived samples	One or more with consistent results
II	Prospective using archived samples	None, or inconsistent results
II	Prospective / observational	Two or more with consistent results
III	Prospective / observational	None, or one with consistent results, or inconsistent results
IV-V	Retrospective / observational	Not applicable*

The Onco*type* DX® assay fulfills the criteria for Level I evidence: More than one prospective validation study using archived samples with consistent results

***Level of evidence IV and V studies will never be satisfactory for determination of medical utility.**

Simon RM, et al. *J Natl Cancer Inst*. 2009;101:1446-1452.

The Onco*type* DX® Breast Cancer Assay for Early Stage Patients: Clinical Relevance

- Chemotherapy benefit is modest in the adjuvant setting (~4%) [1]
- Onco*type* DX identifies patients more or less likely to benefit from chemotherapy
- Independent studies verify that use of Onco*type* DX impacts treatment decisions
- Genomic information is shifting the treatment paradigm for breast cancer

1. *The Lancet*.1996;347(9008):1066-1071.

The Oncotype DX® assay provides reproducible results in relevant patients across a continuum of disease

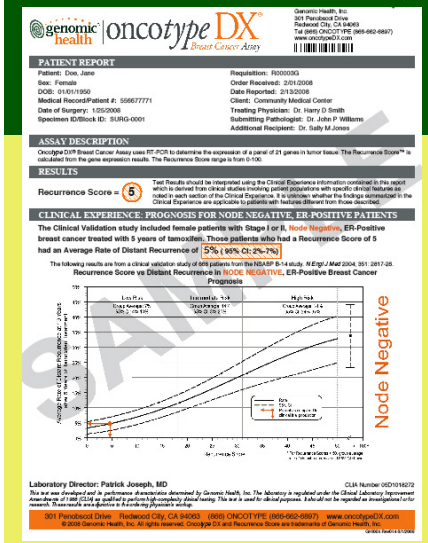
Study	Design	N	Nodal status	Prognostic	Predictive
NSABP B-14[1]	Prospective; tam only	668	Neg	YES	-
Kaiser Permanente[2]	Prospective; case-control	790 cases / controls	Neg	YES	-
NSABP B-14[3]	Prospective; placebo vs tam	645	Neg	YES	YES; Quantitative ER predicts tamoxifen benefit
NSABP B-20[4]	Prospective; tam ± chemo	651	Neg	-	YES; RS predicts chemotherapy benefit
ECOG 2197[5]	Prospective; AC vs AT	776	Neg/Pos	YES	-
SWOG 8814[6]	Prospective; tam ± chemo	367	Pos	YES	YES; RS predicts chemotherapy benefit
TransATAC[7]	Prospective; tam vs AI	1231	Neg/Pos	YES	-

RS, Recurrence Score® result

1. Paik S, et al. *N Engl J Med*. 2004;351:2817-2826.
2. Habel LA, et al. *Breast Cancer Res*. 2006;6:R25-R39.
3. Paik S, et al. *J Clin Oncol*. 2005;23(16S):abstract 510.
4. Paik S, et al. *J Clin Oncol*. 2006; 24:3726-3734
5. Goldstein LJ, et al. *J Clin Oncol*. 2008;26:4063-4071.
6. Albain KS, et al. *Lancet Oncol*. 2010;11:55-65
7. Dowsett M, et al. *J Clin Oncol*. 2010;28:1829-1834.

Continued investment in development increases clinical utility and adoption

Node Negative Recurrence


genomic health | oncotype DX® Breast Cancer Assay

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950
Medical Record/Patient #: 556677771
Date of Surgery: 1/25/2006
Specimen ID/Block ID: SURG-0001

Requisition: R00003G
Order Received: 2/01/2008
Date Reported: 2/13/2008
Client: Community Medical Center
Treating Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Recipient: Dr. Sally M Jones

ASSAY DESCRIPTION

Oncotype DX® Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score™ is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

Recurrence Score = 5

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 5 had an Average Rate of Distant Recurrence of 5% (95% CI: 2%-7%)

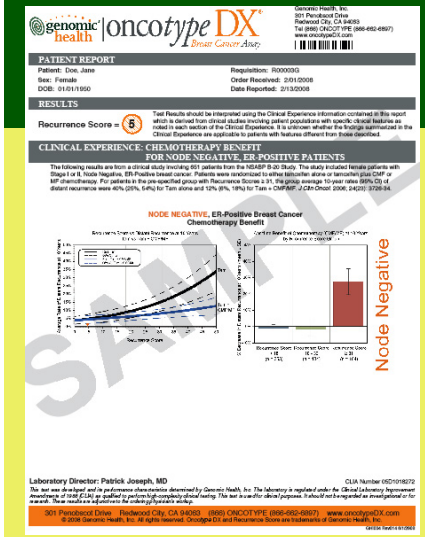
The following results are from a clinical validation study of 668 patients from the NSABP B-14 study. *N Engl J Med* 2004; 351: 2817-26.

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

Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018272

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

Node Negative Chemotherapy Benefit


genomic health | oncotype DX® Breast Cancer Assay

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 2/01/2008
Date Reported: 2/13/2008

RESULTS

Recurrence Score = 5

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: CHEMOTHERAPY BENEFIT FOR NODE NEGATIVE, ER-POSITIVE PATIENTS

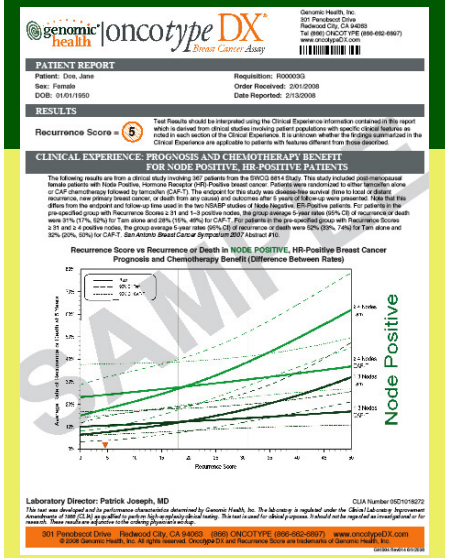
The following results are from a clinical study involving 651 patients from the NSABP B-20 Study. This study included female patients with Stage I or II, Node Negative, ER-Positive breast cancer. Patients were randomized to either tamoxifen alone or tamoxifen plus CMF or MF chemotherapy. For patients 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

Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018272

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

Node Positive Recurrence, Chemotherapy Benefit


genomic health | oncotype DX® Breast Cancer Assay

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 2/01/2008
Date Reported: 2/13/2008

RESULTS

Recurrence Score = 5

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 AND CHEMOTHERAPY BENEFIT FOR NODE POSITIVE, HR-POSITIVE PATIENTS

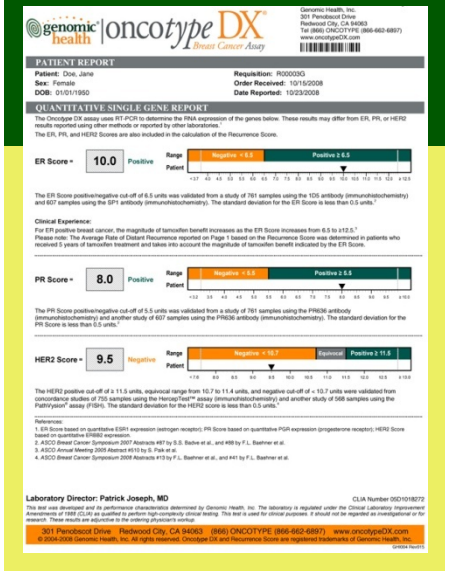
The following results are from a clinical study involving 367 patients from the SWOG 8814 Study. This study included post-menopausal female patients with Node Positive, Hormone Receptor (HR)-Positive breast cancer. Patients were randomized to either tamoxifen alone or CAF chemotherapy followed by tamoxifen (CAF-T). The endpoint for this study was disease-free survival (time to local or distant recurrence, new primary breast cancer, or death from any cause) and outcomes after 5 years of follow-up were presented. Note that this differs from the endpoint and follow-up time used in the two NSABP studies of Node Negative, ER-Positive patients. For patients in the pre-specified group with Recurrence Scores ≥ 31 and 1–3 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 31% (17%, 52%) for Tam alone and 28% (15%, 49%) for CAF-T. For patients in the pre-specified group with Recurrence Scores ≥ 31 and ≥ 4 positive nodes, the group average 5-year rates (95% CI) of recurrence or death were 52% (33%, 74%) for Tam alone and 32% (20%, 50%) for CAF-T. *San Antonio Breast Cancer Symposium 2007* Abstract #10.

Recurrence Score vs Recurrence or Death in NODE POSITIVE, HR-Positive Breast Cancer Prognosis and Chemotherapy Benefit (Difference Between Rates)

Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018272

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

Quantitative Single Gene


genomic health | oncotype DX® Breast Cancer Assay

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950

Requisition: R00003G
Order Received: 10/15/2008
Date Reported: 10/23/2008

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.

ER Score = 10.0 Positive

Range: Negative < 6.5 | Positive ≥ 6.5
Patient

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 ≥10.5.[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.

PR Score = 8.0 Positive

Range: Negative < 6.5 | Positive ≥ 6.5
Patient

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.[1]

HER2 Score = 9.5 Negative

Range: Negative < 10.7 | Equivocal | Positive ≥ 11.5
Patient

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.[1]

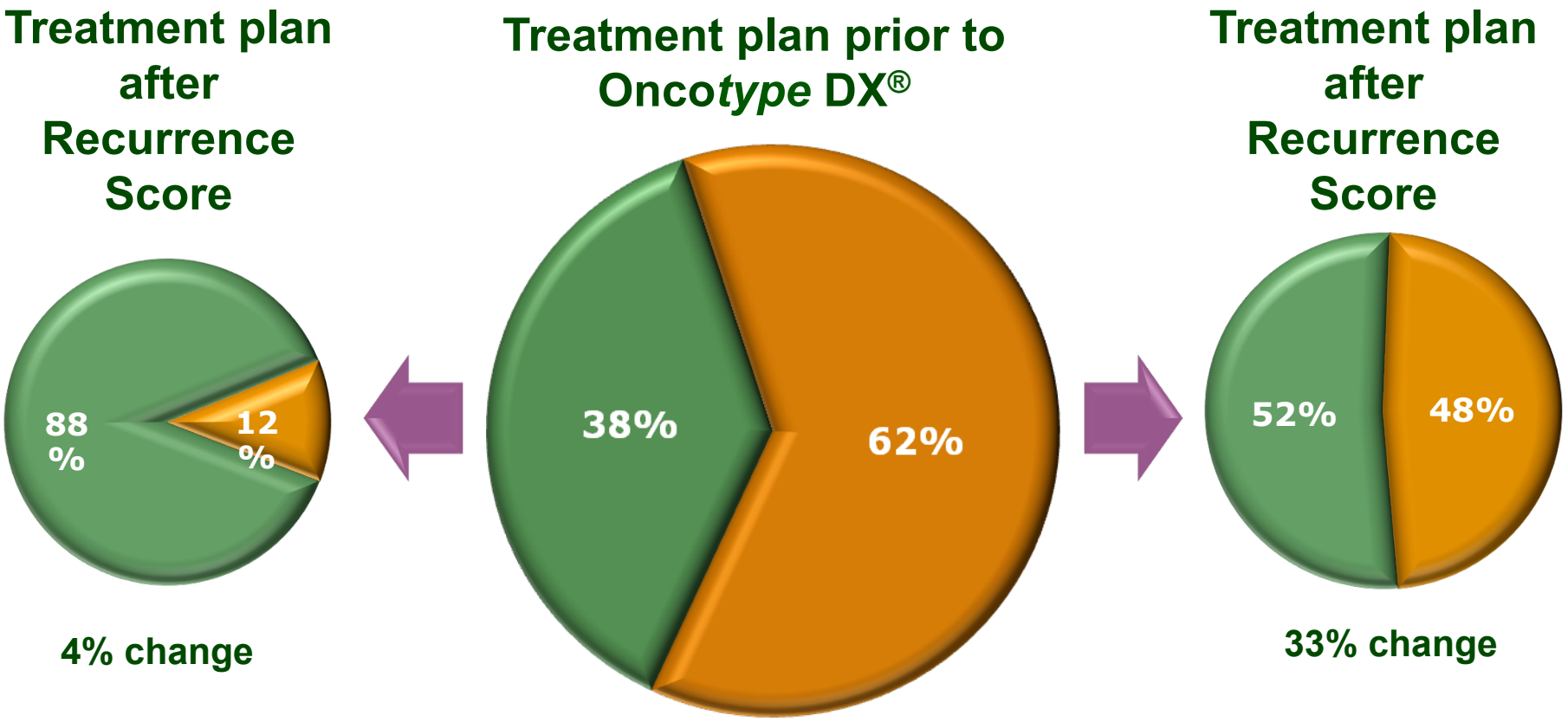
References:

1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.
2. *ASCO Breast Cancer Symposium 2007* Abstracts 497 by S.S. Badve et al., and 498 by F.L. Baehner et al.
3. *ASCO Annual Meeting 2005* Abstract #510 by S. Paik et al.
4. *ASCO Breast Cancer Symposium 2008* Abstracts #13 by F.L. Baehner et al., and #41 by F.L. Baehner et al.

Laboratory Director: Patrick Joseph, MD CLIA Number 05D1018272

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897) www.oncotypeDX.com

Meta-analysis: Overall impact of the Recurrence Score® result on treatment decisions (n=912)



Overall, the Recurrence Score led to a 37% change in treatment decisions

- ***33% from CT+HT→ HT***
- ***4% from HT → CT+HT***

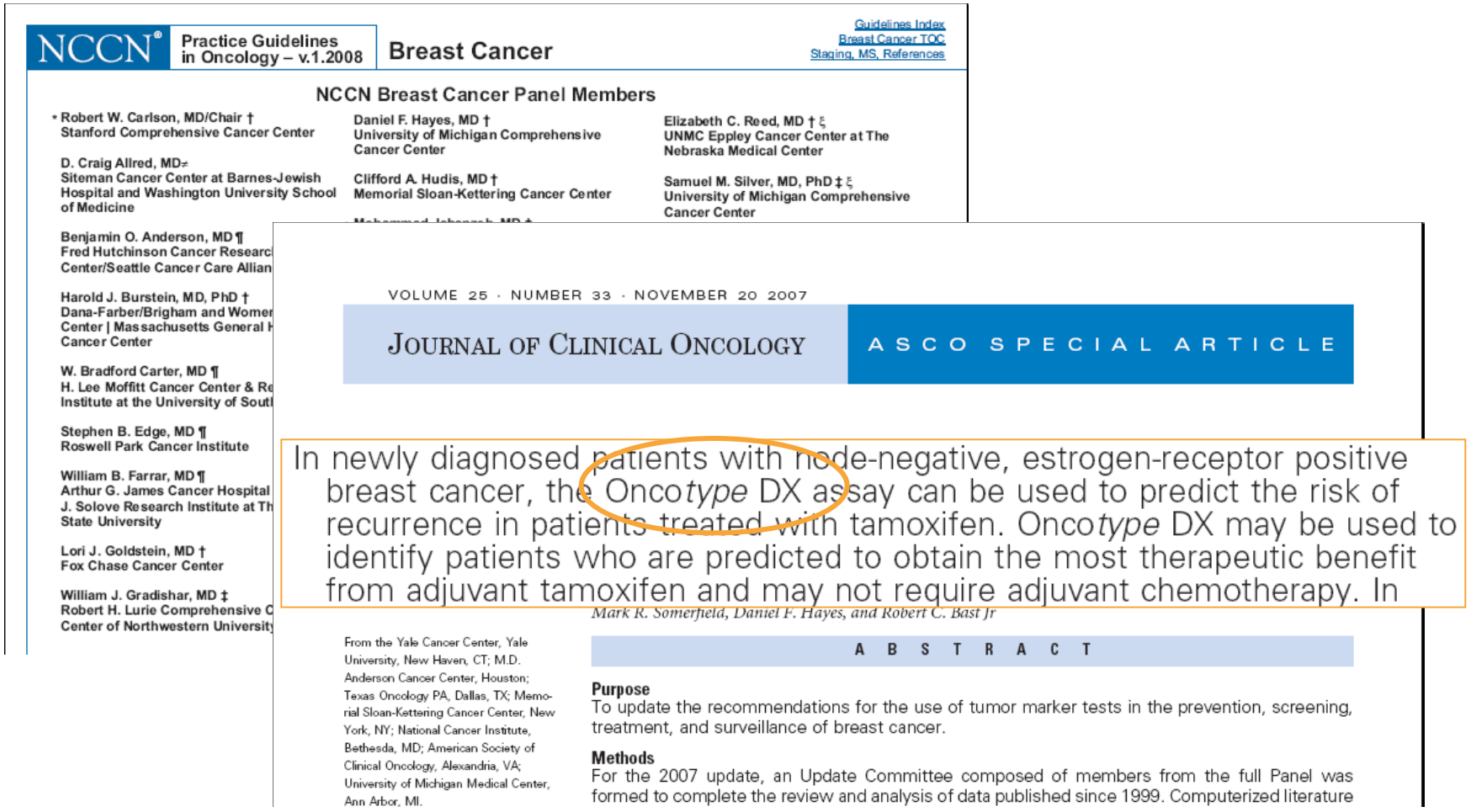
Hornberger J, et al. SABCS 2010. Poster P2-09-06.

Cost savings driven by proven clinical utility: A cost-benefit analysis example for node negative breast cancer ($US)

Input		
No. Lives	1,000,000	1,000,000
Oncotype Penetration	50%	80%
List Cost	$4075	$4075
Decision Impact (CMT=> HT)	30%	30%
Cost Adjuvant Chemo (ASP+6%)	$6460	$6460
Cost Adjuvant Supportive Care	$8580	$8580
Cost Adverse Events	$4748	$4748

Output		
Eligible Population	299	299
pN0	138	249
pN1 mic	11	20
Chemo Savings per Patient	**($1669)**	**($1669)**
Supportive Savings pp	**($2098)**	**($2098)**
A/E Savings pp	**($1304)**	**($1304)**
Recurrence Savings pp	**($2031)**	**($2031)**
Total pp (ex. assay cost)	**($3027)**	**($3027)**
Total Savings per Plan	**($584,892)**	**($935,827)**

Treatment guidelines include the Oncotype DX® assay for breast cancer



NCCN® Practice Guidelines in Oncology – v.1.2008 **Breast Cancer**

Guidelines Index
Breast Cancer TOC
Staging, MS, References

NCCN Breast Cancer Panel Members

• Robert W. Carlson, MD/Chair †
Stanford Comprehensive Cancer Center

D. Craig Allred, MD≠
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Benjamin O. Anderson, MD ¶
Fred Hutchinson Cancer Researc
Center/Seattle Cancer Care Allian

Harold J. Burstein, MD, PhD †
Dana-Farber/Brigham and Wome
Center | Massachusetts General H
Cancer Center

W. Bradford Carter, MD ¶
H. Lee Moffitt Cancer Center & Re
Institute at the University of Soutl

Stephen B. Edge, MD ¶
Roswell Park Cancer Institute

William B. Farrar, MD ¶
Arthur G. James Cancer Hospital
J. Solove Research Institute at Th
State University

Lori J. Goldstein, MD †
Fox Chase Cancer Center

William J. Gradishar, MD ‡
Robert H. Lurie Comprehensive C
Center of Northwestern University

Daniel F. Hayes, MD †
University of Michigan Comprehensive Cancer Center

Clifford A. Hudis, MD †
Memorial Sloan-Kettering Cancer Center

Elizabeth C. Reed, MD † ξ
UNMC Eppley Cancer Center at The Nebraska Medical Center

Samuel M. Silver, MD, PhD ‡ ξ
University of Michigan Comprehensive Cancer Center

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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

Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

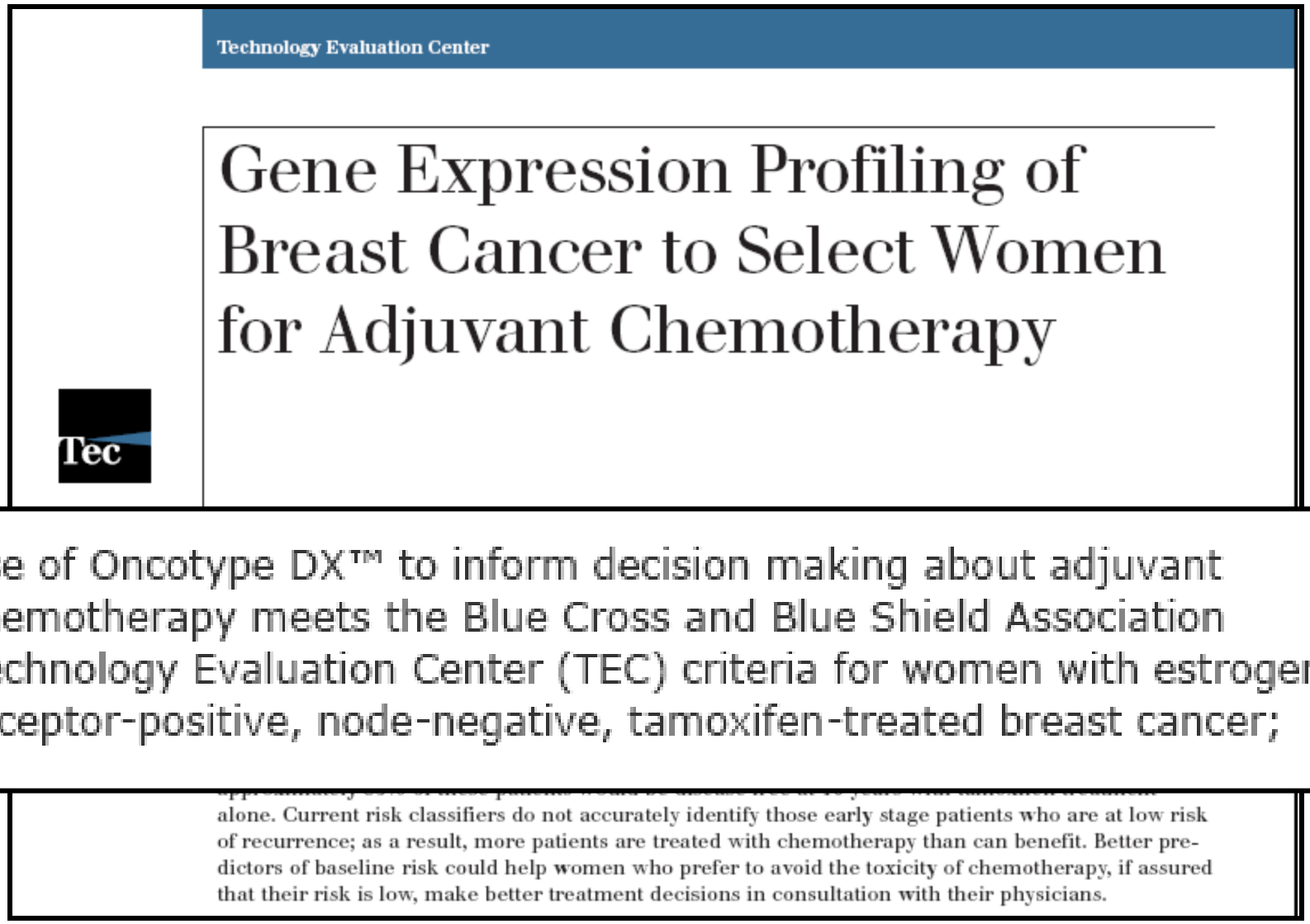
From the Yale Cancer Center, Yale University, New Haven, CT; M.D. Anderson Cancer Center, Houston; Texas Oncology PA, Dallas, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; National Cancer Institute, Bethesda, MD; American Society of Clinical Oncology, Alexandria, VA; University of Michigan Medical Center, Ann Arbor, MI.

A B S T R A C T

Purpose
To update the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of breast cancer.

Methods
For the 2007 update, an Update Committee composed of members from the full Panel was formed to complete the review and analysis of data published since 1999. Computerized literature

BCBS TEC conclusions: April 2008



Technology Evaluation Center

Gene Expression Profiling of Breast Cancer to Select Women for Adjuvant Chemotherapy

Tec

use of Oncotype DX™ to inform decision making about adjuvant chemotherapy meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria for women with estrogen receptor-positive, node-negative, tamoxifen-treated breast cancer;

alone. Current risk classifiers do not accurately identify those early stage patients who are at low risk of recurrence; as a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women who prefer to avoid the toxicity of chemotherapy, if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Managed care plan acceptance of the Onco*type* DX® assay for quality pathways

- CareFirst BlueCross BlueShield in Baltimore
- Integrated Onco*type* DX diagnostic test into breast cancer treatment pathway
- Three-year pilot quality program initiated Aug 2008
  - Onco*type* DX in all N-, ER+, HER-, early stage breast cancer where chemo may be considered
  - Physicians complying with treatment pathway guidelines based on risk stratification will be reimbursed at a higher rate than physicians not following pathway guidelines
  - CareFirst anticipation is that use of the genomic biomarker test will decrease unnecessary chemotherapy, improve patient quality of life and result in health plan cost savings

***Managed Care*. 2008;17(7)(suppl 7).**
http://www.managedcaremag.com/supplements/0807_diagnostics_oncology/MC_0807_diagnostics_oncology.pdf .

Adoption of clinical quality pathways is growing

- The highly ranked UPMC Cancer Centers work in tandem with the University of Pittsburgh Cancer Institute (UPCI), a National Cancer Institute designated Comprehensive Cancer Center

- Their clinical pathways program in oncology was developed and implemented in large part to offer quality, streamlined patient care while at the same time gaining efficiencies that would reduce costs

- This program incorporates both K-RAS testing for colon cancer and the Onco*type* DX® assay for breast cancer

Our tests address critical questions in cancer treatment planning…

Breast Cancer

oncotype DX® Breast Cancer Assay

Launched January 2004

Colon Cancer

oncotype DX® Colon Cancer Assay

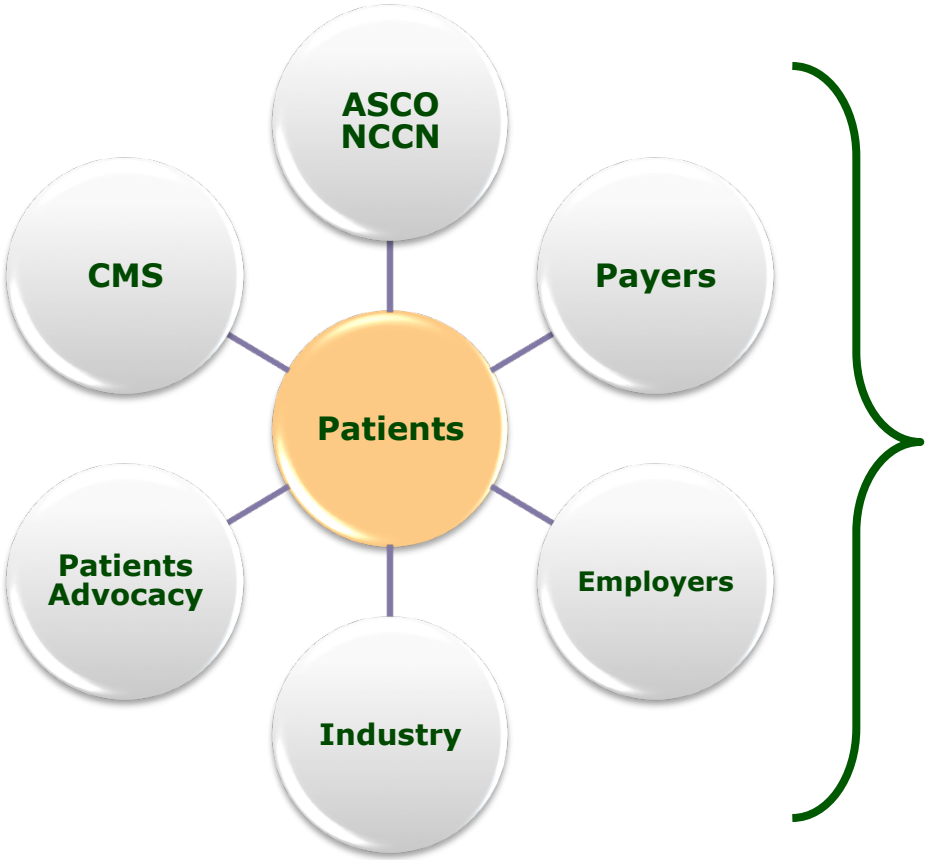
Launched January 2010

Prostate Cancer

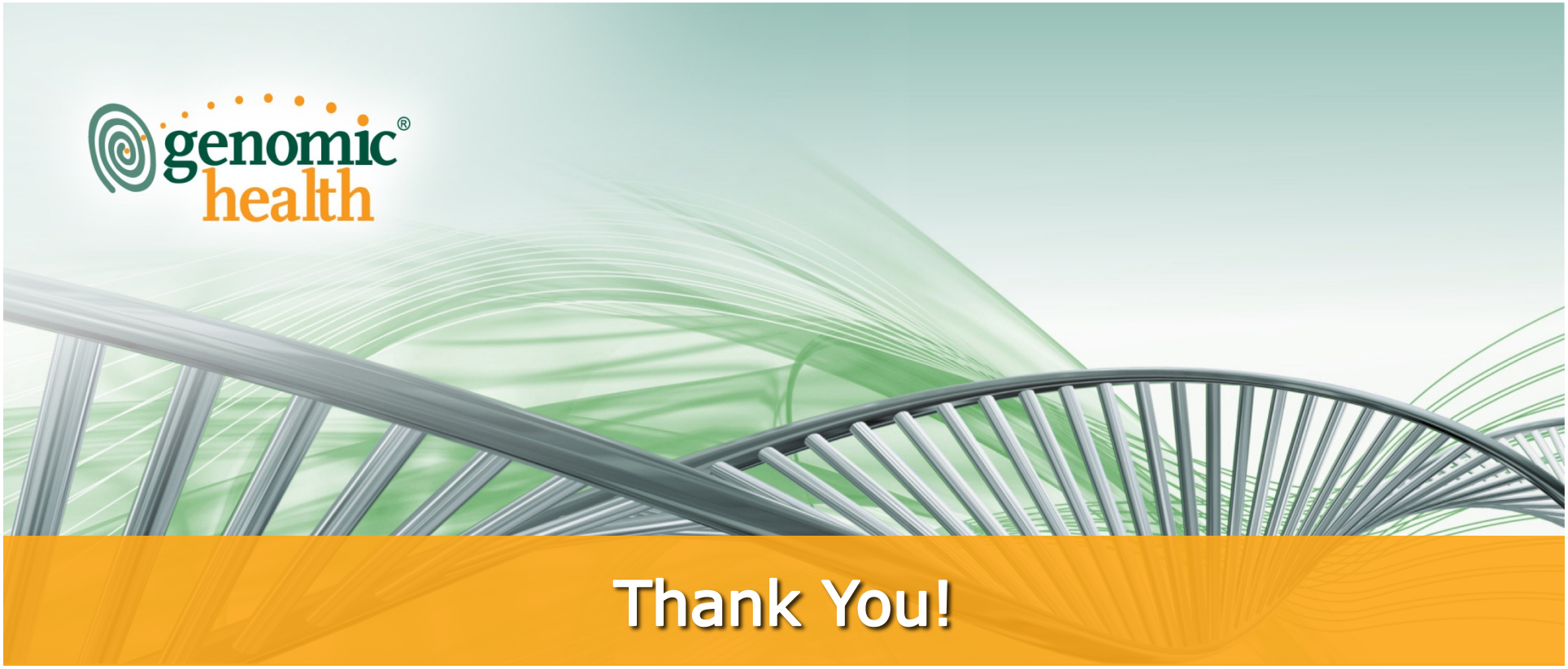
oncotype DX® Prostate Cancer Assay

Gene ID Data 2011

Stakeholders must be aligned toward a common goal



Joint Decision



Thank You!

Clinical Utility Evidence Supports the Clinical Relevance of the Oncotype DX (ex. Node-)

After RS \ Before RS	CT + HT	HT	**Total**
CT + HT	271	41	312
HT	297	303	600
Total	568	344	**912**

- Before RS testing, **62%** of patients (568 of 912) were recommended adjuvant CT+HT

- After RS testing **34%** of patients (312 of 912) were recommended adjuvant CT+HT → **28% net reduction in CT**

RS, Recurrence Score® result

Hornberger J, et al. SABCS 2010. Poster P2-09-06.