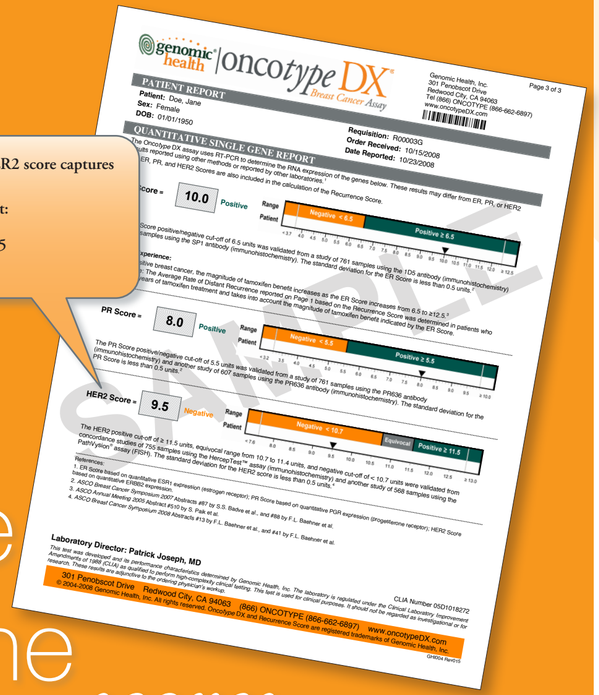
quantitative

- Continuous, quantitative HER2 score captures a wide range of expression
- Interpreting the HER2 Result:
  - Negative: < 10.7
  - Equivocal: ≥ 10.7 to < 11.5
  - Positive: ≥ 11.5


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

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063
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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.* 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

ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) in patients who received tamoxifen. The standard deviation for the ER Score is less than 0.5 units.*

Clinical experience:
In ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.†
‡ The Average Rate of Distant Recurrence reported on Page 1 is based on the Recurrence Score was determined in patients who were aware 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.*

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 588 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.5 units.*

References based on quantitative ER/PR expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.
1. ER score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score
2. ASCO Breast Cancer Symposium 2007 Abstracts #87 by S.S. Badve et al., and #88 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
This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be reported as investigational or for research. These results are qualified to be ordering physician's workup.

CLIA Number 05D1018272

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GHI004 Rev01/08

Single Gene *scores*

HER2

The Oncotype DX® Breast Cancer Assay:

- Predicts the magnitude of chemotherapy benefit
- Quantifies the likelihood of breast cancer recurrence
- Provides clinical experience for multiple patient populations

oncotype DX® Breast Cancer Assay

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Genomic Health is a CLIA-certified, high-volume reference laboratory.

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oncotype DX® Breast Cancer Assay

Accurate, Precise, Reproducible.

oncotype DX® Breast Cancer Assay

The Oncotype DX® Breast Cancer Assay Report to Include a Quantitative HER2 Score

Although the Recurrence Score remains the best tool for assessing prognosis and prediction of chemotherapy benefit, HER2 is an important marker for therapeutic decision-making for patients with breast cancer, and its measurement may significantly impact the chosen course of treatment.

- **Quantitative HER2 Information:**
  The HER2 Score by the Oncotype DX Breast Cancer Assay is another measure for clinicians and patients to determine HER2 status, and it provides further insight into individual patients' breast cancer tumor biology together with the Recurrence Score.
- **Highly Concordant with IHC and FISH:**
  The HER2 score's concordance with IHC and FISH meets or exceeds the ASCO/CAP guidelines requirement of 95% for determination of HER2 status.
- **Added Clinical Information:**
  Many clinicians who rely on the Oncotype DX Breast Cancer Assay for treatment planning have requested that Genomic Health also report the quantitative HER2 Score as this is already a component of the Recurrence Score.
  - To provide further clarification especially in cases of equivocal IHC and/or FISH results or discordance between FISH and IHC.
- **Addressing a Limitation with Current Testing:**
  The impact of preanalytical variability can be minimized by "normalization" strategies used in quantitative gene expression assessment as performed by quantitative RT-PCR by Oncotype DX.

Concordance with IHC:

Oncotype DX Assay and central laboratory

IHC: *95%* (CI: 92%,96%)

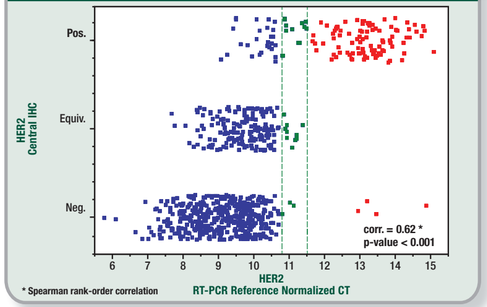
HER 2 Central **IHC*** vs Oncotype DX (Current ASCO/CAP Guidelines)

	IHC +	IHC –	Total
RT-PCR by Oncotype DX +	94 (78%)	4 (1%)	98
RT-PCR by Oncotype DX –	27 (22%)	439 (99%)	466
Total	121	443	564

Concordance: 95%
95% CI (92%,96%)

** IHC analysis using HercepTest®*

HER2 Expression
by Central RT-PCR & Central IHC



- E2197 Study[1]
- N = 755 patients
- The overall range of HER2 expression is approximately 1,000-fold
- Range of HER2 expression for HER2 positive is approximately 16-fold

- 27 (22%) IHC 3+ cases were negative by RT-PCR
- 4 (1%) IHC negative cases were positive by RT-PCR

HER2

[1] Baehner FL et al. HER2 Concordance Between Central Laboratory Immunohistochemistry & Quantitative Reverse Transcription Polymerase Chain Reaction in Intergroup Trial E2197. Presented at the ASCO Breast Cancer Symposium. September 6, 2008; Washington, D.C. Abstract #13

Concordance with FISH:

Oncotype DX Assay and central laboratory

FISH: *97%* (CI: 96%,99%)

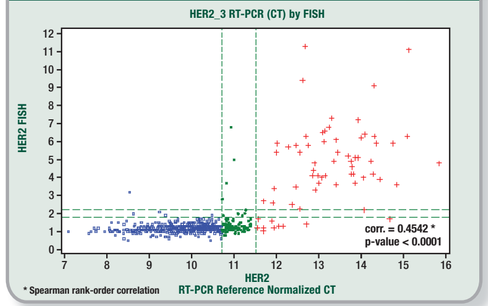
HER 2 Central **FISH*** vs Oncotype DX (Current ASCO/CAP Guidelines)

	FISH +	FISH –	Total
RT-PCR by Oncotype DX +	55 (98%)	11 (3%)	66
RT-PCR by Oncotype DX –	1 (2%)	408 (97%)	409
Total	56	419	475

Concordance: 97%
95% CI (96%,99%)

** FISH analysis using Vysis*

HER2 Expression
Central RT-PCR & Central FISH



- Kaiser Study[2]
- N = 568 patients
- The overall range of HER2 expression is approximately 500-fold
- Range of HER2 expression for HER2 positive is approximately 16-fold

- 1 case (2%) was FISH positive but negative by RT-PCR
- 11 cases (3%) were RT-PCR positive but FISH negative

HER2

[2] Baehner FL et al. HER2 Assessment in a Large Kaiser Permanente Case-Control Study: Comparison of FISH and Quantitative RT-PCR Performed by Central Laboratories. Presented at the ASCO Breast Cancer Symposium. September 6, 2008; Washington, D.C. Abstract #41