

## The impact on the Recurrence Score™ due to patient variation in the quantitative expression of individual genes or gene groups

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**Background:** The Recurrence Score (RS), derived from the quantitative RT-PCR analysis of 21 individual genes, quantifies the likelihood of distant recurrence in tamoxifen-treated patients with estrogen receptor (ER)-positive, node-negative breast cancer. To assess the degree to which components of this multi-gene assay influence the RS, we examined the impact on the RS due to patient variation in quantitative expression for the individual genes and gene groups.

**Material and Methods:** 10,618 tumor specimens successfully examined in the Genomic Health laboratory from January 2004 through March 2006 were included in the analyses. Quantitative expression of 16 individual cancer-related genes was measured by the pre-specified 21-gene *Oncotype DX™* assay on a scale from 0 to 15 (relative to reference genes), where a one-unit increment is associated with a 2-fold change in expression. RS is calculated from a published equation (Paik, et al. *NEJM* 2004) using the quantitative expression of five proliferation-related genes (CCNB1, Ki-67, MYBL2, STK15 and Survivin), four ER-related genes (ER, PR, Bcl2 and SCUBE2), two HER2-related genes (HER2 and GRB7), two invasion-related genes (CTSL2 and STMY3), and three single genes, BAG1, CD68 and GSTM1. Based on the observed distribution of expression among the tumors for each individual gene and group, we determined the range in RSs for low-, intermediate- and high-risk patients.

**Results:** For each individual gene, ranges of expression from 32 to > 2,000-fold were observed. The table shows the range of RSs that may be observed for a low-, intermediate- or high-risk patient by altering any individual gene or gene group over its range.

Gene or Gene Group	RS < 18 Range Expression (log <sub>2</sub> )	RS < 18 RS	RS 18-30 Range Expression (log <sub>2</sub> )	RS 18-30 RS	RS ≥ 31 Range Expression (log <sub>2</sub> )	RS ≥ 31 RS
BAG1	5.2	7.2	5.7	8.0	5.5	7.6
CD68	11.6	11.6	4.7	4.7	6.1	6.1
GSTM1	9.6	15.3	9.5	15.1	8.7	14.0
HER2 Group*	2.0	19.3	2.5	23.1	4.8	44.7
ER Group	4.4	29.7	4.7	31.8	8.6	58.7
Proliferation Group*	0.7	14.2	1.0	20.1	2.3	48.6
Invasion Group	5.2	10.5	6.1	12.2	7.2	14.4

\*HER2 and proliferation gene groups contribute to the RS when the value exceeds a threshold of 8.0 for the HER2 Group and 6.5 for the Proliferation Group

**Discussion:** Conditional on ranges of expression, any single gene or gene group altered the Recurrence Score as much as 5 to 59 RS units. The ER, HER2 and proliferation groups have the largest coefficients used in calculation of the RS. However, the other individual genes with smaller coefficients and wide ranges of expression impacted the RS in a clinically significant way, especially for low-risk patients.