The Effect of Oncotype DX Recurrence Score on Treatment Recommendations for Patients with Estrogen Receptor–Positive Early Stage Breast Cancer and Correlation with Estimation of Recurrence Risk by Breast Cancer Specialists

JENNIFER E. JOH,^a NICOLE N. ESPOSITO,^{a,b,c} JOHN V. KILUK,^a CHRISTINE LARONGA,^a M. CATHERINE LEE,^a LORETTA LOFTUS,^a HATEM SOLIMAN,^a JUDY C. BOUGHEY,^d CAROL REYNOLDS,^e THOMAS J. LAWTON,^f PETER I. ACS,^g LUCIO GORDAN,^g GEZA ACS^{a,b,c,h}

^aDepartment of Women's Oncology, Comprehensive Breast Program, and ^bDepartment of Anatomic Pathology, H. Lee Moffitt Cancer Center, Tampa, Florida, USA; ^cDepartment of Pathology and Cell Biology, University of South Florida College of Medicine, Tampa, Florida, USA; Departments of ^dSurgery and ^ePathology, Mayo Clinic, Rochester, Minnesota, USA; ^fSeattle Breast Pathology Consultants, Seattle, Washington, USA; ^gFlorida Cancer Specialists, Gainesville, Florida, USA; ^hWomen's Pathology Consultants, Ruffolo Hooper & Associates, Tampa, Florida, USA

Key Words. Breast cancer • Risk assessment • Adjuvant chemotherapy • Gene expression profiling

Disclosures: Jennifer E. Joh: None; Nicole N. Esposito: None; John V. Kiluk: None; Christine Laronga: Genomic Health (H, Speaker's Bureau); M. Catherine Lee: None; Loretta Loftus: Honoraria: GlaxoSmithKline, Bristol-Myers Squibb, sanofi-aventis, Genomic Health (Speaker's Bureau) (H); Eli Lilly, Amgen, Schering-Plough, Pfizer (OI); Hatem Soliman: Genomic Health (H, Speaker's Bureau, although no talks or funds have been received to date); Judy C. Boughey: None; Carol Reynolds: None; Thomas J. Lawton: Clarient, Inc. (C/A); Peter I. Acs: None; Lucio Gordan: GlaxoSmithKline, ProStrakan, Eli Lilly (H); Geza Acs: Genomic Health (H).

(C/A), consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder

ABSTRACT

Purpose. The Oncotype DX assay predicts likelihood of distant recurrence and improves patient selection for adjuvant chemotherapy in estrogen receptor–positive (ER-positive) early stage breast cancer. This study has two primary endpoints: to evaluate the impact of Oncotype DX recurrence scores (RS) on chemotherapy recommendations and to compare the estimated recurrence risk predicted by breast oncology specialists to RS.

Methods. One hundred fifty-four patients with ER-positive early stage breast cancer and available RS results were selected. Clinicopathologic data were provided to four surgeons, four medical oncologists, and four pathologists. Participants were asked to estimate recurrence risk category and offer their chemotherapy recommendations initially without and later with knowledge of RS results. The three most important clinico-

pathologic features guiding their recommendations were requested.

Results. Ninety-five (61.7%), 45 (29.2%), and 14 (9.1%) tumors were low, intermediate, and high risk by RS, respectively. RS significantly correlated with tumor grade, mitotic activity, lymphovascular invasion, hormone receptor, and HER2/neu status. Estimated recurrence risk by participants agreed with RS in $54.2\% \pm 2.3\%$ of cases. Without and with knowledge of RS, $82.3\% \pm 1.3\%$ and $69.0\% \pm 6.9\%$ of patients may be overtreated, respectively ($p = 0.0322$). Inclusion of RS data resulted in a 24.9% change in treatment recommendations. There was no significant difference in recommendations between groups of participants.

Conclusions. Breast oncology specialists tended to overestimate the risk of tumor recurrence compared with RS.

Correspondence: Geza Acs, M.D., Ph.D., Department of Anatomic Pathology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, Florida 33612, USA. Telephone: 813-615-7318; Fax: 813-745-5853; e-mail: geza.acs@moffitt.org Received February 22, 2011; accepted for publication July 3, 2011; first published online in *The Oncologist Express* on October 20, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0045>

RS provides useful information that improves patient selection for chemotherapy and changes treatment recom-**mendations in approximately 25% of cases. *The Oncologist* 2011;16:1520–1526****INTRODUCTION**

Traditionally, breast oncology specialists have relied on clinical and pathologic tumor features as well as patient characteristics to determine risk of recurrence and to guide recommendations for adjuvant chemotherapy. However, such treatment decisions remain challenging, especially in patients with estrogen receptor–positive (ER-positive) early stage breast cancer where the absolute benefit of adjuvant chemotherapy is more difficult to perceive. Although studies have shown overall efficacy of adjuvant chemotherapy in the early stage breast cancer population [1], many patients are exposed to the associated risks of chemotherapy without deriving significant benefit from it.

Multiple molecular assays have been developed to help tailor therapeutic strategies for early stage breast cancer [2–4]. One such assay is the Oncotype DX (Genomic Health, Redwood City, CA), a 21-gene breast cancer–specific expression profile which is now being utilized to improve patient selection for adjuvant chemotherapy. With use of a panel of 16 cancer-related genes and 5 reference genes, the likelihood of developing distant recurrence in ER-positive early stage breast cancer is calculated as a recurrence score (RS) ranging from 0 to 100. The RS is based on the assumption that patients will receive adjuvant hormonal manipulation for 5 years and predicts a 10-year distant recurrence risk as a continuous variable. RS can also be subdivided into three risk categories: low (<18), intermediate (18–30), and high (>30) scores.

A validation study utilizing paraffin-embedded tissue samples from a large multicenter prospective trial, the NSABP B-14 tamoxifen-treated cohort of breast cancer patients, demonstrated Kaplan-Meier estimates of risk of distant recurrence at 6.8%, 14.3%, and 30.5% with low, intermediate, and high RS, respectively [5]. Since then, multiple studies worldwide have validated the prognostic capability of this assay [6–8]. A subsequent study explored utilization of Oncotype DX categorical scores for prediction of additive benefit of chemotherapy to hormonal therapy. Patient tumor samples from another large multicenter prospective trial, the NSABP B-20 trial, which compared tamoxifen alone with chemotherapy plus tamoxifen treatment in node-negative, ER-positive, invasive breast cancer were assayed for RS. Patients with low RS (<18) demonstrated no benefit from chemotherapy, whereas high scoring patients (RS >31) had maximum benefit (absolute benefit of 28% reduction in distant metastatic disease development at 10 years) from adjuvant chemotherapy [9].

More recently, the applicability of Oncotype DX RS both in node-positive breast cancer and in predicting local regional recurrence has been studied. The TransATAC study found RS to be independently predictive of distant recurrence and thus prognostic in node-positive breast cancer patients [7]. A retrospective analysis of a subset of node-positive patients in the SWOG-8814 study has demonstrated that the multigene assay

was prognostic and predictive of chemotherapy benefit [10]. The Oncotype DX assay was also studied in the tamoxifen-treated patients from both the NSABP B-14 and B-20 trials to evaluate for association with local regional recurrence and revealed a significant association between RS and risk of local regional recurrence [11].

The current study explores the impact of Oncotype DX RS on recommendations for adjuvant chemotherapy given by 12 breast oncology specialists spanning 3 subspecialties and 5 institutions. The risk of distant recurrence estimated by participants based on traditional clinicopathologic tumor features was compared to the risk category calculated by Oncotype DX. Recommendations for adjuvant chemotherapy offered by participants before and after knowledge of the RS were compared. Differences in treatment recommendations between subspecialties were also examined.

METHODS**Patient Clinical and Pathologic Data**

We selected 154 consecutive patients with early stage ER-positive breast cancer and available Oncotype DX RS from the Surgical Pathology files of the Moffitt Cancer Center, Tampa, Florida, for this retrospective study. All patients had definitive surgical treatment at Moffitt Cancer Center between July 1, 2004 and March 31, 2009. The decision to order Oncotype DX was made based on clinical and surgical pathology features of the cancers by multidisciplinary review by the faculty panel of breast-specific surgical oncologists, medical oncologists, and radiation oncologists at the time of treatment. Study protocols were approved by the Scientific Review Committee of the Moffitt Cancer Center and the Institutional Review Board of the University of South Florida. All H&E-stained slides of all patients were reviewed by a single breast pathologist (G.A.) to confirm the diagnoses, including histologic type and grade, based on established criteria [12–14]. All invasive carcinomas were graded using the modified combined histologic grading system [15]. The number of mitoses was determined in ten consecutive high-power ($\times 400$) fields in the mitotically most active areas of the tumors. Tumors were evaluated to determine the presence or absence of lymphovascular invasion (LVI) based on all available stained slides.

The clinicopathologic features of the tumors are summarized in Table 1. Surgical treatment consisted of partial mastectomy in 91 patients and mastectomy in 63 patients. The median size of invasive carcinomas was 1.4 cm (1.49 ± 0.06 , mean $\pm$ SEM; range 0.4–6.0 cm). Evaluation of nodal status was performed in 153 of 154 (99.4%) cases and consisted of sentinel lymph node biopsy in 143 (93.5%) cases, whereas complete axillary lymph node dissection was performed in 10 (6.5%) cases. All patients with micro- and macrometastatic disease on sentinel lymph node biopsy underwent completion axillary lymph node dissection. Axillary lymph node metasta-

Table 1. Summary of clinicopathologic features				
	RS <18 (n = 95)	RS 18–30 (n = 45)	RS >30 (n = 14)	p
Age (years, median, mean $\pm$ SEM)	54 (55.5 $\pm$ 1.1)	51 (53.4 $\pm$ 1.3)	58.5 (59.1 $\pm$ 3.3)	.1972 ^a
Tumor size (cm, median, mean $\pm$ SEM)	1.3 (1.5 $\pm$ 0.1)	1.5 (1.5 $\pm$ 0.1)	1.6 (1.5 $\pm$ 0.2)	.8848 ^a
Menopausal status				
Premenopausal	40	22	3	.1919 ^b
Postmenopausal	55	23	11	
Histologic type				
Ductal (NST)	70	36	14	.2895 ^b
Lobular	10	3	0	
Special type	14	6	0	
Histologic grade				
Low	42	13	1	<.0001 ^b
Intermediate	50	24	4	
High	3	8	9	
Tubule formation				
1	17	3	0	.0643 ^b
2	29	15	2	
3	49	27	12	
Nuclear pleomorphism				
1	11	2	0	<.0001 ^b
2	72	27	2	
3	12	16	12	
Mitotic activity				
1	89	33	4	<.0001 ^b
2	3	8	4	
3	3	4	6	
No. mitoses per 10 HPF (median, mean $\pm$ SEM)	2 (3.4 $\pm$ 0.6)	4 (8.5 $\pm$ 1.9)	14.5 (22.7 $\pm$ 5.5)	<.0001 ^a
LVI				
Absent	87	40	7	<.0001 ^b
Present	8	5	7	
pN stage				
0(i–)	80	39	11	.6673 ^b
0(i+)	11	4	3	
1 mi/1a	4	1	0	
Percentage of ER reactivity (median, mean $\pm$ SEM)	100 (93.7 $\pm$ 1.0)	90 (88.3 $\pm$ 2.5)	90 (81.4 $\pm$ 5.3)	.0059 ^a
Percentage of PR reactivity (median, mean $\pm$ SEM)	90 (78.1 $\pm$ 2.7)	60 (57.6 $\pm$ 5.7)	42.5 (43.1 $\pm$ 9.5)	.0003 ^a
PR status				
Positive	92	41	12	.1483 ^b
Negative	3	4	2	
HER2/neu status				
Positive	1	2	6	<.0001 ^b
Negative	94	43	8	
Chemotherapy offered				
No	84	14	2	<.0001 ^b
Yes	11	31	12	
Chemotherapy received				
No	88	21	5	<.0001 ^b
Yes	7	24	9	

^aOne-way analysis of variance or Kruskal-Wallis test.
^b χ^2 test.
Abbreviations: ER, estrogen receptor; HPF, high-power fields; LVI, lymphovascular invasion; NST, no special type; PR, progesterone receptor.

sis was present in 23 (15.0%) patients; the median number of positive lymph nodes was 1 (range 1–2). Eighteen of the axillary metastases cases (78.3%) showed isolated tumor cell clusters in sentinel lymph nodes [pN0(i+)]. ER and progesterone receptor (PR) status were evaluated by immunohistochemistry at the time of diagnosis and results were obtained from the pathology reports. HER2/neu evaluation was determined by immunohistochemistry in 31 (20.1%) cases, fluorescence in situ hybridization in 20 (13.0%) cases, or both methods in 103 (66.9%) cases.

Study Participants

A contingent of physicians who specialize in breast cancer diagnosis and management were invited to participate in this study. This group of breast oncology specialists consisted of four surgical oncologists, four medical oncologists, and four pathologists. Each participant was given clinical and pathologic data on which to base their estimation of recurrence risk and recommendations for chemotherapy. Clinicopathologic data included patient age, menopausal status, tumor size, histologic type, grade, mitotic activity, presence of LVI, nodal status, hormone receptor (including percentage of staining values), and HER2/neu status. Participants were asked to predict the risk of distant tumor recurrence (low, intermediate, or high) based on the provided clinicopathologic data for each case. Assuming that all patients were in good general health, participants were also asked to record their treatment recommendation as chemotherapy plus hormone therapy or hormone therapy alone and to provide the three most important features influencing their recommendations. All respondents were initially blinded to the Oncotype DX RS. One month later, the data sheet, now containing the actual RS results but with the order of patients randomized, was redistributed to the participants who were asked to provide their treatment recommendations based on the clinicopathologic features and the actual RS.

Estimation of recurrence risk determined by participants was compared with actual Oncotype DX RS results. Changes in treatment recommendations of participants following inclusion of RS data were also analyzed. Treatment recommendations before and after inclusion of RS results were compared with treatment recommendations based on RS alone, actual treatment recommendations from the patients' treating medical oncologists, and treatments received by the patients.

Statistical Analysis

Clinicopathologic features between groups of tumors were compared using the one-way analysis of variance and the χ^2 tests, when appropriate. Median percentage of ER and PR immunostaining score values were compared using the Kruskal-Wallis one-way analysis of variance by ranks followed by Dunn's multiple comparison test, when appropriate. The rate of agreement between participants' risk assessment with RS and their treatment recommendations was assessed using Cohen's κ and weighted κ statistics, where appropriate. Statistical significance was determined if the two-sided p -value of a test

was $<.05$. Computations were performed using the Graphpad Prism (Version 5, GraphPad Software, San Diego) software.

RESULTS

The clinical and pathologic features of the selected patients and tumors are summarized in Table 1. On the basis of the Oncotype DX RS results, 95 (61.7%), 45 (29.2%), and 14 (9.1%) tumors were classified as low, intermediate, and high risk, respectively. RS showed significant correlation with tumor grade, mitotic activity, presence of LVI, ER, PR, and HER2/neu status. There was no correlation between RS and patient age, menopausal status, tumor size, and histologic type.

The participants' estimates of distant recurrence risk were congruent with Oncotype DX RS results in $54.2\% \pm 2.3\%$ (mean $\pm$ SEM, range 41.6–63.0) of cases. Overestimation and underestimation of recurrence risk compared with RS occurred in $31.8\% \pm 3.1\%$ (mean $\pm$ SEM, range 16.2–43.5) and $14.1\% \pm 1.4\%$ (mean $\pm$ SEM, range 7.1–22.7) of cases, respectively. The rate of overestimation of recurrence risk by participants compared to RS was significantly higher than the rate of underestimation ($p = .0003$). Analysis of the concurrence of participants with RS results showed a mean weighted κ value of 0.2955 (range 0.1506–0.4123) (Supplemental Table 1). There was no statistically significant difference in overall concurrence with RS results between surgical oncologists, medical oncologists, and pathologists (Fig. 1A). Medical oncologists estimated the risk of recurrence to be higher compared with RS ($38.1\% \pm 2.0\%$, mean $\pm$ SEM) more frequently compared with surgical oncologists ($28.7\% \pm 5.9\%$, mean $\pm$ SEM) or pathologists ($27.5\% \pm 7.8\%$, mean $\pm$ SEM); this difference did not reach statistical significance. Participants registered tumor stage/nodal status, hormone receptor status, and tumor size as the most important clinicopathologic features impacting their estimations of recurrence risk.

The participants' recommendations of adjuvant chemotherapy before and after knowledge of RS results are summarized in Supplemental Table 2 and Fig. 1B. Assuming patients with low and intermediate risk RS are unlikely to benefit from chemotherapy, $82.3\% \pm 1.3\%$ (range 75.5–89.0) and $69.0\% \pm 6.9\%$ (range 5.9–85.7) of patients for whom chemotherapy was recommended by the participants would be overtreated without and with the use of RS results ($p = .0322$) [9, 10]. Inclusion of RS data resulted in a 24.9% overall change in chemotherapy recommendations for participants. Without the inclusion of RS data, there was a statistically significant difference between medical oncologists and surgical oncologists in the percentage of chemotherapy recommendations (Figs. 1C,D). Once Oncotype DX results were known, medical oncologists were more likely to use this information to change their treatment recommendations (mostly in favor of hormone therapy alone) (Fig. 1B). Among the various clinicopathologic factors, participants ranked patient age/menopausal status, hormone receptor status, and tumor stage/nodal status to be the most important features when recommending chemotherapy.

With regard to actual treatment of the patients included in this study, adjuvant chemotherapy was recommended by the treating medical oncologists in 11 of 95 (11.6%), 31 of 45

Figure 1. Summary of participants' risk estimation and treatment recommendations without and with knowledge of Oncotype DX RS results. (A): Comparison of specialists' estimated recurrence risk to RS. (B): Comparison of specialists' treatment recommendations without and with knowledge of RS. Comparison of percentage of patients recommended chemotherapy without (C) and with (D) knowledge of RS.

Abbreviations: A, actual treatment received; O, medical oncologist; P, pathologist; R, actual treatment recommendation; RS, recurrence scores; S, surgeon; *, $p < .05$, Mann-Whitney test.

(68.9%), and 12 of 14 (85.7%) patients with low, intermediate, and high RS tumors (Table 1). Adjuvant chemotherapy was refused by patients in four (4.2%), seven (15.6%), and three (21.4%) cases in the low-, intermediate-, and high-risk groups, respectively. The comparison of actual recommended and received treatments by the patients with those recommended by participants is summarized in Supplemental Table 2 and Figs. 1C,D.

DISCUSSION

The main findings of this study are that breast cancer specialists from various multidisciplinary specialties tend to overestimate the risk of tumor recurrence compared with Oncotype DX RS based on traditional clinicopathologic tumor features, resulting in potential significant overtreatment of breast cancer patients with adjuvant chemotherapy. Inclusion of Oncotype DX RS results, as a reflection of the biologic properties of the individual cancers, results in changing the treatment recommendations in approximately 25% of cases. Although the recommendations provided by participants were not applied for actual clinical decision-making purposes, we compared them to the actual treatment offered to and received by the patients. We recognize that the recommendations for adjuvant treatment ultimately remain with the medical oncologist and patient; however, many patients will seek counsel with their surgeon (less so their pathologist) for confirmation of the opinion rendered by the medical oncologist. The use of adjuvant chemotherapy in breast cancer patients can be associated with significant morbidities related to drug toxicities. Although effective antiemetic and growth factor support medications have

contributed to improved tolerability of regimens, chemotherapy still has potential short-term and long-term toxicities. As such, thoughtful consideration is exercised when recommending chemotherapy. Moreover, empiric use of adjuvant systemic therapy in early stage breast cancer can lead to substantially increased costs for the patient and the health care system. In our study, on the basis of clinicopathologic features alone, breast cancer specialists tended to provide a higher estimate of the risk of tumor recurrence compared with Oncotype DX. Because current studies indicate that patients with breast cancers showing low- and intermediate-risk RS gain little benefit from chemotherapy, such overestimation of recurrence risk may result in exposing a significant number of patients to the risks and morbidities of chemotherapy without any significant benefit [9, 10]. Although cost analyses outcomes were not determined in this study, the utilization of RS to guide selective adjuvant chemotherapy has been shown to lower expected cost per life-year compared with empiric chemotherapy [16]. It is notable, however, that prospective studies examining the accuracy of recurrence risk and/or chemotherapy benefit based on traditional clinicopathologic variables versus Oncotype DX have yet to be performed.

Multiple studies have demonstrated that higher tumor stage/nodal status along with tumor size signifies and predicts more advanced disease and higher distant recurrence risk [17–21]. Indeed, similar to general practice and guidelines, these features were considered by participants as some of the most important tumor characteristics to guide distant recurrence risk estimation. The same tumor features, with significant consid-

eration given to general patient characteristics, such as age and general health, played an important part in guiding treatment recommendations by participants as well. However, as our study shows, risk estimates primarily based on these factors tend to overestimate risk compared with RS. Consequently, meaningful clinical management decisions based on these tumor characteristics alone remain relatively unreliable. A small retrospective study evaluating correlation between clinicopathologic features and RS performed at Magee-Women's Hospital revealed multiple features that correlated with RS [22]. Our study also confirms that various pathologic features of breast cancers significantly correlate with RS, and considering tumor features such as mitotic activity, percentage of PR positivity, and the presence of LVI may lead to better risk estimates. In fact, on the basis of a combination of such tumor features, we have been able to construct a nomogram that predicts Oncotype DX RS with high accuracy (Acs et al., unpublished data). A breast cancer prognostic score was recently developed at Duke University as well, incorporating multiple pathologic features, and was found to correlate well with RS [23]. Such composite indices and/or nomograms may have future economic implications if they are validated in larger studies.

Lo and colleagues prospectively studied the impact of RS on chemotherapy recommendations among 17 medical oncologists and found that the multigene assay changed recommendations in 31.5% of cases [24]. Several other studies have similarly determined RS changes adjuvant treatment recommendations by 18%–44% [25–29]. Moreover, the most common change in recommendations was from chemotherapy plus hormonal therapy to hormonal therapy alone. This is congruent with our study that demonstrated higher rates of overestimation and overtreatment with chemotherapy without RS results. Although the design of our study was different, treatment recommendations after inclusion of RS were very similar to actual treatment recommendations offered to patients, suggesting that our results accurately reflect the impact of RS on actual patient management.

Limitations of our study include its retrospective nature. In addition, on the basis of the results of prior studies, tumors showing low and intermediate RS were assumed to not benefit from adjuvant chemotherapy in contrast to tumors with high RS results [9, 10]. This assumption was utilized to calculate the rates of over- and undertreatment; however, the clinical significance of intermediate RS tumors is not known. On the other hand, additional analysis assuming that intermediate RS breast cancers would also benefit from chemotherapy did not significantly change the results. The prospective Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study

was designed to attempt to elucidate the chemotherapy benefit in patients with intermediate RS tumors [30]. Although accrual for the trial was completed in 2010, no results are available yet. Another potential limitation is selection bias of participants in our study. All participants had received subspecialty training in breast oncology and diagnose, manage, and treat breast cancer patients primarily or exclusively. However, one strength of our study design was the inclusion of physicians from varying geographic regions of the country and practicing in a mixture of both academic and private practices. Clinicians who do not frequently care for breast cancer patients may further over- or underestimate risk of distant recurrence.

CONCLUSIONS

In conclusion, the use of Oncotype DX assists in patient selection for adjuvant chemotherapy in breast cancer. Although there are multiple clinicopathologic features that correlate with RS, risk estimation based on traditionally used tumor characteristics results in a high rate of over- and underestimation of distant recurrence risk compared with Oncotype DX. In our study, participants' risk estimates agreed with RS in only 54.2% of cases. With the advent of molecular testing, breast cancer treatment and management continues to progress toward personalized therapy. The use of Oncotype DX and similar commercially available molecular profiling tools, that is, Mammprint and Mammostrat, has eased the integration of this technology into clinical practice. Using the multigene assay, clinicians may expect an almost 25% change in their adjuvant chemotherapy treatment recommendations for their patients. Finally, the use of emerging nomograms aimed at replicating Oncotype DX may be of both clinical and economic utility in the future.

ACKNOWLEDGMENTS

This study was conducted at H. Lee Moffitt Cancer Center and Research Institute.

Presented in part at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 9–13, 2009.

AUTHOR CONTRIBUTIONS

Conception/Design: Christine Laronga, Geza Acs

Collection and/or assembly of data: Nicole N. Esposito, John V. Kiluk, Christine Laronga, M. Catherine Lee, Loretta Loftus, Hatem Soliman, Judy Boughey, Carol Reynolds, Thomas Lawton, Peter Acs, Lucio Gordan, Geza Acs

Data analysis and interpretation: Jennifer E. Joh, Christine Laronga, Geza Acs

Manuscript writing: Jennifer E. Joh, Geza Acs

Final approval of manuscript: Jennifer E. Joh, Nicole N. Esposito, John V. Kiluk, Christine Laronga, M. Catherine Lee, Loretta Loftus, Hatem Soliman, Judy Boughey, Carol Reynolds, Thomas Lawton, Peter Acs, Lucio Gordan, Geza Acs

REFERENCES

1. EBCTCG: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(9472):1687–1717.
2. Turaga K, Acs G, Laronga C. Gene expression profiling in breast cancer. *Cancer Control* 2010;17:177–182.
3. Ross JS, Hatzis C, Symmans WF et al. Commercialized multigene predictors of clinical outcome for breast cancer. *The Oncologist* 2008;13:477–493.
4. Bao T, Davidson NE. Gene expression profiling of breast cancer. *Adv Surg* 2008;42:249–260.
5. Paik S, Shak S, Tang G et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351:2817–2826.
6. Toi M, Iwata H, Yamanaka T et al. Clinical significance of the 21-gene signature (oncotype dx) in hormone receptor-positive early stage primary breast cancer in the Japanese population. *Cancer* 2010;116:3112–3118.
7. Dowsett M, Cuzick J, Wale C et al. Prediction

of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A transatlantic study. *J Clin Oncol* 2010;28:1829–1834.

8. Habel LA, Shak S, Jacobs MK et al. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res* 2006;8:R25.

9. Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24:3726–3734.

10. Albain KS, Barlow WE, Shak S et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11:55–65.

11. Mamounas EP, Tang G, Fisher B et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from nsabp b-14 and nsabp b-20. *J Clin Oncol* 2010;28:1677–1683.

12. Page DL, Anderson TJ, Sakamoto G, eds. Infiltrating carcinoma: major histologic types. London: WB Saunders, 1987:193–235.

13. Rosen PP, Oberman HA: Tumors of the mammary gland. Washington, DC: Armed Forces Institute of Pathology, 1993.

14. Pinder SE, Elston CW, Ellis IO, eds.: *Invasive*

carcinoma - usual histologic types, 3rd ed. Edinburgh: Churchill Livingstone, 1998:283–337.

15. Elston CW, Ellis IO, eds.: *Assessment of histologic grade*, 3rd ed.: Edinburgh, Churchill Livingstone, 1998:365–384.

16. Lyman GH, Cosler LE, Kuderer NM et al. Impact of a 21-gene rt-pcr assay on treatment decisions in early-stage breast cancer: an economic analysis based on prognostic and predictive validation studies. *Cancer* 2007;109:1011–1018.

17. Fisher B, Slack NH, Bross ID. Cancer of the breast: size of neoplasm and prognosis. *Cancer* 1969;24:1071–1080.

18. Adair F, Berg J, Joubert L et al. Long-term followup of breast cancer patients: the 30-year report. *Cancer* 1974;33:1145–1150.

19. Koscielny S, Tubiana M, Le MG et al. Breast cancer: relationship between the size of the primary tumour and the probability of metastatic dissemination. *Br J Cancer* 1984;49:709–715.

20. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181–187.

21. Hilsenbeck SG, Ravdin PM, de Moor CA et al. Time-dependence of hazard ratios for prognostic factors in primary breast cancer. *Breast Cancer Res Treat* 1998;52:227–237.

22. Flanagan MB, Dabbs DJ, Brufsky AM et al. Histopathologic variables predict oncotype dx recurrence score. *Mod Pathol* 2008;21:1255–1261.

23. Geradts J, Bean SM, Bentley RC et al. The on-

cotype dx recurrence score is correlated with a composite index including routinely reported pathobiologic features. *Cancer Invest* 2010;28:969–977.

24. Lo SS, Mumby PB, Norton J et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol* 2010;28:1671–1676.

25. Henry LR, Stojadinovic A, Swain SM et al. The influence of a gene expression profile on breast cancer decisions. *J Surg Oncol* 2009;99:319–323.

26. Oratz R, Paul D, Cohn AL et al. Impact of a commercial reference laboratory test recurrence score on decision making in early-stage breast cancer. *J Oncol Pract* 2007;3:182–186.

27. Kamal A, Loprinzi C, Reynolds C et al. How well do standard prognostic criteria predict oncotype dx (odx) scores? *J Clin Oncol* 2007 (suppl; abstract 576);25:18s.

28. Rayhanabad JA, Difronzo LA, Haigh PI et al. Changing paradigms in breast cancer management: introducing molecular genetics into the treatment algorithm. *Am Surg* 2008;74:887–890.

29. Asad J, Jacobson AF, Estabrook A et al. Does oncotype dx recurrence score affect the management of patients with early-stage breast cancer? *Am J Surg* 2008;196:527–529.

30. Sparano JA. Tailorx: trial assigning individualized options for treatment (rx). *Clin Breast Cancer* 2006;7:347–350.

EDITOR'S NOTE: See the accompanying commentary, "Impact of multigene assays in early stage breast cancer," by S.S. Lo and K.S. Albain, on pages 1482–1483 of this issue.