Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology April 2009

A Multidisciplinary Approach to The Use of Oncotype DX in Clinical Practice

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Abstract

Recently, recommendations for the use of the Oncotype DX assay in estrogen receptor-positive node-negative breast cancer patients were incorporated into guidelines from both the American Society of Clinical Oncology and the National Comprehensive Cancer Network. The Oncotype DX assay is a diagnostic test which measures changes in a set of 21 genes in order to predict the likelihood of disease recurrence and also to predict which patients are most likely to respond to chemotherapy. Oncotype DX has been available commercially since January 2004 and has been used for more than 85,000 patients.

Drs. William J. Gradishar, Nora M. Hansen, and Barbara Susnik answered questions regarding the incorporation of the Oncotype DX breast cancer assay into routine clinical practice. This expert dialog offers an update and clinical insights into when, how, and why clinicians might incorporate the Oncotype DX assay into the management of their breast cancer patients. Also, the latest research into the benefit of the Oncotype DX assay in node-positive patients is discussed. Finally, sample case studies offer clinically relevant examples of the practical application of the Oncotype DX assay.

Sponsored by an educational grant from Genomic Health.

A Multidisciplinary Approach to The Use of Oncotype DX in Clinical Practice

How has the Oncotype DX breast cancer assay affected your management of estrogen receptor-positive breast cancer patients?

Dr. William J. Gradishar I think one of the most obvious changes that has occurred in recent years since the introduction of Oncotype DX is that we are using less chemotherapy, primarily in patients with estrogen receptor (ER)-positive node-negative breast cancer. For example, one recent study showed that Oncotype DX assay results led to a change in the management of 26% of patients.[1] Other studies have also shown a decrease in chemotherapy use following an Oncotype DX assay.[2,3]

The Oncotype DX assay allows us to discriminate which patients would most benefit from chemotherapy. This was demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial, which randomized 651 patients to receive tamoxifen alone or tamoxifen plus chemotherapy.[4] Here, the Recurrence Score® (the product of the Oncotype DX assay) was significantly associated with benefit from chemotherapy (P=.038). Patients who were determined to have a higher risk according to the Oncotype DX assay received the largest benefit from the addition of chemotherapy, whereas low-risk patients had no benefit (mean absolute decrease in 10-year distant recurrence rate, 28% vs -1.1%).

In another study, the Recurrence Score generated from the Oncotype DX assay changed a decision to receive chemotherapy in 31% of 89 patients.[5] Also, the Recurrence Score caused a panel of 5 experts to change their initial recommendations regarding chemotherapy treatment in 24% of cases.[6] However, the influence of the results of the Oncotype DX assay caused a treatment change in as high as 44% of patients in a retrospective study.[7]

Interestingly, patients are aware of the role of the Oncotype DX assay in helping to determine response to therapy. We are finding that some patients are actually requesting the Oncotype DX assay as a way to help them decide on their course of treatment.

Dr. Nora M. Hansen I would agree. In fact, from a surgeon's perspective I am often asked by patients whether they should begin chemotherapy following resection. I review the general guidelines for adjuvant systemic therapy with the patient based on tumor size, nodal status, and prognostic factors, and I also inform the patient about Oncotype DX.

Dr. Barbara Susnik Within our institution, we have seen over a 50% increase in the requests for an Oncotype DX assay from 2006 to 2008. Most of these requests are for women with T1 and T2 tumors. The Oncotype DX is ordered very rarely for T3 tumors at our institution (<5% of requests).

In 2006, most of these requests were for ER-positive, node-negative tumors. However, during the past several months, we observed an increase in the number of requests for women with node-positive disease. Now, nearly 20% of our requests are for women with node-positive disease, and a majority of them are for those with micrometastases.

How has the incorporation of the Oncotype DX assay evolved in your practice?

WJG While we do not have a set policy or algorithm for determining who should receive an assay, the typical patient for whom we would most likely order the test is an ER-positive patient having a tumor measuring between 1 and 3 cm. However, the Oncotype DX assay is validated in larger tumors, and we do order it for patients who have larger tumors. Although it is by no means a universal practice, there are instances where we order it for women with node-positive disease.

NMH We are actually often waiting for pathologic results, such as ER status, when the patient comes to see us.

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WJG And we generally do not have the Recurrence Score available when we meet with the patient for the first time. Instead, it is at that point that we really discuss ordering the Onco*type* DX assay. This occurs together with a discussion of the overall principles of adjuvant therapy and prognosis. Generally, the patient then returns 7–10 days later to finalize a treatment plan.

What is the Recurrence Score, and what does it tell a physician about prognosis and response to chemotherapy?

WJG The Recurrence Score, the resulting number produced from the Onco*type* DX assay, is generated from a mathematical algorithm that predicts the magnitude of chemotherapy benefit and 10-year future risk of distant metastasis in a population of ER-positive node-negative patients.[8] The Onco*type* DX assay uses a set of 21 genes, 16 of which have been determined to be associated with distant breast cancer recurrence, and 5 of which are used as references to normalize the expression of the cancer-related genes.[9-11] The Recurrence Score, which ranges from 0 to 100, is used to predict patient prognosis; lower scores are associated with a better prognosis and minimal if any benefit from chemotherapy, whereas higher scores are linked to a poorer prognosis and significant benefit from chemotherapy. A population-based study showed that the Recurrence Score was significantly associated with risk of breast cancer-related mortality in both tamoxifen-treated (P=.003) and untreated (P=.03) patients.[12] Using the Recurrence Score, patients are categorized as either low risk (score, <18), intermediate risk (score, 18–30), or high risk (score, >30). The clinician uses these scores when considering treatment. For example, patients with Recurrence Scores less than 18 most likely will not experience any benefit from adding chemotherapy to endocrine therapy. Conversely, endocrine therapy alone may likely prove insufficient for higher Recurrence Score patients.

The Recurrence Score is considered to be a continuous predictor, meaning that the risk of distant recurrence increases continuously as the score increases. Thus, within each risk category there is a continuum of patients with comparatively lower and higher risk as well. For example, a patient with a "low risk" Recurrence Score of 17 has a risk that is more similar to an intermediate Recurrence Score of 20 than a patient with a "low risk" Recurrence Score of 5. This ability to report risk on a continuum is an important advantage of the Onco*type* DX assay over other prognostic tests.

NMH For patients that fall within the intermediate risk category it is not yet known if these patients are likely to benefit from chemotherapy or not. Optimally, we encourage these patients to enroll in the ongoing Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study, which has a main goal of determining the benefit of chemotherapy in this particular patient population.[13] However, if the intermediate risk patient is unwilling to enter a clinical study, most medical oncologists make their treatment decision based on the other clinical factors and patient preference.

How do you use the Recurrence Score obtained from the Oncotype DX assay to help identify the optimal treatment approach for patients?

WJG In the case of node-negative disease and a low Recurrence Score, both the patient and the clinician can feel relatively assured that the risk of distant metastases is low and that the patient would not benefit from chemotherapy. Conversely, a significant proportion of patients with a high Recurrence Score are likely to go on to develop distant metastases. And as was clearly shown in the NSABP-14 and NSABP-20 trials, these are the patients most likely to benefit from the addition of chemotherapy to endocrine therapy.[4,14]

Are there other prognostic factors which you integrate with the Recurrence Score in order to predict patient response to chemotherapy?

WJG For many clinicians, the Onco*type* DX assay is probably not the only tool used when considering a treatment strategy. However, it is likely one of the more refined tools available, especially compared with using tumor size and nodal status. Other available tools include Adjuvant! Online, a computer model which estimates the risk of disease recurrence using traditional prognostic factors such as age, tumor size, and receptor status.[15] There have been several studies that have shown that the Recurrence Score and Adjuvant! Online provide independent information.[16,17]

It is also important to point out that despite the usefulness of the Onco*type* DX assay, the clinician should consider the patient's disease from a clinical perspective in combination with the Recurrence Score. For example, if a young patient (<50 years) presents with a large tumor (>4 cm) and a Recurrence Score of 17, many clinicians would consider chemotherapy in spite of a low Recurrence Score because of the young age of the patient.

NMH For ER-positive node-negative patients, other factors to consider when deciding on the use of chemotherapy is HER2 status, tumor grade, and the extent of nodal invasion. However, compared with the traditional factors used to determine patient prognosis such as age, tumor size, and tumor grade, the Recurrence Score generated by the Onco*type* DX assay is a superior predictor of the risk of recurrence. The Onco*type* DX assay remains prognostic regardless of these traditional factors. Also, it is not affected by menopausal status, making it a valid test for both younger and older patients.

WJG Yes. When a patient exhibits discordant findings, for example a low score in the presence of HER2-positive status and nodal invasion, the clinician should not rely on any one of these. Instead, all of these factors should be considered together.

NMH And some patients are adamant about receiving chemotherapy before ever receiving a Recurrence Score. These patients may not benefit from receiving a Recurrence Score, and in this event, the clinician probably should not order an Onco*type* DX assay because it is not going to help with the treatment decision.

WJG And that should be part of the discussion the clinician has with the patient because these results may convince a patient that the benefit of chemotherapy may be substantial.

Who is responsible for educating the patient regarding the Oncotype DX assay?

NMH This discussion generally begins in the surgeon's office, where the Onco*type* DX assay is first introduced as an evaluation tool. At this time, the patient is provided basic information, so that they are familiar with Onco*type* DX when they first meet with their medical oncologist.

In some events, the Onco*type* DX assay is ordered by the surgeon before the patient ever meets with a medical oncologist. In most cases, the patient would then discuss the resulting Recurrence Score with their medical oncologist.

BS Pathologists generally have no communication with the patient regarding the Onco*type* DX assay. Our role is important in that we select the most representative tumor block to send out after receiving a request. Tumor tissue samples should be selected to contain mostly invasive carcinoma, as opposed to benign tissue. All cases are reviewed by pathologists at Genomic Health. In all cases where there are large amounts of benign tissue or biopsy cavities, a board certified surgical pathologist at Genomic Health manually micro-dissects the tumor to enrich for tumor tissue. All manually micro-dissected cases are then checked by a board certified surgical pathologist as part of the quality control process to ensure that the dissection was appropriately performed.

How has the inclusion of the Oncotype DX assay affected the patient's attitudes towards their treatment?

WJG The Onco*type* DX assay offers an objective measure of risk and potential benefit from chemotherapy. The Onco*type* DX assay often serves as a deciding factor for patients, and for this reason it is often reassuring.

NMH There was some encouraging data presented at the 2007 and 2008 San Antonio Breast Cancer Symposia regarding patient attitudes. Mumby, Lo, and colleagues evaluated patient satisfaction following the use of Onco*type* DX assay to determine course of treatment.[20,5] The investigators reported that 95% of patients were glad that they had taken the Onco*type* DX assay, and 83% of patients stated that the assay influenced their treatment decision. Patients also experienced reduced anxiety over their treatment decision, greater satisfaction, and increased confidence in their choice of therapy.

What is the value of the ER, PR, and HER2 scores which are now part of the results from the Oncotype DX assay?

BS Conventionally, ER, progesterone receptor (PR), and HER2 status have been measured using immunohistochemistry (IHC). However, this method is associated with both false positives and false negatives.[21-25] The Onco*type* DX assay uses real-time reverse transcription polymerase chain reaction (RT-PCR) technology to quantitatively determine the expression of ER, PR, and HER2. This method allows for the detection of a greater range of molecular expression, which is not possible by IHC.[26,27] Also, ER, PR, and HER2 measured by RT-PCR by Onco*type* DX have been shown to be highly concordant with IHC and HER2 by FISH.[28-30]

When we compared the ER, PR, and HER2 scores obtained by the Onco*type* DX assay with results at our institution, we found them to be highly concordant. This high concordance may actually serve as a type of quality control, to validate the Recurrence Score generated by the Onco*type* DX. ER and HER2 status was 100% concordant between the Onco*type* DX assay and our laboratory findings. In the case of the PR, we found 5% of cases to be discordant. All discordances were minor and involved "borderline" cases, such as, for example, when a low positive immunohistochemical stain in our laboratory (<10% cells positive for PR) was found to be negative by RT-PCR by Onco*type* DX.

WJG Additionally, the ER score also provides a quantitative measurement of the extent of ER expression. This information may prove useful to understand the probability and extent of benefit from endocrine therapy.

What are the current data regarding the Oncotype DX assay in ER-positive node-positive breast cancer patients?

WJG Most recently, data have begun to emerge from trials which suggest that the Onco*type* DX assay may be effective in determining relatively low-risk patients with node-positive tumors. These patients are considered to be only relatively

Table 1. Rate of 9-year Distant Recurrence Among Node-negative and Node-positive Breast Cancer Patients

Nodal Status	Prognostic Group, According to Recurrence Score		
	Low-Risk	Intermediate-Risk	High-Risk
Node-negative	4%	12%	25%
Node-positive	17%	28%	49%

low risk because they still do carry a substantial risk of distant metastasis, although it is markedly lower than higher risk node-positive patients.

Results from a study by the Southwest Oncology Group (SWOG) showed that the Onco*type* DX assay was also useful in patients with ER-positive, node-positive tumors.[31] These results have generated interest in the possibility that even some node-positive patients may be identified who may not necessarily benefit from chemotherapy. However, this was a small study, and the results need to be validated.

Also, the standards by which we determine node-positive status have changed over recent years. Therefore, if the patients included in the original NSABP trials which validated the Onco*type* DX assay were reassessed using current standards for determining nodal involvement, it would most likely be shown that many patients within these studies had some degree of nodal involvement.

Although the data regarding the Onco*type* DX assay in node-positive patients are interesting and may suggest that this test may be a useful tool for this population, more information is needed before its routine use can be justified for these patients.

NMH I think patient education will be particularly important for these patients. As Dr. Gradishar pointed out, even low-risk node-positive patients still have a 10-year disease-free survival rate of approximately 40%. (Disease-free survival was the endpoint for the SWOG study, thus, the event rate would be expected to be higher here than in the B-14 analysis because it includes local recurrence and death by other cause.) It is therefore very important to realize that these low risk patients are quite different and require special consideration when deciding to treat with chemotherapy.

How is the Oncotype DX assay used in your center for node-positive patients?

NMH We do not have a particular policy regarding the impact of the extent of nodal involvement on the decision to order an Onco*type* DX assay. Definitely a less extensive nodal involvement (fewer positive nodes) would increase the likelihood that we would order the Onco*type* DX assay. However, for a patient with 4 or more positive nodes, it is difficult to imagine not recommending chemotherapy.

WJG We have ordered the Onco*type* DX assay for patients with more extensive nodal involvement, but only in rare cases. There is no data to suggest that patients with multiple positive lymph nodes would not benefit from a treatment strategy including chemotherapy.

I find that the Onco*type* DX assay may be particularly useful for patients with minimal nodal involvement and for whom I would normally recommend chemotherapy but where the patient may be hesitant to receive chemotherapy. The Onco*type* DX assay may prove to be a useful tool to persuade her otherwise. Or in other cases where other factors such as comorbidities may impact a patient's ability to tolerate chemotherapy, a low Recurrence Score may make a clinician more comfortable not administering chemotherapy.

BS Interestingly, when reviewing the data over the past 6 months for our center, we found that nearly 15% of requests for the Onco*type* DX assay were for patients who had micrometastases. Therefore, it seems that the use of the Onco*type* DX assay for this population may be becoming more common.

What is your interpretation of the recently reported results of the TransATAC study?

WJG Data from the TransATAC study were recently presented at the 2008 San Antonio Breast Cancer Symposium.[17] This study evaluated the prognostic ability of the Recurrence Score obtained from the Onco*type* DX assay in patients treated with the aromatase inhibitor anastrozole. The investigators showed that the Onco*type* DX assay was significantly predictive of distant recurrence in both node-positive as well as node-negative patients. Among node-positive patients, the risk of disease-recurrence was calculated to be 17%, 28%, and 49% for patients categorized as low-risk, intermediate-risk, or high-risk, respectively ($P<.001$). Interestingly, as shown in the TransATAC study, the number of nodes provides useful information in combination with Recurrence Score. The Recurrence Score with nodal status provides independent prognostic information, but as reported by Dowsett and colleagues, patients with a low Recurrence Score and 1–3 positive nodes had a less than 10% risk of distant recurrence.[17]

Case Studies

The panel was presented with several cases typically seen in clinical practice, and asked how the Oncotype DX assay might be utilized in each scenario.

Case 1: The patient is 43 years old and premenopausal, presenting with a 2.7 cm grade II invasive ductal carcinoma tumor. The patient is node-negative and ER/PR-positive (ER and PR score of 10.7 and 8.5, respectively).

NMH In this case, the size of the tumor is on the larger side, but the patient would probably benefit from receiving an Oncotype DX assay.

WJG And if the Recurrence Score was in the lower range (ie, score of 12), I would proceed with endocrine therapy only. However, if the score was in the intermediate range (ie, score of 22), I would recommend adding chemotherapy in the absence of the patient entering a clinical trial.

Case 2: The patient is 62 years old and postmenopausal, presenting with a 3.2 cm, well-differentiated invasive lobular carcinoma tumor. The patient has a micrometastasis in one lymph node, and is ER-positive and PR-negative.The patient is also HER2-positive by IHC, but is HER2-negative by FISH.

WJG This is a particularly challenging case. The patient is young enough to receive chemotherapy and has a tumor size that justifies treatment. Resolving the correct HER2 status is important, as that would be important in determining if an anti-HER2 targeted therapy should be used in conjunction with chemotherapy. It is possible that an Oncotype DX assay would be helpful in finding the true HER2 status of the patient.

BS But I think it would be very unlikely for a patient with a well-differentiated lobular carcinoma to be HER2-positive. That would suggest that there was likely a problem with the IHC analysis, and lead me to think that the results by FISH are correct.

NMH Here, a low Oncotype DX Recurrence Score would help to reassure the clinician to not treat the patient with chemotherapy, while a higher score may help to convince the patient to receive chemotherapy.

Case 3: The patient is 37 years old with a poorly differentiated invasive ductal carcinoma tumor measuring 0.7 cm. The patient is node-negative, ER/PR-positive, and HER2-negative.

WJG I would not typically order an Oncotype DX assay for a patient with this small of a tumor. Patients with this tumor size were not typically included in the validation studies. Generally, I try to avoid chemotherapy for tumors smaller than 1 cm. However, if the patient was adamant about an aggressive chemotherapy approach, a low Recurrence Score by the Oncotype DX assay may help to make the argument for avoiding chemotherapy. Another consideration in this case is the poor grade which may indicate that this tumor is more aggressive. Consistent with the recommendation in the NCCN guidelines, for patients with a T1b tumor with poor features a physician should consider an Oncotype DX assay.

Case 4: The patient is 67 years old and postmenopausal, presenting with a 1.4 cm tumor with one positive lymph node, which is strongly ER-positive and moderately differentiated. The patient is very healthy and exercises 3 times per week.

WJG Currently, with any node-positive patient, we order Oncotype DX assay infrequently. However, data is beginning to emerge to support ordering in this patient population. And if the patient had comorbidities which would make it difficult for her to receive chemotherapy, the Oncotype DX assay may also be useful to help make the treatment decision.

NMH We would be more likely to treat this patient with chemotherapy, just on the basis that she is node-positive. I think the use of the Oncotype DX assay here would be to otherwise convince the clinician that chemotherapy may not be necessary if the patient was strongly against receiving treatment. And again, it is important to remember that in node-positive patients even a low risk prognosis resulting from an Oncotype DX assay is still markedly higher compared with a low risk prognosis in node-negative patients.

Case 5: The patient is 61 years old and is referred for a second opinion. She is node-negative and has a 1.4 cm ER-positive tumor that is HER2-positive by FISH but found to be HER2-negative in an Oncotype DX assay, and has a Recurrence Score of 14.

NMH In this situation, the low Recurrence Score would not be weighed as heavily for determining treatment, because of the HER2-positive status. This patient would likely undergo more aggressive treatment. However, it may be worthwhile to retest the FISH results since the testing was not done at our institution.

References

1. Rayhanabad JA, Difronzo LA, Haigh PI, Romero L. Changing paradigms in breast cancer management: introducing molecular genetics into the treatment algorithm. *Am Surg* 2008;74:887-90.
2. Liang H, Brufsky AM, Lembersky BB, et al. A retrospective analysis of the impact of oncotype DX low Recurrence Score results on treatment decisions in a single academic breast cancer center. Presentation at the 30th Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 13-16, 2007:Abstract 2061.
3. Erb C, Fox KR, Patel M, et al. Evaluation of practice patterns in the treatment of node-negative, hormone-receptor positive breast cancer patients with the use of the oncotype DX assay at the University of Pennsylvania. Presentation at the 30th Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 13-16, 2007: Abstract 3082.
4. 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.
5. Lo SS, Norton J, Mumby PB, et al. Prospective multicenter 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. *J Clinl Oncol.* 2007;18S: 577
6. Henry LR, Stojadinovic A, Swain SM, Prindiville S, Cordes R, Soballe PW. The influence of a Gene expression profile on breast cancer decisions. *J Surg Oncol.* 2009.
7. Asad J, Jacobson AF, Estabrook A, et al. Does onco*type* DX Recurrence Score affect the management of patients with early-stage breast cancer? *Am J Surg*. 2008;196: 527-529.
8. Morris SR, Carey LA. Gene expression profiling in breast cancer. *Curr Opin Oncol.* 2007;19:547-551.
9. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406:747-752.
10. Golub TR, Slonim DK, Tamayo P, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science.* 1999;286: 531-537.
11. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Expression profiling predicts outcome in breast cancer. *Breast Cancer Res.* 2003;5:57-58.
12. 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.
13. Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). *Clin Breast Cancer* 2006;7:347-350.
14. 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.
15. Goldstein L, Ravdin P, Gray R, et al. Prognostic utility of the 21-gene assay compared with Adjuvant! in hormone receptor (HR) positive operable breast cancer with 0–3 positive axillary nodes treated with adjuvant chemohormonal therapy (CHT): an analysis of intergroup trial E2197. Presentation at the 30th Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 13–16, 2007:Abstract 63.
16. Goldstein LJ, Gray R, Badve S, et al. Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. *J Clin Oncol*. 2008;26:4063-4071.
17. Dowsett M, Cuzick J, Wales C, et al. Risk of distant recurrence using oncotype DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: a TransATAC study. Presentation at the 31st Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 10-14, 2008:Abstract 53.
18. R Baehner, B Hiller, CY Kim, et al. Use of Macrodissection in Multi-Gene RNA Analysis of Fixed Paraffin- Embedded Tumor Tissue. 2004 USCAP Annual Meeting. Abstract 80.
19. FL Baehner, J Anderson, C Sengali, et al. Biopsy cavities in breast cancer specimens: their impact on quantitative RT-PCR gene expression profiles and recurrence risk assessment. USCAP 2009 Annual Meeting. Abstract TK
20. Mumby PB, Lo SS, Norton J, et al. Prospective multi-center study of the impact of the 21-gene Recurrence Score assay on patient satisfaction, anxiety and decisional conflict for adjuvant breast cancer treatment selection. Presentation at the 30th Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 13–16, 2007:Abstract 1092.
21. Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. *J Clin Oncol.* 2006;24(19):3032-3038; comment in *J Clin Oncol.* 2007; 25(22):e27-28.
22. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;25:118-145; comment and author reply in *J Clin Oncol.* 2007 25: 4020-4023.
23. Rhodes A, Jasani B, Barnes DM, Bobrow LG, Miller KD. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. *J Clin Pathol*. 2000;53:125-130.
24. Allred DC. Commentary: Hormone Receptor Testing in Breast Cancer: A Distress Signal from Canada. *Oncologist.* 2008;13:1134-1136.
25. Gown AM. Current issues in ER and HER2 testing by IHC in breast cancer. Mod Pathol. 2008 May;21 Suppl 2:S8-S15.
26. Badve SS, Baehner FL, Gray R, et al. ER and PR assessment in ECOG 2197: comparison of locally determined IHC with centrally determined IHC and quantitative RT-PCR. Presentation at the 2007 American Society of Clinical Oncology Breast Cancer Symposium; San Francisco, CA;September 7-8, 2007:Abstract 87.
27. Baehner FL, Maddala T, Alexander C, et al. A Kaiser-Permanente population-based study of ER and PR expression by the standard method, immunohistochemistry (IHC), compared to a new method, quantitative reverse transcription polymerase chain reaction (RT-PCR). Presentation at the 2007 American Society of Clinical Oncology Breast Cancer Symposium; San Francisco, CA;September 7-8, 2007:Abstract 88.
28. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and Progesterone-Receptor Status in ECOG 2197: Comparison of Immunohistochemistry by Local and Central Laboratories and Quantitative Reverse Transcription Polymerase Chain Reaction by Central Laboratory. *J Clin Oncol*. 2008;26:2473-2481.
29. Baehner FL, Gray R, Childs B, et al. HER2 Concordance Between Central Laboratory Immunohistochemistry & Quantitative Reverse Transcription Polymerase Chain Reaction in Intergroup Trial E2197. American Society of Clinical Oncology (ASCO) Breast Cancer Symposium. 2008;Abstract 13.
30. Baehner FL, Achacoso, Maddala T, et al. HER2 Assessment in a Large Kaiser Permanente Case-Control Study: Comparison of Fluorescence In Situ Hybridization (FISH) and Quantitative Reverse Transcription Polymerase Chain Reaction (RTPCR) Performed by Central Laboratories.
31. Albain K, Barlow W, Shak S, et al. Prognostic and predictive value of the 21-gene Recurrence Score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100). Presentation at the 30th Annual San Antonio Breast Cancer Symposium; San Antonio, TX;December 13-16, 2007:Abstract 10.


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