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Tissue Biomarkers in the Management of Breast Cancer

Proceedings from a Closed Roundtable Meeting of Clinical Investigators

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Breast Cancer® UPDATE

CME Certified

Tissue Biomarkers in the Management of Breast Cancer

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

It is estimated that approximately 180,000 new invasive breast cancer cases will be diagnosed in 2008, and 41,000 individuals will die as a result of the disease. A major breakthrough in the individualized management of breast cancer has stemmed from the clinician's ability to segment the disease based on tumor-specific prognostic and predictive variables or biomarkers — specifically, cellular expression of ER, PR and/or HER2 and amplification of these and other genes representative of invasion or proliferation — that correlate both with long-term outcome and response to various treatments. The future of targeted and personalized breast cancer treatment algorithms will likely rely upon the incorporation of many additional relevant tumor-specific biomarkers. The utility of these molecular expressions may ultimately reside in the culmination of a signature or profile rather than in the presence of a single upregulated receptor. Additionally, the contributory roles of genetic-based assays that enable quantitative measurements versus historical IHC assays delivering largely qualitative findings have yet to be elucidated. Tools such as the Onco*type* DX® assay have already begun to enable the tailoring of treatment algorithms in the setting of controversial clinical situations, and further efforts to enhance the precision of therapeutic decision-making are underway. A thorough understanding of the evidence-based validation of such tools, in addition to knowledge of the specific populations likely to benefit from their use, is essential to ensuring best-practice patient outcomes. The primary goal of this activity is to provide medical oncologists with the information they need for optimal utilization of these biomarkers and genomic assays in up-to-date patient care strategies.

LEARNING OBJECTIVES

- Compare and contrast the qualitative and quantitative molecular assays currently used to measure ER/PR and HER2 tumor expression, and describe the clinical application and challenges that accompany each method.
- Describe the evidence to support global standardization of ER/PR and HER2 testing, and provide examples of how this consistency may improve patient care.
- Summarize the objectives and recommendations of the ASCO/College of American Pathologists guidelines for HER2 testing.
- Design a clinical algorithm for resolving inconclusive IHC and/or FISH HER2 testing in your practice.
- Appraise the relationship between quantitative ER/PR measurements and response to hormonal therapy.
- Discriminate between the Onco*type* DX and MammaPrint® genomic assays in terms of the tissue requirements, development and validation, and prognostic and predictive capabilities of each.
- Assess the clinical value of biopsying metastases for diagnostic confirmation of disease and/or assessment of biomarker concordance with the primary lesion.

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Challenges in HER2 Testing and Interpretation

Select Excerpts from the Discussion

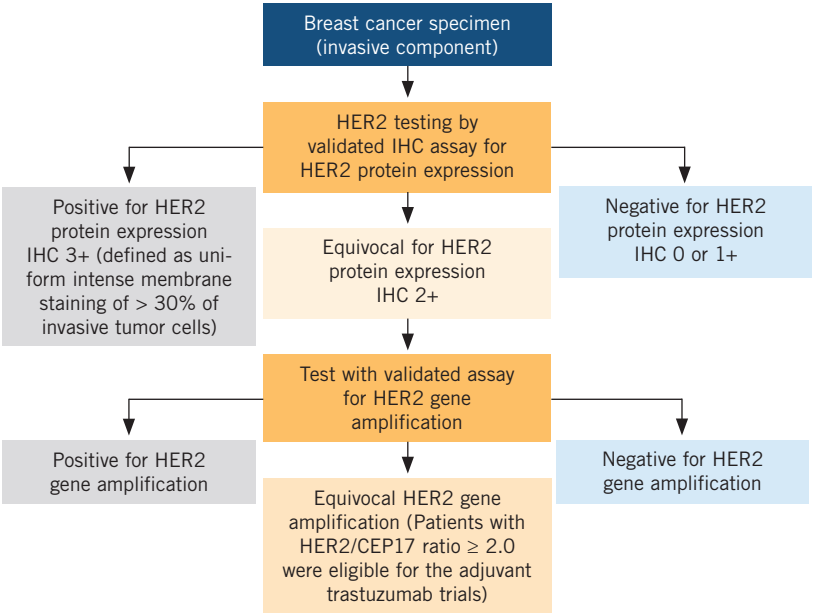
Tracks 3-4

DR LOVE: Antonio, you were the lead author for the paper about HER2 testing that came out of an elite group from ASCO and CAP (Wolff 2007a, 2007b). Would you discuss the conclusions?

DR WOLFF: The panel attempted to answer two questions. First, what is the optimal testing algorithm for the assessment of HER2 status? Second, what strategies can help ensure the optimal performance, interpretation and reporting of assays? Essentially, clinical algorithms were established that recapitulate what has been done in clinical practice (Wolff 2007a; [1.1A, B]).

The panel believed that, for the most part, no evidence supported the superiority of FISH compared to IHC. We decided to emphasize the importance of reflex testing for equivocal FISH results with IHC. We also formalized the definition of the equivocal range for FISH assays as a ratio of HER2 to CEP17 between 1.8 and 2.2 (Wolff 2007a; [1.1B]).

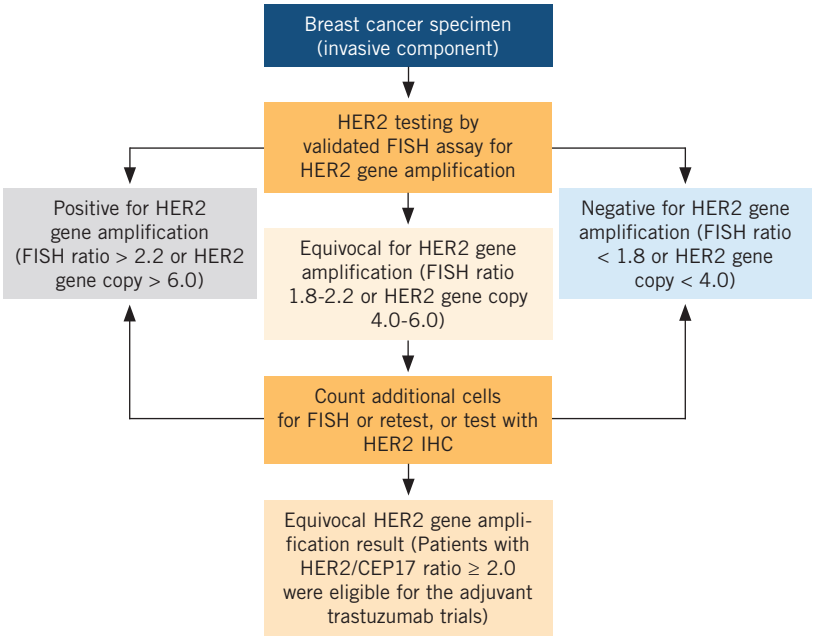
1.1A **Immunohistochemistry (IHC) Testing for HER2 Status: ASCO/CAP Algorithm**



SOURCE: With permission from Wolff AC et al. *J Clin Oncol* 2007a;25(1):118-45. **Abstract**

1.1B

Fluorescence In Situ Hybridization (FISH) Testing for HER2 Status: ASCO/CAP Algorithm



SOURCE: With permission from Wolff AC et al. *J Clin Oncol* 2007a;25(1):118-45. **Abstract**

DR WOLFF: We are also increasingly paying attention to the fixation of a tumor specimen, a key issue that applies to other markers as well, such as ER. The currently available HER2 assays have been validated using samples that have been fixed in neutral buffered formalin between six and 48 hours. This has huge implications from a practical standpoint for those women who have their breast surgery on a Friday afternoon. The pathologist must continue processing the tissue sample over the weekend, rather than waiting until Monday morning.

DR LOVE: What usually happens over the weekend? Could the tumor sit without being placed in formalin?

DR ALLRED: We hope that doesn't happen. The tumor usually is put in formalin, but it isn't sliced well. Sometimes it isn't sliced at all. In a typical scenario, the operating room nurse drops the entire piece of tissue in a big bucket of formalin, but formalin can't permeate within the tissue quickly. Then the outside of the tumor is overfixed and the inside is underfixed.

DR LOVE: Is there anything in the published literature about this?

DR WOLFF: Liz Hammond, who has a reference laboratory in Salt Lake City,

presented a study about this issue at the 2005 San Antonio Breast Cancer Symposium. She evaluated the prevalence of ER-negative test results in a homogeneous population across seven facilities (Nkoy 2005; [1.2]).

She reported by hospital and demonstrated variability, which indicates inconsistency in the time from tissue acquisition until it arrives in the laboratory for fixation. She also reported according to when the specimens were obtained. The specimens from the surgeries performed on Friday or Saturday had a lower prevalence of ER-positive results (Nkoy 2005; [1.2]).

1.2 Prevalence of ER-Negative Test Results According to Day of Breast Cancer Surgery in 5,028 Women

Healthcare facility	Specimen removed Sunday through Thursday	Specimen removed Friday or Saturday
LDHS (reference lab)	20%	18%
AFH	26%	39%
AVH	20%	26%
CWH	24%	26%
DXH	23%	30%
MKH	15%	29%
UVRMC	23%	25%
All facilities	20%	24%*

*$p = 0.03$

SOURCE: Nkoy FL et al. San Antonio Breast Cancer Symposium 2005;**Abstract 5107**.

Tracks 5-7, 9-10

DR LOVE: Craig, what are some of the key issues related to quality control with IHC and FISH for HER2?

DR ALLRED: It's important to understand that both IHC and FISH are inherently difficult tests to control. Even the experts have to work hard to keep the sensitivity and reproducibility of the tests at an acceptable level. One needs to know, what are those acceptable levels? How closely does your laboratory reproduce the biological distribution of the test results? How do the results vary from week to week, month to month, year to year?

Testing kits have been designed to remove most of the guesswork for the pathology laboratory in terms of the analytical and postanalytical or interpretive variables. But one must adhere closely to the recommended testing procedures, which is not always easy to do. In many laboratories, technicians don't realize that a minor variation in the procedure can have a major effect on the test result. This is as true for FISH as it is for IHC.

DR LOVE: Do we know where HER2 testing is being done?

DR WOLFF: I don't have a sense of how much is being done by local laboratories versus how much is being sent out. Community laboratories tend to perform the IHC locally and send samples to a central laboratory for FISH

testing. One of the proposed benefits of the new chromogenic assay is that you can perform the in situ hybridization test in your own community lab.

Clinicians in the community assume that FISH is more accurate and more predictive, but nothing could be further from the truth. It has more to do with whether you're performing the test correctly than whether you perform a particular test.

A perfect example was Michael Press's experience with the recent study of capecitabine with or without lapatinib. When HER2 testing by FISH was done by a large commercial laboratory, a suggestion emerged that some patients with HER2-negative disease benefited from the addition of lapatinib. Michael retested all the samples in his own lab by FISH. He found that many of the tumors that were labeled HER2-negative by the central reference laboratory were in fact HER2-positive, which had led to the implication that patients with HER2-negative disease were benefiting from lapatinib (Press 2008; [1.3]).

When he investigated further, it appeared that most of the interpretation of the results of the FISH assay in the large commercial laboratory was not being done by a pathologist but by a technologist. His strong recommendation was that you need a pathologist not only to supervise the test but also to make the interpretation (Press 2008). I believe the key issue for the clinician in the community to remember is that simply because a tumor is tested with FISH doesn't mean it is a better test.

DR LOVE: How can a laboratory assure themselves that they are providing accurate HER2 results? What should be the proportion of 2+ results with IHC for a laboratory?

DR ALLRED: As a clinician and a pathologist at a local institution, I would want to convince myself that the distribution of results was within expected range. One of the most sensitive indications is the proportion of 2+ results you obtain with IHC.

1.3

Progression-Free Survival Benefit Associated with the Addition of Lapatinib to Capecitabine for Women with Metastatic Breast Cancer

HER2 status assessed by a medical technologist in a large commercial laboratory

	HER2-positive (n = 255)	HER2-negative (n = 86)
Hazard ratio (95% CI)	0.47 (0.32-0.67)	0.54 (0.30-0.99)
p-value	<0.001	0.046

HER2 status assessed by a board-certified pathologist in a small academic laboratory

	HER2-positive (n = 271)	HER2-negative (n = 47)
Hazard ratio (95% CI)	0.46 (0.33-0.65)	0.94 (0.39-2.28)
p-value	<0.001	0.888

SOURCE: Press MF et al. *Proc ASCO* 2008;**Abstract 1007**.

Based on the data I have the most faith in, it's probably about 10 to 20 percent. So I would say that 15 percent is the average rate for a 2+ result with IHC. That is a number that repeatedly comes out of expert academic laboratories as roughly correct. The frequency of 2+ results with IHC coming out of commercial laboratories varies from 10 to 60 percent. If you have around a 15 percent rate for 2+ results with IHC and you send the tumor for FISH analysis, if 30 to 50 percent come back amplified, you're probably doing it right.

At the 2005 San Antonio Breast Cancer Symposium, two poster discussions dealt with FISH assay validation of HER2 2+ IHC results. One poster was from an academic laboratory, and it included approximately 2,000 patients. The other poster was from a large commercial laboratory, and it included approximately 10,000 patients.

The algorithm was for 2+ IHC — on which the initial screening was always based — to be sent for FISH analysis. In the academic laboratory, 15 percent of tumor samples went on to FISH, and around 30 percent were positive. In the commercial laboratory, 60 percent of the tumor samples were 2+ by IHC. Among the 60 percent, a far smaller proportion ended up being amplified by follow-up FISH.

Next you should check your results against other laboratories and participate in the CAP accreditation programs, which have become much more rigorous, especially with the new ASCO/CAP guidelines (Wolff 2007a; [1.4]). Some pathologists, especially those in smaller institutions, use the word *onerous* rather than rigorous, because they don't handle enough cases to meet the quality-control guidelines.

DR SIMON: It would be nice to have national certification of HER2 testing in individual laboratories. This would involve a central organization that randomly sent out standardized materials with a known HER2 status and then provided feedback regarding the sensitivity and specificity of HER2 testing in

1.4 ASCO/CAP Guidelines: Proficiency Testing Requirements for HER2 Assays

"All laboratories reporting HER2 results must participate in a guideline concordant proficiency testing (PT) program specific for each assay method used (ie, separate programs for IHC, FISH, brightfield ISH, image analysis). To be concordant with this guideline, PT programs must distribute specimens at least twice per year including a sufficient number of challenges (cases) to ensure adequate assessment of laboratory performance.

For programs with 10 or more challenges per event, satisfactory performance requires correct identification of at least 90% of the graded challenges in each testing event. Laboratories with less than 90% correct responses on graded challenges in a given PT event are at risk for the next event. Laboratories that have unsatisfactory performance will be required to respond according to accreditation program requirements up to and including suspension of HER2 testing for the applicable method until performance issues are corrected."

SOURCE: Wolff AC et al. *J Clin Oncol* 2007a;25(1):118-45. **Abstract**

that laboratory. It would be voluntary on the part of the laboratory, but physicians wouldn't have to use laboratories that didn't volunteer to participate in national certification.

Track 13

DR LOVE: Joe, the Onco*type* DX® assay is now reporting quantitative HER2 results. What are the issues related to assessing HER2 status with RT-PCR? What is actually being measured compared to when HER2 is assessed with FISH and IHC?

DR SPARANO: IHC measures protein expression. Gene amplification is measured by FISH. In general, when FISH indicates gene amplification, protein overexpression is almost always present.

RT-PCR is a semiquantitative way of examining expression of RNA, the intermediary. It's just another way of analyzing the same pathway. Information is emerging about the correlation between RNA expression and both gene amplification and protein overexpression.

DR BUDD: We need correlation between RT-PCR and response to trastuzumab in the setting of a randomized trial, which is forthcoming. Ultimately, we're trying to determine whether this test will predict response to a specific therapy. The best way to evaluate the tests is in trials.

Track 18

DR LOVE: How should the assessment of HER2 status be approached in clinical practice?

DR SIMON: Today, a reasonable algorithm would be the following: If the tumor is HER2-positive, then I go with that. If it is HER2-negative, then I ask for it to be sent out a second time. From what I see, the downside of having a false-negative result is greater than the downside of having a false-positive one.

DR WOLFF: It actually goes both ways, because a false-positive result, which occurred anywhere from 12 to 18 percent of the time in NCCTG-N9831 (Perez 2006), means you run the risk of potentially receiving a costly and toxic placebo.

DR SIMON: But if my tumor is HER2-positive, the treatment will benefit me. If my tumor is HER2-negative, it won't benefit me and I'll be subject to some toxicity. On the other hand, if my tumor is HER2-positive and it is actually labeled HER2-negative, to have that drug withheld, I believe, is a greater cost.

DR GOSS: However, $100,000 and a serious cardiac event for the wrong reason are extremely important.

DR LOVE: Also, many patients end up receiving chemotherapy because their tumor is HER2-positive.

DR SPARANO: We also have evidence that those patients with tumors that are called HER2-positive by one laboratory and HER2-negative by another laboratory may benefit from adjuvant trastuzumab (Paik 2008; [1.5]). ■

1.5 **HER2 Status and the Efficacy of Adjuvant Trastuzumab in NSABP-B-31**

Endpoint	ACT	ACTH	Relative risk (95% CI)	*p*-value	*p*-value for the interaction
	Number of events/ total number of events				
Disease progression					
HER2-positive	163/875	85/804	0.47 (0.37-0.62)	<0.001	0.47
HER2-negative	20/92	7/82	0.34 (0.14-0.80)	0.014	
Death					
HER2-positive	55/875	38/804	0.66 (0.43-0.99)	0.047	0.08
HER2-negative	10/92	1/82	0.08 (0.01-0.64)	0.017	

ACT = doxorubicin/cyclophosphamide → paclitaxel; ACTH = doxorubicin/cyclophosphamide → paclitaxel/trastuzumab

SOURCE: Paik S et al. *N Engl J Med* 2008;358(13):1409-11. No abstract available

SELECT PUBLICATIONS

Nkoy FL et al. **Day of surgery affects estrogen receptor test results in women with breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 5107**.

Paik S et al. **HER2 status and benefit from adjuvant trastuzumab in breast cancer.** *N Engl J Med* 2008;358(13):1409-11. No abstract available

Perez EA 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):3032-8. **Abstract**

Press MF et al. **Correlation of HER2 gene amplification, HER2 and EGFR expression (protein and mRNA) with lapatinib efficacy in women with metastatic breast cancer.** *Proc ASCO* 2008;**Abstract 1007**.

Wolff AC 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* 2007a;25(1):118-45. **Abstract**

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *Arch Pathol Lab* Med 2007b;131(1):18. **Abstract**

Assessment of Estrogen Receptor Status

Select Excerpts from the Discussion

Tracks 20-22

DR LOVE: Craig, can you discuss the study by Kim on ER testing?

DR ALLRED: Kim and colleagues compared three assays for the measurement of ER status in patients with node-negative, ER-positive breast cancer. The three assays were a ligand-binding assay, IHC and quantitative RT-PCR. This study was based on a subset of 297 patients treated with tamoxifen in NSABP-B-14, one of the pivotal trials demonstrating the efficacy of adjuvant tamoxifen in patients with node-negative, ER-positive breast cancer (Kim 2006).

The ligand-binding assay, performed at the study sites, required fresh or frozen tissue. IHC was performed on formalin-fixed tissue sections in a central laboratory at NSABP with an FDA-approved, validated kit — the DakoCytomation ER/PR pharmDx™. They used computerized-image analysis to quantify results three ways: percent of positive cells, average intensity of positive cells and the product of both. Quantitative RT-PCR required formalin-fixed tissue and was performed at Genomic Health as part of the Onco*type* DX 21-gene panel. ER is one of those genes (Kim 2006).

The aim of the study was to determine the level of correlation between the different assays and the relationship of each assay to the clinical outcome of distant recurrence-free interval. The correlation between the assays varied, and the correlations between all of the assays and the overall Onco*type* DX Recurrence Score were weak (Kim 2006).

This retrospective study demonstrated a notable difference in the ability of these tests to predict the distant recurrence-free interval with tamoxifen. The ligand-binding assay performed most poorly, with a hazard ratio of 0.86 that was not statistically significant. The different methods for scoring the IHC assay demonstrated hazard ratios ranging from about 0.3 to 0.6, and they were all statistically significant in univariate analysis. RT-PCR was remarkably predictive in this single study. The hazard ratio was 0.14 and highly statistically significant (Kim 2006; [2.1]).

2.1

Measures of ER Status and Hazard Ratio for Distant Recurrence-Free Interval Among Women with ER-Positive, Node-Negative Breast Cancer Who Were Treated with Adjuvant Tamoxifen

ER measures	Hazard ratio	95% CI	*p*-value
Ligand binding (fmol/mg/100)	0.86	0.70-1.08	0.191
IHC % cells (%/50)	0.63	0.43-0.94	0.022
IHC intensity (score/500)	0.32	0.15-0.71	0.005
IHC % cells x intensity (value/50,000)	0.44	0.21-0.89	0.023
Quantitative RT-PCR (expression/6)	0.14	0.07-0.29	<0.0001

CI = confidence interval; IHC = immunohistochemistry; RT-PCR = reverse transcriptase-polymerase chain reaction

SOURCE: Kim C et al. San Antonio Breast Cancer Symposium 2006;**Abstract 3116**.

These are promising preliminary results, suggesting that evaluating ER by quantitative RT-PCR is more predictive — compared to IHC or the ligand-binding assay — of response to tamoxifen in patients with ER-positive disease. However, this is only one study.

Quantitative RT-PCR performed almost too well: Hazard ratios as low as 0.14 are almost unbelievable. We've never seen anything like that before. It's wonderful if it's true and reproducible, but we don't know that yet.

Recently some of the same investigators published a similar study evaluating ER status assessed by IHC versus RT-PCR in ECOG-E2197, a trial for patients with high-risk breast cancer who received chemotherapy with or without tamoxifen based on hormone receptor status (Badve 2008; [2.2]). RT-PCR was a significant predictor of recurrence, but it didn't have a hazard ratio anywhere near 0.14 that was seen in the Kim paper (Kim 2006; [2.1]).

I wrote an editorial about that paper (Allred 2008; [2.3]). The performance of IHC and RT-PCR were similar. We saw a trivial statistical advantage to RT-PCR, but they both did well. So that raises the question, does this just happen to be a sampling bias in this particular retrospective study? I don't know. I believe the results, but these aren't the same results as those from another study conducted by some of the same people.

2.2

ECOG-E2197: Assessment of ER Status by IHC and RT-PCR

"The relationship between recurrence risk and ER expression by central IHC and central RT-PCR was explored. Five-year recurrence rate estimates were obtained for all patients, and separately for the ER-positive patients who received chemohormonal therapy. As expected, ER by both central IHC and central RT-PCR were significantly associated with relapse when all patients were included in the analysis ($P < .0001$ for both). When the ER-positive subgroup was analyzed, ER expression by central IHC AS [Allred Score] was marginally associated with recurrence, while ER expression by central RT-PCR was significantly associated with recurrence."

SOURCE: Badve SS et al. *J Clin Oncol* 2008;26(15):2473-81. **Abstract**

2.3

Dr Allred on the Assessment of ER Status by IHC and RT-PCR in ECOG-E2197

"The importance of the Badve et al study stems from its investigation of alternative methods for evaluating receptors that may be more reliable and accurate. In the limited scope of this study, it was successful by demonstrating that RT-PCR is at least equivalent to IHC in its ability to identify receptor-positive cases (considering ER and PR combined), marginally superior in predicting outcome in ER-positive patients, and superior in technical precision, which are all encouraging results."

SOURCE: Allred DC. *J Clin Oncol* 2008;26(15):2433-5. No abstract available

Track 24

DR LOVE: The Onco*type* DX assay now reports quantitative ER. Are there situations in which that information might change what you do?

DR BUDD: Not for me right now. The following decisions need to be made: Do we or do we not use hormonal therapy? Do we or do we not use chemotherapy? If the patient has ER-positive disease, we will use hormonal therapy. Then the decision is whether to use chemotherapy. To make that decision, you're using the whole Onco*type* DX Recurrence Score.

DR SPARANO: I believe at the least it provides greater transparency.

You struggle when you have a midrange Recurrence Score. If you had the information regarding ER and PR and they were high, as a clinician you'd feel more confident in recommending to that patient, "I believe you'll be okay with endocrine therapy alone."

I believe it will be more helpful for the patients who have intermediate Recurrence Scores because we already know from a great deal of experience what happens at the extremes. The proportion of patients with intermediate Recurrence Scores, no matter how you define it, can be anywhere from 45 to 70 percent, depending on how you select your patients.

DR GOSS: I agree with Tom. The decision to use chemotherapy based on the Onco*type* DX assay is primarily driven by the Recurrence Score overall, and the Recurrence Score has the ER level built into it.

I don't believe the decision to use chemotherapy for patients with intermediate Recurrence Scores should be influenced by the quantitative ER results, but you could argue that the choice of endocrine therapy or the type of endocrine therapy might be so influenced.

DR SPARANO: I take the opposite view. We know that a continuous relationship exists between the Recurrence Score and benefit from chemotherapy — the higher the score, the greater the benefit. We don't know at what threshold you do not benefit from chemotherapy. So for the 40 to 70 percent of patients with intermediate Recurrence Scores, I would have more confidence relying on endocrine therapy alone if I had a higher level of ER and/or PR expression.

Tracks 26-27

DR LOVE: Craig, can you comment on the new analysis for the P024 study by Ellis evaluating neoadjuvant endocrine therapy?

DR ALLRED: In P024, postmenopausal patients with Stage II/III, ER-positive disease were randomly assigned to neoadjuvant tamoxifen or letrozole for four months. Then the tumor was surgically removed, usually by lumpectomy, and thereafter all patients received tamoxifen for up to five years. The median

follow-up at the time of this analysis was about 62 months, slightly over five years (Ellis 2008).

Tissues were sampled twice for proliferation rate, hormone receptor status, grade, tumor size and nodal status, first at the initial diagnosis by core biopsy and then from the excised tumor after four months of neoadjuvant hormonal therapy. The analysis included looking for univariate correlations, developing a multivariate model and performing internal validation on all of these parameters, which are standard in a neoadjuvant setting (Ellis 2008).

Rather than conducting this core biopsy analysis on the primary tumor, it was done on the tumor after four months of therapy. So theoretically you have a chance to measure the response of the tumor under the pressure of therapy. The variables all correlated with both relapse-free and breast cancer-specific survival. In the new update, the investigators have also had an opportunity to validate their prognostic model in an independent data set (Ellis 2008).

On multivariate analysis, only four parameters — tumor size, node status, Ki-67 proliferation rate and ER status — remained significant for relapse-free survival. When the endpoint was changed to breast cancer-specific survival, the same four variables remained significant on multivariate analysis. The investigators remodeled only those four variables to recalculate the hazard ratios, which were strengthened and remained significant (Ellis 2008).

2.4 **Calculation of the Preoperative Endocrine Prognostic Index (PEPI) Score**

The total PEPI score assigned to each patient is the sum of the risk points derived from the pathologic tumor size, pathologic node status, Ki-67 level and ER status

Pathology, biomarker status	RFS HR	Points	BCSS HR	Points
Pathological tumor size				
T1 or T2	—	0	—	0
T3 or T4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki-67 level				
0% to 2.7%	—	0	—	0
>2.7% to 7.3%	1.3	1	1.4	1
>7.3% to 19.7%	1.7	1	2.0	2
>19.7% to 53.1%	2.2	2	2.7	3
>53.1%	2.9	3	3.8	3
ER status, Allred score				
0 to 2	2.8	3	7.0	3
3 to 8	—	0	—	0

A hazard ratio (HR) in the range of 1 to 2 receives one risk point; an HR in the 2 to 2.5 range, two risk points; an HR greater than 2.5, three risk points. RFS = relapse-free survival; HR = hazard ratio; BCSS = breast cancer-specific survival

SOURCE: Ellis MJ et al. *J Natl Cancer Inst* 2008;100(19):1380-8. **Abstract**

Then they used these hazard ratio data to create what they referred to as the preoperative endocrine prognostic index (PEPI). They followed a strategy from the cardiovascular literature that developed a numerical score for predicting outcomes for patients who experienced myocardial infarctions.

They measured multiple variables and assigned points based on the magnitude of the hazard ratios. If a hazard ratio was between one and two, it was assigned one point. If it was between two and 2.5, it had two points, and so on (Ellis 2008; [2.4]).

The PEPI score showed remarkable ability to predict response to therapy. At five years, recurrence-free survival among patients in the lowest-risk tertile (PEPI risk group 1) was almost 95 percent. This led the authors to conclude that these patients could be treated without adjuvant chemotherapy. Survival was much worse in the PEPI risk groups 2 and 3 (Ellis 2008; [2.5]).

For independent validation, investigators applied the PEPI model to patients in the IMPACT trial, which evaluated treatment for three months with anastrozole, tamoxifen or the combination before surgery. Relapse-free survival was 100 percent in the PEPI risk group 1, with much poorer results in the higher PEPI risk groups (Ellis 2008).

The authors concluded, and I agree with most of their conclusions, that the PEPI score is a powerful and inexpensive tool for predicting relapse in postmenopausal women with Stage II/Stage III ER-positive breast cancer.

After neoadjuvant hormonal therapy, patients with a PEPI score of zero, which accounts for approximately 10 percent of the patient population, can probably be treated without adjuvant chemotherapy and remain on hormonal therapy alone. This would be a major change in therapeutic strategy. ■

2.5 **PEPI Score Predicts Risk of Relapse and Risk of Breast Cancer Death**

PEPI score	PEPI risk group	Risk of relapse*	Risk of breast cancer death*
0	1	10%	2%
1-3	2	23%	11%
≥ 4	3	48%	17%

* $p < 0.001$

"Ultimately, the clinical significance of the PEPI model lies in its ability to identify patients at low risk of relapse in the absence of adjuvant chemotherapy (group 1) and patients at very high relapse risk that should mandate all appropriate adjuvant treatments (group 3). More confidence around the estimates of relapse risk assigned to PEPI group 2 will require studies with larger sample sizes and longer follow-up."

SOURCE: Ellis MJ et al. *J Natl Cancer Inst* 2008;100(19):1380-8. **Abstract**

SELECT PUBLICATIONS

Allred DC. **Problems and solutions in the evaluation of hormone receptors in breast cancer.** *J Clin Oncol* 2008;26(15):2433-5. No abstract available

Badve SS 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(15):2473-81. **Abstract**

Ellis MJ et al. **Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics.** *J Natl Cancer Inst* 2008;100(19):1380-8. **Abstract**

Ellis MJ et al. **Outcome prediction for clinical stage II and III ER+ breast cancer based on treatment response, pathological stage, tumor grade, Ki67 proliferation index, and estrogen receptor status after neoadjuvant endocrine therapy.** San Antonio Breast Cancer Symposium 2007;**Abstract 62**.

Kim C et al. **A comparison of estrogen receptor (ER) measurement by three methods in node negative, estrogen receptor (ER) positive breast cancer: Ligand binding (LB), immunohistochemistry (IHC), and quantitative RT-PC.** San Antonio Breast Cancer Symposium 2006;**Abstract 3116**.

Evolving Role of Genomic Assays in Breast Cancer

Select Excerpts from the Discussion

Track 38

DR LOVE: Joe, can you discuss the ASCO Guidelines Committee's recommendations, published in the November 2007 *Journal of Clinical Oncology*, about the use of tumor markers in breast cancer?

DR SPARANO: The panel found sufficient evidence to recommend multiparameter gene expression analysis. They also found sufficient evidence to recommend measuring urokinase plasminogen activator (uPA) or plasminogen activator inhibitor 1 (PAI-1) using ELISA, which requires a minimum of 300 milligrams of fresh or frozen tissue. Low levels of uPA/PAI-1 are associated with a good prognosis with tamoxifen alone for patients with ER-positive disease (Harris 2007), although issues exist regarding the effect of core biopsies on the results.

DR LOVE: What are uPA and PAI-1?

DR SPARANO: They are an index of the fibrinolytic system and biological processes involved in metastasis. In terms of other markers, the panel found insufficient evidence for the use of IHC-based markers as they relate to measuring proliferation, including Ki-67, cyclin D, cyclin E, p27, p21, thymidine kinase and topoisomerase II (Harris 2007).

They also found insufficient evidence for the use of other markers that have been recently published, including cyclin E fragments, proteomic analysis and circulating tumor cells.

Regarding multiparameter gene-expression analysis, the ASCO panel

concluded that the Onco*type* DX assay can be used to predict the risk of recurrence in newly diagnosed patients with node-negative, ER-positive breast cancer who are treated with tamoxifen. In addition, it may be used to identify patients who are predicted to attain the most therapeutic benefit from adjuvant tamoxifen and may not require chemotherapy. Conversely, they concluded that patients with tumors with a high Recurrence Score achieve more benefit from adjuvant chemotherapy, specifically CMF, than from tamoxifen alone (Harris 2007; [3.1]).

The MammaPrint® assay appears to identify groups of patients with a particularly good or particularly poor prognosis. However, considering the design of studies used to validate the assay, it is uncertain whether the data pertain to an inherently favorable outcome in untreated patients, to patients whose prognosis is favorable due to therapy or to those with poor outcomes in the absence of treatment or despite treatment.

In addition, the need for fresh or frozen tissue makes this assay challenging in current clinical practice. The panel concluded that more definitive recommendations for the use of the MammaPrint assay in clinical practice will require data from more clearly directed studies (Harris 2007).

3.1

2007 ASCO Recommendations: Use of Multiparameter Gene-Expression Analysis in Breast Cancer

"In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Onco*type* DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Onco*type* 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 addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from tamoxifen.

There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens. The precise clinical utility and appropriate application for other multiparameter assays, such as the MammaPrint assay, the "Rotterdam Signature," and the Breast Cancer Gene Expression Ratio are under investigation."

CMF = cyclophosphamide, methotrexate and fluorouracil

SOURCE: Harris L et al. *J Clin Oncol* 2007;25(33):5287-312. **Abstract**

Track 40

DR LOVE: Do we have any data correlating the MammaPrint assay with benefit from chemotherapy?

DR SPARANO: I believe that's one of the critical and key differences between how the MammaPrint and the Onco*type* DX assays were developed and validated. They may be equally fine in terms of predicting outcomes, but they were developed in different ways.

The Onco*type* DX assay was developed using data from prospective randomized trials comparing tamoxifen to placebo (Paik 2004) or tamoxifen to tamoxifen with CMF (Paik 2006), which is different from how the groups of patients were studied with the MammaPrint assay (van 't Veer 2002; van de Vijver 2002).

A second key difference is how the tissue is processed. For the MammaPrint assay, or any assay that requires collection of fresh tissue, you have to know in advance that the patient is a potential candidate for the test. A third important issue is the transparency of Onco*type* DX as opposed to MammaPrint. MammaPrint involves a Pandora's box of 70 genes that we know nothing about. In contrast, Onco*type* DX involves a much more manageable number of genes that are familiar to us as clinicians — they make sense.

Track 41

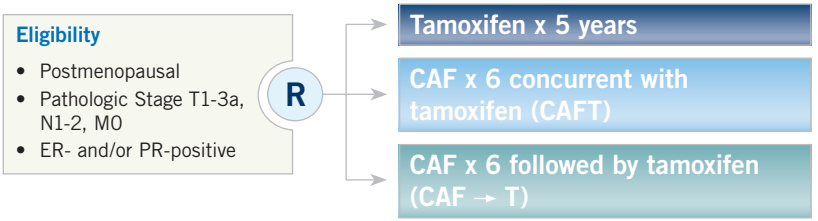
DR LOVE: Joe, can you discuss the potential role of Onco*type* DX for patients with node-positive disease?

DR SPARANO: At the 2004 San Antonio Breast Cancer Symposium, Kathy Albain presented the results from SWOG-8814, evaluating five years of tamoxifen alone or in combination with CAF for postmenopausal patients with node-positive, ER-positive disease. A better outcome was demonstrated for those who received CAF followed by sequential tamoxifen compared to those who received tamoxifen alone (Albain 2004; [3.2]).

3.2

SWOG-8814: A Phase III Randomized Trial of Tamoxifen Alone versus Tamoxifen Concurrent or Sequential with CAF for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer

Protocol IDs: SWOG-8814, CAN-NCIC-MA9, CLB-9194, EST-4188, NCCTG-883051, INT-0100, MA9
Accrual: 1,477 (Closed)



Treatment arm	Estimated 10-year disease-free survival
CAF → T	60%
CAFT	53%
Tamoxifen	48%

CAF = oral cyclophosphamide, doxorubicin, 5-FU

SOURCES: Albain K et al. San Antonio Breast Cancer Symposium 2004. No abstract available; NCI Physician Data Query, January 2008.

More recently, she evaluated whether the Onco*type* DX assay provided information additional to the clinical features in a subset of about 40 percent of the patients in the parent trial (Albain 2007).

In SWOG-8814, patients with a Recurrence Score of 31 or higher obtained a significant reduction in the risk of recurrence with the addition of chemotherapy. Those who had a low Recurrence Score obtained no benefit.

Among those with intermediate Recurrence Scores, a trend appeared toward benefit from the addition of chemotherapy, but the *p*-value was not statistically significant (Albain 2007; [3.3]). Examining these data with Forest plots reveals a strong trend favoring the administration of chemotherapy to patients who have an intermediate Recurrence Score (Albain 2007). ■

3.3

Impact of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to the Onco*type* DX Recurrence Score

	10-year disease-free survival estimates	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low Recurrence Score (<18)	60%	64%
Intermediate Recurrence Score (18-30)	49%	63%
High Recurrence Score (≥31)	43%	55%

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Albain K et al. **Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen (ER) and/or progesterone (PgR) receptor positive breast cancer: Mature outcomes and new biologic correlates on Phase III Intergroup trial 0100 (SWOG-8814).** San Antonio Breast Cancer Symposium 2004. No abstract available

Harris L et al. **American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer.** *J Clin Oncol* 2007;25(33):5287-312. **Abstract**

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Van de Vijver MJ et al. **A gene-expression signature as a predictor of survival in breast cancer.** *N Engl J Med* 2002;347(25):1999-2009. **Abstract**

Van 't Veer LJ et al. **Gene expression profiling predicts clinical outcome of breast cancer.** *Nature* 2002;415(6871):530-6. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the 2007 ASCO/CAP guidelines for HER2 testing, which assay is considered superior for the assessment of HER2 status?**
   a. FISH
   b. IHC
   c. None of the above

2. **The 2007 ASCO/CAP guidelines for HER2 testing recommend that proficiency testing be conducted _____.**
   a. Annually
   b. Twice per year
   c. Quarterly
   d. Monthly

3. **In a retrospective analysis of NSABP-B-14, Kim and colleagues demonstrated that ER measurement by _____ was the strongest predictor of distant recurrence-free interval for women with node-negative, ER-positive breast cancer who received adjuvant tamoxifen.**
   a. Ligand binding assay
   b. IHC
   c. Quantitative RT-PCR

4. **In the P024 study, women received four months of neoadjuvant _____.**
   a. Letrozole
   b. Anastrozole
   c. Tamoxifen
   d. Either a or c
   e. Either b or c

5. **Which of the following is not included in the calculation of the PEPI score?**
   a. Pathological tumor size
   b. Node status
   c. PR status
   d. Ki-67 level

6. **In the P024 study, the PEPI score was predictive of _____.**
   a. Relapse-free survival
   b. Breast cancer-specific survival
   c. Both a and b

7. **High levels of uPA/PAI-1 are associated with a good prognosis with tamoxifen alone for patients with ER-positive, node-negative disease.**
   a. True
   b. False

8. **The 2007 ASCO Update of Recommendations for the Use of Tumor Markers in Breast Cancer found sufficient evidence to recommend the use of IHC-based markers, such as ____.**
   a. Ki-67
   b. Cyclin E
   c. Topoisomerase II
   d. None of the above

9. **The 2007 ASCO Update of Recommendations for the Use of Tumor Markers in Breast Cancer supports the use of the _____ to identify patients who may not require adjuvant chemotherapy.**
   a. Onco*type* DX assay
   b. MammaPrint assay
   c. Both a and b
   d. None of the above

10. **Which of the following assays requires fresh or frozen tumor tissue?**
    a. Onco*type* DX
    b. MammaPrint
    c. Both a and b
    d. None of the above

Post-test answer key: 1c, 2b, 3c, 4d, 5c, 6c, 7b, 8d, 9a, 10b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Tissue Biomarkers in the Management of Breast Cancer — Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- **Objectives and recommendations of the ASCO/CAP guideline recommendations for HER2 testing** 4 3 2 1
- **Importance of timing in tissue acquisition and fixation in ER and HER2 assessment** . . 4 3 2 1
- **Effectiveness of quantitative RT-PCR for ER assessment compared to IHC and ligand-binding assays with regard to prediction of benefit from hormonal therapy** . . . 4 3 2 1
- **Preoperative Endocrine Prognostic Index (PEPI)** 4 3 2 1
- **Development and clinical utility of the Onco*type* DX assay in node-negative and node-positive breast cancer** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- **Objectives and recommendations of the ASCO/CAP guideline recommendations for HER2 testing** 4 3 2 1
- **Importance of timing in tissue acquisition and fixation in ER and HER2 assessment** . . 4 3 2 1
- **Effectiveness of quantitative RT-PCR for ER assessment compared to IHC and ligand-binding assays with regard to prediction of benefit from hormonal therapy** . . . 4 3 2 1
- **Preoperative Endocrine Prognostic Index (PEPI)** 4 3 2 1
- **Development and clinical utility of the Onco*type* DX assay in node-negative and node-positive breast cancer** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . . . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Compare and contrast the qualitative and quantitative molecular assays currently used to measure ER/PR and HER2 tumor expression, and describe the clinical application and challenges that accompany each method. . . . . 4 3 2 1 N/M N/A
- Describe the evidence to support global standardization of ER/PR and HER2 testing, and provide examples of how this consistency may improve patient care. . . . . 4 3 2 1 N/M N/A
- Summarize the objectives and recommendations of the ASCO/College of American Pathologists guidelines for HER2 testing. . . . . 4 3 2 1 N/M N/A
- Design a clinical algorithm for resolving inconclusive IHC and/or FISH HER2 testing in your practice. . . . . 4 3 2 1 N/M N/A
- Appraise the relationship between quantitative ER/PR measurements and response to hormonal therapy. . . . . 4 3 2 1 N/M N/A
- Discriminate between the Onco*type* DX and MammaPrint® genomic assays in terms of the tissue requirements, development and validation, and prognostic and predictive capabilities of each. . . . . 4 3 2 1 N/M N/A
- Assess the clinical value of biopsying metastases for diagnostic confirmation of disease and/or assessment of biomarker concordance with the primary lesion. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

What additional information or training do you need on the activity topics or other oncology-related topics?

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G Thomas Budd, MD	4 3 2 1	4 3 2 1
Paul E Goss, MD, PhD	4 3 2 1	4 3 2 1
Richard Simon, DSc	4 3 2 1	4 3 2 1
Joseph A Sparano, MD	4 3 2 1	4 3 2 1
Antonio C Wolff, MD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the moderator and faculty for this activity:

.....

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