



AMERICAN SOCIETY OF CLINICAL ONCOLOGY



**2007 UPDATE OF ASCO
RECOMMENDATIONS FOR
THE USE OF TUMOR MARKERS IN
BREAST CANCER**

American Society of Clinical Oncology
Clinical Practice Guideline

Introduction

- ASCO convened an Update Committee to review and update recommendations for the use of tumor markers in breast cancer.
- ASCO previously published these guidelines in 1996 and updated them previously in 1997 and 2000.
- The 2007 Update expands the scope of the guideline to include six new markers in breast cancer.

Harris L., et al. J Clin Oncol. 2007

Guideline Methodology (cont'd): Panel Members

- Robert C. Bast, Jr., MD, *Co-Chair* MD Anderson Cancer Center
- Daniel F. Hayes, MD, *Co-Chair* University of Michigan Medical Center
- Lyndsay Harris, MD, *Subcommittee Chair* Yale Cancer Center
- Dean F. Bajorin, MD Memorial Sloan-Kettering Cancer Center
- Jonathan S. Berek, MD UCLA School of Medicine
- Ross S. Berkowitz, MD Brigham & Women's Hospital
- Roy Beveridge, MD Fairfax Northern VA Hem/Onc
- Herbert Fritsche, Jr., PhD MD Anderson Cancer Center
- Timothy Gilligan, MD Dana Farber Cancer Institute
- Stanley Hamilton, MD MD Anderson Cancer Center
- Jules Harris, MD Rush-Presbyterian St. Luke's Medical Center
- John M. Jessup, MD Georgetown Univ. Medical Center

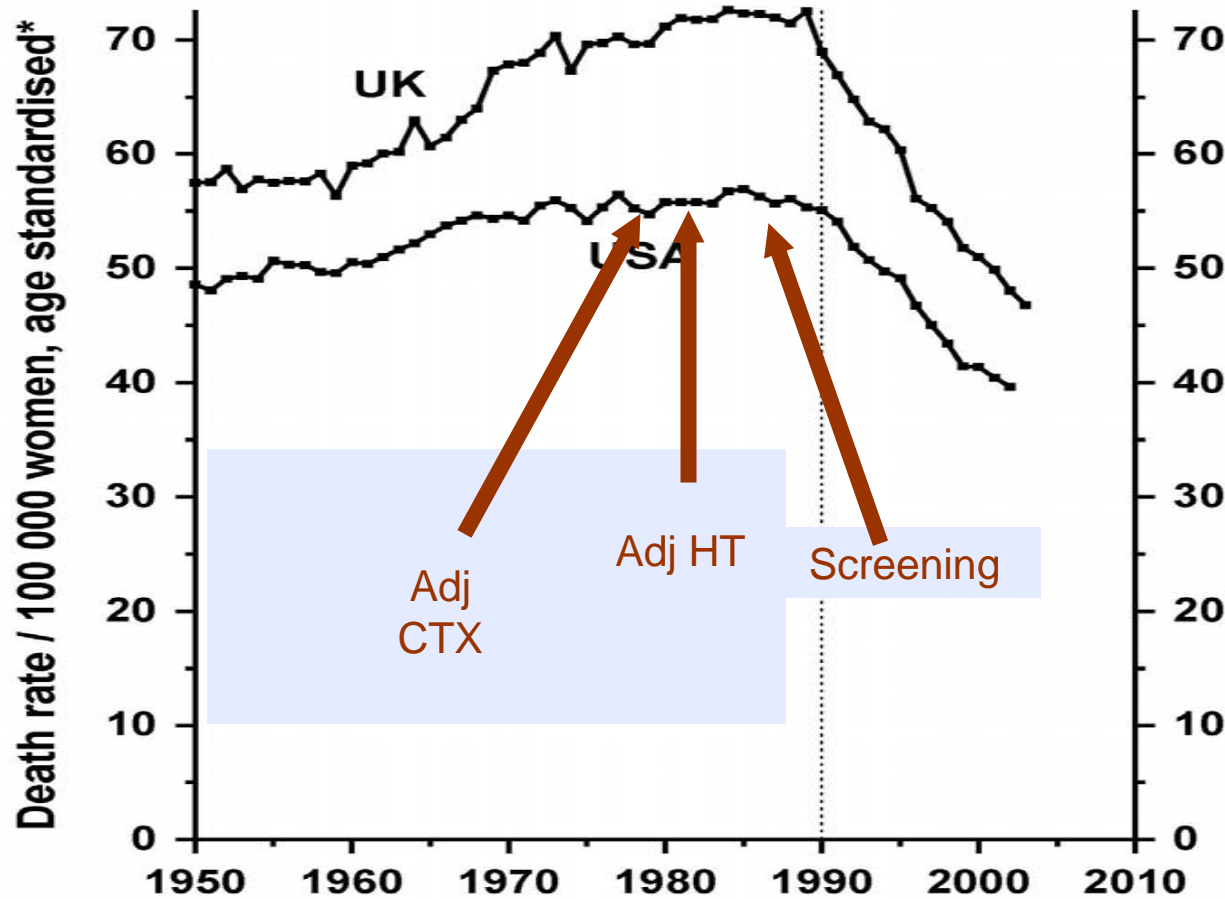
Guideline Methodology (cont'd): Panel Members

- Philip W. Kantoff, MD
Dana-Farber Cancer Institute
- Nancy E. Kemeny, MD
Memorial Sloan-Kettering Cancer Center
- Ann Kolker
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- Susan Leigh, BSN, RN
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- Gershon Y. Locker, MD
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- Pam McAllister, PhD
Science Advocate, Colorectal Cancer Coalition
- Robert G. Mennel, MD
Texas Oncology PA
- Larry Norton, MD
Memorial Sloan-Kettering Cancer Center
- Peter Ravdin, MD
San Antonio, TX
- Sheila Taube, PhD
National Cancer Institute

Guideline Methodology: Systematic Review

- An ASCO Update Committee completed a review and analysis of data published since 1999 to February 2007 (or from 1966 to February 2007 for new markers):
 - ✓ MEDLINE
 - ✓ Cochrane Collaboration Library

Recent decrease in UK and USA breast cancer mortality at ages 35-69 years



*Mean of annual rates in the seven component 5-year age groups

Source: WHO mortality & UN population estimates

Modified from Peto et al. Lancet 355:1822, 2000

■ Should All Patients Receive All Therapy?

- If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything*
- If pt is willing to forego SOME benefit to avoid SOME toxicity: *then select therapy carefully*

■ Depends on:

- Prognostic and Predictive Factors
- Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy

■ How much absolute benefit is needed to justify Rx?

- AdjuvantOnline!

Ravdin et al. J Clin Oncol 19:980-91, 2001

TMUGS: Levels of Evidence

<u>Level</u>	<u>Definition</u>
I	Prospective, Marker Primary Objective, Well-powered OR Meta-analysis
II	Prospective, Marker Secondary Objective
III	Retrospective, Outcomes, Multivariate Analysis
IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Marker, No Outcomes

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

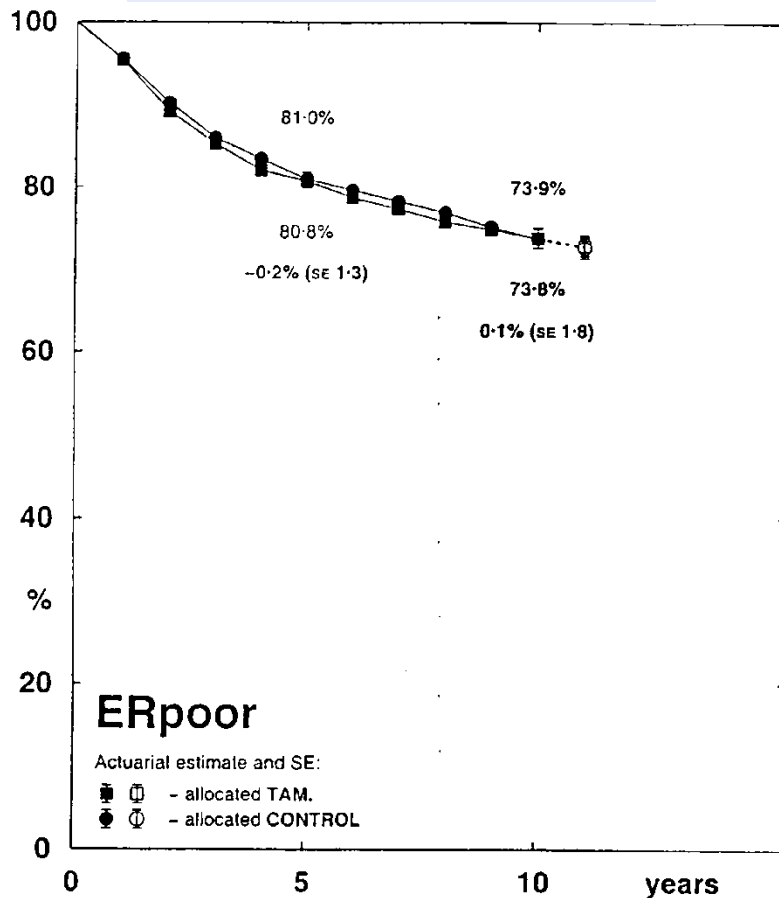
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When is a Marker Clinically Useful?

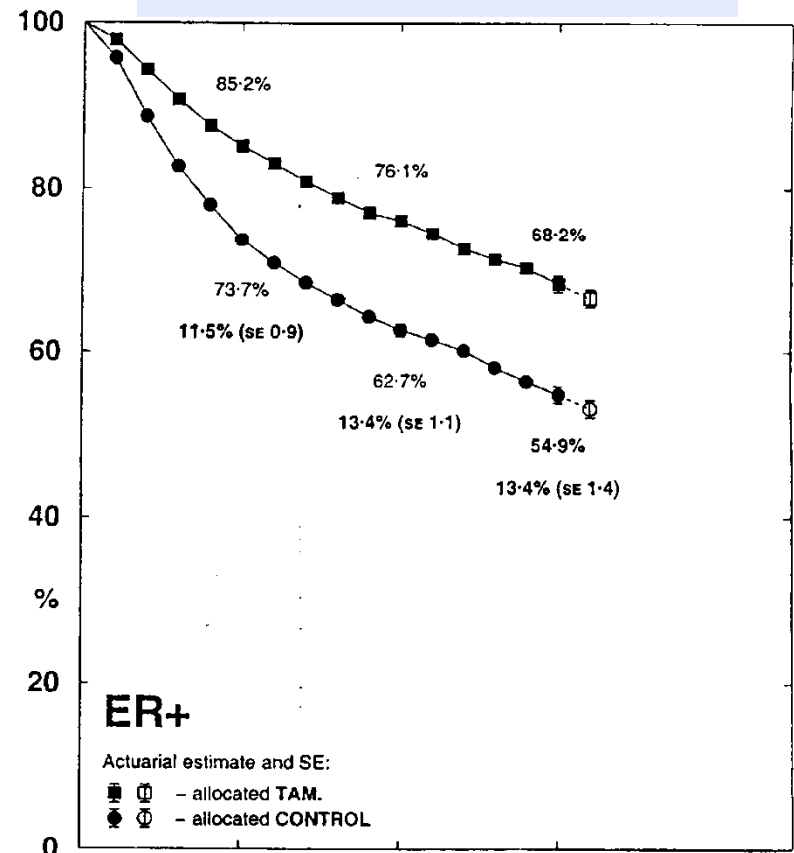
- It is either **prognostic** or **predictive**
- The **magnitude** of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
 - *Greater chance for benefit*
 - *Smaller toxicity risk*
- The estimate of magnitude of effect is **reliable**
 - *Assay is reproducible*
 - *Clinical trial/marker study design is appropriate*
 - *Results are validated in subsequent well-designed studies*

Tamoxifen vs. Not: RECURRENCES

ER POOR



ER POSITIVE



Prognostic Factors: Clinical Utility

- How much added benefit is required to justify treatment?
 - or, “how much benefit are you willing to give up to avoid cost and toxicity?”
 - Depends on toxicity of treatment
 - Depends on perspective of patients

2007 Updated Recommendations for Breast Cancer Tumor Markers

- CA 15-3 and CA 27.29
- Carcinoembryonic Antigen (CEA)
- Estrogen receptors and Progesterone receptors (ER and PgR)
- DNA flow cytometry-based proliferation markers
- Immunohistochemically-based markers of proliferation **NEW!**
- HER2
- p53 as a marker for breast cancer
- Cathepsin D
- Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1) **NEW!**
- Cyclin E **NEW!**
- Proteomic Analysis **NEW!**
- Multiparameter gene expression analysis **NEW!**
- Bone marrow micrometastases **NEW!**
- Circulating Tumor Cells **NEW!**

CA 15-3 and CA 27.29 as Markers for Breast Cancer

Screening	<p>CA 15-3 and CA 27.29 are not recommended to use as screening tests for breast cancer.</p>
Diagnosis/ Staging	<p>CA 15-3 and CA 27.29 are not recommended for diagnosing or staging breast cancer.</p>
Monitoring Response to Therapy	<ul style="list-style-type: none"> ■ For monitoring patients with metastatic disease during active therapy, CA 15-3 and CA 27.29 can be used in conjunction with diagnostic imaging, history, and physical exam. ■ Present data are insufficient to recommend use of CA 15-3 and CA 27.29 <u>alone</u> for monitoring response to treatment. ■ When no readily measurable disease, increasing levels of CA 15-3 and CA 27.29 may be used to indicate treatment failure. ■ Use caution while monitoring during the first 4-6 weeks of a new therapy to avoid spurious early rises.
Surveillance	<p>CA 15-3 and CA 27.29 are not recommended for monitoring patients for recurrence after primary breast cancer therapy.</p>

CEA as a Marker for Breast Cancer

Screening	CEA is not recommended to use as a screening test for breast cancer.
Diagnosis/ Staging	CEA is not recommended for diagnosing or staging breast cancer.
Monitoring Response to Therapy	<ul style="list-style-type: none"> ■ For monitoring patients with metastatic disease during active therapy, CEA can be used in conjunction with diagnostic imaging, history, and physical exam. ■ Present data are insufficient to recommend use of CEA <u>alone</u> for monitoring response to treatment. ■ When no readily measurable disease, an increasing CEA may be used to indicate treatment failure. ■ Use caution while monitoring during the first 4-6 weeks of a new therapy to avoid spurious early rises.
Surveillance	CEA is not recommended to use for routine surveillance of breast cancer.

ER and PgR as Markers for Breast Cancer

- Should be measured on every primary invasive breast cancer.
- May be measured on metastatic lesions.
- Use ER and PgR status to identify patients most likely to benefit from endocrine therapy (both early and metastatic disease).
- For patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.

DNA Flow Cytometry-Based Proliferation Markers for Breast Cancer

■ Present data are insufficient to recommend use of DNA content, S phase, or other flow-cytometry-based markers of proliferation to assign patients to prognostic groupings.

NOT RECOMMENDED	
DNA content	S Phase

Immunohistochemically-based markers of proliferation

■ Present data are insufficient to recommend measurement of Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation to assign patients to prognostic groupings.

NOT RECOMMENDED

Screening	Diagnosis	Staging	Prognosis	Surveillance	Monitoring
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HER2 Evaluation in Breast Cancer

- HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer, to guide selection of trastuzumab.
- Not recommended as prognostic in early breast cancer in absence of systemic therapy.
- Refer to “ASCO/CAP Clinical Practice Guidelines on HER2 Testing in Breast Cancer” regarding analysis of tissue HER2 status. (*Wolff A.C., et al. J Clin Oncol. 25:118-45, 2007*)
- Use IHC (expression) or FISH (amplification) tests to identify HER2 levels and identify benefit (or lack thereof) of trastuzumab therapy, in either adjuvant or metastatic settings.

HER2 Evaluation in Breast Cancer (cont'd)

- If considering chemotherapy for a patient with HER2 positive breast cancer who will not receive trastuzumab, strongly consider an anthracycline (if no contraindications).
- Use of HER2 not recommended to guide use of adjuvant taxane chemotherapy.
- Should not be used to withhold endocrine therapy for a patient with hormone-receptor positive breast cancer, nor should it be used to select one specific type of endocrine therapy over another.
- Measuring circulating extracellular domain of HER2 is not currently recommended for any clinical setting.

p53 as a Marker for Breast Cancer

■ Present data are insufficient to recommend use of *p53* measurements for screening, diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer.

NOT RECOMMENDED

Screening

Diagnosis

Staging

Prognosis

Surveillance

Monitoring

Cathepsin D as a Marker for Breast Cancer

■ Present data are insufficient to recommend use of Cathepsin D measurements for screening, diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer.

NOT RECOMMENDED

Screening

Diagnosis

Staging

Prognosis

Surveillance

Monitoring

uPA and PAI-1 as Markers for Breast Cancer

<p>Prognosis</p>	<p>Can be used to determine prognosis in patients with newly diagnosed, node negative breast cancer using ELISA with a minimum of 300 mg of fresh or frozen breast tissue.</p>
<p>Treatment Planning</p>	<ul style="list-style-type: none"> ■ Low levels of both markers are associated with a sufficiently low risk of recurrence, especially for women with hormone receptor positive cancer who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. ■ CMF-based adjuvant chemotherapy provides substantial benefit, compared to observation alone, in patients with high risk of recurrence as determined by high levels of uPA and PAI-1.

Cyclin E as a Marker for Breast Cancer

■ Present data are insufficient to recommend use of whole length or fragment measurements of Cyclin E for screening, diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer.

NOT RECOMMENDED

Screening

Diagnosis

Staging

Prognosis

Surveillance

Monitoring

Proteomic Analysis as a Marker for Breast Cancer

■ Present data are insufficient to recommend use of proteomic patterns for screening, diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer.

NOT RECOMMENDED

Screening

Diagnosis

Staging

Prognosis

Surveillance

Monitoring

Multiparameter Gene Expression Analysis for Breast Cancer

- Oncotype DX[™] can be used to determine prognosis in newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer who will receive tamoxifen. Indications:
 - To predict risk of recurrence in patients considering treatment with tamoxifen
 - To identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy
 - Patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically CMF) than from tamoxifen
- Conclusions may not be generalizable to hormonal therapies other than tamoxifen, or to other chemotherapy regimens.
- Several other multi-parameter assays have been reported and a few are commercially available, including Mammaprint and the Rotterdam Signature. However, the Committee felt that the precise clinical utility and appropriate application for these other assays were insufficiently defined to recommend their use.

Bone Marrow Micrometastases as a Marker for Breast Cancer

■ Present data are insufficient to recommend use of bone marrow micrometastases for screening, diagnosis, staging, prognosis, surveillance, or monitoring treatment of patients with breast cancer.

NOT RECOMMENDED

Screening

Diagnosis

Staging

Prognosis

Surveillance

Monitoring

Circulating Tumor Cell Assays as a Marker for Breast Cancer

- The measurement of circulating tumor cells (CTC) should not be used to make the diagnosis of breast cancer or to influence any treatment decisions in patients with breast cancer.
- The use of the recently FDA-cleared test for CTC (Cell Search, Veridex) in patients with metastatic breast cancer is not recommended until further validation confirms the clinical value of this test.

NOT RECOMMENDED

Diagnosis

Treatment Planning

Summary	Not Recommended	Recommended
CA 15-3, CA 27.29 (Circulating)	Screening, diagnosis, staging, prognosis, or surveillance. Using alone for monitoring.	For monitoring patients with metastatic disease during active therapy, in conjunction with diagnostic imaging, history, and physical exam.
CEA (Circulating)	Screening, diagnosis, staging, prognosis, or surveillance. Using alone for monitoring.	For monitoring patients with metastatic disease during active therapy, conjunction with diagnostic imaging, history, and physical exam.
ER (tissue), PgR (tissue)	For women with DCIS who are candidates for hormonal therapy.	For diagnosis, treatment planning – on every primary invasive breast cancer and on metastatic lesions if would influence treatment planning.
DNA Flow Cytometry-based proliferation (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
HER2 (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring. Should not be used to withhold or select one specific type of endocrine treatment. Not to Guide use of adjuvant taxane treatment.	For treatment planning, identification of patients who may benefit from trastuzumab and/or from anthracycline-based adjuvant therapy.
Circulating Extracellular Domain of HER2	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	

Summary	Not Recommended	Recommended
P53 (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Cathepsin D (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
uPA and PAI-1 (tissue)	Screening, diagnosis, staging, surveillance, or monitoring.	To determine prognosis. For treatment planning. To guide use of CMF-based adjuvant chemotherapy.
Cyclin E Fragments (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Proteomic Analysis (tissue)	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Multiparameter Gene Expression Analysis (tissue)	Screening, diagnosis, staging, surveillance, or monitoring. Not for prediction of hormonal therapies other than tamoxifen or other chemotherapy regimens.	Oncotype™ for prognosis for patients with node-negative, ER positive breast cancer who will receive tamoxifen. Guiding use of adjuvant tamoxifen and adjuvant chemotherapy (specifically CMF).
Multiparameter Gene Expression Analysis, (tissue) other	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Bone Marrow Micrometastases	Screening, diagnosis, staging, prognosis, surveillance, or monitoring.	
Circulating tumor cell assays	Screening, diagnosis, staging, prognosis, surveillance, predicting or monitoring.	

Breast Cancer Tumor Markers Recommendations by Diagnosis State

Diagnosis State	Recommended	Not Recommended
Newly Diagnosed Primary Invasive	ER/PgR test, HER2 test	(See Summary slides above)
Newly Diagnosed Metastatic Invasive	ER/PgR test, HER2 test, CA 15-3 and CA 27.29 (in conjunction with diagnostic imaging, history and physical exam), CEA (in conjunction with diagnostic imaging, history and physical exam)	Using CA 15-3 and CA 27.29 alone; Using CEA alone
Newly Diagnosed Primary Invasive Node Negative and either ER and/or PR positive	Oncotype DX™, uPA and PAI-1 test	Other multiparameter gene expression assays
Newly Diagnosed Primary Invasive Node Negative and ER and PR negative	uPA and PAI-1 test	(See Summary slides above)
Recurrent Primary Invasive	HER2 test	ER/PgR test; Oncotype DX™; uPA and PAI-test
DCIS	n/a	ER/PgR test

Additional ASCO Resources

The full-text guideline as well as the following tools and resources including the following are available at <http://www.asco.org/guidelines/breasttm>:

- Guideline Summary
- Revisions Table, other summary tables
- Tumor Markers Matrix

- Patient-friendly information on *People Living With Cancer* website for at <http://www.plwc.org>
- ASCO/College of American Pathologists (CAP) Guideline Recommendations for HER2 Testing in Breast Cancer available at <http://www.asco.org/guidelines/her2>
- 2006 Update of the Breast Cancer Follow-up and Management Guideline in the Adjuvant Setting, available at <http://www.asco.org/breastfollowup>
- ASCO CME Curriculum “Cancer Genetics & Cancer Predisposition: The 2nd Edition”



ASCO Guidelines

It is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.