

# ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

	Previous Recommendation (2000)	Current Recommendation (2007)	Changes in 2007
<b>Guideline Title</b>	2000 Update of Recommendations for the Use of Tumor Markers in Breast and Colorectal Cancer: Clinical Practice Guidelines for the Use of Tumor Markers in Breast and Colorectal Cancer (JCO Vol 19, No. 19 (Mar.) 2001)	ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer	
<b>Markers Recommended in 2000</b>			
<b>Estrogen receptors and progesterone receptors (ER/PgR)</b>	<p>Estrogen and progesterone receptors are recommended to be measured on every primary breast cancer and may be measured on metastatic lesions if the results would influence treatment planning.</p> <p>In both pre- and postmenopausal patients, steroid hormone receptor status may be used to identify patients most likely to benefit from endocrine forms of adjuvant therapy and therapy for recurrent or metastatic disease.</p>	<p>ER and PgR should be measured on every primary invasive breast cancer and may be measured on metastatic lesions if the results would influence treatment planning.</p> <p>In both pre- and post-menopausal patients, steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine forms of therapy in both the early breast cancer and metastatic disease settings.</p>	Changed diagnoses likely to benefit from recurrent or metastatic to <i>early breast cancer</i> and metastatic disease settings
<b>ER/PgR, continued</b>		For patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.	DCIS
<b>HER2 evaluation in breast cancer</b>	c-erbB-2 overexpression should be evaluated on every primary breast cancer either at the time of diagnosis or at the time of recurrence. Measures of c-erbB-2 amplification may also be of value.	HER2 expression and/or amplification should be evaluated in every primary invasive breast cancer either at the time of diagnosis or at the time of recurrence, principally to guide selection of trastuzumab in the adjuvant and/or metastatic setting.	Use of the term HER2 (rather than c-erbB-2). Specific reference to trastuzumab in the adjuvant and/or metastatic setting.

<p><b>Methods for measuring HER2</b></p>	<p>Because of the uncertain interchangeability, reproducibility, and clinical utility of different c-erbB-2 tests, it is important that clinical laboratories report not only an estimate c-erbB-2 but also a statement about the test's quality controls, the method, the specific kit or critical reagents, details of the scoring system, a statement regarding reproducibility, sensitivity, and specificity of the assay, and a reference to the clinical validation of the assay or its correlation with a clinically validated c-erbB-2 test.</p>	<p>A separate Expert Panel convened jointly by the College of American Pathologists and the American Society of Clinical Oncology has recently published a set of guideline recommendations regarding analysis of tissue HER2 status, in which it was strongly recommended that laboratories offering this service be accredited on an annual basis.<sup>1</sup> The Update Committee endorses the ASCO-CAP guideline; hence, this topic was not covered further in the present guideline update.</p>	<p>The completion of CAP/ASCO guideline.<sup>ii</sup></p>
<p><b>HER2 to determine sensitivity to anti-HER2-based therapy</b></p>	<p>High levels of c-erbB-2 expression or c-erbB-2 amplification can be used to identify patients for whom trastuzumab may be of benefit for the treatment of metastatic, recurrent, and/or treatment-refractory unresectable locally advanced breast cancer.</p>	<p>High levels of tissue HER2 expression or HER2 gene amplification should be used to identify patients for whom trastuzumab may be of benefit for treatment of breast cancer in the adjuvant or metastatic disease settings.</p>	<p>Slight changes:</p> <ul style="list-style-type: none"> <li>• Recommendation for use of this marker is stronger.</li> <li>• Diagnosis state narrowed to adjuvant or metastatic disease settings.</li> </ul>
<p><b>Utility of HER2 for predicting response to specific chemotherapeutic agents</b></p>	<p>The question of whether <i>c-erbB-2</i> overexpression affects the relative benefits of adjuvant cyclophosphamide methotrexate, and fluorouracil chemotherapy remains open, and the update committee cannot make a definitive practice recommendation at present.</p> <p>High levels of <i>c-erbB-2</i>, as determined by immunohistochemistry, may identify patients who particularly benefit from anthracycline-based therapy, but levels of <i>c-erbB-2</i> expression should not be used to exclude patients from anthracycline treatment.</p>	<p>Level II evidence (prospective therapeutic trials in which marker utility is a secondary study objective) suggests that overexpression of HER2 (3+ by protein or &gt; 2.0 FISH ratio by gene amplification) identifies patients who have greater benefit from anthracycline-based adjuvant therapy. If a clinician is considering chemotherapy for a patient with HER2 positive breast cancer, it is recommended that an anthracycline be strongly considered, assuming there are no contraindications to anthracycline therapy. In the context of trastuzumab therapy, there is Level I evidence (single, high-powered, prospective, randomized controlled trials specifically designed to test the marker or a meta-analyses of well-designed studies) that a non-anthracycline regimen may produce similar outcomes. At present, the Update Committee does not recommend that HER2 be used to guide use of taxane chemotherapy in the adjuvant setting.</p>	<ul style="list-style-type: none"> <li>• 2007 recommendation addresses evidence on anthracycline therapy.</li> <li>• Full-text guideline addresses CMF.</li> <li>• The taxane recommendation has not changed.</li> </ul>

<b>New Markers Recommended in 2007 (in selected applications)</b>	
<b>uPA and PAI as a marker for breast cancer</b>	<p>uPA/PAI-1 measured by ELISAs on a minimum of 300 mg of fresh or frozen breast cancer tissue may be used for the determination of prognosis in patients with newly diagnosed, node negative breast cancer. IHC for these markers is not accurate, and the prognostic value of ELISA using smaller tissue specimens has not been validated. Low levels of both markers are associated with a sufficiently low risk of recurrence, especially in hormone receptor positive women who will receive adjuvant endocrine therapy, that chemotherapy will only contribute minimal additional benefit. Furthermore, 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.</p>
<b>Multiparameter gene expression analysis for breast cancer</b>	<p>In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the <i>Oncotype DX™</i> assay can be used to predict the risk of recurrence in patients treated with tamoxifen. <i>Oncotype DX™</i> 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 (C)MF) 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.</p>
<b>New Markers Not Recommended in 2007</b>	
<b>Ki67, Cyclin D, Cyclin E, p27, p21, thymidine kinase, topoisomerase II, or other markers of proliferation</b>	<p>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.</p>
<b>Cyclin E fragments as markers for breast cancer</b>	<p>Present data are insufficient to recommend use of whole length or fragment measurements of cyclin E for management of patients with breast cancer.</p>
<b>Proteomic analysis for breast cancer</b>	<p>Present data are insufficient to recommend use of proteomic patterns for management of patients with breast cancer.</p>
<b>Bone marrow micrometastases as markers for breast cancer</b>	<p>Present data are insufficient to recommend assessment of bone marrow micrometastases for management of patients with breast cancer.</p>
<b>Circulating tumor cell assays as markers for breast cancer</b>	<p>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. Similarly, the use of the recently FDA-cleared test for CTC (Cell Search, Veridex) in patients with metastatic breast cancer cannot be recommended until further validation confirms the clinical value of this test.</p>

<b>Recommended Tumor Markers– No Change From 2000 (in selected applications)</b>	
<b>CA 15-3 and CA 27.29 to contribute to decisions regarding therapy for metastatic breast cancer</b>	For monitoring patients with metastatic disease during active therapy, CA 27.29 or CA 15-3 can be used in conjunction with diagnostic imaging, history, and physical exam. Present data are insufficient to recommend use of CA 15-3 or CA 27.29 <u>alone</u> for monitoring response to treatment. However, in the absence of readily measurable disease, an increasing CA 15-3 or CA 27.29 may be used to indicate treatment failure. Caution should be used when interpreting a rising CA 27.29 or CA 15-3 level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.
<b>CEA to contribute to decisions regarding therapy for metastatic breast cancer</b>	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. However, in the absence of readily measurable disease, an increasing CEA may be used to indicate treatment failure. Caution should be used when interpreting a rising CEA level during the first 4-6 weeks of a new therapy, since spurious early rises may occur.

<b>Markers Not Recommended– No Change From 2000</b>
CA 15-3 and CA 27.29 as Markers for Breast Cancer as screening, diagnostic, or staging tests or for detecting recurrence.
CEA for screening, diagnosis, staging, or routine surveillance of breast cancer patients after primary therapy.
DNA low cytometry-based proliferation markers
HER2 to define prognosis for early stage breast cancer patients in the absence of systemic therapy
HER2 to determine sensitivity to endocrine therapy
HER2 to predict response to taxane-based therapy
Utility of circulating extracellular domain of HER-2
P53 as a marker for breast cancer
Cathepsin D as a marker for breast cancer

This table is derived from recommendations in the ASCO 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer. This table is a practice tool based on ASCO® practice guidelines and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the practice guidelines and this table are voluntary. The practice guideline and additional information are available at <http://www.asco.org/guidelines/breasttm>.  
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<sup>i</sup> American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor 2 Testing in Breast Cancer, Journal of Clinical Oncology, January 2007, Vol. 25(1).

<sup>ii</sup> Ibid