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Prognostic and predictive factors in early, non-metastatic breast cancer

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INTRODUCTION

The widespread application of adjuvant systemic therapy has reduced mortality from breast cancer in the Western world [1-4]. Unfortunately, many patients are not treated appropriately, with some overtreated (when they would have been cured solely with local therapy) and others undertreated (eg, not treated in the adjuvant setting or treated with drugs that are ultimately not active). It would be of great value to have reliable prognostic factors that could help select those patients most at risk for recurrence. In addition, clinically applicable predictive factors would aid in the personalization of adjuvant therapy by identifying which therapies would be most likely of benefit to patients and which patients would not benefit, potentially sparing them from the unnecessary exposure to potentially toxic and expensive therapies.

This topic will review prognostic and predictive factors that are relevant for patients diagnosed with early, non-metastatic breast cancer. An overview of the treatment of breast cancer and relevant factors for patients with metastatic breast cancer is discussed separately.

- (See "[Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer](#)".)
- (See "[Overview of the approach to metastatic breast cancer](#)".)

DEFINITIONS OF PREDICTIVE AND PROGNOSTIC FACTORS

The field of marker discovery in oncology is evolving rapidly, driven by the better understanding of tumor biology and knowledge of the human genome. However, only a small proportion of markers have ultimately proven to be clinically useful.

By definition, a **prognostic** factor is capable of providing information on clinical outcome at the time of diagnosis, independent of therapy. Such markers are usually indicators of growth, invasion, and metastatic potential [5,6]. By contrast, a **predictive** factor is capable of providing information on the likelihood of response to a given therapeutic modality. Such markers are either within the target of the treatment or serve as modulators or epiphenomena related to expression and/or function of the target. Although they can be separately classified, several factors in breast cancer are both prognostic and predictive (eg, the presence of overexpression of the human epidermal growth factor receptor 2 [HER2]).

Markers that are either predictive or prognostic must demonstrate three factors to be of clinical use [7,8]:

- **Analytical validity** – Analytical validity refers to the technical aspects of a test, including accuracy, reproducibility, dependence of pre-analytical issues (eg, the Biospecimen Reporting for Improved Study Quality [BRISQ] recommendations for biospecimens [9]), and reliability.
- **Clinical validity** – Clinical validity is the ability of a factor to separate a population of interest into two or more subgroups that differ in biologic or clinical outcomes. However, clinical validity does not imply that a factor should be used in direct patient care.
- **Clinical utility** – Clinical utility implies that a factor is useful for patient care. A factor has clinical utility based on evidence that it impacts outcomes when compared with clinical use without it. Clinical utility requires an assumption of a specific use or context in which the factor is relevant (eg, determination of prognosis in patients with pathologically node-negative cancer).

Although high-quality data are preferred in determining clinical utility of a proposed prognostic factor [10], it is now generally agreed that sufficient evidence to support the clinical utility of a proposed marker can be obtained by a retrospective study of prospectively collected material, ideally from randomized clinical trials [11]. This is a time- and cost-effective strategy, compared with the previous requirement of a new trial with the marker as the primary endpoint, which will hopefully yield more promising results.

In addition, a useful prognostic factor in breast cancer should have the following characteristics [12]:

- It provides significant and independent prognostic value, validated by clinical testing
- Its determination must be feasible, reproducible, and widely available, with quality control
- The results should be readily interpretable by the clinician
- Measurement must not consume tissue needed for other tests, particularly routine histopathologic evaluation

PREDICTIVE FACTORS

Factors that may enable personalization of adjuvant treatment recommendations are of utmost importance because they would ideally allow for the selection of patients for a particular therapy while sparing others from potentially ineffective therapies. Unfortunately, the identification of clinically useful predictive markers has not been as successful as the identification of prognostic ones. For example, factors traditionally used by many clinicians for the selection of adjuvant therapy were analyzed in a meta-analysis that included over 100,000 patients involved in 123 randomized controlled trials [1]. The report concluded that the relative benefit of adjuvant chemotherapy is independent of age, estrogen receptor (ER) status, grade, tumor size, nodal involvement, and use of adjuvant [tamoxifen](#).

The most well-established predictive markers in early breast cancer thus far are the ER (for endocrine therapy) and human epidermal growth factor receptor 2 (for HER2-directed therapy). These are discussed below. Data supporting the predictive role of the Oncotype DX Recurrence Score (RS) in the choice of who should undergo adjuvant chemotherapy (though not what type of therapy they should receive) are discussed elsewhere. (See "[Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer](#)", section on 'Recurrence Score'.)

ER predicting response to endocrine therapy — Estrogen receptor (ER) expression predicts patients who will benefit from endocrine therapy. Although patients with progesterone receptor (PR)-positive tumors also have better outcomes when treated with endocrine therapy, PR status is heavily dependent on ER [2]. Therefore, it does not appear that PR has independently predictive value, especially when the ER status is known [2]. *ESR1* mutations are an adverse predictive factor for response to endocrine therapy in the metastatic setting, as discussed elsewhere. (See "[Mechanisms of action of selective estrogen receptor modulators and down-regulators](#)", section on 'ESR1 gene mutations'.)

The predictive value of ER is clearly demonstrated by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of randomized trials of adjuvant [tamoxifen](#) [2]. In patients with ER-positive disease, tamoxifen significantly reduced the risk of recurrence by 39

percent (rate ratio 0.61) and death by 30 percent (rate ratio 0.696) throughout 15 years of follow-up. The benefit was independent of PR status, age, nodal status, or use of adjuvant chemotherapy. By contrast, tamoxifen had no impact on relapse or survival rates among patients with ER-negative breast cancer.

Whether ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists improves breast cancer outcomes for women with breast cancer is not entirely clear, though there is a more established role for its use in subsets of patients with high-risk, hormone receptor-positive rather than hormone receptor-negative disease [13-17] (see ["Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive breast cancer"](#), section on ["Ovarian suppression plus endocrine therapy"](#)). Any potential therapeutic role for GnRH agonists in hormone receptor-negative breast cancer requires further investigation.

In keeping with American Society of Clinical Oncology (ASCO) guidelines, ER/PR analysis should be performed routinely in all invasive breast cancers [18]. Unfortunately, reproducibility of immunohistochemistry measurements of ER is an issue, with reports of moderate interobserver and interlaboratory concordance for strongly positive tumors, but lower concordance for weakly ER-positive tumors [19]. (See ["Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy"](#) and ["Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer"](#) and ["Treatment for hormone receptor-positive, HER2-negative advanced breast cancer"](#).)

HER2 predicting response to HER2-directed therapy — Following the introduction of [trastuzumab](#), human epidermal growth factor receptor 2 (HER2) is mainly used as a predictive factor, identifying those patients who might benefit from treatments that target HER2, both in the adjuvant and metastatic disease settings. The predictive value of HER2 is evident in all major adjuvant [20-22] and metastatic [23-25] trials of HER2-directed therapies.

Guidelines for HER2 testing from a joint ASCO/College of American Pathologists (CAP) consensus panel [26], the data on HER2 status, and treatment of HER2-positive breast cancer are covered separately. (See ["HER2 and predicting response to therapy in breast cancer"](#), section on ["Testing for HER2 expression"](#) and ["Adjuvant systemic therapy for HER2-positive breast cancer"](#) and ["Systemic treatment for HER2-positive metastatic breast cancer"](#).)

Although HER2 overexpression is an established tool for determining response to HER2-directed therapies, some evidence suggests its limitations. For example, the intrinsic subtype may identify HER2-positive tumors that are less likely to respond to HER2-directed therapy. In a study of almost 1400 tumor samples from patients with clinically identified HER2-positive disease (either by immunohistochemistry or fluorescent in situ hybridization), those with basal-like

intrinsic subtype did not experience improved recurrence-free survival with the addition of [trastuzumab](#) (hazard ratio 1.06, 95% CI 0.53-2.13) [27]. Although intrinsic subtype cannot replace conventional histopathologic evaluation of HER2 status, it may identify a subset of HER2-positive, basal-like cancers for which alternative treatment strategies may be appropriate.

Gene expression profiles in predicting response to chemotherapy in hormone receptor-positive/HER2 negative cancers — The decision of whether to recommend adjuvant chemotherapy should be based on anatomic prognoses (nodal status, tumor size) and biology of the tumor. Patients with ER-, PR-, and HER2-negative cancers should in general receive adjuvant chemotherapy, especially if they have positive lymph nodes or tumors >1 cm.

The National Comprehensive Cancer Network notes that although several **prognostic** assays are available to estimate recurrence risk (eg, Oncotype DX RS, EndoPredict, Predictor Analysis of Microarray 50 [PAM50], the Breast Cancer Index, and the Amsterdam 70-gene profile [MammaPrint]), only the RS has been validated for **predicting** the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence [28].

The use of gene expression profiles in deciding whether to use chemotherapy in hormone receptor-positive, HER2-negative disease is discussed in detail elsewhere. (See "[Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer](#)", section on 'Node-negative disease'.)

Tumor infiltrating lymphocytes — Observational analyses have demonstrated a correlation between the extent of lymphocytic infiltration in the tumor or surrounding stroma, referred to as tumor-infiltrating lymphocytes (TILs), and the likelihood of achieving a pathologic complete response with neoadjuvant chemotherapy (NACT), particularly in HER2-negative and triple negative breast cancers [29]. This is discussed in more detail elsewhere. (See "[Neoadjuvant therapy for patients with HER2-positive breast cancer](#)", section on 'Tumor prognostic features'.)

PROGNOSTIC FACTORS IN ROUTINE CLINICAL USE

Approach to use of prognostic markers — For women with newly diagnosed, non-metastatic breast cancer, we routinely utilize the following clinical factors to help determine prognosis:

- Age and race (see '[Patient features](#)' below)
- Pathologic factors, including tumor stage (see '[Pathologic factors](#)' below)
- Tissue markers, including hormone receptor expression and/or human epidermal growth factor receptor 2 (HER2) overexpression (see '[Receptor status](#)' below and '[ER predicting](#)

[response to endocrine therapy](#)' above and ['HER2 predicting response to HER2-directed therapy'](#) above)

Beyond clinical factors, gene expression profiling is increasingly utilized in selected patients. Assays that are in clinical use, as well as those that are under investigation, are discussed elsewhere. (See ["Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer"](#), section on ["Node-negative disease"](#).)

There is overlap between prognostic markers, but some still retain independent variables (eg, estrogen receptor [ER], grade, Oncotype DX Recurrence Score [RS], Ki-67).

Patient features — Both younger and older age at diagnosis have been associated with a worse prognosis [30]. However, contemporary studies suggest that recurrences among young women diagnosed with breast cancer have become less frequent over time [31].

Differences exist on the impact of age among breast cancer subtypes. For example, for patients with HER2-positive breast cancer, age is not associated with early relapse or survival, with or without [trastuzumab](#) treatment [32].

- **Age** – Overall, age alone should not be a factor in whether a patient should or should not receive specific types of local or systemic therapies.

The impact of age on prognosis is demonstrated in the following studies:

- Patients age <35 years have a worse overall survival (OS) and recurrence-free survival [33]. For example, in one study five-year survival rates for women <35 years were 75 percent, versus 84 to 88 percent in women 35 to 69 years [34]. These patients generally present with a later stage, have ER-negative disease in a higher proportion, and receive more aggressive treatment. However, even after adjustment for stage, tumor characteristics (grade, ER status), and treatment, patients in this age group experience a relative increase in breast cancer mortality of at least 70 percent [34], indicating a more aggressive tumor biology in these patients [35].
- Age may be of greater prognostic significance in patients with luminal cancers than in other types of breast cancer. In a study of approximately 17,500 women with stage I to III breast cancer, women ≤ 40 years of age at diagnosis had increased breast cancer mortality relative to older patients (hazard ratio [HR] 1.4, 95% CI 1.2-1.7), with the most significant increases observed in patients with luminal A and B cancers, and no differences seen in patients with HER2 subtypes [36].

- Several population-based studies and randomized trials demonstrate increased breast cancer mortality in older adult patients (>65 years) [37-39]. This is attributed to a later stage at diagnosis, higher comorbidity, and treatment discrepancies [38]. (See ["Treatment of metastatic breast cancer in older women"](#).)
- **Menopausal status** – Among premenopausal patients who received adjuvant chemotherapy, chemotherapy-induced amenorrhea and lack of resumption of menstrual cycles after chemotherapy is associated with improved survival, after controlling for standard prognostic variables, particularly for hormone receptor-positive disease [40].
- **Race** – Racial disparities in breast cancer outcomes may be due in part to socioeconomic reasons [41], but may also relate to a more aggressive tumor biology among African Americans. However, there is no evidence that African American women should receive different chemotherapy regimens than women of other races with the same biologic subset of breast cancer.

In a retrospective cohort study with over 23,000 participants with triple-negative breast cancer, African American patients had lower odds of receiving surgery (odds ratio [OR], 0.69) and chemotherapy (OR, 0.89) after adjustment for sociodemographic, clinicopathologic, and county-level factors [42]. The HR of breast cancer mortality was 1.28 for African American individuals after adjustment for sociodemographic factors.

Studies have also suggested more aggressive biology in tumors occurring in African American patients. In a retrospective study of 280,000 women with non-metastatic breast cancer showed that although African American women were more likely to receive neoadjuvant chemotherapy than White women, they were less likely to experience a pathologic complete response (pCR) for triple-negative and HER2-positive breast cancers [43]. Evidence also suggests that African American women are more often diagnosed with the biologically aggressive basal-like subtype of breast cancer [44,45].

- **Smoking** – Cigarette smoking, both before and after breast cancer diagnosis, has been linked to increased breast cancer mortality. In a study including almost 21,000 women diagnosed with non-metastatic breast cancer, during a median follow-up of 12 years, approximately 2900 patients died of breast cancer [46]. Patients who smoked actively during the year prior to their breast cancer diagnosis were more likely than never-smokers to die of breast cancer (HR 1.25, 95% CI 1.13-1.37). Furthermore, the 10 percent of women who continued to smoke after diagnosis were more likely than never-smokers to die of breast cancer (HR 1.72, 95% CI 1.13-2.60). When compared with women who continued to smoke after diagnosis, those who quit smoking had lower breast cancer mortality (HR

0.67, 95% CI 0.38-1.19), suggesting that among women who smoke, smoking cessation may improve outcomes after a diagnosis of breast cancer.

Mammographic features — Screen-detected breast cancers have a better prognosis than those identified by clinical exam [47-49]. This is generally due to the stage of disease at diagnosis, with those tumors detected by screening more likely to be smaller and not involving the regional nodes.

Although breast density on mammogram is a well-recognized risk factor for breast cancer, it is not prognostic for women diagnosed with breast cancer [50]. (See '[Tumor stage](#)' below.)

Whether multifocal (ie, invasive tumors identified within the same breast quadrant) or multicentric (ie, invasive tumors identified in separate breast quadrants) tumors influence prognosis is controversial. While some evidence suggests they are associated with a poor prognosis [51], other data suggest that multifocality does not influence prognosis [52]. Regardless of method of detection (eg, by mammogram, ultrasound, or magnetic resonance imaging), findings of multifocality or multicentricity should not by themselves be included in the decision regarding adjuvant therapy for patients with newly diagnosed, non-metastatic breast cancer.

Pathologic factors

Tumor stage — In general, stage is a prognostic factor. Breast cancer is staged according to tumor size, whether and how many nodes are involved, and whether metastatic disease is present (Tumor, Node, Metastasis [TNM] system (([table 1](#) and [table 2](#) and [table 3](#))).

In validation cohorts of the American Joint Committee on Cancer (AJCC) eighth edition staging system, the five-year disease-free survival (DFS) rates, according to anatomic stage, were as follows: for stage I disease, 98 to 100 percent; for stage II disease, 85 to 98 percent; and for stage III disease, approximately 70 to 95 percent [53]. (See "[Tumor, node, metastasis \(TNM\) staging classification for breast cancer](#)".)

Tumor size — Tumor size (T), defined as the largest diameter of the primary breast tumor, was recognized early as an important prognostic factor in breast cancer [54-56].

Tumor size is correlated with nodal involvement, but the prognostic value of the two factors is independent. In a meta-analysis of 88 trials involving over 62,000 patients with ER-positive breast cancer who were disease-free after five years of scheduled endocrine therapy, the risk of distant recurrence was correlated with the original tumor size over years 5 to 20 [57]. Among those with no involved lymph nodes, the risk of distant recurrence for T1 versus T2 tumors was

13 versus 19 percent, respectively. Among those with one to three involved nodes, the risks among those with T1 versus T2 tumors were 20 versus 26 percent; and among those with four to nine involved nodes, the risks for T1 and T2 tumors were 34 versus 41 percent, respectively. In triple-negative tumors, the correlation of tumor size with nodal status and with prognosis is much weaker [58]. (See ['Nodal involvement'](#) below.)

The impact of multifocal (ie, invasive tumors identified within the same breast quadrant) or multicentric (ie, invasive tumors identified in separate breast quadrants) tumors on prognosis is controversial, with some evidence that they are associated with a poor prognosis [51] and other data suggesting they do not impact prognosis [52]. The eighth edition TNM staging system does not assign independent value to multifocality or multicentricity and uses the diameter of the largest lesion to assign T stage [53].

Inflammatory breast cancer (IBC, T4d) is a rare but highly aggressive form of breast cancer characterized by a clinical picture of inflammation in the breast and a poor prognosis. The hallmark of diagnosis is made by skin biopsy demonstrating dermal lymphatic invasion. IBC should not be confused with the histologic presence of inflammation or inflammatory cells in a breast cancer, which is considered a good prognostic feature. (See ["Inflammatory breast cancer: Clinical features and treatment"](#) and ['Pathologic factors'](#) above.)

Nodal involvement — Nodal involvement (ie, the number of ipsilateral axillary nodes with metastatic tumor growth) is a strong and independent negative prognostic factor.

Among women with no evidence of metastatic disease (M0), the five-year survival rate for those who present with localized (ie, breast only) versus regional disease (ie, pathologic node involvement) is 99 and 85 percent, respectively [59]. Even small tumors (<2 cm) have a worse prognosis in the presence of pathologic node involvement. In the meta-analysis discussed above including over 62,000 patients with ER-positive breast cancer who were recurrence free after five years of endocrine therapy, the risk of distant recurrence over years 5 to 20 for those with T1 tumors was 13 percent in the absence of lymph node involvement, 20 percent among those with one to three involved lymph nodes, and 34 percent among those with four to nine involved nodes [57].

While lymph node macrometastasis is a well-established independent prognostic factor, the significance of metastatic disease <2 mm (micrometastases, pN1_{mic}) or isolated tumor cells (ITC, pN0_{ITC}) in axillary nodes is less clear. However, the evidence suggests that patients with pN1_{mic} breast cancer have a worse outcome compared with those with node-negative breast cancer while the presence of isolated tumor cells does not influence prognosis. This is demonstrated in the following studies:

- In a prospective cohort study of 3369 patients with breast cancer, patients with pN1_{mic} disease (n = 123) had a significantly lower breast cancer-specific five-year survival compared with N0 patients (80 versus 87 percent) [60]. However, there was no difference in survival among patients with pN0_{ITC} and N0 disease. In addition, the presence of pN1_{mic} and not pN0_{ITC} was associated with a trend towards a worse OS compared with patients with pN0 breast cancer.
- The prognostic impact of micrometastatic nodal involvement was shown in a large meta-analysis of 58 studies [61]. Patients with microscopic pathologic node involvement were at an increased risk of death compared with patients with pN0 disease (pooled HR of death 1.44, 95% CI 1.29-1.62). In addition, this study also suggested there was a negative prognostic impact of occult metastases on survival when identified by the retrospective examination of what were initially determined to be negative sentinel nodes (pooled HR for mortality 1.45, 95% CI 1.11-1.88).
- In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, occult metastasis was an independent prognostic factor for relapse; however, it had no meaningful effect on OS (94.6 versus 95.8 percent) [62].

Metastatic disease — The presence of metastatic disease is a poor prognostic factor. Women with newly diagnosed breast cancer and evidence of metastatic disease, regardless of whether it was detected clinically or radiographically, should be treated as having metastatic breast cancer. The prognostic factors and the approach to patients with metastatic disease are discussed separately. (See "[Prognostic and predictive factors in metastatic breast cancer](#)" and "[Overview of the approach to metastatic breast cancer](#)" and "[The role of local therapies in metastatic breast cancer](#)".)

Tumor morphology — The most common type is invasive ductal carcinoma (IDC), accounting for greater than 70 percent of all cases, followed by invasive lobular carcinoma (ILC), with a frequency of about 10 percent [63]. ILC has a distinctive biology and clinical behavior compared with IDC, although the prognostic impact of histology appears to vary with time. This was shown in a pooled analysis of over 9000 patients with extended follow-up that reported a 16 percent lower risk of recurrence for ILC compared with IDC during the first six years of follow-up; however, ILC conferred a 54 percent higher risk of relapse after six years [64].

Other subtypes of invasive breast cancer have been described. Tubular, papillary, mucinous, medullary, and adenoid cystic carcinoma have been associated with a good prognosis; by contrast, micropapillary and metaplastic carcinomas appear to confer a worse prognosis. (See "[Pathology of breast cancer](#)".)

Histologic grade — The grade of breast cancer is assigned using the Elston-Ellis grading system, which characterizes the degree of tumor differentiation by the percentage of tubule formation, nuclear pleomorphism, and mitotic activity [65]. (See "[Pathology of breast cancer](#)".)

In the original report, this system was found to be prognostic [65], and this has been independently confirmed by others [66]. For example, in a study including over 2200 operable breast cancer cases, there was a correlation between histologic grade and worsened outcomes, with an HR for worsened breast cancer-specific survival (BCSS) of 1.6 for grade 2 versus 1 cancers (95% CI 1.1-2.5) and 3.9 for grade 3 versus grade 1 cancers (95% CI 2.6-5.8) [66]. The correlation persisted after multivariate adjustment for other prognostic indications, including lymph node involvement, tumor size, and vascular invasion.

Peritumoral lymphovascular invasion — The presence of lymphovascular invasion appears to be a poor prognostic indicator, particularly in higher-grade tumors. This was shown in a cohort study of 1704 patients that did not receive any systemic adjuvant therapy, in which peritumoral lymphovascular invasion (PLVI) was an independent risk factor for local recurrence and death [67].

However, more contemporary reports are less clear about whether PLVI is of independent prognostic value [68,69].

- In a population-based study of more than 15,000 patients, PLVI was significantly associated with other adverse prognostic factors (tumor size, grade, positive nodal status, ductal histology, ER negativity). In the absence of these other factors, PLVI had no effect on survival. At five years, 98 percent of patients without PLVI were alive (versus 94.1 percent for the patients with PLVI) [68].
- In another retrospective analysis of 2754 patients treated in two adjuvant therapy trials, PLVI was associated with worse DFS, but its prognostic value was abrogated by adjuvant endocrine therapy [69].

Taken together, these studies indicate that PLVI has a prognostic value, but its clinical utility remains to be determined.

Ki-67 — The relationship between Ki-67 status and prognosis in early breast cancer has been extensively studied [70]. Despite heterogeneity in clinical trials and Ki-67 assessment methods used, the results of two large meta-analyses are consistent with the independent prognostic value of Ki-67 [71,72]. According to an international working group, Ki-67 has clinical validity but concluded that clinical utility is evident only for prognosis estimation in anatomically favorable estrogen receptor-positive/HER2-negative cancers to identify those who do not need adjuvant

chemotherapy [73]. In this T1-2, N0-1 patient group, the consensus was that Ki-67 ≤ 5 , or ≥ 30 percent, can be used to estimate prognosis. Ki-67 can also be considered in the selection of patients with high-risk hormone receptor-positive, HER2-negative breast cancer for adjuvant [abemaciclib](#), as discussed elsewhere. (See "[Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer](#)", section on '[CDK 4/6 inhibitors for select patients with high risk disease](#)'.)

As an example of available data, one meta-analysis that included 46 studies (and over 12,000 patients) reported that high Ki-67 levels were associated with [71]:

- A higher risk of relapse in both node-positive (HR 1.59, 95% CI 1.35-1.87) and node-negative disease (HR 2.31, 95% CI 1.83-2.92).
- Worse breast cancer survival in node-positive (HR for death 2.33, 95% CI 1.83-2.95) and node-negative disease (HR 2.54, 95% CI 1.65-3.91).

An analysis of samples from randomized controlled trials with central determination of Ki-67 confirmed the independent prognostic value of Ki-67 (multivariate HR 1.05-1.72 for relapse) [70].

Receptor status

Hormone receptors — ER and PR expression are generally associated with improved breast cancer outcomes, at least over the short term. ER should be used to determine if a patient should or should not receive adjuvant endocrine therapy. (See '[ER predicting response to endocrine therapy](#)' above.)

Data suggest that OS, DFS, and time to treatment failure are all positively related to ER and PR levels [74-76]. However, while the annual rate of recurrence for ER-positive cancers is lower in the first five years after initial treatment compared with ER-negative cancers, studies suggest it may be higher with longer-term follow-up [77,78]. For example, in a study of over 4000 patients with operable breast cancer enrolled in International Breast Cancer Study Group clinical trials I to V, patients with ER-positive disease had a lower annual risk of recurrence during the first five years after their initial treatment compared with those with ER-negative disease (9.9 versus 11.5 percent). However, after five years, patients with ER-positive disease had a higher annual risk of recurrence (5 to 10 years: 5.4 versus 3.3 percent; 10 to 15 years: 2.9 versus 1.3 percent; 15 to 20 years: 2.8 versus 1.2 percent) [78]. Other data have shown the breast cancer recurrences in women with early-stage, ER-positive breast cancers continue to occur steadily after five years of endocrine therapy to at least 20 years, with the risk of distant recurrences being strongly correlated with the original cancer stage [57]. The long-term recurrence risk of ER-positive

cancers has given rise to interest in extended endocrine therapy courses. (See ["Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer"](#), section on 'Duration of endocrine treatment'.)

ER status is also associated with specific site(s) of metastatic spread. For unclear reasons, ER-positive tumors are more likely to develop clinically apparent metastases in bone, soft tissue, or the reproductive/genital tracts; by contrast, ER-negative tumors more commonly metastasize to brain and liver, sites that are associated with shorter survival [79].

ER-positive tumors are more likely to be histologically well-differentiated [80-82], to have a lower fraction of dividing cells, and to be diploid [83]. They are also less likely to be associated with mutations, loss, or amplification of breast cancer-related genes such as *p53* [84,85], *HER2* [86-88], or *HER1* (the epidermal growth factor receptor [*EGFR*]) [89,90], all of which have been associated with a poorer prognosis. (See ["HER2 and predicting response to therapy in breast cancer"](#), section on 'HER2 status and predicting treatment response'.)

PR appears to be prognostic and independent of ER [91,92]. This was shown in a large population-based cohort study that included over 1000 women with early breast cancer, all of whom underwent primary surgery with curative intent [92]. Absent PR expression was associated with poorer prognosis for OS, BCSS, and DFS, even within the ER-positive, lymph node-negative group (HR for BCSS 3.17, 95% CI 1.43-7.01), and was not influenced by endocrine therapy. These data are supported by the finding that patients with ER-positive, PR-negative disease have a more aggressive subtype of hormone receptor-positive breast cancer [92], and often fall into the luminal B subtype of tumors [93].

In general, tumors that are singly hormone receptor positive (ie, ER positive and PR negative, or PR positive and ER negative) appear to have a worse prognosis than those that are ER positive and PR positive. [94].

HER2 overexpression — Assay for human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification is a routine part of the diagnostic work-up on all primary breast cancers [18,26]. HER2 overexpression contends an unfavorable prognosis, particularly if patients are not treated with chemotherapy and HER2-directed agents. However, the added value of this information in clinical practice is questionable because outcomes are heavily influenced by the administration of therapy [18]. In women with breast cancer, the main benefit of HER2 testing is its predictive value for appropriate candidates who should receive HER2-directed agents. (See ["HER2 and predicting response to therapy in breast cancer"](#) and ['Predictive factors'](#) above.)

In the absence of systemic therapy, HER2 overexpression is a marker of poor prognosis in patients with pathologically node-positive [87,95] and node-negative breast cancer [96]. In addition, data suggest that HER2 retains prognostic value even in the presence of small tumors ≤ 1 cm.

Tumor infiltrating lymphocytes — Tumor-infiltrating lymphocytes (TILs) have been shown to be an adverse prognostic factor for survival in luminal-HER2-negative breast cancer [29]. Guidelines for standardized assessment of TILs have been published [97].

Gene expression-based and clinical prognostic profiles — The emergence of genomics (which evaluate DNA) and transcriptomics (which evaluate RNA) techniques and the ability to simultaneously measure the expression of thousands of genes has led to the identification of biology-based prognostic profiles, several of which have been validated and are in clinical use, for example the Oncotype Dx Recurrence Score (RS). While prognostic contributions of specific genes in the RS (or their combinations) are unknown, the panel overall is better at prognostication than clinicopathologic features such as grade or Ki-67. The RS and other gene-expression based profiles are discussed in detail elsewhere. (See "[Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer](#)".)

The field is under development with intensive research efforts ongoing, aiming to define the clinical utility and the indications for each of the prognostic profiles in routine practice [11]. Furthermore, a next generation of molecular profiles should be anticipated with the implementation of advances in large-scale sequencing of tumor genomes [98-103]. (See '[Global genomic profiling](#)' below.)

Additionally, clinical risk prediction calculators exist that allow the user to input patient and tumor characteristics and garner prognostic information. As examples:

- The ESTIMATE online tool was derived from a registry of over 264,000 women with invasive, non-metastatic breast cancer, and estimates the residual cumulative risk of breast cancer specific mortality (BCSM) and non-BCSM to year 20, after any specified time from initial diagnosis [104,105].
- The CTS5 categorizes patients who have been disease free for five years into low, intermediate, and high risk and estimates an absolute risk for developing distant recurrences between 5 and 10 years [106], although one study notes that it overestimates the risk in high-risk patients [107].
- The UK [PREDICT](#) tool estimates risks of recurrence based on clinical features and predicts benefit of therapy, as discussed elsewhere. (See "[Deciding when to use adjuvant](#)"

[chemotherapy for hormone receptor-positive, HER2-negative breast cancer", section on 'Clinical features that guide the use of chemotherapy'.\)](#)

OTHER PROGNOSTIC FACTORS

Global genomic profiling — The cellular and molecular heterogeneity of breast cancer and the large number of genes involved in controlling cell growth, death, and differentiation emphasize the importance of studying multiple genetic alterations in concert. Global gene expression profiling allows the simultaneous measurement of the activity (expression) of thousands of genes in a breast cancer cell, but is not routinely applied in clinical care. Future applications of high-throughput examinations will doubtless take the same approach to proteins (proteomics), genome-wide germline variability (single-nucleotide polymorphisms), or cellular metabolism (metabolomics).

Gene expression studies have identified several distinct breast cancer subtypes that differ markedly in prognosis and in the therapeutic targets they express [103,108-115]. The list of genes that differentiates these subtypes is called the intrinsic list and is made up of several clusters of genes relating to estrogen receptor (ER) expression (the luminal cluster), human epidermal growth factor receptor 2 (HER2) expression, and a unique cluster of genes called the basal cluster. Others are being identified as investigators continue to study the genomic data derived from breast cancer specimens.

The intrinsic subtypes segregate into two groups that correspond to expression of hormone receptor-related genes. This segregation is consistent with both the literature and clinical experience that show ER-positive and ER-negative cancers define biologically distinct phenotypes that may derive from different progenitor cells [112]. However, the analytical validity and clinical utility of determining the intrinsic subtypes depend on the specific assay and the precise clinical use in which the assay will be applied. The Predictor Analysis of Microarray 50 (PAM50) assesses intrinsic subtype [116]. (See "[Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer", section on 'PAM50 risk of recurrence score'.\)](#)

A brief review of the genomic profiles in breast cancer is covered below.

Luminal subtypes — Luminal A- and luminal B-expressed genes are associated with luminal epithelial cells of normal breast tissue and overlap with ER-positive breast cancers defined by clinical assays.

The name "luminal" derives from similarity in gene expression between these tumors and the luminal epithelium of the breast; they typically express luminal cytokeratins 8 and 18. These are the most common subtypes, make up the majority of ER-positive breast cancer, and are characterized by expression of ER, progesterone receptor (PR), and other genes associated with ER activation. Despite comprising the majority of ER-positive breast cancers, the luminal A and luminal B subtypes have some important molecular and prognostic distinctions.

- Luminal A tumors, which probably make up about 40 percent of all breast cancers, usually have high expression of ER-related genes, low expression of the HER2 cluster of genes, and low expression of proliferation-related genes [117,118]. Luminal A tumors are the most common subtype and, in general, carry the best prognosis of all breast cancer subtypes [112-114,119-121]. Despite this, most breast cancer deaths are from ER-positive, HER2-negative disease, and racial disparity in outcome is particularly found in this subset [122].
- The less common (approximately 20 percent) luminal B tumors have relatively lower (although still present) expression of ER-related genes, variable expression of the HER2 cluster, and higher expression of the proliferation cluster. Luminal B tumors carry a worse prognosis than luminal A tumors [120]. Most luminal B cancers have high recurrence scores as assessed by the 21-gene recurrence score assay and poor 70-gene prognostic signatures [117].

HER2-enriched — The human epidermal growth factor receptor 2 (HER2)-enriched subtype (previously the HER2-positive/ER-negative subtype) makes up about 10 to 15 percent of breast cancers and is characterized by high expression of the HER2 and proliferation gene clusters and low expression of the luminal and basal clusters. For this reason, these tumors are most often negative for ER and PR, and positive for HER2.

However, the HER2-enriched subtype is not synonymous with clinically HER2-positive breast cancer. While clinical HER2-positive breast cancers are typically HER2 enriched, studies have shown that a large percentage of HER2-positive tumors are not HER2 enriched [123-126]. While the impact of HER2 targeting in these tumors is being studied, it is possible that at least some represent *HER2* mutations or other events in the HER2 signaling pathway producing a similar expression phenotype without *HER2* amplification or protein overexpression. Further discussion of the HER2-enriched subtype, and its utility as a predictive factor for neoadjuvant HER2-directed therapy, is discussed elsewhere. (See "[Neoadjuvant therapy for patients with HER2-positive breast cancer](#)", section on 'Tumor prognostic features'.)

ER-negative subtypes — The estrogen receptor (ER)-negative genomic profile includes multiple subtypes, such as basal-like, claudin-low [108], interferon-rich [127], and mesenchymal and luminal androgen receptor subtypes [128], among others. Most of these fall under the category of triple-negative breast cancers because they are also PR negative and HER2 negative.

Of these, the best described is the claudin-low subtype. The basal-like subtype, so-called because of some similarity in gene expression to that of the basal epithelial cells of normal breast tissue, makes up about 15 to 20 percent of breast cancers. It is characterized by low expression of the luminal and HER2 gene clusters. For this reason, these tumors are typically ER negative, PR negative, and HER2 negative on clinical assays, which has prompted the nickname "triple-negative breast cancers" to describe them. However, while most triple-negative breast cancers are basal-like, and most basal-like tumors are triple-negative, there is significant discordance (up to 30 percent) between these two classification methods that must be kept in mind when evaluating studies focused upon basal-like breast cancer.

Triple-negative breast cancer is reviewed in detail separately. (See ["ER/PR negative, HER2-negative \(triple-negative\) breast cancer"](#).)

Markers of proliferation — The proliferative rate of breast cancer appears to be prognostic. There are a variety of methods used to assess this, including mitotic counts, S-phase fractions as determined by flow cytometry, and immunohistochemistry using monoclonal antibodies to antigens found in proliferating cells. However, the most commonly studied method is to perform immunohistochemistry of the nuclear antigen Ki-67. (See ["Ki-67"](#) above.)

Others are discussed in the sections below.

Urokinase plasminogen activator system — Urokinase plasminogen activator (uPA) is a serine protease with an important role in cancer invasion and metastases [129]. When bound to its receptor (uPAR), uPA converts plasminogen into plasmin and mediates degradation of the extracellular matrix during tumor cell invasion. High levels of uPA and uPAR, as well as the plasminogen activator inhibitor PAI-1, have been associated with shorter survival in women with breast cancer [130]; by contrast, high levels of PAI-2 appear to be associated with better outcomes [129,131-133]. American Society of Clinical Oncology guidelines include the option for using uPA and PAI-1 to guide decisions on adjuvant systemic therapy for patients with node-negative, hormone receptor-positive, HER2-negative disease, but not for patients with HER2-positive or triple-negative disease [134].

A prospective trial involving almost 650 women with node-negative breast cancer was performed to evaluate the prognostic ability of cytosolic uPA and/or PAI-1 levels [135,136]. The

results were then used to determine whether or not adjuvant chemotherapy was administered. At a median follow-up of 9.4 years, the following results were noted:

- Among women who were not treated with systemic chemotherapy (n = 409), the 10-year recurrence rate was significantly lower for those with low expression of both uPA and PAI-1 (13 versus 23 percent) [136].
- Among women with high expression of either protein, adjuvant chemotherapy resulted in a lower risk of disease recurrence compared with observation only (21 versus 28 percent; hazard ratio 0.74, 95% CI 0.44-1.27) [136].

Despite these results, the enthusiasm for the use of uPA and PAI-1 as prognostic indicators in the United States is tempered by issues involving the assay methodology:

- The analysis requires a large volume of tissue obtained at the time of surgery rather than paraffin-embedded blocks.
- Tissue must be frozen in order to proceed with enzyme-linked immunosorbent assay (ELISA), but the equipment and supplies to allow for freezing and storage are not generally available.

There are some data suggesting analysis can be performed on fresh tissue obtained at the time of core biopsy [137]. In addition, preliminary data suggest that immunohistochemistry staining for uPA and PAI-1 can be done using cryostat specimens [138]. However, further validation of these newer methods to analyze for both of these factors is required.

Other markers of invasion and metastasis — Many other markers of invasion and metastatic potential have been proposed and/or studied in retrospective reports. For example, the prognostic role of p53 abnormalities in breast cancer has been evaluated. While the predictive value of somatic tumor protein p53 (*TP53*) is unclear, and we do not analyze tumors for this genetic alteration [18], data suggest that patients with germline mutations in *TP53* have a worse prognosis compared with other patients, independent of tumor size, node status, and hormone receptor status [139-141]. (See "[Overview of hereditary breast and ovarian cancer syndromes](#)", [section on 'TP53 \(Li-Fraumeni syndrome\)'](#).)

Others include measurement of the soluble extracellular domain of HER2 in serum, nm23, E-cadherin, the catenins, tissue inhibitors of metalloproteinases, prostate-specific antigen, tissue factor, and osteopontin [142-151]. Allelic loss, microsatellite instability, or methylation silencing of tumor suppressor genes may also provide prognostic information [152-155]. All of these

potential indicators of prognosis require further evaluation and validation. None should be considered routine in the evaluation of breast cancer specimens.

Disseminated and circulating tumor cells — Disseminated and/or circulating tumor cells (DTCs/CTCs) are likely to play an important role in the development of distant metastases in breast cancer. In contrast to clinically overt metastases, which represent a relatively late event in the natural history of solid tumors such as breast cancer, circulation of tumor cells in the bloodstream and/or their identification in bone marrow can be detected much earlier and are thought to be an early indicator of tumor spread [156,157]. While DTCs/CTCs both carry a poor prognosis [158-169], many patients with detectable DTCs/CTCs will not develop advanced breast cancer [165-167,170,171]. We do not routinely assess for DTCs/CTCs in the absence of high-quality data suggesting that this information improves outcomes in early breast cancer [18,170,172-177].

The investigative use of CTCs to predict benefit from adjuvant chemotherapy is discussed elsewhere. (See "[Deciding when to use adjuvant chemotherapy for hormone receptor-positive, HER2-negative breast cancer](#)", section on 'Investigational assays'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: Breast cancer](#)".)

SUMMARY AND RECOMMENDATIONS

- **Terminology**
 - By definition, a **prognostic** factor is capable of providing information on clinical outcome at the time of diagnosis, independent or in the absence of further therapy. By contrast, a **predictive** factor is capable of providing information on the likelihood of response to a given therapeutic modality. Although they can be separately classified, several factors in breast cancer are both prognostic and predictive (eg, the presence of overexpression of the human epidermal growth factor receptor 2 [HER2]). (See '[Introduction](#)' above and '[Definitions of predictive and prognostic factors](#)' above.)
 - Potential markers must demonstrate three factors to be of clinical use: analytical validity, clinical validity, and clinical utility. In addition, they should be able to provide significant and independent value; be determined feasibly, reproducibly, and widely

available; be readily interpretable; and must not consume tissue needed for other tests. (See ['Definitions of predictive and prognostic factors'](#) above.)

- **Predictive factors**

- All women with newly diagnosed, non-metastatic breast cancer should undergo tumor testing for hormone receptor expression and HER2 overexpression. In addition to being prognostic, this information can be used to tailor individualized plans for adjuvant therapy. (See ['Receptor status'](#) above and ['ER predicting response to endocrine therapy'](#) above and ['HER2 predicting response to HER2-directed therapy'](#) above.)
- Gene expression studies have identified several distinct breast cancer subtypes that differ markedly in prognosis. The major clusters are those relating to estrogen receptor expression (the luminal cluster), HER2 expression, and a unique cluster of genes called the basal cluster. Others are being identified as investigators continue to study the genomic data derived from breast cancer specimens.

- **Prognostic factors**

- Both younger and older age at diagnosis is associated with a worse prognosis. In addition, African American women have a worse prognosis compared with White women, even after controlling for disease characteristics at presentation. (See ['Patient features'](#) above.)
- Among pathologic factors, tumor stage (tumor size, nodal status, and whether or not metastatic disease is present) is the most important prognostic indicator. (See ['Pathologic factors'](#) above.)
- The enumeration of circulating tumor cells (CTCs) is prognostic for women with early, non-metastatic breast cancer. However, it is not clear how this information can be used to guide clinical care, and we do not routinely measure CTCs in this population. (See ['Disseminated and circulating tumor cells'](#) above.)

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Topic 782 Version 72.0

GRAPHICS

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA

T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Breast carcinoma TNM clinical prognostic stage groups AJCC UICC 8th edition

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the clinical prognostic stage group is...
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB

				Negative	IB
T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1 ^Δ M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA

				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1 ^Δ M0 T3 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
T2 N1 ^Δ M0 T3 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1 ^Δ M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1 ^Δ M0	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA

T3 N2 M0		Negative	Positive	Positive	IIA		
				Negative	IIIA		
			Negative	Positive	IIIA		
				Negative	IIIB		
T0 N2 M0	G3	Positive	Positive	Positive	IIB		
T1* N2 M0				Negative	IIIA		
T2 N2 M0			Negative	Positive	IIIA		
T3 N1 ^Δ M0				Negative	IIIA		
T3 N2 M0		Negative	Positive	Positive	IIIA		
				Negative	IIIB		
			Negative	Positive	IIIB		
				Negative	IIIC		
T4 N0 M0	G1	Positive	Positive	Positive	IIIA		
T4 N1 ^Δ M0				Negative	IIIB		
T4 N2 M0			Negative	Positive	IIIB		
Any T N3 M0				Negative	IIIB		
			Negative	Positive	Positive	IIIB	
					Negative	IIIB	
			Negative	Positive	Positive	IIIB	
					Negative	IIIC	
	T4 N0 M0		G2	Positive	Positive	Positive	IIIA
	T4 N1 ^Δ M0					Negative	IIIB
T4 N2 M0	Negative	Positive			IIIB		
Any T N3 M0		Negative			IIIB		
		Negative		Positive	Positive	IIIB	
					Negative	IIIB	
		Negative		Positive	Positive	IIIB	
					Negative	IIIC	
T4 N0 M0	G3	Positive	Positive	Positive	IIIB		
T4 N1 ^Δ M0				Negative	IIIB		
T4 N2 M0			Negative	Positive	IIIB		

Any T N3 M0		Negative	Positive	Negative	IIIB
				Positive	IIIB
			Negative	Negative	IIIC
				Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

NOTES:

1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with the clinical prognostic staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (eg, T0 N1, etc) or with breast ductal carcinoma *in situ* (eg, Tis N1, etc), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the clinical prognostic stage group table.
4. The prognostic value of these prognostic stage groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* T1 includes T1mi.

¶ N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Δ N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

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Breast carcinoma TNM pathologic prognostic stage groups AJCC UICC 8th edition

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the pathological prognostic stage group is...
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T0 N1 [¶] M0 T1* N1 [¶] M0 T2 N0 M0	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T2 N1 ^Δ M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

T2 N1 ^Δ M0 T3 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1 ^Δ M0 T3 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1 ^Δ M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1 ^Δ M0 T3 N2 M0	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1 ^Δ M0 T3 N2 M0	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC
T4 N0 M0 T4 N1 ^Δ M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
T4 N0 M0 T4 N1 ^Δ M0 T4 N2 M0 Any T N3 M0	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1 ^Δ M0 T4 N2 M0 Any T N3 M0	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

Any T Any N M1	Any	Any	Any	Any	IV
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NOTES:

1. For cases with lymph node involvement with no evidence of primary tumor (eg, T0 N1, etc) or with breast ductal carcinoma *in situ* (eg, Tis N1, etc), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the pathological prognostic stage group table.
3. The prognostic value of these prognostic stage groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Genomic profile for pathologic prognostic staging

When OncotypeDx score is less than 11...

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the pathological prognostic stage group is...
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

NOTES:

1. Obtaining genomic profiles is NOT required for assigning pathological prognostic stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned pathological prognostic stage group IA.
2. If OncotypeDx is not performed, or if it is performed and the OncotypeDx score is not available, or is 11 or greater for patients with T1-2 N0 M0 HER2-negative, ER-positive cancer, then the prognostic stage group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx is the only multigene panel included to classify pathologic prognostic stage because prospective level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to prognostic stage groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* T1 includes T1mi.

¶ N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Δ N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

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