

# Identification of Patients with Early HR+ HER2– Breast Cancer at High Risk of Recurrence

## Identifizierung von Patientinnen mit HR+, HER2– Brustkrebs im Frühstadium mit hohem Rezidivrisiko



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### ABSTRACT

Breast cancer incidence has increased in the last two decades and, simultaneously, survival has improved due to earlier detection and improved treatment options. Despite this improvement, locoregional recurrences and distant metastases occur in up to 10 and 30% of women diagnosed with early breast cancer, respectively. Around 70% of breast cancers are hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–), and associated with a persistent risk of relapse up to 20 years after diagnosis/initial treatment. We conducted a narrative review by combining PubMed searches with our clinical experience to describe patient characteristics, biomarkers, and genomic profiling tools available to clinicians for the identification of patients with HR+, HER2– early breast cancer at high risk of recurrence and to provide recommendations to classify patients into recurrence risk categories. National and international treatment guidelines are also summarised. Accurate assessment of the risk of recurrence in these patients is crucial as the predicted

risk guides treatment decisions; imprecise estimations can result in over- or undertreatment, with either scenario having negative consequences for patients. Multiple prognostic tools and factors are recommended for early breast cancer, and no single test provides accurate prognosis in isolation. Since no single test can provide accurate prognosis in isolation, a combination of tools should be used. Risk thresholds are important to guide optimised and balanced therapeutic decisions in HR+, HER2- early breast cancer. However, prognostic assessment should be performed on a case-by-case basis, making patient-specific prognostic approaches essential to avoid over- or undertreatment.

## ZUSAMMENFASSUNG

Die Inzidenz von Brustkrebs ist in den letzten 2 Jahrzehnten gestiegen; gleichzeitig hat sich das Überleben durch frühere Erkennung und bessere Therapiemöglichkeiten verbessert. Trotz dieser Verbesserungen treten lokoregionäre Rezidive sowie Fernmetastasen bei bis zu 10 resp. 30% aller mit Brustkrebs im Frühstadium diagnostizierten Frauen auf. Rund 70% aller Brustkrebsfälle sind HR+ (hormonrezeptorpositiv), HER2- (humane epidermale Wachstumsfaktorrezeptor 2 negativ) und sind somit mit einem anhaltenden Rezidivrisiko assoziiert, das bis zu 20 Jahren nach der Diagnose/Erstbehandlung anhält. Wir führten eine narrative Übersichtsarbeit durch und kombinierten dabei unsere Suche in PubMed mit unseren kli-

nischen Erfahrungen, um die Patientinnencharakteristika, Biomarker und Instrumente zur Analyse von Genomprofilen, die Klinikärztinnen und -ärzten zur Identifizierung von Patientinnen mit HR+, HER2- frühem Mammakarzinom mit einem hohen Rezidivrisiko zur Verfügung stehen, zu beschreiben und Empfehlungen zur Klassifizierung von Patientinnen gemäß ihrem Rezidivrisiko aufzustellen. Es wurden auch nationale und internationale Behandlungsrichtlinien zusammengefasst. Die korrekte Einschätzung des Rezidivrisikos ist für diese Patientinnen wichtig, weil das prognostizierte Risiko die nachfolgenden Therapieentscheidungen steuern wird; unpräzise Einschätzungen können zur Über- bzw. Untertherapie führen, und beide Szenarien haben negative Konsequenzen für Patientinnen. Es gibt zahlreiche prognostische Werkzeuge und Faktoren, die für die Analyse von Brustkrebs im Frühstadium empfohlen werden; es gibt aber keinen Test, der für sich genommen eine akkurate Prognose bieten kann. Da es keinen Test gibt, der für sich allein genommen imstande ist, eine akkurate Prognose zu bieten, sollte eine Kombination verschiedener Testverfahren verwendet werden. Risikoschwellen sind wichtig, da diese die Entscheidung für eine optimierte, ausgewogene Therapie bei HR+, HER2- frühem Mammakarzinom lenkt. Dennoch sollte jede prognostische Evaluierung individuell durchgeführt werden, da ein patientenspezifisches prognostisches Vorgehen wichtig ist, um eine Über- oder Untertherapie zu vermeiden.

## Introduction

Breast cancer is one of the most diagnosed cancers worldwide, representing around 12% of all new cancer cases and approximately 25% of the total number of new cancer cases in women in 2020 [1]. Estimates for Europe show a similar trend, where breast cancer represented 13% of all new cancer cases in 2020 and is estimated to account for 29% of all new cancers in women [2,3].

Early breast cancer, defined as cancer confined to the breast or that has only spread to the axillary lymph nodes, accounts for more than 90% of breast cancer diagnoses [4]. Earlier detection and improved treatment options in recent years have contributed to increased survival for patients with breast cancer. However, this improvement in survival, coupled with the rising incidence, also means that more patients are at risk of recurrence (ROR) than ever before [3].

Between 8 and 10% of women diagnosed with breast cancer will present with locoregional recurrences, and 15–30% will develop distant metastases [5–7]. Mortality after local recurrence varies by disease stage, with 15-year mortality rates of 16, 32, and 59% for stage 0, I, and II, respectively [8].

Recurrence in breast cancer can appear early (usually defined as within 5 years of diagnosis) or late (beyond 5 years). Patients with hormone receptor-positive (HR+) tumours (which include tumours with oestrogen receptor positivity [ER+] with or without progesterone receptor positivity [PR+]) have a lower ROR soon after diagnosis, but their risk persists longer than for patients with HR- tumours. Cases that are also human epidermal growth factor

receptor 2 (HER2)-negative (HER2-) clearly have a higher risk of late recurrence than treated HER2-positive (HER2+) individuals [9,10] as a consequence of effective anti-HER2 treatment for HER2+ patients. HR+, HER2- breast cancer constitutes around 70% of all breast cancers [4,11]. More than half of women (55%) have been reported to remain disease free in the first 10 years after diagnosis, and more than 10% of these individuals will go on to develop recurrences after 10 years [12]. In women with breast cancer aged 60–74 years, the estimated recurrence rates within 5 years were 2.5, 9.6, and 34.5% for stage I, II, and III HR+ tumours, and 6.5, 20.2, and 48.5% for stage I, II, and III HR- tumours, respectively [10]. Estimated recurrence rates for stage I, II, and III HR+ tumours were 5.2, 16.6, and 45.5% within 10 years and 7.8, 21.4, and 50.7% within 15 years, respectively. For stage I, II, and III HR- tumours, estimated recurrence rates were 9.7, 23.5, and 51.9% within 10 years and 11.2, 24.6, and 53.1% within 15 years, respectively [10]. A meta-analysis comparing 5 years' treatment with aromatase inhibitors versus tamoxifen in early breast cancer found that both endocrine therapies provided significant benefits in reducing the ROR and breast cancer mortality during years 0–9 versus no endocrine treatment. There was a significantly greater reduction in recurrence risk for aromatase inhibitors versus tamoxifen (by about 30% [proportionately]) during years 0–4 but no difference in years 5–9 [13].

Breast cancer is a highly heterogeneous disease, with subtypes exhibiting substantial differences with regards to their disease presentation, patterns of metastasis, drug sensitivity, timing of recurrence and prognosis. Treatment recommendations have been

adapted to take this heterogeneity into account, being more biology centred, with treatment strategies differing according to the tumour subtype. Therapeutic strategies for HR+, HER2- patients may focus on the need for treatment de-escalation to reduce their adverse effects and sequelae, with the identification of patients who can safely be excluded from additional adjuvant chemotherapy and/or extended adjuvant endocrine therapy being a high priority.

The vast majority of ER+ patients do receive adjuvant endocrine therapy, which reduces the ROR and improves overall survival (OS); however, the recurrence rate remains  $\geq 20\%$  in the first 10 years in ER+ patients [14, 15].

For patients with HR+, HER2- early breast cancer, current standard treatments include a combination of surgery, with or without (neo)adjuvant chemotherapy, radiation therapy, and adjuvant endocrine therapy; neoadjuvant or adjuvant chemotherapy is given to patients who are at increased ROR [16, 17]. It is also recommended to treat postmenopausal women, or women receiving ovarian suppression therapy, with bisphosphonates to both prevent cancer treatment-induced bone loss and reduce the risk of disease recurrence [18].

Risk of distant recurrence is the main determinant of recommendations for chemotherapy, and the risk of disease recurrence is significantly reduced with adjuvant chemotherapy [19]. Determining what constitutes high recurrence risk in early breast cancer is challenging because of individual patient factors and the large number of prognostic methods that may or may not be available to a particular clinician. Consequently, most treatment guidelines do not recommend “one size fits all” risk thresholds [17, 20, 21]. In the MINDACT trial, high ROR was defined as high-risk gene expression signature results with no to three involved lymph nodes, involvement of four or more lymph nodes or a  $> 10\%$  risk of breast cancer-specific mortality at 10 years [22], but these thresholds have not been established in clinical practice. Another approach to assessing whether chemotherapy should be recommended is by determining the absolute 10-year survival benefit from chemotherapy. For example, the Cambridge Breast Unit (UK) considers that chemotherapy is not recommended if the 10-year survival benefit is  $< 3\%$ ; chemotherapy is discussed as a treatment option when the 10-year survival benefit is 3–5%, and chemotherapy is recommended when the 10-year survival benefit is  $> 5\%$  [23]. Some patients may overestimate their ROR, which can have a negative impact on quality of life. Therefore, it is important to communicate recurrence risk to patients, particularly for those at lower risk [24]. Since the risk–benefit balance of chemotherapy can become unfavourable in low-risk patients because of treatment toxicity or in patients with a high benefit from endocrine therapy [19, 25], low-risk patients benefit from de-escalation of chemotherapy [26].

As described, the ROR influences the treatment decisions for patients with HR+, HER2- early breast cancer. For example, the American Society of Clinical Oncology (ASCO) guidelines recommend extended adjuvant endocrine therapy for patients at high ROR (although “high risk” is not defined) [27, 28]. The ASCO guidelines were recently updated to recommend offering abemaciclib for 2 years plus endocrine therapy for  $\geq 5$  years to patients with resected, HR+, HER2-, node-positive early breast cancer at

high ROR [29] based on results from the phase III monarchE study [30]. Recently those results were updated with 5-year follow up data and therapy effects were maintained over time [31]. Similarly, the National Comprehensive Cancer Network guidelines for breast cancer were recently updated for patients with HR+/HER2-, high-risk breast cancer to recommend that 2 years of adjuvant abemaciclib be considered in combination with endocrine therapy. In these guidelines, high risk is defined as patients with four or more positive lymph nodes, or one to three positive lymph nodes with one or more of the following: grade 3 disease, tumour size  $\geq 5$  cm, or a Ki-67 score of  $\geq 20\%$  [32].

Given the importance of estimating the ROR for treatment strategies, several molecular tests to classify patients with breast cancer into different recurrence risk groups have been developed in recent years [33]. Some uncertainty remains as to which markers are reliable for identifying high-risk patients and for the differentiation of early and late recurrence [34].

This review presents a summary of the currently available tools and patient characteristics that can be used by clinicians to identify patients with HR+, HER2- early breast cancer at high ROR to guide optimised and balanced therapeutic decisions.

## Review

### Prognostic factors defining outcome

#### Prognostic and predictive factors

A prognostic biomarker is a characteristic (clinical or biological) that can be used to estimate the likely patient health outcome, regardless of any treatment. In oncology, a prognostic factor is a marker that can be used to estimate the outcomes for a patient with a cancer, usually either recurrence, progression, or death [35]. A predictive biomarker indicates the likely benefit of a treatment for a patient [36]. Some markers can be both prognostic and predictive, such as ER, PR, and HER2 expression, whereas others are only prognostic, such as tumour size and lymph node status [37].

Prognostic biomarkers help determine which patients should receive particular treatments such as chemotherapy, hormone therapy, or neither. For patients selected to receive systemic therapy, predictive biomarkers will help identify the most appropriate treatment or combination of treatments [38].

The current range of prognostic factors for recurrence in patients with early breast cancer include patient and tumour characteristics in addition to histological markers and gene expression signatures. These prognostic factors are used to assess a patient's risk of an event; predictive factors help select treatment options that may reduce that risk. The main classical clinicopathological and molecular prognostic factors in breast cancer are described below.

#### Routine clinicopathological prognostic factors

Tumour size (T), lymph node involvement (N), and the status concerning distant metastases (M) are among the factors with the greatest prognostic relevance. These three characteristics are used to make up the TNM staging system, which has to be determined for every patient with breast cancer [39, 40].

## Tumour size

Tumour size is one of the most important prognostic factors in breast cancer; tumours are categorised according to size as T0 (no evidence of primary tumour), T1 ( $\leq 20$  mm in greatest dimension), T2 ( $> 20$  but  $\leq 50$  mm in greatest dimension), T3 ( $> 50$  mm in greatest dimension), and T4 (any size with direct extension to the chest wall and/or to the skin) [41]. There is a well-established correlation between primary tumour size and the risk of developing metastases [42]. Tumour size is an independent prognostic factor of recurrence in breast cancer, with patients who have larger tumours (T2–T4) having a greater ROR than those with smaller tumours (T0–T1) [43].

## Lymph node involvement

Regional lymph node involvement has long been recognised as an important prognostic factor in early breast cancer. Prognosis worsens as the number of lymph nodes involved increases; the higher the number of axillary lymph nodes involved, the higher the risk of local and distant recurrence [44] and the shorter the disease-free survival (DFS) and OS times [45]. The status of the regional lymph nodes (N stage) is determined according to the extent of nodal involvement; axillary, internal mammary, and ipsilateral supraclavicular lymph nodes can be involved, but the ipsilateral axillary lymph node is the most common site of involvement, making it a strong negative prognostic factor significantly related to high recurrence risk [46, 47]. Axillary lymph node involvement is associated with tumour size, histological grade and subtype in early breast cancer. Definition of axillary lymph node level is based on the relationship with the pectoralis minor muscle; level I nodes are on the lateral border, level II nodes are between the medial and lateral borders, and level III lymph nodes are on the medial border of the pectoralis minor muscle [46]. Clinical lymph node assessment is categorised according to stage as N0 (no regional lymph node metastases), N1 (metastases to movable ipsilateral level I, II axillary lymph node[s]), N2 (metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in absence of clinically evident axillary lymph node metastases), N3 (metastases in ipsilateral infraclavicular [level III axillary] lymph node[s] with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node[s] with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node[s] with or without axillary or internal mammary lymph node involvement) [41, 46].

Pathological lymph node assessment is the lymph node assessment most commonly taken into consideration for prognosis and categorises findings according to stage as pN0 (no regional lymph node metastasis identified or isolated tumour cell clusters only), pN1 (micrometastases, or metastases in one to three axillary lymph nodes and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy), pN2 (metastases in four to nine axillary lymph nodes, or positive ipsilateral internal mammary nodes by imaging in the absence of axillary lymph node metastases), pN3 (metastases in ten or more axillary lymph nodes, or in infraclavicular [level III axillary] lymph nodes, or positive ipsilateral internal mammary

lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes, or in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral mammary lymph nodes, or in ipsilateral supraclavicular lymph nodes) [41, 46].

## Tumour grade

The Nottingham grading system (also called the Elston–Ellis modification of the Scarff–Bloom–Richardson grading system) is one of the most commonly used grading systems for breast cancer. It stratifies tumours into low-, intermediate-, or high-grade categories by scoring three features:

1. the proportion of tubule (and gland) formation,
2. the nuclear pleomorphism, and
3. the mitotic counts.

Each feature is given a score of 1–3, then the individual scores are added together, giving a possible total score of 3–9 points. Tumours are classified as grade 1 (low grade, 3–5 points), grade 2 (intermediate grade, 6–7 points), or grade 3 (high grade, 8–9 points) [48]. Well-differentiated tumours are associated with the best prognosis, with patients with poorly–moderately differentiated tumours having poorer survival [49]. Tumour grading is partly subjective, and this can lead to some disagreements in grading between pathologists [50] and between different hospitals. Grading has demonstrated limited reproducibility, so whether decisions on therapy should be based on this marker is under debate [51].

Both increasing tumour size and grade are associated with a significant long-term risk of distant recurrence. In a clinical trial of tamoxifen, patients with larger tumours and higher-grade tumours had significantly worse long-term survival than patients with smaller tumours and lower-grade tumours [52]. Colleoni et al. [53] studied the ROR at 5-year intervals over 25 years and found that, although in the first 5 years patients with grade 3 tumours had a numerically higher hazard of recurrence than patients with grade 1 or 2 tumours, this risk difference decreased beyond 5 years, with the hazard of recurrence for patients with grade 3 tumours being at least equal to that of those with a grade 1 tumour [53].

## ER and PR expression

ER and PR are involved in normal breast development and in mammary tumorigenesis [54]. A feasible method to measure the expression of both receptors is immunohistochemistry (IHC), and breast cancer tissue samples are considered positive (hormone therapy responsive) for ER or PR if 1–100% of tumour nuclei are positive for the receptors. ER and PR are commonly used as prognostic markers in breast cancer, with the presence of PR expression in ER+ patients being associated with a better prognosis [55]. However, patients who are ER-“low” positive (1–10% of cells staining ER+) can still be at high ROR, with some clinical and biological similarities with triple-negative patients [55, 56]. Furthermore, low expression of PR (defined as  $< 20\%$ ) is associated with a high risk of relapse [56]. Patients with ER+/PR+ tumours have lower risks of disease-related mortality than those with ER+/PR-

ER-/PR+, or ER-/PR- tumours [57]. Compared with ER-/PR- tumours, ER+/PR+ breast cancers generally have less aggressive clinicopathological features and have a better prognosis since they benefit from endocrine treatment [58, 59].

### HER2 status

HER2 is a transmembrane tyrosine kinase receptor expressed in breast tissues. The amplification of its gene leads to HER2 overexpression and mammary tumorigenesis and has been associated with an unfavourable prognosis [60]. HER2 is usually assessed to decide for or against an anti-HER2 therapy. An algorithm incorporating IHC and in situ hybridization is used: stained breast cancer tissue samples are given a score of 0 to 3+, where a score of 0–1+ (no staining or incomplete, faint/barely perceptible staining) is considered HER2- and a score of 3+ (complete, intense, circumferential staining) is considered HER2+. A score of 2+ (weak to moderate complete membrane staining) is considered equivocal and requires analysis of the gene amplification by in situ hybridization [61, 62]. Patients with low HER2 expression levels that do not reach the HER2-positivity threshold may also benefit from some HER2-targeted therapies [63–65]. HER2 has been found to be overexpressed in approximately 15–20% of breast cancers [63]. HER2 overexpression is associated with an unfavourable prognosis and correlates with a lower frequency of hormone receptor expression and a higher histopathological grade [6, 66].

### Clinical factors

#### Age

Both young age (normally defined as <35–40 years) and older age ( $\geq 65$  years) are associated with poor prognosis in breast cancer [4, 68]. Older patients tend to have more favourable disease characteristics (e.g. smaller tumours and lower grade) [68]. Furthermore, patients aged  $\geq 75$  years are less likely to be given adjuvant therapy and have a higher risk of death than treated patients [69, 70]. Older patients also have a greater likelihood of presenting with comorbidities, and this has a negative effect on their survival [69]. The influence of comorbidities in the OS estimates for elderly patients suggests that breast cancer-specific survival rates should be measured instead [71]. Similarly, the survival benefits of chemotherapy may be masked when looking at OS in this population because of the competing causes of mortality, and comorbidities may prompt the use of chemotherapy with lower toxicity than standard agents. However, more tolerable chemotherapy comes at a cost of reduced efficacy [72].

### Additional biomarkers of potential use in clinical routine

#### Ki-67

Ki-67 is an immunohistochemical marker of cell proliferation, labelling nuclei of cycling cells from G1 to M phase of the cell cycle. Ki-67 correlates well with tumour grade [73] and with results from molecular profiling systems [74, 75].

Higher levels of Ki-67 expression are associated with poor prognosis in breast cancer. No consensus has yet been reached as to which threshold for Ki-67 labelling index defines high risk [76]. Ki-67 values  $\leq 10\%$  are generally considered low risk. Different investigators have proposed a value of  $\geq 20\%$  to define high risk for DFS prognosis [77], but it is not generally accepted. In a

decentralised observational study [78] and a central setting within the frame of a prospective study [79], unfavourable prognosis and high-risk recurrence score (RS) were encountered in tumours with a Ki-67 labelling index exceeding 35%. High and low levels of Ki-67 correlate well with classical prognostic markers; however, correlation is less clear for intermediate levels of Ki-67 from 15 to 35% [73].

Ki-67 has been suggested to differentiate between types of breast cancer, with a cut-off Ki-67 index  $< 14\%$  proposed to distinguish luminal A-like tumours from luminal B-like tumours [80, 81]. The St. Gallen consensus temporally adopted this threshold but discarded it in subsequent meetings. No consensus has yet been reached on a parameter to discriminate luminal A from luminal B tumours. Proliferation suppression by short-term pre-operative endocrine therapy has yielded a novel prognostic and predictive marker based on Ki-67. Currently, Ki-67 response to endocrine therapy represents a predictive biomarker to indicate that endocrine therapy alone without chemotherapy might be sufficient for treatment of premenopausal women with breast cancer. Furthermore, in the WSG-ADAPT-HR+/HER2- trial, Oncotype DX RS (discussed later) was combined with 3-week Ki-67 response to endocrine therapy to guide systemic therapy, and it was found that Ki-67 can be used to identify patients with a higher RS that can be spared chemotherapy [82].

Scoring of Ki-67 for routine clinical practice can be challenging, with manual scoring methods having high inter- and intra-user variability, so it is not routinely used in clinical practice in all countries. Automated scoring methods have been developed to help with this issue [83]. As with ER, PR, and HER2 determination, quality assurance trials for Ki-67 have demonstrated that regular participation will improve concordance rates among pathologists [84].

Together with the described prognostic markers, Ki-67 plays an important role in therapy recommendations for patients with early breast cancer [85]. Importantly, Ki-67 may help to provide a more accurate prognosis in patients with an intermediate prognosis according to clinical factors (particularly stage II disease) and identify patients who are at high ROR and who may benefit from further therapy [86]. To improve inter-observer concordance and to provide a platform for both training and testing of capacity to read Ki-67 labelling in breast cancer, a novel digital pathology tool has been established [87].

### Prognostic biomarkers under investigation

#### Circulating tumour cells

Circulating tumour cells (CTCs) are intact, viable non-haematological cells with malignant features that have been shed from the primary tumour or a metastatic lesion into the bloodstream as single cells or clusters. In breast cancer, CTCs can provide information about disease progression and response to therapy in patients with metastases [88]. Detection of CTCs is rare in early breast cancer, but it has been validated as a prognostic marker for metastasis. CTCs were shown to be a prognostic marker for reduced DFS, distant DFS, breast cancer-specific survival, and OS before the start of systemic treatment and for DFS after completion of adjuvant chemotherapy in the SUCCESS (Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treat-



ment, as well as Extended Bisphosphonate and Surveillance-Trial) prospective trial [89]. Detection of CTCs is not routinely used in clinical practice, and further studies, including prospective trials, are needed to assess its utility [90].

### **Bone marrow involvement – disseminated tumour cells**

Although bone marrow involvement is not assessed in routine clinical practice, studies have shown that in patients with stage I–III breast cancer, the presence of occult cytokeratin-positive metastatic cells in bone marrow detected by IHC is associated with an increased risk of relapse. Furthermore, the presence of these disseminated tumour cells (DTCs) in the bone marrow following chemotherapy is associated with a poor prognosis in early and metastatic breast cancer [91,92]. An international pooled analysis showed that DTC detection was an independent prognostic marker for OS, DFS, and distant DFS [93]. On the other hand, the presence of DTCs in bone marrow was not significantly associated with the risk of locoregional relapse in some studies [92, 93], while another one established an association [94].

### **Circulating tumour DNA**

Circulating tumour DNA (ctDNA) is fragmented cell-free DNA that is released from necrotic and apoptotic cancer cells and that may contain cancer-specific mutations that have occurred in the originating cell. Elevated ctDNA levels have been associated with poorer outcomes in patients with early, locally advanced, and metastatic breast cancer [95]. A meta-analysis found that ctDNA is a strong prognostic marker in breast cancer; high levels of ctDNA and the presence of ctDNA were significantly associated with poor DFS/recurrence-free survival (RFS) and OS in patients with breast cancer [96], and ctDNA is used to identify patients in the ongoing ZEST trial of niraparib [97]. However, like CTCs, ctDNA is not used in routine clinical practice.

### **Prognostic scoring systems and models**

Several prognostic scoring systems have been developed for breast cancer, including the Nottingham Prognostic Index (NPI), Adjuvant! Online, PREDICT, Clinical Treatment Score post-5 years (CTS5), IHC, and CanAssist Breast.

#### **NPI**

The NPI is a widely used, validated, and clinically relevant tool for classifying patients with early breast cancer into three or more prognostic groups [98]. The NPI is calculated based on tumour size and grade and the number of lymph nodes involved. It is used to predict 5-year survival [99] and can be used to predict benefits of adjuvant therapy [100]. The NPI was devised in 1982 and validated in prospective cohorts and independent multicentre studies. It has been refined over the years to include ER and HER2 status, which are now considered essential predictive factors, to create NPI+, which has been verified in independent European studies [100, 101].

#### **Adjuvant! Online**

The Adjuvant! Online score is an open access computer program, developed using the Surveillance, Epidemiology, and End Results (SEER) registry, that assists decision making regarding adjuvant

therapy in patients with early breast cancer by predicting 10-year risks for recurrence, breast cancer-specific mortality, and mortality due to other causes, including the expected benefit of adjuvant systemic treatments based on patient- and tumour-related factors [102]. However, this model was found to overestimate [103, 104] or underestimate [105] OS and breast cancer-specific and event-free survival and is no longer available for clinical use [106].

#### **PREDICT**

The PREDICT breast cancer prognostication and treatment benefit prediction model (V1) was developed in 2010 using cancer registry data from the UK and was based on positive attributes of the Adjuvant! model. The model predicts 5-year and 10-year OS in early breast cancer following surgery based on patient- and tumour-related characteristics. PREDICT also provides information on the expected benefits of chemotherapy and endocrine therapy. The PREDICT model provides a high degree of discrimination across different prognostic groups [107]. A newer version of PREDICT (V2) has been developed with improved calibration in patients diagnosed before 40 years of age, and both V1 and V2 versions have been validated [108, 109]. The latest version in development at the time of writing (V2.3) incorporates PR status, which improved model performance and provides more accurate absolute treatment benefit predictions [110].

#### **CTS5**

The CTS5 is a tool based on clinicopathological information such as age, tumour size, histological grade, and lymph node involvement that estimates the risk of distant recurrence after 5 years and can help with the identification of patients who could benefit from extended endocrine therapy (> 5 years); the CTS5 stratifies patients into low risk (<5%), intermediate risk (5–10%), or high risk (> 10%) of late distant recurrence [111]. The CTS5 has been validated in postmenopausal patients but has not been sufficiently validated in premenopausal patients; further calibration in this population is still required. CTS5 is recommended for postmenopausal women treated for ER+, HER2– breast cancer who are free of distant recurrence at 5 years [112].

#### **IHC**

IHC is an immunohistochemical score that can be calculated from three to four of the following stains: ER, PR, HER2, and Ki-67 [113, 114]. IHC scores can be combined with a clinical score that includes factors such as patient's age, tumour grade, and nodal burden. IHC4 has been compared with several multigene tests and can produce similar prognostic values to some of the multigene tests, specifically in nodal-negative patients [115].

#### **CanAssist Breast**

CanAssist Breast was first developed in patients of Indian origin and ethnicity and validated in the same population along with a wider exposure in Caucasian patients; it combines the data of five immunohistochemical biomarkers (CD44, N-cadherin, pan-cadherin, ABCC4, and ABCC11) with tumour size, grade, and node status to calculate recurrence risk. CanAssist Breast predicts risk of distant recurrence at 5 years from diagnosis by segregating the

patients into low- and high-risk groups for distant recurrence [116].

### Genomic profiling for prognosis

In recent years, several genomic prognostic assays have been developed to estimate recurrence risk in breast cancer in addition to classical clinicopathological factors and to help decide treatment in the adjuvant setting [117]. The prognostic information provided by these assays is complementary to standard breast cancer clinicopathological parameters. The UK National Institute for Health and Care Excellence recommends a molecular profiling system to lower adjuvant chemotherapy rates as the calculations from multigene systems generally identify fewer patients with a high ROR than risk calculations based on patient demographics and tumour characteristics [118]. A prospective study in Canada found that, when genomic profiling was used to guide treatment decisions for patients with early breast cancer, a smaller proportion of patients actually receive chemotherapy (42%) than the proportion who were recommended chemotherapy before genomic profiling guidance (79%), which is a decrease of 36%. Increased confidence in the adjuvant treatment recommendations was reported for 49% of physicians and 54% of patients [119]. A similar study in Lebanon reported that use of genomic profiling resulted in a treatment change in 35% of patients, with 25% of patients having de-escalation of planned therapy to avoid chemotherapy [120].

Although choice of adjuvant treatments in treatment guidelines can differ among countries, the association between using molecular profiling assays and a change in treatment decisions and an overall reduction in chemotherapy use is consistent [22, 121–123]. By avoiding chemotherapy treatments, improvements in patients' quality of life and overall cost savings for health systems can be achieved, despite the negative economic impact in the short term caused by the cost of the molecular tests [124, 125].

### Oncotype DX

The Oncotype DX RS, also called the 21-gene RS, is one of the most well-established genomic profiling assays. The Oncotype DX RS stratifies the 5- or 10-year risk of distant relapse into low risk (RS 0–10; expected small benefit from chemotherapy), intermediate risk (RS 11–25; uncertain whether the beneficial effects of chemotherapy outbalances the toxic effects of chemotherapy), and high risk (RS > 25 in women aged < 50 years, RS > 15 and high clinical risk, or RS > 21, independent of the clinical risk; high probability of cancer recurrence, and benefits of chemotherapy should surpass the risk of treatment toxicity) [33]. However, it is important to note that the patient data used to define these risk categories were from studies from several years ago. This may therefore result in overestimation of the risk in the context of contemporary clinical practice. A study into the influence of Oncotype DX in decision making found that treatment choices were changed for approximately 25% of patients with early breast cancer, with most of these changes to use lower-intensity treatment regimens than originally chosen [126], reducing adjuvant chemotherapy use in routine clinical practice [127]. In contrast, a comparison of Oncotype DX RS with IHC4 found that the IHC4 score provided similar

prognostic information [113]. A separate study comparing Oncotype DX RS with IHC4, MammaTyper, NexCourse Breast, PAM50, and MammaPrint (the latter two profiles are discussed below) found that, although these tests provide similar prognostic information at the population level, there can be notable discordance in risk categorisation when individual patients are assessed with multiple tests, with 61% of tumours in the study classified in more than one risk group across the six different prognostic tests [128].

### MammaPrint

MammaPrint is a 70-gene signature endorsed by several practice guidelines that classifies patients with breast cancer into high-risk (patients with risk of developing distant metastases within 5 years after diagnosis) and low-risk (patients with a high probability of metastasis-free survival) groups [129]. MammaPrint has been reported to provide similar predictions to Oncotype DX, despite focusing on different genes [130] and is more widely used in some European countries. In the MINDACT trial, MammaPrint was used to identify women classed as at high risk of relapse by Adjuvant! Online who could be spared chemotherapy, discussed later in this review [22].

### EndoPredict

EndoPredict is a 12-gene molecular signature that measures the expression of eight cancer-related genes, three RNA reference genes, and one DNA reference gene. The EndoPredict score ranges between 0 and 15 with a cut-off score of 5 to discriminate low and high risk. The EndoPredict risk score can be combined with tumour size and nodal status to allow the calculation of a comprehensive risk score (Epiclin). EndoPredict can be used to guide treatment decisions for both chemotherapy and extended anti-hormonal therapy [131], although it has not been validated in phase III studies.

### Prosigna/PAM50

Prosigna/PAM50 was developed in premenopausal and postmenopausal women treated without any adjuvant systemic therapy and covers 50 genes (and five reference genes). The PAM50 ROR combines the PAM50 profile and clinical features such as tumour size and proliferation. ROR stratifies the risk of recurrence into low ( $\leq 40$ ), intermediate (41–60), and high ( $> 60$ ) [123]. When the PAM50 ROR was compared with the Oncotype DX RS for the prediction of risk of distant recurrence after endocrine therapy, more patients were scored as at high risk and fewer as at intermediate risk by ROR than by RS [15].

### Breast Cancer Index

The Breast Cancer Index (BCI) was developed in postmenopausal patients with ER+ lymph node-negative breast cancer as a predictive test for the likelihood of benefit from extended adjuvant endocrine therapy. It is an algorithmic gene expression-based signature comprising two functional biomarker panels. Individuals are categorised as low risk ( $< 5.1$ ), intermediate risk (5.1 to  $< 6.5$ ), or high risk ( $\geq 6.5$ ) [132, 133].

A secondary analysis of the Translational Study of Anastrozole or Tamoxifen Alone or Combined (TransATAC) randomised clinical trial of patients with HR+ early-stage breast cancer treated with

► **Table 1** Characteristics of the most used molecular profiling systems in early breast cancer.

Profiling system	Number of genes assessed	Patient characteristics suitable for adjuvant chemotherapy assessment	Clinical application	Recommended by	Classification
Oncotype DX Recurrence Score	21 genes (16 breast cancer-related genes and five reference genes)	ER/PR+, HER2- N- ER/PR+, HER2-, N+	Prognostic, endocrine treated, HR+, HER2-, N±	NCCN ASCO NICE St. Gallen ESMO AGO IQWiG	RS0-100: Low risk (0-10) Intermediate risk (11-25) High risk (> 25 in women aged < 50 years, > 15 and high clinical risk or > 21, independent of the clinical risk)
MammaPrint	70 genes	ER/PR+, HER2-, N- ER/PR+, HER2-, N+	Prognostic, age < 70 years, HR+, HER2-, N±	NCCN ASCO St. Gallen ESMO AGO	MammaPrint Index: Low risk High risk
Prosigna/PAM50	50 genes (and five reference genes)	ER/PR+, HER2-, N-	Prognostic, endocrine treated, postmenopausal, HR+, HER2-, N±	NCCN ASCO NICE St. Gallen ESMO AGO	ROR 0-100: Low risk (< 40) Intermediate risk (41-60) High risk (61-100)
EndoPredict	12 genes (8 cancer-related, 3 reference genes, and 1 control gene for DNA contamination)	ER/PR+, HER2-, N-	Prognostic, endocrine treated, (pre-) postmenopausal, HR+, HER2-, N±	NCCN ASCO NICE St. Gallen ESMO AGO	EP molecular score 0-15: Low risk (< 5) High risk (> 5) Epclin score (with tumour size and nodal status): Low risk (< 3.3) High risk (≥ 3.3)
Breast Cancer Index	Two functional biomarker panels	ER/PR+, HER2-, N-	Prognostic, endocrine treated, HR+, HER2-, N±	NCCN ASCO St. Gallen AGO	Low risk (< 5.1) Intermediate risk (5.1- < 6.5) High risk (≥ 6.5)

Adapted from Gluz et al. [147] and Puppe et al. [134].

AGO: German Gynaecological Oncology Group, ASCO: American Society of Clinical Oncology, EP: EndoPredict score, Epclin: EndoPredict score + tumour size and nodal status, ER: oestrogen receptor, ESMO: European Society for Medical Oncology, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, IQWiG: Institute for Quality and Efficiency in Health Care, N: lymph nodes, NCCN: National Comprehensive Cancer Network, NICE: UK National Institute for Health and Care Excellence, PR: progesterone receptor, ROR: risk of recurrence, RS: recurrence score

5 years of tamoxifen or anastrozole compared the prognostic value of Oncotype DX RS, PAM50 ROR, BCI, Epclin, CTS, and IHC4. For 5- to 10-year recurrence, there was prognostic value in adding PAM50 ROR, BCI, or Epclin to the CTS. However, there was no prognostic value in adding IHC4 or Oncotype DX RS to the CTS [115].

Further details for the recommended genomic tests used to measure ROR are presented in ► **Table 1**. Molecular profiling provides a standardised and reproducible estimate of the ROR. However, the results do not necessarily correlate with the prognosis given by classical clinicopathological markers. The values provided by these tests must be carefully interpreted by the clinician on a case-by-case basis rather than simply being used as an indication of high or low risk. Rather than replacing clinicopathological markers, molecular profiling tests are complementary to classical clinicopathological markers. Therefore, the integration of ge-

nomics assays with clinicopathological prognostic factors may be the best approach [75, 134].

### Multigene tests versus non-genomic scoring systems

Currently, genomic methods are a commonly recommended method to predict ROR. However, genomic methods can be expensive and require specialised equipment. Several studies have compared IHC scoring systems with these newer genomic profiling methods and have found that the prognostic value of non-genomic scoring systems can be equivalent to that of the modern genomic methods and can still be used as an alternative when genomic methods are not available or affordable [135]. For example, patients grouped into low-, intermediate-, and high-risk categories by Oncotype DX RS were found to have significantly different tumour grade, PR expression, and Ki-67 index between risk catego-



ries [136]. An analysis of the TransATAC dataset found that, for ER+, HER2- patients, late distant recurrence risk was significantly predicted by PAM50 ROR and IHC4 but not by Oncotype DX RS [43].

### Prospective clinical trials with multigene tests

Although OS can be considered the most clinically relevant endpoint in cancer trials, DFS is usually used as a surrogate endpoint for breast cancer [137, 138], and DFS is the most commonly reported clinical endpoint in breast cancer studies [139]. This is because of the relatively long expected survival time of treated patients with breast cancer, especially the patients with ER+, HER2-disease, which makes an OS endpoint impractical in this patient population within the timeframe of a clinical trial [140].

Recurrence endpoints include DFS-ductal carcinoma in situ, invasive DFS (IDFS), RFS, recurrence-free interval (RFI), breast cancer-free interval, invasive breast cancer-free survival, distant DFS, distant relapse-free survival, and distant RFI [141, 142].

In addition to these end points, quality of life is becoming an increasingly important end point in breast cancer. Health-related quality of life is a patient-reported measure that demonstrates clinical benefit of a treatment. Quality of life can be used as a secondary end point to compare treatments that have similar beneficial effects on disease but differences in toxicity [138].

### TAILORx

The predictive ability of a combination of molecular profiling with a clinicopathological factor (nodal involvement) has been assessed in clinical studies. The prospective Trial Assigning Individualized Options for Treatment (TAILOR-X) study evaluated the classification of recurrence risk in patients with early breast cancer with HR+, HER2-, and axillary node-negative tumours to identify patients likely to benefit from chemotherapy [106, 143]. Treatment choice was stratified according to Oncotype DX RS. Analysis of IDFS from TAILORx showed that endocrine therapy was non-inferior to adjuvant chemotherapy plus endocrine (chemoendocrine) therapy in HR+, HER2-, and axillary node-negative patients with an RS of 11–25 [143]. Exploratory analyses indicated that women aged  $\leq 50$  years with an RS of 16–25 might benefit from chemotherapy with respect to both locoregional and distant recurrences. The trial also showed a low percentage of women with distant recurrence (3%) at 9 years with endocrine therapy alone if the RS was  $< 16$ , irrespective of age [106].

### MINDACT

The MINDACT trial, which included women with early breast cancer who were lymph node negative or one to three lymph nodes positive, used MammaPrint for molecular profiling. Patients received either endocrine therapy alone or adjuvant chemotherapy plus endocrine therapy. Patients were categorised as having high or low genomic risk and high or low clinical risk. In the case of discordant results (i.e. high clinical risk and low genomic risk, or low clinical risk and high genomic risk), patients were randomly assigned to chemotherapy or no chemotherapy based on either the clinical result or the genomic result. The primary outcome was distant RFI. This study showed that chemotherapy could be avoided in patients at high clinical risk for relapse according to Adjuvant! Online but who had a low genomic risk for recurrence ac-

ording to MammaPrint (corresponding to 46% of patients in the MINDACT trial [22].

### RxPonder

The RxPonder trial used Oncotype DX to determine which patients with HR+, HER2- breast cancer and nodal positivity (one to three positive lymph nodes) and an RS of 0–25 would benefit from chemotherapy and which could safely avoid it. The primary objective was to determine the effect of chemotherapy on IDFS. In RxPonder, data were analysed according to menopausal status; results showed that postmenopausal women with an RS of  $\leq 25$  derived no further benefit from chemotherapy added to endocrine therapy and can safely avoid adjuvant treatment with it. On the other hand, premenopausal patients with an RS of  $\leq 25$  benefited from the addition of chemotherapy at 5 years [144].

### OPTIMA

The OPTIMA study is an ongoing international randomised controlled trial comparing standard treatment with chemotherapy followed by endocrine therapy versus undergoing Prosigna testing; participants with high Prosigna score ( $> 60$ ) tumours receive standard treatment, and those with low-score tumours receive endocrine therapy alone. The investigators aim to randomise 2250 patients in each arm to demonstrate non-inferiority of test-directed treatment, defined as not more than 3% below the estimated 85% 5-year IDFS for the control arm [145]. To date, more than 3000 patients have been recruited [146].

### Decision making in HR+, HER2- breast cancer

A summary of recommendations on the use of prognostic markers to guide adjuvant therapy in patients with early breast cancer is presented in ► **Tables 2 to 4**.

According to the European Society for Medical Oncology clinical practice guidelines for diagnosis, treatment, and follow-up in early breast cancer, the decision to start chemotherapy should in part be based on an individual's risk of relapse, which depends on tumour burden and tumour biology [17]. Guidelines vary in their recommendations for identification of patients at high risk of relapse, particularly regarding Ki-67 testing. To summarise this, we provide a table of national and international guideline recommendations for prognosis in early breast cancer (► **Tables 2 to 4**). This highlights that no single test provides accurate prognosis in isolation, and a combination of tools should therefore be used.

### Conclusions

Our review highlights that no single test provides accurate prognosis in isolation, and a combination of tools should therefore be used. Risk thresholds are important to guide optimised and balanced therapeutic decisions in HR+, HER2- early breast cancer. However, prognostic assessment should be performed on a case-by-case basis, considering patient factors as well as choice of treatment, making patient-specific prognostic approaches essential to avoid over- or undertreatment. Prediction of recurrence risk and risk thresholds to guide treatment decisions continues to evolve with the improving availability and accuracy of prognostic tests and the increased availability of treatments with more favourable efficacy-to-adverse-event balances.

► **Table 2** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): genomic profiling assay.

Guideline	Oncotype DX (RS; 21 genes)	MammaPrint (70 genes)	Prosigna (PAM50; 50 genes)	EndoPredict (EpClin; 12 genes)	Breast Cancer Index
AGO [20, 148]	<p>✓</p> <p>May be included in the decision criteria for the definition of high risk of recurrence.</p> <p>Can be used in luminal early breast cancer with 0–3 involved lymph nodes for indicating the use of chemotherapy if the use of routine prognostic factors is not conclusive.</p>	<p>✓</p> <p>May be included in the decision criteria for the definition of high risk of recurrence.</p> <p>Can be used in luminal early breast cancer with 0–3 involved lymph nodes for indicating the use of chemotherapy if the use of routine prognostic factors is not conclusive.</p>	<p>✓</p> <p>May be included in the decision criteria for the definition of high risk of recurrence.</p> <p>Can be used in luminal early breast cancer with 0–3 involved lymph nodes for indicating the use of chemotherapy if the use of routine prognostic factors is not conclusive.</p>	<p>✓</p> <p>May be included in the decision criteria for the definition of high risk of recurrence.</p> <p>Can be used in luminal early breast cancer with 0–3 involved lymph nodes for indicating the use of chemotherapy if the use of routine prognostic factors is not conclusive.</p>	Not specified
ASCO [21, 149]	<p>✓ &amp; ✗</p> <p>For patients &gt; 50 years whose tumours have Oncotype DX RSs &lt; 26 and for patients ≤ 50 years whose tumours have Oncotype DX RSs &lt; 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone.</p> <p>For patients ≤ 50 years with Oncotype DX RSs of 16–25, clinicians may offer chemotherapy.</p> <p>Patients with Oncotype DX RSs &gt; 30 should be considered candidates for chemotherapy, and patients with Oncotype DX scores of 26–30 may be offered chemotherapy.</p> <p>If a patient has ER/PR+, HER2- (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multi-parameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC4) to guide decisions about extended endocrine therapy.</p> <p>If a patient has ER/PR+, HER2- (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use Oncotype DX to guide decisions about extended endocrine therapy.</p>	<p>✓ &amp; ✗</p> <p>MammaPrint may be used in those older than 50 and with high clinical risk breast cancer that is node-negative or node-positive with 1–3 positive nodes to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.</p> <p>MammaPrint should not be used in patients aged ≤ 50 years and with high clinical risk, node-negative or node-positive with 1–3 positive nodes breast cancer to inform decisions on withholding adjuvant systemic chemotherapy because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer.</p> <p>If a patient has ER/PR+, HER2-, node-positive breast cancer, MammaPrint may be used in patients with 1–3 positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.</p> <p>If a patient has ER/PR+, HER2-, node-positive breast cancer, MammaPrint should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy.</p> <p>If a patient has ER/PR+, HER2- (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use Oncotype DX to guide decisions about extended endocrine therapy.</p>	<p>✓ &amp; ✗</p> <p>If a patient is postmenopausal and has node-negative breast cancer, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy.</p> <p>If a patient is premenopausal and has node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy.</p> <p>If a patient is postmenopausal and has node-positive breast cancer with 1–3 positive nodes, the clinician should not use the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy.</p> <p>If a patient has node-positive breast cancer with ≥ 4 positive nodes, evidence on the clinical utility of routine use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use.</p>	<p>✓ &amp; ✗</p> <p>If a patient is postmenopausal and has node-negative or node-positive breast cancer with 1–3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy.</p> <p>If a patient is premenopausal and has node-negative or node-positive breast cancer with 1–3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy.</p> <p>If a patient has breast cancer with ≥ 4 positive nodes, evidence on the clinical utility of routine use of the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient.</p>	<p>✓ &amp; ✗</p> <p>If a patient has ER/PR+, HER2-, node-negative breast cancer, the clinician may use the Breast Cancer Index to guide decisions about adjuvant systemic chemotherapy.</p> <p>If a patient has ER/PR+, HER2-, node-positive breast cancer, the clinician should not use the Breast Cancer Index to guide decisions about adjuvant systemic therapy.</p> <p>If a patient has breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use Breast Cancer Index to guide decisions about extended endocrine therapy.</p>

► **Table 2** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): genomic profiling assay. (Continued)

Guideline	Oncotype DX (RS; 21 genes)	MammaPrint (70 genes)	Prosigna (PAM50; 50 genes)	EndoPredict (EpClin; 12 genes)	Breast Cancer Index
ECIBC [150]	<p>✓ &amp; ✗</p> <p>Recommended to guide the use of chemotherapy for women with node-negative invasive breast cancer.</p> <p>Not recommended for women with node-positive invasive breast cancer.</p>	<p>✗</p> <p>Not recommended for women with node-negative or ≤3 node-positive invasive breast cancer to guide the use of chemotherapy.</p>	Not specified	Not specified	Not specified
ESMO [17]	<p>✓</p> <p>Recommended in cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of all clinical and pathological factors).</p>	<p>✓</p> <p>Recommended in cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of all clinical and pathological factors).</p>	<p>✓</p> <p>Recommended in cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of all clinical and pathological factors).</p>	<p>✓</p> <p>Recommended in cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of all clinical and pathological factors).</p>	<p>✓</p> <p>Recommended in cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of all clinical and pathological factors).</p>
NICE [151, 152]	<p>✓</p> <p>Recommended as an option for guiding adjuvant chemotherapy decisions for individuals with node-negative disease (including micrometastatic disease), only if:</p> <ul style="list-style-type: none"> <li>they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index.</li> <li>information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference.</li> </ul>	<p>✗</p> <p>Not recommended for guiding adjuvant chemotherapy decisions for individuals in this patient population with node-negative disease because it is not cost effective.</p>	<p>✓</p> <p>Recommended as an option for guiding adjuvant chemotherapy decisions for individuals with node-negative disease (including micrometastatic disease), only if:</p> <ul style="list-style-type: none"> <li>they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index.</li> <li>information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy, taking into account their preference.</li> </ul>	<p>✓</p> <p>Recommended as an option for guiding adjuvant chemotherapy decisions for individuals with node-negative disease (including micrometastatic disease), only if:</p> <ul style="list-style-type: none"> <li>they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index.</li> <li>information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy, taking into account their preference.</li> </ul>	Not specified

Continued next page

► **Table 2** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): genomic profiling assay. (Continued)

Guideline	Oncotype DX (RS; 21 genes)	MammaPrint (70 genes)	Prosigna (PAM50; 50 genes)	EndoPredict (EpClin; 12 genes)	Breast Cancer Index
Ontario Health [153]	<p>Should be considered to help guide the use of systemic therapy.</p> <p>In patients with early-stage node-negative disease, clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy.</p> <p>In patients with node-negative disease, clinicians may use a high-risk result to support a decision to offer chemotherapy. A high recurrence score is capable of predicting adjuvant chemotherapy benefit.</p> <p>In postmenopausal patients with ER+/HER2- tumours and 1–3 nodes involved, clinicians may withhold chemotherapy based on a low-risk score if the decision is supported by other clinical, pathological, or patient-related factors.</p>	<p>Should be considered to help guide the use of systemic therapy.</p> <p>In patients with early-stage node-negative disease, clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy.</p> <p>In postmenopausal patients with ER+/HER2- tumours and 1–3 nodes involved, clinicians may withhold chemotherapy based on a low-risk score if the decision is supported by other clinical, pathological, or patient-related factors.</p>	<p>Should be considered to help guide the use of systemic therapy.</p> <p>In patients with early-stage node-negative disease, clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy.</p>	<p>Should be considered to help guide the use of systemic therapy.</p> <p>In patients with early-stage node-negative disease, clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy.</p>	<p>Should be considered to help guide the use of systemic therapy.</p> <p>In patients with early-stage node-negative disease, clinicians may use a low-risk result to support a decision not to use adjuvant chemotherapy.</p> <p>Clinicians may consider using a Breast Cancer Index high assay result to support a decision to extend adjuvant endocrine therapy if the decision is supported by other clinical, pathological, or patient-related factors.</p>
SEOM guidelines [154]	<p>May be used for prediction of the risk of distant recurrence at 9 years in patients treated with adjuvant endocrine therapy only.</p> <p>May be used for prediction of the benefit of adjuvant chemotherapy.</p>	<p>May be used for prediction of the risk of distant recurrence at 5 years in patients treated with adjuvant endocrine therapy only.</p>	<p>May be used for prediction of the risk of distant recurrence at 10 years in patients treated with adjuvant endocrine therapy only for 5 years.</p> <p>May be used for prediction of the risk of late distant recurrence (years 5–10) in patients treated with adjuvant endocrine therapy only for 5 years.</p>	<p>May be used for prediction of the risk of distant recurrence at 10 years in patients treated with adjuvant endocrine therapy only for 5 years.</p> <p>May be used for prediction of the risk of late distant recurrence (years 5–10) in patients treated with adjuvant endocrine therapy only for 5 years.</p>	Not specified
St. Gallen [16]	Serves as a prognostic marker for recurrence risk.	Serves as a prognostic marker for recurrence risk.	Not specified	Not specified	Not specified

✓ indicates recommended; ✗ indicates not recommended.

AGO: German Gynaecological Oncology Group, ASCO: American Society of Clinical Oncology, ECIBC: European Commission Initiative on Breast Cancer, EPclin: EndoPredict score + tumour size and nodal status, ER: oestrogen receptor, ESMO: European Society for Medical Oncology, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, IHC: immunohistochemistry, IHC4+C: IHC4 plus clinical and pathological features, NICE: UK National Institute for Health and Care Excellence, PR: progesterone receptor, RS: recurrence score

► **Table 3** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): clinicopathological prognostic factor.

Guideline	Lymph node involvement	Tumour size	Tumour grade	Age	ER and PR expression level (in patients who are HR+, HER2-)	Ki-67	Circulating tumour cells	Bone marrow involvement
AGO [20, 148]	<input checked="" type="checkbox"/> May be included in the decision criteria for the definition of high risk of recurrence.	<input checked="" type="checkbox"/> May be included in the decision criteria for the definition of high risk of recurrence.	Not specified	<input checked="" type="checkbox"/> Patients aged < 50 years have increased risk.	Not specified	Not specified	Not specified	Not specified
ASCO [21, 29, 149]	<input checked="" type="checkbox"/> Node positivity can be used in conjunction with genomic profiling assays or Ki-67 score to estimate prognosis and guide treatment.	<input checked="" type="checkbox"/> Can be used in conjunction with Ki-67 score to guide chemotherapy in high-risk patients.	<input checked="" type="checkbox"/> Can be used in conjunction with Ki-67 score to guide chemotherapy in high-risk patients.	<input checked="" type="checkbox"/> Age can be used in conjunction with genomic profiling assays to estimate prognosis and guide treatment.	Not specified	<input checked="" type="checkbox"/> & <input checked="" type="checkbox"/> Ki-67 should not be used to guide choice of adjuvant chemotherapy, apart from patients with node-positive early breast cancer with a high risk of recurrence, where individuals with a Ki-67 score of ≥ 20% may be offered 2 years of abemaciclib plus endocrine therapy.	<input checked="" type="checkbox"/> The clinician should not use circulating tumour cells to guide decisions about adjuvant systemic therapy.	Not specified
ECIBC [150]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
ESMO [17]	<input checked="" type="checkbox"/> One of the most important prognostic factors in early breast cancer.	<input checked="" type="checkbox"/> One of the most important prognostic factors in early breast cancer.	<input checked="" type="checkbox"/> One of the most important prognostic factors in early breast cancer.	<input checked="" type="checkbox"/> Age should be taken into consideration in conjunction with other factors and should not be the sole determinant for withholding or recommending a treatment.	<input checked="" type="checkbox"/> One of the most important prognostic factors in early breast cancer.	<input checked="" type="checkbox"/> Use of Ki-67 is recommended. However, there is no final consensus on cut-off; values < 10% are considered low and > 30% are considered high.	Not specified	Not specified

Continued next page



► **Table 3** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): clinicopathological prognostic factor. (Continued)

Guideline	Lymph node involvement	Tumour size	Tumour grade	Age	ER and PR expression level (in patients who are HR+, HER2-)	Ki-67	Circulating tumour cells	Bone marrow involvement
NICE [151, 152]	<p>✓</p> <p>Can be used in conjunction with genomic profiling assays to guide treatment.</p>	<p>✓</p> <p>Can be used to guide treatment.</p>	<p>✓</p> <p>Can be used to guide treatment.</p>	Not specified	Not specified	Not specified	Not specified	Not specified
Ontario Health [153]	<p>✓</p> <p>Node positivity can be used in conjunction with genomic profiling assays to estimate prognosis and guide treatment.</p>	<p>✓</p> <p>Can be used in conjunction with genomic profiling assays to estimate prognosis and guide treatment.</p>	<p>✓</p> <p>Can be used in conjunction with genomic profiling assays to estimate prognosis and guide treatment.</p>	<p>✓</p> <p>Patients aged &lt; 50 years may still benefit from chemotherapy despite low-risk scores from multigene assay testing. Premenopausal patients aged &lt; 50 years have a significant benefit from chemotherapy despite low-risk scores from multigene assay testing. Risk scores should be interpreted with caution, and decisions should be made while considering other clinical, pathological, or patient-related factors.</p>	Not specified	Not specified	Not specified	Not specified
SEOM guidelines [154]	<p>✓</p> <p>Node positivity indicates high risk.</p>	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified

Continued next page

► **Table 3** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): clinicopathological prognostic factor. (Continued)

Guideline	Lymph node involvement	Tumour size	Tumour grade	Age	ER and PR expression level (in patients who are HR+, HER2-)	Ki-67	Circulating tumour cells	Bone marrow involvement
St. Gallen [16]	<input checked="" type="checkbox"/> Node positivity can be used in conjunction with genomic profiling assays to estimate prognosis and guide treatment.	<input checked="" type="checkbox"/> Panellists recommended adjuvant endocrine therapy for nearly all patients with ER-positive tumours that were even only micro-invasive or ≥ 1 mm in size, for reducing distant recurrence, in-breast recurrence, and second breast cancers.	<input checked="" type="checkbox"/> Serves as a prognostic marker for recurrence risk.	<input checked="" type="checkbox"/> Age can be used to guide some treatment approaches.	<input checked="" type="checkbox"/> Lower ER expression indicates less favourable tumour biology.	<input checked="" type="checkbox"/> Serves as a prognostic marker for recurrence risk. The Panel could not define a consistent Ki-67 threshold between 10% and 25% for recommending chemotherapy in ER-positive, node-negative breast cancer, and a large fraction of the Panel believe that such a threshold was simply not known.	Not specified	Not specified

indicates recommended;  indicates not recommended.

AGO: German Gynaecological Oncology Group, ASCO: American Society of Clinical Oncology, ECIBC: European Commission Initiative on Breast Cancer, EPclin: EndoPredict score + tumour size and nodal status, ER: oestrogen receptor, ESMO: European Society for Medical Oncology, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, IHC: immunohistochemistry, IHC4+C: IHC4 plus clinical and pathological features, NICE: UK National Institute for Health and Care Excellence, PR: progesterone receptor, RS: recurrence score

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## Conflict of Interest

Professor Fasching: Personal fees from Novartis, grants from BioNTech, personal fees from Pfizer, personal fees from Daiichi Sankyo, personal fees from AstraZeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from Seattle Genetics, personal fees from Roche, personal fees from Hexal.

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► **Table 4** Summary of national and international guideline recommendations on prognostic testing in early breast cancer (ER+, HER2-): prognostic scoring system/model.

Guideline	Nottingham Prognostic Index	Adjuvant! Online	PREDICT	CTS5	IHC3 and IHC4	CanAssist Breast
AGO [20, 148]	Not specified	Not specified	 Can be used in luminal early breast cancer to estimate prognosis.	 May be included in the decision criteria for the definition of high risk of recurrence.	 May be included in the decision criteria for the definition of high risk of recurrence.	Not specified
ASCO [21, 149]	Not specified	Not specified	Not specified	Not specified	 If a patient has ER/PR+, HER2- (node-positive or node-negative) breast cancer, the clinician <b>should not use</b> IHC4 to guide decisions about adjuvant systemic chemotherapy. If a patient has ER/PR+, HER2- (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician <b>should not use IHC4</b> to guide decisions about extended endocrine therapy.	Not specified
ECIBC [150]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
ESMO [17]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
NICE [151, 152]	 Can be used in conjunction with genomic profiling assays to guide treatment.	Not specified	 Can be used in conjunction with genomic profiling assays to guide treatment.	Not specified	 <b>Not recommended</b> for guiding adjuvant chemotherapy decisions for individuals in this patient population with node-negative disease because the analytical validity of the test is uncertain.	Not specified
Ontario Health [153]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
SEOM guidelines [154]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified
St. Gallen [16]	Not specified	Not specified	Not specified	Not specified	Not specified	Not specified

 indicates recommended;  indicates not recommended.

AGO: German Gynaecological Oncology Group, ASCO: American Society of Clinical Oncology, ECIBC: European Commission Initiative on Breast Cancer, EPclin: EndoPredict score + tumour size and nodal status, ER: oestrogen receptor, ESMO: European Society for Medical Oncology, HER2: human epidermal growth factor receptor 2, HR: hormone receptor, IHC: immunohistochemistry, IHC4+C: IHC4 plus clinical and pathological features, NICE: UK National Institute for Health and Care Excellence, PR: progesterone receptor, RS: recurrence score

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