ASCO special articles

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

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abstract

PURPOSE To update recommendations on appropriate use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer.

METHODS An updated literature search identified randomized clinical trials and prospective-retrospective studies published from January 2016 to October 2021. Outcomes of interest included overall survival and disease-free or recurrence-free survival. Expert Panel members used informal consensus to develop evidence-based recommendations.

RESULTS The search identified 24 studies informing the evidence base.

RECOMMENDATIONS Clinicians may use Onco*type* DX, MammaPrint, Breast Cancer Index (BCI), and EndoPredict to guide adjuvant endocrine and chemotherapy in patients who are postmenopausal or age > 50 years with early-stage estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative (ER+ and HER2–) breast cancer that is node-negative or with 1-3 positive nodes. Prosigna and BCI may be used in postmenopausal patients with node-negative ER+ and HER2– breast cancer. In premenopausal patients, clinicians may use Onco*type* in patients with node-negative ER+ and HER2– breast cancer. Current data suggest that premenopausal patients with 1-3 positive nodes benefit from chemotherapy regardless of genomic assay result. There are no data on use of genomic tests to guide adjuvant chemotherapy in patients with ≥ 4 positive nodes. Ki67 combined with other parameters or immunohistochemistry 4 score may be used in postmenopausal patients without access to genomic tests to guide adjuvant therapy decisions. BCI may be offered to patients with 0-3 positive nodes who received 5 years of endocrine therapy without evidence of recurrence to guide decisions about extended endocrine therapy. None of the assays are recommended for treatment guidance in individuals with HER2-positive or triple-negative breast cancer. Treatment decisions should also consider disease stage, comorbidities, and patient preferences.

Additional information is available at www.asco.org/breast-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Since the 2016 guidelines on biomarkers for breast cancer, several publications have provided additional perspectives on use of specific assays broadly, or in women on the basis of menopausal status or age.[1] This guideline update provides evidence-based recommendations to optimally use currently available biomarkers in the population of women presenting with early-stage breast cancer with known estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status. In 2016, ASCO endorsed the use of genomic tests (Onco*type* Dx, MammaPrint, Prosigna, EndoPredict, and Breast Cancer Index [BCI]) in patients with early-stage breast cancer to guide decisions of adjuvant endocrine and chemotherapy. The 2016 guideline was further updated by two focused guidelines on the use of MammaPrint[2] and Onco*type* Dx[3] following the publication of the MINDACT and TAILORx trials, respectively. In the past few years, new data have allowed for further guidance on the use of these tests according to the age of patients and the number of involved lymph nodes. In addition, new biomarkers (eg, programmed cell death receptor ligand-1 [PD-L1], tumor-infiltrating lymphocytes [TILs], and circulating tumor DNA [ctDNA]) and new applications (eg, to guide

THE BOTTOM LINE

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

Guideline Questions

1. For patients with early-stage ER-positive, HER2-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy for a newly diagnosed cancer or in the extended setting?
2. For patients with early-stage HER2-positive breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy?
3. For patients with early-stage triple-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant chemotherapy?

Target Population

Women with early-stage invasive breast cancer being considered for adjuvant endocrine and chemotherapy.

Target Audience

Medical, surgical, and radiation oncologists; oncology nurses and physician assistants; pathologists; general practitioners; and patients.

Methods

An Expert Panel was convened to update the clinical practice guideline recommendations on the basis of a review of recently published literature (2016-2021).

Recommendations. A summary of the clinical application of the recommendations is presented in Table 1 and in Figure 1. Refer to Appendix Table A4 (online only) for a summary of recommendations including the 2016 guidelines recommendations that did not require an update.

Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer

Oncotype DX (21-gene recurrence score, 21-gene RS).

Recommendation 1.1. If a patient has node-negative breast cancer, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. In the group of patients in Recommendation 1.1 with Oncotype DX recurrence score ≥ 26, the clinician should offer chemoendocrine therapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX recurrence score 16 to 25, the clinician may offer chemoendocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX recurrence score is ≥ 26 (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, the Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.7. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

MammaPrint (70-gene signature).

Recommendation 1.8. If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

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THE BOTTOM LINE (CONTINUED)

Recommendation 1.9. If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.11. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).
Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

EndoPredict (12-gene risk score).

Recommendation 1.12. If a patient is postmenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.13. If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 1.14. 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 (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Prosigna (PAM50).

Recommendation 1.15. If a patient is postmenopausal and has breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.16. If a patient is premenopausal and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.18. 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 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Ki67.

Recommendation 1.19. If a patient is postmenopausal and has stage I-II breast cancer, the clinician may use Ki67 expression in conjunction with other clinical and pathologic parameters to guide decisions on adjuvant endocrine and chemotherapy when multigene assays are not available. Ki67 expression levels are most informative for prognosis when the level is < 5% (low proliferation) or > 30% (high proliferation) because technical reliability of distinguishing values within this range is limited (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.20. If a patient is postmenopausal and has breast cancer, there is insufficient evidence to use baseline Ki67 expression or Ki67 level after 2 weeks of neoadjuvant aromatase inhibitor (AI) therapy to guide decisions on adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.21. Despite the limitations associated with Ki67 testing, a patient with node-positive breast cancer with a high risk of recurrence and a Ki67 score of ≥ 20% as determined by a US Food and Drug Administration (FDA)–approved test may be offered 2 years of abemaciclib plus endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Immunohistochemistry 4.

Recommendation 1.22. If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes, the clinician may use immunohistochemistry 4 (IHC4) score to guide decisions for adjuvant endocrine and chemotherapy if the score has been validated in the performing laboratory and if multigene assays are not available (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Extended Endocrine Therapy for ER-Positive HER2-Negative Breast Cancer

Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4.

Recommendation 1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Breast Cancer Index.

Recommendation 1.24. If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.25. If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical treatment score post-5 years.

Recommendation 1.26. If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the clinical treatment score post-5 years (CTS5) web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10), which could assist in decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

HER2-Positive Breast Cancer or Triple-Negative Breast Cancer

Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4.

Recommendation 1.27. If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Emerging Biomarkers

Tumor-infiltrating lymphocytes.

Recommendation 1.28. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use TILs to guide decisions for (neo)adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

PD-L1 testing.

Recommendation 1.29. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use PD-L1 testing to guide decisions for (neo)adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Circulating tumor cells.

Recommendation 1.30. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use circulating tumor cells (CTC) to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Circulating tumor DNA.

Recommendation 1.31. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use ctDNA to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Tables A2 and A3 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

TABLE 1. Biomarkers to Guide Decisions on Endocrine and Chemotherapy for Patients With Early-Stage Invasive Breast Cancer

ER+ and HER2–	Premenopausal or Age ≤ 50 Years (evidence quality/strength of recommendation)	Postmenopausal or Age > 50 Years (evidence quality/strength of recommendation)
Node-negative	Oncotype DX (*high/strong*)	Oncotype DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Prosigna (*intermediate/moderate*) Ki67[b] (*intermediate/moderate*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
1-3 positive nodes	Insufficient evidence to recommend a biomarker for use	Oncotype DX (*high/strong*) MammaPrint[a] (*intermediate/strong*) EndoPredict (*intermediate/moderate*) Ki67[b] (*intermediate/strong*) IHC4[b] (*intermediate/moderate*) BCI[c] (*intermediate/moderate*)
≥ 4 positive nodes	Insufficient evidence to recommend a biomarker for use	
HER2+ (ER+ or ER–)	No mature evidence to recommend use of any other biomarker for this patient population	
ER–/HER2–	No mature evidence to recommend use of any other biomarker for this patient population	

Abbreviations: BCI, Breast Cancer Index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC4, immunohistochemistry 4.
[a]Only in women with high clinical risk.
[b]Only if locally validated and together with other parameters in patients who do not have access to genomic tests.
[c]May also be offered to women who received 5 years of endocrine therapy without evidence of recurrence.

extended endocrine therapy) have been developed. This report aims to provide more precise guidelines on how to use previously endorsed genomic tests and to provide recommendations on the use of new biomarkers to guide endocrine and chemotherapy recommendations in individuals with ER-positive, HER2-negative tumors, and in those with HER2-positive or triple-negative breast cancer (TNBC). In recent months, several new systemic therapies have demonstrated benefit in patients with early-stage breast cancer, including olaparib and pembrolizumab. The use of these agents is not discussed in this update.

GUIDELINE QUESTIONS

This clinical practice guideline addresses three overarching clinical questions: (1) For patients with early-stage ER-positive, HER2-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy for a newly diagnosed cancer or in the extended setting? (2) For patients with early-stage HER2-positive breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy? (3) For patients with early-stage triple-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant chemotherapy?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology (JCO)* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed (January 2016 to October 2021) and Cochrane Library (January 2016 to October 2021) of phase III randomized clinical trials (RCTs), prospective-retrospective studies, and clinical experience. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: women with early-stage invasive breast cancer being considered for adjuvant endocrine and chemotherapy, with analyses on patient groups with:

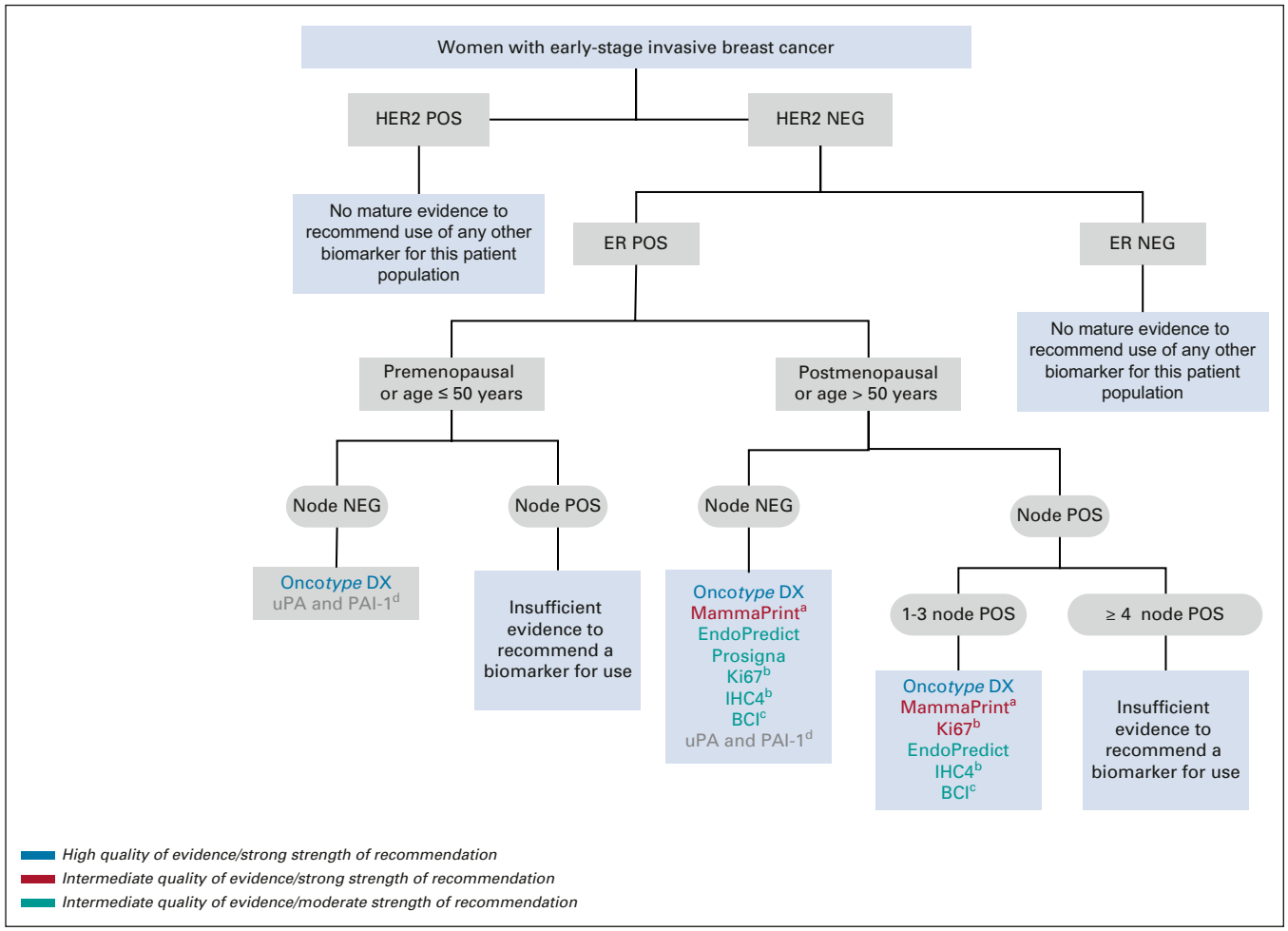

FIG 1. Algorithm on biomarkers to guide decisions on adjuvant endocrine and chemotherapy. [a]Only in patients with high clinical risk per MINDACT categorization. [b]Only if locally validated and together with other parameters in patients who do not have access to genomic tests. [c]May also be offered to patients who received 5 years of endocrine therapy without evidence of recurrence. [d]This biomarker is no longer in use. BCI, Breast Cancer Index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC4, immunohistochemistry 4; NEG, negative; PAI-1, plasminogen activator inhibitor-1; POS, positive; uPA, Urokinase plasminogen activator.

- ER-positive, HER2-negative disease, for a newly diagnosed cancer or in the extended setting
- HER2-positive disease (ER-positive or -negative)
- TNBC (ER-negative, progesterone receptor [PR]–negative, and HER2-negative)
- Clinical risk and menopausal status or age

- Publications were included if they reported rigorously conducted systematic reviews (with or without meta-analyses), RCTs, and retrospective biomarker analyses of samples from completed prospective RCTs

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.[4] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, and evidence quality are provided with each recommendation (Appendix Tables A2 and A3).

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

In contrast to previous guidelines, we refer to potentially endocrine therapy sensitive cancers as ER+ regardless of PR status. PR positivity in the absence of ER positivity is

very rare and should alert physicians for possible technical errors in the staining process.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 562 articles were identified in the updated literature search. After applying the eligibility criteria, 24 articles remained, forming the evidentiary basis for the guideline recommendations. The identified trials included 14 RCTs (three studies with multiple publications)[5-18] and 10 prospective-retrospective studies.[19-28]

The identified trials were published between 2016 and 2021. The trials included interventions exploring various biomarkers including, Onco*type* DX, MammaPrint, EndoPredict, Prosigna, Ki67, IHC4, BCI, CTC, ctDNA, TILs, and PD-L1. Characteristics of the studies' participants are in the Data Supplement (online only).

The primary outcomes in most of these studies included disease-free survival (DFS), recurrence-free survival (RFS), event-free survival, pathologic complete response, and overall survival (OS). No studies evaluated adverse outcomes of biomarker testing or reported on changes in quality-of-life outcomes attributable to biomarker testing.

Data analysis regarding unchanged recommendations is reviewed in the 2016, 2017, and 2019 versions of the guideline.[1-3]

Study Quality Assessment

Study design aspects related to individual study quality, quality of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Manual for more information and for definitions of ratings for overall potential risk of bias.

Study quality was formally assessed for the 14 RCTs identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results.

RECOMMENDATIONS

Clinical Question 1

For patients with early-stage ER-positive, HER2-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy for a newly diagnosed cancer or in the extended setting?

Newly diagnosed ER-positive, HER2-negative breast cancer. **Onco*type* DX (21-gene recurrence score, 21-gene RS).**

Recommendation 1.1. If a patient has node-negative

breast cancer, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2. In the group of patients in Recommendation 1.1 with Oncotype DX recurrence score greater or equal to 26, the clinician should offer chemoendocrine therapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX recurrence score 16 to 25, the clinician may offer chemoendocrine therapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX recurrence score is ≥ 26 (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.7. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine Oncotype DX to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

Literature review and clinical interpretation. In TAILORx, participants with ER-positive, HER2-negative, lymph node-negative breast cancer who had an intermediate Oncotype DX 21-gene recurrence score (RS) of 11-25 were randomly assigned to adjuvant endocrine therapy alone or chemotherapy followed by endocrine therapy (chemoendocrine therapy).[16] The trial demonstrated no chemotherapy benefit in patients with intermediate RS age > 50 years; however, if age ≤ 50 years, there was detectable benefit from adjuvant chemotherapy if the RS was 16-25. For patients age ≤ 50 years, the absolute benefit increased as the RS increased (invasive DFS [IDFS] rate at 5 years: 92% *v* 94.7% for RS 16-20, and 86.3% *v* 92.1% for RS 21-25) for endocrine versus chemoendocrine therapy, respectively. In TAILORx, patients with an RS of 26-100 were treated with chemoendocrine therapy, mostly with taxane and/or anthracycline-based chemotherapy, and had an estimated IDFS rate of 87.6% and freedom of distant recurrence (DR) of 93% at 5 years.[12] These rates were superior to those anticipated with endocrine therapy alone. Although knowledge generated from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG or Oxford Overview) provides evidence for a benefit of adjuvant chemotherapy in patients with ER-positive, HER2-negative breast cancer, the RS cutoff above which such benefit occurs is still unknown in postmenopausal women. This has been fixed at 26 on the basis of TAILORx trial. Incorporating clinical risk offered additional prognostic information to the RS and further informed the absolute benefit of chemotherapy in patients age ≤ 50 years with an RS of 11-25.[16] Please refer to previous guideline update for more details.[3] RSClin was developed as a tool that integrates RS 0-100 with tumor grade, tumor size, and age to further individualize risk and guide discussions regarding adjuvant chemotherapy benefit for women with ER-positive, HER2-negative, lymph node–negative breast cancer.[29]

In the RxPONDER trial, participants with ER-positive, HER2-negative breast cancer, 1-3 axillary lymph nodes positive, and RS 0-25 were randomly assigned to endocrine therapy alone or taxane and/or anthracycline-based chemoendocrine therapy.[30] In the overall population of participants with RS 0-25, there was no improvement in 5-year IDFS with the addition of adjuvant chemotherapy to endocrine therapy. At the third planned interim analysis, chemotherapy benefit for IDFS differed by menopausal status in a prespecified analysis, leading to separate analyses. In the 67% of participants who were postmenopausal, 5-year IDFS rates were 91.9% and 91.3%, for endocrine and chemoendocrine therapy, respectively, with no chemotherapy benefit (hazard ratio [HR] = 1.02; 95% CI, 0.82 to 1.26; $P = .89$). In premenopausal women (33.2% of RxPONDER participants), the 5-year IDFS rates were 89.0% and 93.9% for endocrine therapy and chemoendocrine therapy (HR = 0.60; 95% CI, 0.43 to 0.83; $P = .002$), with similar improvement in distant DFS (HR = 0.58; 95% CI, 0.39 to 0.87, $P = .009$). In premenopausal women, chemotherapy benefit was seen across subgroups. Although relative chemotherapy benefit did not increase with higher RS, there was greater absolute chemotherapy benefit observed with higher RS in premenopausal women with RS 0-25. There are no randomized trials evaluating the clinical utility of the RS in patients with ≥ 4 lymph nodes.

The prognostic utility of the RS in premenopausal women with node-negative and node-positive breast cancer was demonstrated in other prospective cohorts.[31] The TAILORx and RxPONDER trials were not designed to test whether chemotherapy can be replaced by ovarian function suppression (OFS) in premenopausal women with node-positive breast

cancer or lymph node–negative disease with RS 16-25. The rate of OFS was limited in both TAILORx and RxPONDER. Within 2 years of study entry in TAILORx, OFS alone or with an AI was used in 4% and 7%, respectively, in premenopausal women randomly assigned to endocrine therapy alone. In premenopausal participants randomly assigned to endocrine therapy alone in RxPONDER, the rate of OFS plus tamoxifen, OFS with an AI, or OFS plus tamoxifen and an AI within 1 year of study entry was 5%, 12%, and 3%, respectively. It is possible that therapy-induced amenorrhea contributes to the benefit but it should be noted that many women with chemotherapy-induced amenorrhea continue to have premenopausal estradiol levels.[32] Therefore, direct antitumor effects of chemotherapy also likely contribute to the observed benefit.

MammaPrint (70-gene signature).

Recommendation 1.8. If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.9. If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.11. If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making.

Literature review and clinical interpretation. The clinical utility of the 70-gene signature MammaPrint has been evaluated in a prospective randomized trial (MINDACT),[14] which included 6,693 women with node-negative or 1-3 node-positive, early-stage breast cancer. Patients were eligible irrespective of breast cancer subtype, but the majority had ER-positive tumors. Patients were classified as having high or low clinical risk (Appendix Table A5, online only). The primary objective was to test whether the lower boundary of 95% CI for the 5-year distant metastasis-free survival (DMFS) was above 92% in patients with clinically high risk and genomic low risk tumors, who did not receive adjuvant chemotherapy. The initial publication[5] reported that the trial met its primary objective. Indeed, the 5-year DMFS was 94.4% (95% CI, 92.5 to 96.2) in the population of interest. In this initial report, a 1.5% difference was observed in the 5-year DMFS between patients treated or not with adjuvant chemotherapy, and presenting with a clinically high-risk, genomic low-risk breast cancer. A recent update of MINDACT reported results according to age (≤ 50 or > 50 years).[14] In the subgroup of women presenting with ER-positive, HER2-negative early-stage breast cancer with 0-3 axillary nodes involved and a high clinical risk, low genomic risk, adjuvant chemotherapy was associated with a benefit in women age ≤ 50 years but not in the ones age > 50 years. In the group of women ≤ 50 ($n = 464$), the 8-year DMFS were 93.6% (95% CI, 89.3 to 96.3) for patients who received adjuvant chemotherapy versus 88.6% (95% CI, 83.5 to 92.3) for those without chemotherapy. Conversely, the 8-year DMFS were 90.2% (95% CI, 86.8 to 92.7) and 90.0% (95% CI, 86.6 to 92.6) in patients > 50 years ($n = 894$) who received adjuvant chemotherapy versus those who did not. On the basis of these data, the Panel does not recommend the use of MammaPrint in patients age ≤ 50 years presenting with a high clinical risk, ER-positive, HER2-negative early-stage breast cancer with 0-3 positive nodes. In patients age ≤ 50 years with 0-3 positive nodes and high clinical risk, there is no evidence that ordering a MammaPrint would guide adjuvant endocrine and chemotherapy recommendations.

A remaining question was whether patients with low clinical risk could benefit from testing their tumors with MammaPrint. In the group of patients presenting with a low clinical risk, high genomic risk, adjuvant chemotherapy did not improve DMFS (HR = 0.85; 95% CI, 0.53 to 1.37). Nevertheless, the sample size was small ($n = 690$) and did not allow formal conclusions. The utility of using MammaPrint to determine whether to recommend chemo-endocrine therapy in patients with low clinical risk is, therefore, an open research question. Please refer to previous guideline update for more details.[2]

EndoPredict (12-gene risk score).

Recommendation 1.12. If a patient is postmenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.13. If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 1.14. 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 (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. EPclin is a tool that integrates both genomic prognostic factors (eight cancer-related genes, three reference genes, and one control gene by reverse transcriptase polymerase chain reaction [PCR]) and anatomic prognostic factors (tumor size and nodal status) to generate a risk score. This risk score can identify patients at such low risk of late recurrence that systemic chemotherapy or extended endocrine therapy may not be indicated. Unlike MammaPrint and Onco*type* DX, which have to be centrally determined, EndoPredict can be performed reliably in local laboratories, which can decrease cost and logistical issues. Furthermore, EndoPredict can be performed on presurgical biopsies and on surgical specimens with good correlation coefficients.

Prognostic value of the EPclin score in women with ER-positive, HER2-negative breast cancer. The prognostic value of EndoPredict (EPclin) has been validated in several prospective-retrospective trials of women with ER-positive, HER2-negative breast cancer including two trials of 5 years of adjuvant endocrine therapy alone (ABCSG 6 and 8 and TransATAC)[17,33] and one trial of chemoendocrine therapy in lymph node–positive women (GEICAM 9906).[34]

In the ABCSG 6/8 cohort, EPclin was evaluated in 1,702 women with ER-positive, HER2-negative breast cancer who received 5 years of endocrine therapy alone.[17] Of those, 77.8% of patients had node-negative disease and 35% of patients had 1-3 positive nodes. The 10-year DR-free rates for patients with low risk EPclin were 95.5% (94.0 to 97.1) with node-negative disease and 95.6% (92.2 to 99.1) with 1-3 positive nodes. Similar data were seen in a study of invasive lobular carcinoma demonstrating that in patients with low-risk EPclin, the 10-year DR rate was 4.6% (2.5 to 8.4) for node-negative disease and 6.4% (1.6 to 23.5) for node-positive disease.[35] These results are consistent with data from the TransATAC trial in which postmenopausal women with 1-3 positive nodes and EPclin low-risk classification had a DR-free rate of 94.4% when treated with endocrine therapy alone.[33] EPclin may identify a population of women with 0-3 positive nodes who have low enough risk of DR at 10 years and can be treated with 5 years of endocrine therapy alone.

Predictive value of the EPclin score in women with ER-positive, HER2-negative breast cancer. A comparative, nonrandomized analysis of EPclin in women who received adjuvant endocrine therapy alone (ABCSG 6/8, TransATAC) compared with those receiving chemoendocrine therapy (GEICAM 2003-02/9906) was performed to determine the predictive power of EPclin for chemotherapy benefit.[36] In the 3,746 women who were included in the joint analysis, those with high-risk EPclin had a significant improvement in 10-year distant recurrence–free interval (DRFI) with the addition of chemotherapy to endocrine therapy (12% 10-year DRFI) versus endocrine therapy alone (20% 10-year DRFI). This indirect comparison suggested that a high-risk EPclin score could predict chemotherapy benefit in women with ER-positive, HER2-negative disease. A meta-analysis from the EBCTCG of 2,185 samples tested by Myriad Genetics showed similar results of an absolute chemotherapy benefit for women with high-risk EPclin score of between 5.3% and 7.3%.[37] A small prospective study of 373 women with ER-positive, HER2-negative breast cancer with 0-3 positive nodes has also demonstrated benefit of chemotherapy with high-risk EPclin when patients underwent adjuvant chemoendocrine therapy (3-year DFS of 96.3%; 95% CI, 92.2 to 100) in contrast to patients who underwent endocrine therapy only (3-year DFS of 91.5%; 95% CI, 82.7 to 100).[38] These analyses demonstrate that rates of DR with high-risk EPclin can be reduced by administration of adjuvant chemotherapy. Two prospective, randomized trials (UNIRAD and RESCUE) are currently accruing, which will evaluate EPclin prognostic and predictive efficacy.

As data specifically for premenopausal women and patients with > 3 positive nodes have not been assessed in a prospective, randomized trial, the Panel does not recommend the routine use of EndoPredict to guide decisions on adjuvant endocrine and chemotherapy in this patient population.

Prosigna (PAM50).

Recommendation 1.15. If a patient is postmenopausal and has breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.16. If a patient is premenopausal and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.18. 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 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review and clinical interpretation. Prosigna (PAM50) assesses the breast cancer molecular subtypes using the nanostring technology. When integrated with tumor size, it leads to the risk-of-recurrence score (ROR). The strongest evidence for Prosigna and ROR are coming from retrospective analyses of prospective randomized trials and from population-based studies. Nevertheless, as opposed to some other genomic tests, there are no data from prospective randomized trials testing its clinical utility.

In the TransATAC study,[33] 774 postmenopausal women with ER-positive, HER2-negative breast cancer were included. In this study, a high-ROR score was associated with inferior outcome (distant metastases; HR = 2.56; 95% CI, 1.96 to 3.35). The 10-year risk of DR in node-negative patients was 3% (95% CI, 1.6 to 5.8), 14% (95% CI, 9.4 to 20.8), and 32% (95% CI, 23.4 to 43.8) in patients presenting a low-, intermediate-, or high-ROR, respectively. In patients with 1-3 positive axillary nodes, the 10-year risk of DR was 0%, 20.7% (95% CI, 12 to 34), and 30.7% (95% CI, 22 to 41) in patients with low-, intermediate-, and high-ROR scores, respectively. Importantly, only 15 (8%) of the patients with 1-3 positive nodes presented a low-ROR score, suggesting that using ROR score in patients with 1-3 positive nodes is unlikely to change treatment recommendations in more than 90% of patients. In the same study, ROR was associated with an increased risk of distant relapse occurring between 5 and 10 years of follow-up (HR = 2.77; 95% CI, 1.93 to 3.96) in patients with node-negative disease. In a population-based study from Denmark,[39] samples from 2,558 women with ER-positive, HER2-negative were analyzed for Prosigna. All patients age 50 years or older received 5 years of endocrine therapy. In node-negative disease, the 10-year risks of distant relapse were 5.0% (95% CI, 2.9 to 8.0), 7.3% (95% CI, 4.8 to 10.6), and 17.8% (95% CI, 14.0 to 22.0) in patients with low-, intermediate-, and high-risk ROR score, respectively. In 1-3 node-positive disease, the 10-year risks of DR were 3.5% (95% CI, 1.9 to 6.1), 11.5% (95% CI, 8.0 to 15.6), and 22.1% (95% CI, 18.6 to 25.8) in patients with low-, intermediate-, and high-risk ROR scores, respectively. In the retrospective analysis of the prospective observational study,[40] ROR score was associated with a poor outcome (HR = 6.82; 95% CI, 2.62 to 17.81; $P < .001$ for high-ROR *v* low-ROR). Only 33% of patients had a diagnosis of node-positive disease in this study not allowing for any clinical conclusions. Finally, Jensen et al[41] reported that ROR score was predictive for the efficacy of cyclophosphamide, epirubicin, and fluorouracil versus cyclophosphamide, methotrexate, and fluorouracil (CMF) in the Danish DBCG89D trial. The HRs for cyclophosphamide, epirubicin, and fluorouracil efficacy over CMF were 1.01 (95% CI, 0.59 to 1.73), 0.78 (95% CI, 0.53 to 1.15), and 0.54 (95% CI, 0.36 to 0.80) in patients with low-, intermediate-, and high-ROR scores, respectively.

One study assessed the clinical validity of Prosigna and ROR in premenopausal women (N = 460).[19] This analysis is a retrospective analysis of a prospective randomized trial.[42] In this analysis, ROR score was associated with prognosis in patients who did not receive systemic treatment (HR = 1.23; 95% CI, 1.09 to 1.39; $P < .001$ for a 10-point difference). Among the patients receiving CMF chemotherapy, a significant interaction was reported between ROR score and efficacy of CMF. CMF benefit appears to be greater in patients with basal-like breast cancer (HR = 0.14; 95% CI, 0.06 to 0.32). Validation of these findings is recommended through the additional testing of Prosigna and ROR in existing or ongoing chemotherapy clinical trials.

Ki67.

Recommendation 1.19. If a patient is postmenopausal and has stage I-II breast cancer, the clinician may use Ki67 expression in conjunction with other clinical and pathologic parameters to guide decisions on adjuvant endocrine and chemotherapy when multigene assays are not available. Ki67 expression levels are most informative for prognosis when the level is $< 5\%$ (low proliferation) or $> 30\%$ (high proliferation) because technical reliability of distinguishing values within this range is limited (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.20. If a patient is postmenopausal and has breast cancer, there is insufficient evidence to use baseline Ki67 expression or Ki67 level after 2 weeks of neoadjuvant AI therapy to guide decisions on adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.21. Despite the limitations associated with Ki67 testing, a patient with node-positive breast cancer with a high risk of recurrence and a Ki67 score of $\geq 20\%$ as determined by an FDA-approved test may be offered two years of abemaciclib plus endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Tumor proliferation has been linked in multiple studies to prognosis and chemotherapy sensitivity. All clinically validated multigene prognostic assays include a proliferation module that contains proliferation-related genes such as *MKI67*. Ki67 is a quantitative measure of proliferation, and higher expression levels of Ki67 have been associated with greater response to neoadjuvant chemotherapy (NACT) and inferior long-term survival. It has not been examined as a predictor of chemotherapy benefit in large adjuvant clinical trials. However, expression of Ki67 has been challenging to standardize across laboratories, and clinical studies examining Ki67 as a

prognostic or predictive marker have used differing cutoffs. Therefore, use of Ki67 expression has had limited clinical utility.

Many studies have been performed examining associations between Ki67 expression levels and both prognosis and prediction in hormone receptor–positive breast cancer. Essentially, all studies show that among ER-positive cancers, the higher the Ki67, the worse the long-term survival. Also, the higher the Ki67, the higher the likelihood of pathologic complete response to NACT. However, unlike ER or HER2, the expression distribution of Ki67 is not bimodal, and there is no natural threshold to define high or low Ki67 status. Different studies have used different definitions of high Ki67, which makes interpretation of the literature challenging. Interobserver and interlaboratory variability in Ki67 assessment and a lack of standards further hinder setting a universal Ki67 threshold. In an attempt to standardize a prognostic threshold, the St Gallen International Consensus on the Primary Therapy of Early Breast Cancer recommended ≥ 20% as the threshold to define high risk. In the past decade, the International Ki67 Breast Cancer Working Group has attempted to standardize Ki67 testing. The group recently reported that expression levels of Ki67 < 5% or > 30% can be reliably reported, but levels between those thresholds are unreliable.[43] Ki67 IHC results are most informative at the extreme ends of the spectrum (eg, Ki67 < 5% or > 30%). Ki67 percent positivity alone has modest prognostic and predictive value and must be interpreted in the context of other variables including age, grade, extent of ER positivity, HER2 status, size, and nodal status. Also, most studies of Ki67 expression have been conducted using samples from primarily postmenopausal women and in women with stage 1 or 2 breast cancer. It remains unclear whether these results can be extrapolated to premenopausal women or those with higher-stage breast cancer.

Ki67 expression has also been tested in the neoadjuvant endocrine therapy setting to guide adjuvant endocrine and chemotherapy recommendations for postmenopausal women. In the POETIC trial,[11] women with ER-positive, HER2-negative, stage 1-3 breast cancer whose tumors had Ki67 expression levels < 10% before any systemic therapy or that decreased to < 10% after 2 weeks of neoadjuvant AI therapy had 5-year breast cancer recurrence risk of 4.3% (95% CI, 2.9 to 6.3). This is in contrast to patients with Ki67 expression level > 10% at baseline; patients whose tumors' Ki67 expression level decreased to < 10% in 2 weeks had a 5-year recurrence of 8.4% (95% CI, 6.8 to 10.5) and those whose tumors' Ki67 expression level did not decrease had a 5-year recurrence of 21.5% (95% CI, 17.1 to 27.0). However, given the challenges with quantification of Ki67 expression levels described above, the use of Ki67 expression levels to guide care in the neoadjuvant setting remains investigational and should not be routinely used to guide care on the basis of currently available evidence.[43]

In 2021, the FDA approved abemaciclib in combination with endocrine therapy for the adjuvant treatment of patients with ER-positive, HER2-negative, node-positive breast cancer at high risk of recurrence and with a Ki67 score ≥ 20% as determined by an FDA-approved test (currently Agilent Technologies [formerly DAKO], Santa Clara, CA, MIB-1 anti-Ki67 antibody in a proprietary automated platform). We note that broad implementation of the FDA-approved platform will be challenging and considering the substantial experience with Ki67 staining in many pathology laboratories, laboratory-developed tests may perform equally well when cross-validated. There are also analytical differences between the way Ki67 was measured in the pivotal monarchE trial and the recommended method from the International Ki67 Breast Cancer Working Group about which pathologists should be aware.

Finally, it also should be noted that in the monarchE trial, patients with tumors that were Ki67 low (< 20%) and Ki67 high (> 20%) benefited similarly from abemaciclib (HR = 0.7 and HR = 0.63, respectively), although with different absolute reduction in cancer recurrence because of different baseline risk.[13] Therefore, Ki67 functions as a prognostic test to define individuals at higher risk of disease recurrence, rather than as a predictive assay to define any potential treatment-sensitive cancers. When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity and financial cost).

Immunohistochemistry 4.

Recommendation 1.22. If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes, the clinician may use IHC4 score to guide decisions for adjuvant endocrine and chemotherapy if the score has been validated in the performing laboratory and if multigene assays are not available (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. The IHC4 algorithm combines ER, PR, HER2, and Ki67 into a single score that provides information on residual risk of recurrence in patients treated with endocrine therapy. The algorithm was originally developed on the TransATAC cohort.[44] In the original report, the IHC4 algorithm was shown to provide similar evidence to that provided by the 21-gene RS when the four IHC markers were assessed in a central laboratory. The IHC4 algorithm was then validated on samples from postmenopausal women with hormone receptor–positive breast cancer treated on the Tamoxifen Versus Exemestane Adjuvant Multicenter (TEAM) Trial, and was shown to provide prognostic value when added to standard clinical prognostic factors.[45] However, in all published studies IHC4 was determined in central highly specialized laboratories. As noted above, there remain analytic concerns about the

assessment of Ki67 expression and the reproducibility, accuracy, and clinical validity of IHC4 in the community setting is unknown. Therefore, use of the IHC4 algorithm is not routinely recommended, but may be helpful in decision making if the assay is performed in an experienced clinical pathology laboratory and if better standardized multiparameter genomic assays are not available.

Extended endocrine therapy for ER-positive, HER2-negative breast cancer.

Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4.

Recommendation 1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 tests to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. Several retrospective studies have shown a prognostic value to predict relapse in individuals who have received endocrine therapy for 5 versus more than 5 years. Nevertheless, these studies are sparse and did not test the value of the genomic tests in the context of multiple randomized trials testing efficacy of extended adjuvant endocrine therapy.

Breast Cancer Index.

Recommendation 1.24. If a patient has node-negative or node-positive with 1-3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.25. If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Extended adjuvant endocrine therapy (beyond 5 years) has demonstrated improved outcomes albeit with modest absolute benefit and added toxicity and tolerability challenges. Furthermore, although extended endocrine therapy is endorsed by several clinical practice guidelines, clear guidance on individualized approaches to optimize patient selection for prolonged endocrine regimens remains limited. This underscores the need for prognostic and predictive information from genomic analysis that can help guide this important clinical decision.

Proof-of-concept and validation of the prognostic performance of the BCI with prespecified risk groups for predicting early (0-5 years) and late (> 5 years) DRs was provided from retrospective analyses of two cohorts: first, tumor samples from tamoxifen-treated, ER-positive, node-negative, postmenopausal women enrolled in the Stockholm trial (N = 317) and second, a multi-institutional cohort consisting of ER-positive, node-negative, tamoxifen-treated premenopausal (30%) and postmenopausal (70%) women from two academic medical centers (N = 358).[46] On the Stockholm tamoxifen-treated arm, BCI classified 64, 20, and 16% of women into low-, intermediate-, and high-risk groups, respectively. The overall 10-year distant RFS (DRFS) was 95.2% (95% CI, 92.2 to 98.3), 88.3% (95% CI, 80.5 to 96.9), and 78.9% (95% CI, 68.0 to 91.5), respectively ($P = .0004$).

The predictive component of BCI, the (HOXB13/IL17BR [H/I]) ratio, predicted benefit from an additional 5 years of letrozole after 5 years of adjuvant tamoxifen on the basis of the prospective-retrospective, nested case-control study in a subset of patients from NCIC Clinical Trials Group MA.17 trial.[47] The parent trial enrolled postmenopausal women, defined as age at least 50 years at the start of adjuvant tamoxifen therapy, age ≥ 50 years at the start of tamoxifen therapy but postmenopausal at the initiation of tamoxifen therapy, age < 50 years at the start of tamoxifen therapy but had undergone bilateral oophorectomy, premenopausal, and age< 50 years at the start of tamoxifen therapy but became amenorrheic during chemotherapy or treatment with tamoxifen, or any age but had postmenopausal levels of luteinizing hormone or follicle-stimulating hormone before study entry. The cohort that was included for the BCI analyses consisted of 83 patients with local, regional, or DR (cases) matched with 166 patients without recurrence (control; total N = 249), with majority of patients age ≥ 50 years (cases: age < 50 years 5%, control: age < 50 years 3%) with T1 or T2 tumors and node-positive disease (approximately 58%) who did not receive adjuvant chemotherapy. In the adjusted model, which included all clinicopathologic factors as covariates, high H/I ratio was statistically significantly associated with patient benefit from letrozole (odds ratio = 0.33; 95% CI, 0.15 to 0.73; $P = .006$), which represented a 67% reduction in the risk of recurrence with extended letrozole treatment compared with placebo. Additionally, patients with high H/I-expressing tumors had a 16.5% reduction in the absolute risk of recurrence at 5 years when taking letrozole, compared with placebo. The details of nodal status (1-3 positive nodes *v* ≥ 4 positive nodes) were not provided in this analysis or in the parent MA.17 trial.

The study by Bartlett et al,[20] Trans-aTTom, a multi-institutional, prospective-retrospective study evaluated tumors from 583 ER-positive, node-positive patients (15% were age < 50 years; 4% of women were premenopausal, 86% were postmenopausal, and 4% were perimenopausal) and demonstrated that 49% classified as BCI-High derived a significant benefit from 10 versus 5 years of tamoxifen treatment (HR = 0.35; 95% CI, 0.15 to 0.86; 10.2% absolute

risk reduction on the basis of recurrence-free interval [RFI]; $P = .027$). BCI-low patients showed no significant benefit from extended endocrine therapy (HR = 1.07; 95% CI, 0.69 to 1.65; −0.2% absolute risk reduction; $P = .768$). Furthermore, although continuous BCI levels predicted the magnitude of benefit from extended tamoxifen, centralized ER and PR did not. After adjusting for clinicopathologic factors, the interaction between extended tamoxifen treatment and BCI (H/I) was statistically significant ($P = .012$). The details of nodal status (1-3 positive nodes $v \geq 4$ positive nodes) were not provided in this analysis.

The Investigation on the Duration of Extended Letrozole (IDEAL) trial was a randomized controlled trial conducted in postmenopausal women and was designed to directly examine the potential benefit of extended durations of AI therapy.[8] In the prospective-retrospective translational study of the randomized IDEAL trial (N = 908; 50% of the parent trial population), 33% were age < 50 years, 73% node-positive (1-3 positive nodes 47%, 4-9 lymph nodes 11%, and > 10 lymph nodes 3%), 45% pT1, 48% pT2, 43% grade 2, 34% grade 3, and 9% were HER2-positive. The BCI gene expression assay predicted benefit from extended endocrine therapy in patients with ER-positive early-stage breast cancer. Significant differences in outcome from randomized treatment of an additional 5 versus 2.5 years of letrozole were dependent on classification by BCI (H/I) ratio. BCI-high patients experienced a 58% and 66% reduction in relative risk of recurrence in the overall cohort (N = 908) and in the subset treated with primary adjuvant AIs (n = 794), respectively, whereas BCI-low patients did not show benefit from extended endocrine therapy. In patients with node-positive disease, the 46% (n = 307) that were classified as BCI-high demonstrated a statistically significant benefit from 5 years versus 2.5 years of letrozole with an HR of 0.30 (95% CI, 0.12 to 0.77) and absolute benefit of 10.8% ($P = .008$), whereas the 54% of node-positive patients (n = 357) classified as BCI-Low showed no significant benefit (HR = 0.88; 95% CI, 0.50 to 1.53; $P = .644$).[28]

The NSABP B-42 study (N = 3,933; 58% node-negative, 78% HER2-negative) aimed to determine whether extended letrozole treatment improves DFS after 5 years of AI-based therapy in patients with postmenopausal breast cancer. After a median follow-up of 6.9 years, letrozole did not significantly improve DFS compared with placebo in patients initially treated with an AI or tamoxifen for ≤ 3 years, followed by an AI for the remainder of 5 years. At the 10-year analysis, after a median follow-up of 9.3 years, the use of extended letrozole after 5 years of hormonal therapy led to a statistically significant improvement in DFS with an absolute improvement of 3.3%. Extended letrozole provided statistically significant reduction in breast cancer–free interval HR = 0.75, $P = .003$, 2.7% absolute improvement, and DR HR = 0.72, $P = .01$, 1.8% absolute improvement. It is important to note that the DFS benefit observed in NSABP B-42 was primarily driven by contralateral prevention and a modest benefit for preventing DRs. The BCI-B-42 translational study was set out to determine whether BCI (H/I) status (high *v* low) is predictive of benefit from 5 years of extended letrozole therapy with a primary end point of RFI. The primary end point for the study (RFI) was not met. However, the analysis was underpowered (50% powering) and 60% of the patients in B-42 trial were node-negative. In the B-42 parent trial, a delayed treatment effect of extended letrozole therapy on DR was observed at around 4 years after random assignment. In time-dependent DR analyses, BCI (H/I) significantly predicted benefit of extended letrozole therapy 4 years after random assignment with an absolute benefit in DRS with BCI (H/I) high of 3.6% compared with 1.8% in the unselected cohort. BCI (H/I) prediction of extended letrozole therapy benefit after 4 years was more apparent in the HER2-negative subset, with statistically significant treatment-by-BCI (H/I) interaction ($P = .043$). In conclusion, this translational study supports previous findings that BCI (H/I) can be used to identify patients that are likely to derive a DR prevention benefit from longer duration endocrine therapy.

The collective evidence from these five studies suggests that BCI has consistently demonstrated a predictive benefit for extended endocrine therapy for three distinct groups: 5 years of tamoxifen followed by an additional 5 years of the same drug, those who should receive 5 years of tamoxifen followed by an additional 5 years of an AI, and those who will benefit from 5 years with an AI followed by an additional 5 years of the same drug class, in postmenopausal, early-stage ER-positive breast cancer with node-negative and 1-3 node-positive breast cancer. Since most of these trials had patients who were either node-negative or with 1-3 positive nodes, the evidence to support the utility of BCI in patients with > 3 positive lymph nodes is limited. Majority of patients in the above trials are postmenopausal. Hence, similar recommendations for premenopausal and perimenopausal women also cannot be definitively made.

Clinical treatment score post-5 years.

Recommendation 1.26. If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the CTS5 web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10) that could assist in decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation. The CTS5 multivariate predictor was developed to estimate the risk of DR after 5 years of endocrine therapy (ie, late recurrence) without further therapy in postmenopausal women using routine clinical and histologic variables from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial. The model was validated in the BIG (Breast International Group) 1-98 trial and showed a 3.6%, 6.9%, and 17.3% average

risk of DR in years 5-10 in the low-, intermediate-, and high-risk cohorts, respectively.[25] The final CTS5 model was built from the combined ATAC and BIG 1-98 data and requires tumor size, number of nodal metastases, tumor grade, and age at diagnosis as input and provides a percent estimate of risk of DR between years 5-10 and also assigns a low-, intermediate-, or high-risk category. The tool is freely available.[48] Several independent studies validated the prognostic value of CTS5 and suggest that it may also predict late recurrence in premenopausal women; however, additional calibration may be required.[49-51] Clinicians could consider recommending extended endocrine therapy for postmenopausal women with high CTS5 scores since their prognostic risk is high and the absolute benefit from extended therapy could be substantial. CTS5 should not be used to estimate residual risk after receiving extended endocrine therapy because it overestimates risk.[52] The clinical variable–based CTS5 predictor and molecular assays such as BCI can provide discordant results and therefore, performing both can make decision making more difficult.[51,53]

Clinical Questions 2 and 3

For patients with early-stage HER2-positive breast cancer, which biomarkers should be used to guide decisions on adjuvant endocrine and chemotherapy?

For patients with early-stage triple-negative breast cancer, which biomarkers should be used to guide decisions on adjuvant chemotherapy?

HER2-positive breast cancer or triple-negative breast cancer. **Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4.**

Recommendation 1.27. If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review and clinical interpretation. Oncotype DX, EndoPredict, BCI, Prosigna, Ki67, and IHC4 were studied primarily in women with ER-positive breast cancer and cannot be recommended for use in HER2-positive breast cancer or TNBC.

MammaPrint in HER2-positive breast cancer and TNBC. The MINDACT trial included 6,693 participants, out of which 640 and 638 presented with a TNBC or HER2-positive breast cancer, respectively. Given the small numbers, the Panel recommends not to interpret the results of MINDACT within the groups of women with TNBC or HER2-overexpressing breast cancer.

Emerging biomarkers.

Use of immune biomarkers in the (neo) adjuvant setting. Biomarkers capturing the influence and impact of the immune system activation on breast cancer prognosis and therapeutic outcome are in active development. The most mature of these emerging biomarkers includes measurement of stromal TILs from baseline diagnostic tumor tissue, as well as testing the tumor cells or the immune cells for the presence of PD-L1. These biomarkers have not yet demonstrated a role in ER-positive breast cancer and have been best studied in HER2-positive or TNBC. The majority of data evaluating these biomarkers have been generated through retrospective analyses of samples from prospective studies. Emerging work using serial tissue samples is evaluating the kinetics of these biomarkers with therapeutic exposure and, in the future, may provide greater dimension and accuracy to results.

Tumor-infiltrating lymphocytes.

Recommendation 1.28. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use TILs to guide decisions for (neo)adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review and clinical interpretation. There are no data from studies meeting our criteria to recommend the use of TILs to guide decisions for adjuvant endocrine and chemotherapy.

TILs in HER2-positive breast cancer. Measurement of TILs from diagnostic HER2-positive tumor tissue may have prognostic and predictive capacity. The presence of increased TILs from baseline tissue is associated with improved survival outcomes for HER2-positive disease treated with trastuzumab,[21,54] and TIL level may ultimately help to identify patients with an excellent prognosis for whom de-escalation of systemic therapy is possible. Additionally, an increased TIL level at diagnosis is associated with greater responsiveness to preoperative[54] as well as adjuvant[55] HER2-directed systemic therapy. Currently, TIL levels from baseline tissue do not provide information that supports treatment pathways other than current practice patterns. Additionally, TIL assessment can be subjective and operator dependent, although efforts are in place by an international group to standardize measures.[56] Therefore, the Panel determined that the evidence is currently not sufficiently strong to recommend routine use of TILs as a predictive test for therapy selection for HER2-positive breast cancer outside of a research setting.

TILs in TNBC. Baseline measurement of TILs has a prognostic role in TNBC, as a greater presence of TILs is highly correlated with a decreased risk of disease recurrence.[24,55,57-59] This relationship exists in the presence and absence of systemic treatment. Patients with residual TNBC after neoadjuvant systemic therapy are known to be at higher risk of recurrence, but those with higher TILs in residual disease have an improved prognosis.[60,61] TIL level at the time of diagnosis is also predictive of response to preoperative systemic

chemotherapy, with higher level of TILs predicting improved pathologic response at surgery independent of chemotherapy regimen used.[62-64] Early data have also suggested that higher TIL level predicts response to the inclusion of preoperative immunotherapy.[65] Despite emerging data, the Panel determined that the current evidence is insufficient to support routine use of TILs in therapy selection for TNBC outside of a research setting.

PD-L1 testing.

Recommendation 1.29. If a patient has node-negative or node-positive ER-positive, HER2-positive, or triple-negative breast cancer, the clinician should not use PD-L1 testing to guide decisions for (neo)adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Literature review and clinical interpretation. Testing for PD-L1, either on tumor or immune stromal cells, is an important process in the management of metastatic TNBC and other cancer types. Despite biologic relevance, testing may be limited by tumor heterogeneity, lack of inter-reader reproducibility, and availability of several commercial assays without diagnostic concordance. Although testing for PD-L1 is an important part of management for metastatic TNBC, utility in the early setting is not clear. Higher baseline PD-L1 has been associated with higher likelihood of pathologic response at surgery using an immunotherapy-containing regimen.[65,66] However, larger randomized studies have suggested that an increase in pathologic response rate with the addition of preoperative PD-1 or PD-L1 inhibition appears independent of tumor PD-L1 status.[67,68] It is not known if PD-L1 tumor status will predict any survival benefit from the addition of an immune-oncology drug in the (neo)adjuvant setting for TNBC. At this time, the Panel determined that the evidence is insufficient to recommend the use of PD-L1 testing in the early TNBC setting to guide therapy decisions.

Circulating tumor cells.

Recommendation 1.30. If a patient has node-negative or node-positive ER-positive, HER2-positive, or triple-negative breast cancer, the clinician should not use CTC test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. Emerging data suggest that CTCs may provide prognostic value in early-stage breast cancer. In a prospective study, investigators evaluated the presence in CTCs in patients with early-stage breast cancer after surgery and before adjuvant chemotherapy, as well as after chemotherapy from the Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment, and Extended Bisphosphonate and Surveillance-Trial (SUCCESS) using the CellSearch System.[69] The SUCCESS investigators compared fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel versus fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel plus gemcitabine, and 2 versus 5 years of treatment with zoledronic acid in 3,754 women with node-positive or high-risk node-negative early-stage breast cancer. CTCs were positive (≥ 1 CTC per 30 mL of blood) in 21.5% of patients (435/2,026) before chemotherapy, and in 22.1% of patients (330/1,493) after chemotherapy. The presence of CTCs was associated with inferior DFS at 36 months (88% *v* 94%; log-rank test $P < .0001$), distant DFS (88% *v* 94%; log-rank test $P < .001$), breast cancer–specific survival (94% *v* 98%; log-rank test $P = .008$), and OS (93% *v* 97%, log-rank test, $P = .0002$), and was an independent prognostic factor for DFS (HR = 2.11; 95% CI, 1.49 to 2.99; $P < .0001$) and OS (HR = 2.18; 95% CI, 1.32 to 3.59; $P = .002$). Prognosis was worse in patients with ≥ 5 CTCs per 30 mL blood (DFS: HR = 4.51; 95% CI, 2.59 to 7.86; OS: HR = 3.60; 95% CI, 1.56 to 8.45). Subsequently, CTCs were evaluated in 1,087 patients 2 years after completion of chemotherapy.[9] CTCs were positive in 198 (18.2%) of patients and was associated with inferior OS (HR = 3.91; 95% CI, 2.04 to 7.52; $P < .001$) and DFS (HR = 2.31; 95% CI, 1.50 to 3.55, $P < .001$).

In another prospective study, investigators enumerated CTCs using the CellSearch System from chemonaive patients with early-stage breast cancer before surgery.[70] CTCs were identified in 24% (73/302) patients and its detection (≥ 1 CTCs) were predictive for inferior progression-free survival (log-rank $P = .005$; HR = 4.62; 95% CI, 1.79 to 11.9) and OS (log-rank $P = .01$; HR = 4.04; 95% CI, 1.28 to 12.8). Similarly, in a prospective study, detection of CTCs by CellSearch System in patients with ER-positive early-stage breast cancer before surgery was an independent prognostic factor for DRFS.[71]

In the secondary analysis of E5103 study, phase III trial of doxorubicin and cyclophosphamide followed by paclitaxel with bevacizumab or placebo in high-risk HER2-negative breast cancers, patients who were without clinical evidence of recurrence between 4.5 and 7.5 years were evaluated for the presence of CTCs using the CellSearch system.[27] One or more CTCs per 7.5 mL of blood was considered positive. Among the 547 patients included in the analysis, CTCs were observed in 5.1% (18/353) of patients with ER-positive breast cancer. The recurrence rates per person-year of follow-up in the CTC-positive and CTC-negative groups were 21.4% (seven recurrences per 32.7 person-years) and 2.0% (16 recurrences per 796.3 person-years), respectively. Positive CTC assay was associated with a 13.1-fold higher risk of recurrence (HR = 13.1; 95% CI, 4.7 to 36.3). Seven of 23 patients (30.4%, 95% CI, 13.2 to 52.9) with ER-positive disease had a positive CTC assay result before recurrence with a median time to recurrence of 2.8 years (range, 0.1-2.8 years). None of eight patients with ER-negative disease and a positive CTC assay had a recurrence. In a prospective assessment of CTCs in

patients with early-stage TNBC, identification of ≥ 2 CTCs predicted shorter progression-free survival (log-rank $P <$ .001; HR = 8.30; 95% CI, 2.61 to 26.37) and OS (log rank $P = .0004$; HR = 7.19; 95% CI, 1.98 to 26.06).[72]

However, none of the aforementioned studies were designed to analyze the benefit of adjuvant therapy in patients who had detectable CTCs, and hence, use of CTCs is not recommended at this time, because of lack of evidence for clinical utility.

Circulating tumor DNA.

Recommendation 1.31. If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use ctDNA test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation. In a prospective, multicenter study of patients with early-stage breast cancer, investigators evaluated the role of serial ctDNA measurements to predict the likelihood of early recurrence after NACT and surgery.[73] Patient-specific digital PCR assays were developed to detect mutations in plasma DNA. Patients scheduled to receive NACT (n = 140) consented to sample collection before chemotherapy, whereas patients who received adjuvant chemotherapy (n = 30) consented after surgery and before chemotherapy. Samples were obtained every 3 months for the first year and subsequently every 6 months until 5 years of follow-up. Detection of ctDNA at baseline before neoadjuvant or adjuvant chemotherapy was associated with inferior RFS (HR = 5.8; 95% CI, 1.2 to 27.1; $P = .01$). ctDNA detection had a median lead time of 10.7 months (95% CI, 8.1 to 19.1) compared with clinical relapse. Median RFS among patients with ctDNA-detected molecular residual disease was 38.0 months (95% CI, 20.8 to undetermined), with the median not reached in patients without ctDNA-detected molecular residual disease (standard HR = 16.7; 95% CI, 3.5 to 80.5; $P <$ .001).

In a retrospective study of serial monitoring of ctDNA postsurgery in patients with early-stage breast cancers, ctDNA detection preceded clinical detection of metastasis in 86% of patients with an average lead time of 11 months (range, 0-37 months), whereas patients with long-term DFS had undetectable ctDNA postoperatively.[74] In EBLIS, a multicenter, prospective cohort study, serial ctDNA was monitored in patients with early-stage breast cancer following surgery and adjuvant therapy. Plasma ctDNA, obtained using customized patient-specific 16-plex PCR reaction on the basis of whole-exome sequencing of primary tissue of each patient, was detected ahead of clinical or radiologic relapse in 16 of the 18 relapsed patients (sensitivity 89%) with a lead time of up to 2 years (median, 8.9 months; range, 0.5-24.0 months) for prediction of metastatic recurrence.[75]

In a preplanned secondary analysis of 196 patients in BRE12-158, a phase II trial that randomly assigned patients with early-stage TNBC who had residual disease after NACT to receive genomically directed therapy versus treatment of physician's choice, investigators obtained ctDNA and CTCs at the time of treatment assignment.[10] ctDNA was obtained using the Foundation One Liquid assay, whereas CTCs were enumerated using EpCAM-based, positive selection assay. ctDNA and CTCs were observed in approximately 60% and 40% of patients, respectively. Detection of ctDNA was significantly associated with inferior distant DFS (median distant DFS, 32.5 months *v* not reached; HR = 2.99; 95% CI, 1.38 to 6.48; $P = .006$). At 2 years, distant DFS probability was 56% for ctDNA-positive compared with 81% for ctDNA-negative patients. Detection of ctDNA was associated with inferior DFS (HR = 2.67; 95% CI, 1.28 to 5.57; $P = .009$) as well as inferior OS (HR = 4.16; 95% CI, 1.66 to 10.42; $P = .002$). Patients who were ctDNA- and CTC-positive had significantly inferior outcomes compared with those who were negative: DFS (HR = 3.15; 95% CI, 1.07 to 9.27; $P = .04$) and OS (HR = 8.60; 95% CI, 1.78 to 41.47; $P = .007$).

Although the above studies provide some evidence for clinical validity for ctDNA mutation tracking, they do not demonstrate clinical utility. A recent review from ASCO and College of American Pathologists Expert Panel recommends against using ctDNA assays in early-stage cancers for treatment monitoring or residual disease detection because of lack of evidence of clinical utility.[76] Although there is great enthusiasm for utilization of ctDNA, routine use in practice requires evidence of clinical utility. Consequently, use of ctDNA to assess molecular relapse in early-stage breast cancer is not recommended for clinical practice at this time. ctDNA assays could play a future role in early-stage breast cancers when demonstrated to have clinical utility. Therefore, we currently cannot support the use of ctDNA in nonmetastatic breast cancer, but neoadjuvant and adjuvant clinical trials should consider adding ctDNA sample biorepositories to help clarify ctDNA's value as a prognostic biomarker, as well as its promise as a potential predictive and response biomarker.

PATIENT AND CLINICIAN COMMUNICATION

Clinicians should educate patients, family members, and/or caregivers about the results of pathology and genomic tests and how these tests results are used to develop a treatment plan tailored to the biology of their cancer. Most patients with a newly diagnosed breast cancer are under emotional stress and may be unaccustomed to complex medical terminology. The use of easily understood language at an educational level that the patient can understand is key to clear communication. This is often termed health literacy. Asking patients to repeat back key pieces of information, providing

written or recorded notes, and using visual aids can also help ensure information is effectively communicated. Patients should be provided with a copy of their pathology report and ER, HER2, and, if available, Oncotype DX, EndoPredict, Prosigna, BCI, Ki67, or other test results when useful. The clinician should review the individual results with the patient, discuss any issues with the test interpretation or performance, and ask the patient if he or she has any additional questions about the results. Information on health literacy and using numbers to explain risk can be found online.[77]

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[78]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Vulnerable populations, including racial and ethnic minorities, often experience delays in cancer screening, diagnosis, and initiation of treatment. These patients suffer disproportionately from multiple comorbidities, are more likely to be uninsured, present with more advanced disease, and face significant disparities in quality of care, resulting in higher mortality rates.[79-82] For example, in the TAILORx trial, despite Black patients only representing 7.1% of the eligible participants, they had higher rates of DR (HR = 1.60; 95% CI, 1.07 to 2.41) and inferior OS in the RS 11 to 25 cohort (HR = 1.51; 95% CI, 1.06 to 2.15) compared with non-Hispanic White patients.[83] However, similar to non-Hispanic Whites, Black participants did not overall benefit from the addition of chemotherapy if the RS was 11-25. Hispanic ethnicity and Asian race were associated with improved clinical outcomes. These data demonstrate the need for further elucidation of the clinical utility of RS testing in various races and ethnicities, and this is also needed in other biomarker test studies.

Many patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Advancements in medical care and an aging population have resulted in an increased number of patients who are diagnosed with breast cancer who also have multiple chronic medical conditions.

Given the advancements in medical therapies and the aging population, there are many patients diagnosed with breast cancer who have multiple chronic conditions (MCC). Patients with MCC are a complex and heterogeneous population.

Patients with MCCs have historically been excluded from RCTs to avoid potential pharmacologic interactions or confounding results associated with their chronic medical conditions. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care of this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to consider the complexity and uncertainty created by the presence of MCC and highlight the importance of shared decision making with the oncologist, the patient, and the patient's other physicians regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account before ordering specific biomarker tests and formulating the treatment plan.

Considering the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, as a qualifying statement for recommended care. This may mean that some or all the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[84,85] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[86,87]

Discussion of cost can be an important part of shared decision making.[88] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[88]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[88]

As part of the guideline development process, ASCO may opt to search the literature for published cost effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-

effective analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; or are industry-sponsored. Two cost-effectiveness systematic review analyses were identified to inform this guideline topic.[89,90] The systematic review by Blok et al[89] included the MammaPrint, Onco*type* DX, Prosigna, and EndoPredict assays. They identified 147 studies and summarized those economic evaluations estimate genomic testing to cause a moderate increase in total costs, but that these costs are acceptable in relation to the expected improvement in patient outcome. They also reported that Prosigna and EndoPredict showed comparable prognostic capacities, but with less economical and clinical utility studies. However, no level IA trial data are available yet for these assays compared with MammaPrint and OncotypeDx. The other systematic review by Wang et al[90] focused on Onco*type* DX. This review identified 27 studies, 15 of which were industry-funded. Although this review reported their analysis favoring Onco*type* DX to be cost-effective, they also highlight some concerns about the designs of the included studies to be a potential source of an increased risk of bias.

OPEN COMMENT REVIEW

The draft recommendations were released to the public for open comment from August 17, 2021, through August 31, 2021. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with 39 written comments received. There were 12 respondents in total. There was representation from medical oncology (41%), gynecologic oncology (25%), hematologic oncology (17%), and pathology (17%). A total of 80%-91% of the responses either agreed or agreed with slight modifications to the recommendations, whereas 9% of responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Evidence Based Medicine Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the Panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

LIMITATION OF THE RESEARCH AND FUTURE RESEARCH

A limitation of this guideline is the inability to provide complete guidance on all adjuvant systemic therapy. Several new systemic therapies have been reported to demonstrate benefit in women with early-stage breast cancer. These include abemaciclib, olaparib, and pembrolizumab. Also, there are limited data on biomarker testing for adjuvant therapy for male patients with breast cancer and these are areas that require further research and guidance.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer[91] (http://ascopubs.org/doi/10.1200/JCO.2015.61.1459)
- Integration of Palliative Care into Standard Oncology Care[92] (https://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[78] (https://ascopubs.org/doi/full/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

EQUAL CONTRIBUTION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
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Manuscript writing: All authors
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REFERENCES

1. Harris LN, Ismaila N, McShane LM, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:1134-1150, 2016
2. Krop I, Ismaila N, Andre F, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 35:2838-2847, 2017
3. Andre F, Ismaila N, Henry NL, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline update—Integration of results from TAILORx. J Clin Oncol 37:1956-1964, 2019
4. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
5. Cardoso F, van't Veer LJ, Bogaerts J, et al: 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717-729, 2016
6. Sgroi DC, Chapman JA, Badovinac-Crnjevic T, et al: Assessment of the prognostic and predictive utility of the Breast Cancer Index (BCI): An NCIC CTG MA.14 study. Breast Cancer Res 18:1, 2016
7. Nitz U, Gluz O, Christgen M, et al: Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: Five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 165:573-583, 2017
8. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al: Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 110, 2018
9. Trapp E, Janni W, Schindlbeck C, et al: Presence of circulating tumor cells in high-risk early breast cancer during follow-up and prognosis. J Natl Cancer Inst 111:380-387, 2019
10. Radovich M, Jiang G, Hancock BA, et al: Association of circulating tumor DNA and circulating tumor cells after neoadjuvant chemotherapy with disease recurrence in patients with triple-negative breast cancer: Preplanned secondary analysis of the BRE12-158 randomized clinical trial. JAMA Oncol 6: 1410-1415, 2020
11. Smith I, Robertson J, Kilburn L, et al: Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): An open-label, multicentre, parallel-group, randomised, phase 3 trial. Lancet Oncol 21:1443-1454, 2020
12. Sparano JA, Gray RJ, Makower DF, et al: Clinical outcomes in early breast cancer with a high 21-gene recurrence score of 26 to 100 assigned to adjuvant chemotherapy plus endocrine therapy: A secondary analysis of the TAILORx randomized clinical trial. JAMA Oncol 6:367-374, 2020
13. Harbeck N, Rastogi P, Martin M, et al: Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: Updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 31:1571-1581, 2021
14. Piccart M, van 't Veer LJ, Poncet C, et al: 70-gene signature as an aid for treatment decisions in early breast cancer: Updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 22:476-488, 2021
15. Gluz O, Nitz UA, Christgen M, et al: West German Study Group phase III PlanB trial: First prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol 34:2341-2349, 2016
16. Sparano JA, Gray RJ, Ravdin PM, et al: Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. N Engl J Med 380:2395-2405, 2019
17. Filipits M, Dubsky P, Rudas M, et al: Prediction of distant recurrence using EndoPredict among women with ER(+), HER2(-) node-positive and node-negative breast cancer treated with endocrine therapy only. Clin Cancer Res 25:3865-3872, 2019
18. Sparano JA, Gray RJ, Makower DF, et al: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111-121, 2018
19. Jensen MB, Lænkholm AV, Nielsen TO, et al: The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. Breast Cancer Res 20:79, 2018
20. Bartlett JMS, Sgroi DC, Treuner K, et al: Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-to Offer More? (aTTom) trial. Ann Oncol 30:1776-1783, 2019
21. Dieci MV, Conte P, Bisagni G, et al: Association of tumor-infiltrating lymphocytes with distant disease-free survival in the ShortHER randomized adjuvant trial for patients with early HER2+ breast cancer. Ann Oncol 30:418-423, 2019
22. Varga Z, Li Q, Jochum W, et al: Ki-67 assessment in early breast cancer: SAKK28/12 validation study on the IBCSG VIII and IBCSG IX cohort. Sci Rep 9:13534, 2019

23. Liu MC, Pitcher BN, Mardis ER, et al: PAM50 gene signatures and breast cancer prognosis with adjuvant anthracycline- and taxane-based chemotherapy: Correlative analysis of C9741 (Alliance). NPJ Breast Cancer 2:15023, 2016
24. Pruneri G, Gray KP, Vingiani A, et al: Tumor-infiltrating lymphocytes (TILs) are a powerful prognostic marker in patients with triple-negative breast cancer enrolled in the IBCSG phase III randomized clinical trial 22-00. Breast Cancer Res Treat 158:323-331, 2016
25. Dowsett M, Sestak I, Regan MM, et al: Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor-positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol 36:1941-1948, 2018
26. Hepp P, Andergassen U, Jäger B, et al: Association of CA27.29 and circulating tumor cells before and at different times after adjuvant chemotherapy in patients with early-stage breast cancer—The SUCCESS trial. Anticancer Res 36:4771-4776, 2016
27. Sparano J, O'Neill A, Alpaugh K, et al: Association of circulating tumor cells with late recurrence of estrogen receptor-positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 4:1700-1706, 2018
28. Noordhoek I, Treuner K, Putter H, et al: Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR(+) early-stage breast cancer for 10 years of endocrine therapy. Clin Cancer Res 27:311-319, 2021
29. Sparano JA, Crager MR, Tang G, et al: Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer. J Clin Oncol 39:557-564, 2021
30. Kalinsky K, Barlow WE, Gralow JR, et al: 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. New Engl J Med 385:2336-2347, 2021
31. Poorvu PD, Gelber SI, Rosenberg SM, et al: Prognostic impact of the 21-gene recurrence score assay among young women with node-negative and node-positive ER-positive/HER2-negative breast cancer. J Clin Oncol 38:725-733, 2020
32. Ganz PA, Cecchini RS, Fehrenbacher L, et al: NRG oncology/NSABP B-47 menstrual history study: Impact of adjuvant chemotherapy with and without trastuzumab. NPJ Breast Cancer 7:55, 2021
33. Sestak I, Buus R, Cuzick J, et al: Comparison of the performance of 6 prognostic signatures for estrogen receptor-positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 4:545-553, 2018
34. Martin M, Brase JC, Calvo L, et al: Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: Results from the GEICAM 9906 trial. Breast Cancer Res 16:R38, 2014
35. Sestak I, Filipits M, Buus R, et al: Prognostic value of EndoPredict in women with hormone receptor-positive, HER2-negative invasive lobular breast cancer. Clin Cancer Res 26:4682-4687, 2020
36. Sestak I, Martín M, Dubsky P, et al: Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat 176:377-386, 2019
37. Soliman H, Flake DD II, Magliocco A, et al: Predicting expected absolute chemotherapy treatment benefit in women with early-stage breast cancer using EndoPredict, an integrated 12-gene clinicomolecular assay. JCO Precis Oncol 10.1200/PO.18.00361
38. Ettl J, Anders SI, Hapfelmeier A, et al: First prospective outcome data for the second-generation multigene test Endopredict in ER-positive/HER2-negative breast cancer. Arch Gynecol Obstet 302:1461-1467, 2020
39. Lænkholm AV, Jensen MB, Eriksen JO, et al: PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol 36:735-740, 2018
40. Ohnstad HO, Borgen E, Falk RS, et al: Prognostic value of PAM50 and risk of recurrence score in patients with early-stage breast cancer with long-term follow-up. Breast Cancer Res 19:120, 2017
41. Jensen MB, Lænkholm AV, Balslev E, et al: The Prosigna 50-gene profile and responsiveness to adjuvant anthracycline-based chemotherapy in high-risk breast cancer patients. NPJ Breast Cancer 6:7, 2020
42. Dombernowsky P, Andersen JA, Andersen KW, et al: Adjuvant chemotherapy in premenopausal and menopausal high-risk patients with breast cancer. 4. Results of the DBCG (Danish Breast Cancer Cooperative Group) 77B study [in Danish]. Ugeskr Laeger 153:2280-2283, 1991
43. Nielsen TO, Leung SCY, Rimm DL, et al: Assessment of Ki67 in breast cancer: Updated recommendations from the international Ki67 in breast cancer working group. J Natl Cancer Inst 113:808-819, 2021
44. Cuzick J, Dowsett M, Pineda S, et al: Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol 29:4273-4278, 2011
45. Bartlett JM, Christiansen J, Gustavson M, et al: Validation of the IHC4 breast cancer prognostic algorithm using multiple approaches on the multinational TEAM clinical trial. Arch Pathol Lab Med 140:66-74, 2016
46. Zhang Y, Schroeder BE, Jerevall PL, et al: A novel breast cancer index for prediction of distant recurrence in HR(+) early-stage breast cancer with one to three positive nodes. Clin Cancer Res 23:7217-7224, 2017
47. Sgroi DC, Sestak I, Cuzick J, et al: Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 14:1067-1076, 2013
48. CTS5 Calculator. www.cts5-calculator.com
49. Wang C, Chen C, Lin Y, et al: Validation of CTS5 model in large-scale breast cancer population and the impact of menopausal and HER2 status on its prognostic value. Sci Rep 10:4660, 2020
50. Sestak I, Crager M, Cuzick J, et al: Validation of the clinical treatment score post 5 years (CTS5) in women with hormone receptor positive, HER2-negative, node-negative disease from the TAILORx study. Cancer Res 80:GS4-03, 2020 (abstr)
51. Richman J, Ring A, Dowsett M, et al: Clinical validity of clinical treatment score 5 (CTS5) for estimating risk of late recurrence in unselected, non-trial patients with early oestrogen receptor-positive breast cancer. Breast Cancer Res Treat 186:115-123, 2021
52. Noordhoek I, Blok EJ, Meershoek-Klein Kranenbarg E, et al: Overestimation of late distant recurrences in high-risk patients with ER-positive breast cancer: Validity and accuracy of the CTS5 risk score in the TEAM and IDEAL trials. J Clin Oncol 38:3273–-3281, 2020
53. Foldi J, O'Meara T, Marczyk M, et al: Defining risk of late recurrence in early-stage estrogen receptor-positive breast cancer: Clinical versus molecular tools. J Clin Oncol 37:1365-1369, 2019
54. Salgado R, Denkert C, Campbell C, et al: Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: A secondary analysis of the NeoALTTO trial. JAMA Oncol 1:448-454, 2015
55. Loi S, Michiels S, Salgado R, et al: Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: Results from the FinHER trial. Ann Oncol 25:1544-1550, 2014
56. Dieci MV, Radosevic-Robin N, Fineberg S, et al: Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: A report of the International Immuno-Oncology Biomarker Working Group on breast cancer. Semin Cancer Biol 52:16-25, 2018

57. Kolberg-Liedtke C, Gluz O, Heinisch F, et al: Association of TILs with clinical parameters, Recurrence Score® results, and prognosis in patients with early HER2-negative breast cancer (BC)-a translational analysis of the prospective WSG PlanB trial. Breast Cancer Res 22:47, 2020
58. Adams S, Gray RJ, Demaria S, et al: Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol 32:2959-2966, 2014
59. Loi S, Sirtaine N, Piette F, et al: Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 31:860-867, 2013
60. Luen SJ, Salgado R, Dieci MV, et al: Prognostic implications of residual disease tumor-infiltrating lymphocytes and residual cancer burden in triple-negative breast cancer patients after neoadjuvant chemotherapy. Ann Oncol 30:236-242, 2019
61. Dieci MV, Criscitiello C, Goubar A, et al: Prognostic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: A retrospective multicenter study. Ann Oncol 25:611-618, 2014
62. Issa-Nummer Y, Darb-Esfahani S, Loibl S, et al: Prospective validation of immunological infiltrate for prediction of response to neoadjuvant chemotherapy in HER2-negative breast cancer—A substudy of the neoadjuvant GeparQuinto trial. PLoS One 8:e79775, 2013
63. Denkert C, Loibl S, Noske A, et al: Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 28:105-113, 2010
64. Denkert C, von Minckwitz G, Brase JC, et al: Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol 33:983-991, 2015
65. Schmid P, Salgado R, Park YH, et al: Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: Results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol 31:569-581, 2020
66. Wimberly H, Brown JR, Schalper K, et al: PD-L1 expression correlates with tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy in breast cancer. Cancer Immunol Res 3:326-332, 2015
67. Schmid P, Cortes J, Pusztai L, et al: Pembrolizumab for early triple-negative breast cancer. N Engl J Med 382:810-821, 2020
68. Loibl S, Untch M, Burchardi N, et al: A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: Clinical results and biomarker analysis of GeparNuevo study. Ann Oncol 30:1279-1288, 2019
69. Rack B, Schindlbeck C, Juckstock J, et al: Circulating tumor cells predict survival in early average-to-high risk breast cancer patients. J Natl Cancer Inst 106: dju066, 2014
70. Lucci A, Hall CS, Lodhi AK, et al: Circulating tumour cells in non-metastatic breast cancer: A prospective study. Lancet Oncol 13:688-695, 2012
71. Magbanua MJM, Yau C, Wolf DM, et al: Synchronous detection of circulating tumor cells in blood and disseminated tumor cells in bone marrow predicts adverse outcome in early breast cancer. Clin Cancer Res 25:5388-5397, 2019
72. Karhade M, Hall C, Mishra P, et al: Circulating tumor cells in non-metastatic triple-negative breast cancer. Breast Cancer Res Treat 147:325-333, 2014
73. Garcia-Murillas I, Chopra N, Comino-Mendez I, et al: Assessment of molecular relapse detection in early-stage breast cancer. JAMA Oncol 5:1473-1478, 2019
74. Olsson E, Winter C, George A, et al: Serial monitoring of circulating tumor DNA in patients with primary breast cancer for detection of occult metastatic disease. EMBO Mol Med 7:1034-1047, 2015
75. Coombes RC, Page K, Salari R, et al: Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence. Clin Cancer Res 25: 4255-4263, 2019
76. Merker JD, Oxnard GR, Compton C, et al: Circulating tumor DNA analysis in patients with cancer: American Society of Clinical oOncology and College of American Pathologists joint review. J Clin Oncol 36:1631-1641, 2018
77. Center for Disease Control and Prevention: Health Literacy: Accurate, and actionable health information for all, 2022. http://www.cdc.gov/healthliteracy/
78. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
79. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute, 2016
80. US Cancer Statistics Working Group: United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-Based Report. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2015
81. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, The Commonwealth Fund, 2008
82. American Cancer Society: Cancer Facts and Figures for African Americans 2016-2018. Atlanta, GA, American Cancer Society, 2016
83. Albain KS, Gray RJ, Makower DF, et al: Race, ethnicity, and clinical outcomes in hormone receptor-positive, HER2-negative, node-negative breast cancer in the randomized TAILORx trial. J Natl Cancer Inst 113:390–399, 2021
84. Schnipper LE, Davidson NE, Wollins DS, et al: Updating the American Society of Clinical Oncology value framework: Revisions and reflections in response to comments received. J Clin Oncol 34:2925-2934, 2016
85. Schnipper LE, Davidson NE, Wollins DS, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 33:2563-2577, 2015
86. Streeter SB, Schwartzberg L, Husain N, et al: Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. J Oncol Pract 7:46s-51s, 2011
87. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32: 306-311, 2014
88. Meropol NJ, Schrag D, Smith TJ, et al: American Society of Clinical Oncology guidance statement: The cost of cancer care. J Clin Oncol 27:3868-3874, 2009
89. Blok EJ, Bastiaannet E, van den Hout WB, et al: Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. Cancer Treat Rev 62:74-90, 2018
90. Wang SY, Dang W, Richman I, et al: Cost-effectiveness analyses of the 21-gene assay in breast cancer: Systematic review and critical appraisal. J Clin Oncol 36: 1619-1627, 2018
91. Van Poznak C, Somerfield MR, Bast RC, et al: Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 33:2695-2704, 2015
92. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update

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APPENDIX

TABLE A1. Breast Biomarker Guideline Update Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
Fabrice Andre, MD (cochair)	Institute Gustave Roussy, Paris, France	Medical Oncology
Vered Stearns, MD, FASCO (cochair)	Johns Hopkins University, Baltimore, MD	Medical Oncology
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Kimberly Allison, PhD	Stanford University Medical Center, Stanford, CA	Breast Pathology
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Anya Litvak, MD	Cancer Center at Saint Barnabas Medical Center, Livingston, NJ	PGIN representative
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Nofisat Ismaila, MD, MSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. ASCO: Evidence Quality Rating Definitions

Term	Definitions
Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits versus harms), and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

TABLE A3. ASCO: Recommendation Rating Definitions

Term	Definitions
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (eg, benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (eg, benefits exceed harms); b) consistent results with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (eg, benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

TABLE A4. Summary of Old and Updated Recommendations

Recommendation	Evidence Rating
Clinical question 1: For patients with operable invasive breast cancer and with known ER and HER2 status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant endocrine and chemotherapy?	
Oncotype DX (21-gene RS, 21-gene RS)	
If a patient has node-negative breast cancer, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: high; strength of recommendation: strong
In the group of patients in Recommendation 1.1 with Oncotype DX recurrence score ≥ 26, the clinician should offer chemoendocrine therapy	Type: evidence-based; evidence quality: high; strength of recommendation: strong
In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX recurrence score 16-25, the clinician may offer chemoendocrine therapy	Type: evidence-based; evidence quality: high; strength of recommendation: moderate
If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use the Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: high; strength of recommendation: strong
In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX recurrence score is ≥ 26	Type: evidence-based; evidence quality: high; strength of recommendation: strong
If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, the Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy. *Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making*	Type: evidence-based; evidence quality: high; strength of recommendation: moderate
If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use	Type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate
MammaPrint (70-gene signature)	
If a patient is older than 50 and has high clinical risk breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: strong
If a patient is 50 years of age or younger and has high clinical risk, node-negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: high; strength of recommendation: strong
If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient has node-positive breast cancer with ≥ 4 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use. *Qualifying statement: The genomic assay is prognostic and may be used for shared patient-physician treatment decision making*	Type: informal consensus; evidence quality: insufficient; strength of recommendation: strong
EndoPredict (12-gene risk score)	
If a postmenopausal patient has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy	Type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate

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TABLE A4. Summary of Old and Updated Recommendations (continued)

Recommendation	Evidence Rating
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	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
Prosigna (PAM50)	
If a patient is postmenopausal and breast cancer that is node-negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient is premenopausal, and has node-negative or node-positive breast cancer, the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy	Type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate
If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of the Prosigna test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient has node-positive breast cancer with ≥ 4 positive nodes, the 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	Type: informal consensus; evidence quality: insufficient; strength of recommendation: strong
Mammostrat	
There is insufficient evidence to recommend use Mammostrat to guide decisions about adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
BCI	
If a patient has ER-positive, HER2-negative, node-negative breast cancer, postmenopausal or age > 50 years, the clinician may use the BCI to guide decisions for adjuvant endocrine and chemotherapy.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient has ER-positive, HER2-negative, node-positive breast cancer, the clinician should not use the BCI to guide decisions about adjuvant endocrine and chemotherapy. NOTE. Based on new information regarding other assays, if a patient is premenopausal and has node-negative or node-positive breast cancer, the clinician should refrain from using the BCI test to guide decisions for adjuvant systemic chemotherapy.	Type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate
Ki67	
If a patient is postmenopausal and has stage I-II breast cancer, the clinician may use Ki67 expression in conjunction with other clinical and pathologic parameters to guide decisions on adjuvant endocrine and chemotherapy when multigene assays are not available. Ki67 expression levels are most informative for prognosis when the level is < 5% (low proliferation) or > 30% (high proliferation) because technical reliability of distinguishing values within this range is limited.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient is postmenopausal and has breast cancer, there is insufficient evidence to use baseline Ki67 expression or Ki67 level after 2 weeks of neoadjuvant AI therapy to guide decisions on adjuvant endocrine and chemotherapy	Type: informal consensus; evidence quality: low; strength of recommendation: weak
Despite the limitations associated with Ki67 testing, a patient with node-positive breast cancer with a high risk of recurrence and a Ki67 score of ≥ 20% as determined by an FDA-approved test may be offered 2 years of abemaciclib plus endocrine therapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: strong

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TABLE A4. Summary of Old and Updated Recommendations (continued)

Recommendation	Evidence Rating
IHC4	
If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes, the clinician may use IHC4 score to guide decisions for adjuvant endocrine and chemotherapy if the score has been validated in the performing laboratory and if multigene assays are not available	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
uPA and PAI-1	
If a patient has ER-positive, HER2-negative (node-negative) breast cancer, the clinician may use the uPA and PAI-1 to guide decisions about adjuvant endocrine and chemotherapy.	Type: evidence-based; evidence quality: high; strength of recommendation: weak
If a patient has HER2-positive breast cancer or TNBC, the clinician should not use the uPA and PAI-1 to guide decisions about adjuvant endocrine and chemotherapy.	Type: informal consensus; evidence quality: insufficient; strength of recommendation: weak
Extended endocrine therapy for ER-positive HER2-negative breast cancer	
Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4	
If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
BCI	
If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
If a patient has node-positive breast cancer with ≥ 4 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI	Type: evidence-based; evidence quality: intermediate; strength of recommendation: strong
CTS5	
If a patient is postmenopausal, has breast cancer, and is recurrence-free after 5 years of adjuvant endocrine therapy, the CTS5 web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10), which could assist in decisions about extended endocrine therapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
HER2-positive breast cancer or TNBC	
Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4	
If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy	Type: informal consensus; evidence quality: insufficient; strength of recommendation: strong
Emerging biomarkers	
TILs	
If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use TILs test to guide decisions for (neo)adjuvant endocrine and chemotherapy	Type: informal consensus; evidence quality: insufficient; strength of recommendation: strong
PD-L1 testing	

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TABLE A4. Summary of Old and Updated Recommendations (continued)

Recommendation	Evidence Rating
If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use PD-L1 testing to guide decisions for (neo)adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: high; strength of recommendation: strong
CTC	
If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use CTC test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: strong
ctDNA	
If a patient has node-negative or node-positive ER-positive, HER2-positive, or TNBC, the clinician should not use ctDNA test to guide decisions for adjuvant endocrine and chemotherapy	Type: evidence-based; evidence quality: intermediate; strength of recommendation: strong
The following recommendations are now archived	
Clinical question 2: For women with early-stage invasive breast cancer and with known ER and HER2 status, which additional biomarkers have demonstrated clinical utility to guide choice of specific drugs or regimens for adjuvant systemic therapy?	
The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
The clinician should not use p27 expression by IHC to guide adjuvant endocrine therapy selection.	Type: informal consensus; evidence quality: low; strength of recommendation: strong
The clinician should not use Ki67 labeling index by IHC to guide type of adjuvant endocrine therapy selection.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
The clinician should not use MAP-Tau mRNA expression or mRNA expression by IHC to guide selection of type of adjuvant chemotherapy.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
The clinician should not use HER1/EGFR expression by IHC to guide selection of type of adjuvant chemotherapy.	Type: evidence-based; evidence quality: low; strength of recommendation: moderate
The clinician should not use TOP2A gene amplification or TOP2A protein expression by IHC to guide selection of type of adjuvant chemotherapy.	Type: evidence-based; evidence quality: high; strength of recommendation: moderate
The clinician should not use HER2 and TOP2A gene coamplification, CEP17 duplication, TIMP-1, FOXP3, or p53 to guide selection of type of adjuvant chemotherapy.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
In patients with HER2-positive breast cancer, the clinician should not use PTEN to guide adjuvant therapy selection.	Type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate
In patients with HER2-positive breast cancer, the clinician should not use soluble HER2 levels to guide selection of type of adjuvant therapy.	Type: evidence-based; evidence quality: low; strength of recommendation: moderate

Abbreviations: AI, aromatase inhibitor; BCI, Breast Cancer Index; CTC, circulating tumor cells; ctDNA, circulating tumor DNA; CTS5, Clinical treatment score post-5 years; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC4, immunohistochemistry 4; MAP, microtubule-associated protein; PAI-1, plasminogen activator inhibitor type-1; PD-L1, programmed cell death receptor ligand-1; RS, recurrence score; TIL, tumor-infiltrating lymphocyte; TNBC, triple-negative breast cancer; uPA, urokinase plasminogen activator.

TABLE A5. Classification of Patients According to Clinical Risk Assessment by the Modified Version of Adjuvant!Online

ER Status	HER2 Status	Grade	Nodal Status	Tumor Size (cm)	Clinical Risk in MINDACT
ER-positive	HER2-negative	Well differentiated	N–	≤ 3	C-low
				3.1-5	C-high
			1-3 positive nodes	≤ 2	C-low
				2.1-5	C-high
		Moderately differentiated	N–	≤ 2	C-low
				2.1-5	C-high
			1-3 positive nodes	Any size	C-high
		Poorly differentiated or undifferentiated	N–	≤ 1	C-low
				1.1-5	C-high
			1-3 positive nodes	Any size	C-high
	HER2-positive	Well differentiated or moderately differentiated	N–	≤ 2	C-low
				2.1-5	C-high
			1-3 positive nodes	Any size	C-high
		Poorly differentiated or undifferentiated	N–	≤ 1	C-low
				1.1-5	C-high
			1-3 positive nodes	Any size	C-high
ER-negative	HER2-negative	Well differentiated	N–	≤ 2	C-low
				2.1-5	C-high
			1-3 positive nodes	Any size	C-high
		Moderately differentiated or poorly differentiated or undifferentiated	N–	≤ 1	C-low
				1.1-5	C-high
			1-3 positive nodes	Any size	C-high
	HER2-positive	Well differentiated or moderately differentiated	N–	≤ 1	C-low
				1.1-5	C-high
			1-3 positive nodes	Any size	C-high
		Poorly differentiated or undifferentiated	Any	Any size	C-high

NOTE. As reported by Cardoso et al.[5]

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; N–, node-negative.