ASCO special article

Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: Update of the ASCO Endorsement of the Cancer Care Ontario Guideline

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abstract

PURPOSE To update the American Society of Clinical Oncology endorsement of the Cancer Care Ontario recommendations on the Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer.

METHODS Two phase III trials—the Trial Assigning Individualized Options for Treatment (TAILORx) in women with hormone receptor–positive, node-negative tumors and the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial—provided the evidence for this update.

UPDATED RECOMMENDATIONS Shared decision making between clinicians and patients is appropriate for adjuvant systemic therapy for breast cancer. For patients older than age 50 years and whose tumors have Onco*type* DX recurrence scores less than 26, and for patients age 50 years or younger whose tumors have Onco*type* DX recurrence scores less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone for these patients. For patients age 50 years or younger with recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy. Patients with recurrence scores greater than 30 should be considered candidates for chemoendocrine therapy. Based on informal consensus, the Panel recommends that oncologists may offer chemoendocrine therapy to patients with Onco*type* DX scores of 26 to 30.

The MammaPrint assay could be used to guide decisions on withholding adjuvant systemic chemotherapy in patients with hormone receptor–positive lymph node–negative breast cancer and in select patients with lymph node–positive cancers. In both patients with node-positive and node-negative disease, evidence of clinical utility of the MammaPrint assay was only apparent in those determined to be at high clinical risk; the Panel thus did not recommend use of MammaPrint assay in patients determined to be at low clinical risk. Remaining recommendations from the 2016 ASCO guideline endorsement are unchanged.

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

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ASSOCIATED CONTENT

Appendix

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

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published an endorsement of the Cancer Care Ontario (CCO) guideline on the role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer in July 2016.[1] The results of two large-scale, randomized, phase III trials—the Trial Assigning Individualized Options for Treatment (TAILORx)[2] and the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial[3]—prompted this focused update. The goal of this update of the 2016 ASCO endorsement of the CCO recommendations is to provide oncologists and other clinicians with a summary of this evidence and revised recommendations for practice based on the data. This update focuses solely on new evidence pertaining to the question, "What risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer?" The complete list of the original and updated recommendations is available in Table 1, in the Bottom Line Box, and at www.asco.org/breast-cancer-guidelines. Of note, the biomarker testing Expert Panel will review the pertinent literature on the use of Onco*type* DX in women with node-positive breast cancer in the coming months to address perceived practice variation

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THE BOTTOM LINE

Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: Update of the ASCO Endorsement of the Cancer Care Ontario Guideline

Guideline Question

What risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer?

Target Population

Female patients who are being considered for, or who are receiving, systemic therapy for early-stage invasive breast cancer (stages I to IIA, T1N0-1, T2N0, T2N1).

Target Audience

Medical oncologists, pathologists, surgeons, oncology nurses, patients/caregivers.

Updated and New Recommendations

Shared decision making between clinicians and patients is appropriate for decisions concerning adjuvant systemic therapy for breast cancer.

Oncotype DX Updated Recommendations

All recommendations refer to patients who present with hormone receptor–positive, Human Epidermal Growth Factor Receptor 2 not overexpressed, axillary node–negative early breast cancer.

- For patients older than age 50 years and whose tumors have Onco*type* DX recurrence scores less than 26, and for patients age 50 years or younger whose tumors have Onco*type* DX recurrence scores less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For patients age 50 years or younger with Onco*type* DX scores of 16 to 25, clinicians may offer chemo-endocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Patients with Onco*type* DX recurrence scores greater than 30 should be considered candidates for chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

MammaPrint Assay Recommendations from the ASCO 2017 Biomarkers Guideline

- If a patient has estrogen receptor (ER)/progesterone receptor (PR)–positive, human epidermal growth factor receptor 2 (HER2)-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PR–positive, HER2-negative, node-negative breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

- If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- If a patient has ER/PR–negative and HER2-negative (triple-negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Cancer Care Ontario Guideline Recommendations from 2016 Endorsement

For making adjuvant therapy decisions for women with early-stage breast cancer, the Cancer Care Ontario guideline recommends that (a) lymph node status, T stage, ER status, PR status, HER status, tumor grade, and presence of tumor lymphovascular invasion (LVI) are relevant (prognostic or predictive); (b) Onco*type* DX score (for hormone receptor–positive, N0 or N1mic or ITC [isolated tumor cells], and HER2-negative cancers) and Adjuvant! Online may be used as risk stratification tools; and (c) age, menopausal status, and medical comorbidities should be considered.

In patients in whom chemotherapy would likely be tolerated and is acceptable to the patient, adjuvant chemotherapy should be considered for patients with the following tumor characteristics: lymph node positive (one or more lymph nodes with a macrometastatic deposit $>$ 2 mm), ER negative with tumor greater than 5 mm, HER2-positive tumor, high-risk lymph node–negative tumors with tumor size greater than 5 mm and another high-risk feature, and Adjuvant! Online 10−year risk of death from breast cancer greater than 10%.

For patients with lymph node–negative tumors with T greater than 5mm, grade 3, triple-negative (ER-negative, PR-negative, and HER2-negative) status, LVI positivity, Onco*type* DX recurrence score associated with an estimated distant relapse risk of greater than 15% at 10 years, and HER2-positive status should be considered high-risk features and thus considered candidates for chemotherapy.

Patients with T less than 5 mm, lymph node–negative status, and no other high-risk features may not benefit from adjuvant chemotherapy; finally, adjuvant chemotherapy may not be required in patients with HER2-negative, strongly ER-positive and PR-positive breast cancer and any of the following additional characteristics: lymph node–positive status with micrometastasis ($<$ 2 mm) only, or T less than 5 mm, or an Onco*type* DX recurrence score associated with an estimated distant relapse risk of less than 15% at 10 years.

Additional Resources

More information, including 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.

around the use of this biomarker test in this population of women with breast cancer.

GUIDELINE ENDORSEMENT UPDATE PROCESS

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff with health research methodology expertise (Appendix Table A1, online only). All funding for the administration of the project was provided by ASCO.

ASCO uses a signals approach to facilitate guideline updating.[22] This approach is intended to identify new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO guideline panel members to identify signals. The high quality of the reported evidence and the potential for its clinical impact prompted the ASCO Expert Panel to revise one of the guideline recommendations. The Methodology Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach.

The Expert Panel communicated via e-mail to consider the new evidence relevant to the update. The revised guideline was circulated in draft form to the Expert Panel and

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TABLE 1. CCO Clinical Practice Guideline Recommendations on Patient and Disease Factors in the Selection of Adjuvant Therapy for Women With Early-Stage Breast Cancer

CCO Clinical Question	CCO Recommendation	CCO Qualifying Statements	ASCO Panel Discussion Points and 2019 Updated Recommendations
1. Which disease characteristics (histopathologic parameters) are considered relevant (either prognostic or predictive) when making a decision regarding adjuvant systemic therapies for breast cancer?	Lymph node status T stage ER status PR status HER2 status Tumor grade Presence of tumor LVI	PR Status: The EBCTCG meta-analysis[4] found that PR status was not an important independent factor in determining response to endocrine therapy with tamoxifen. The consensus panel members cautioned that PR status in the studies for the EBCTCG meta-analysis might have been analyzed using older pathology methods and compared with ER analysis might not be as well standardized. Disease that is ER-negative and PR-positive is very rare, such that a pathology result with that profile usually requires retesting and confirmation. The method used to ascertain ER and PR status is important, and positivity should be determined according to the guidelines from CCO, ASCO, and the College of American Pathologists.[5,6] The EBCTCG meta-analysis did not address disease response to endocrine agents other than tamoxifen in patients with ER-negative, PR-positive cancer. Nonetheless, PR status might still have prognostic value even if it is not deemed useful in determining tamoxifen response. LVI: LVI predicted worse outcome in some studies[7,8] and might therefore be useful as a prognostic factor. According to the St Gallen Consensus Conference,[9] it is not sufficient to decide chemotherapy. The panel wondered whether LVI results are reproducible from one laboratory to another. Other characteristics without consensus: Ki-67: Measurement of Ki-67 is currently considered more clinically useful in other cancers, such as lymphoma. Analytically reproducibility of Ki-67 in breast cancer is generally poor from one center to another, because testing methods are not standardized and no clear cutoff values have been defined. Some studies show a prognostic role for Ki-67, and Ki-67 has been incorporated into some molecular gene signatures, such as Oncotype DX (Genomic Health, Redwood City, CA). Finally, Ki-67 has not been prospectively validated. It is premature to recommend its use as a standard parameter for patient risk stratification, although it could be evaluated in clinical trials. Intrinsic subtype: Intrinsic breast cancer subtypes that correlate with prognosis (luminal A, luminal B, HER2-enriched, basal, and normal) have been established. Several retrospective analyses describe response by those subtypes to various systemic treatments. However, the utility of the subtypes (beyond measurement of ER, PR, HER2, and grade) is not clear. At the time of writing, the use of the subtypes in clinical decision making outside of a clinical trial is not recommended.	For making decisions about adjuvant systemic therapy, the CCO guideline recommendations highlight key tumor-related factors that should be considered to avoid over- or under-treatment of patients. In addition to the listed factors, the ASCO panel noted that some data suggest that certain uncommon breast cancer subtypes (eg, tubular, mucinous) have favorable prognoses and that this histologic information could also be relevant for making decisions about systemic therapy. However, large data sets are not currently available to confirm how best to treat these patients. Chemotherapy should be considered for selected patients. However, there was no lower size limit provided in the CCO guideline for HER2-positive tumors, and the ASCO panel noted that there are no definitive data for use of chemotherapy and/or trastuzumab for HER2-positive tumors ≤ 5 mm. In addition, in the opinion of the ASCO Panel, some of the factors, such as grade 3 and presence of LVI, should generally not be used to drive decision making when considered in isolation and must be interpreted in the overall clinical context. The ASCO Panel also felt, consistent with the 2015 St Gallen International Expert Consensus,[10] that tumors that are well differentiated, especially those that are luminal A-like, should also be considered for omission from chemotherapy.
2. What risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer?	Oncotype DX score (for HR-positive, N0 or N1mic or ITC, and HER2-negative cancers) Adjuvant! Online (www.adjuvantonline.com)	The Oncotype DX assay uses real-time reverse-transcription polymerase chain reaction to analyze expression of a panel of 21 genes. In a report from the CCO Molecular Oncology Advisory Committee, the assay was compared with other molecular tests. Oncotype DX includes five reference genes and 16 genes found to correlate with distant relapse in HR-positive breast cancer. The test was initially validated in the patient cohorts of three independent trials. Tumors tested using Oncotype DX are stratified as having a low, intermediate, or high recurrence score, and each individual score is associated with a distinct 10-year distant relapse rate, assuming 5 years of endocrine therapy with tamoxifen. The additional benefit of chemotherapy varies by recurrence score, whereby patients with low scores experience little to no benefit and those with high scores experience the most benefit.[11] The utility of chemotherapy in the intermediate recurrence score zone is currently less clear, although a phase III clinical trial (TAILORx), once reported, might help address that question. The test is most useful in patients with HR-positive, HER2-negative, lymph node–negative cancer. Studies have retrospectively evaluated the use of Oncotype DX in patients with lymph node-positive cancer, but those studies are not entirely robust from a statistical standpoint.[12,13]	The ASCO Panel notes that, in addition to the Oncotype DX assay, there are now multiple risk stratification tools available for routine clinical use and that this is a rapidly evolving field. The Panel recommends that providers refer to the current ASCO guideline on use of biomarkers for decision making for treatment of patients with early-stage breast cancer[14] for recommendations about use of several other risk stratification tools and in the setting of other disease characteristics, such as lymph node–positive breast cancer. ***2019 Oncotype DX Updated Recommendations*** For the 2019 update, the ASCO Panel added these new recommendations for practice: **All recommendations refer to patients who present with a HR-positive, HER2 not overexpressed, axillary node–negative early breast cancer.** For patients older than age 50 years and whose tumors have Oncotype DX recurrence scores < 26, and for patients age ≤ 50 years whose tumors have Oncotype DX recurrence scores < 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone. For patients age ≤ 50 years with Oncotype DX scores of 16 to 25, clinicians may offer chemoendocrine therapy. Patients with Oncotype DX recurrence scores > 30 should be considered candidates for chemoendocrine therapy.

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TABLE 1. CCO Clinical Practice Guideline Recommendations on Patient and Disease Factors in the Selection of Adjuvant Therapy for Women With Early-Stage Breast Cancer (continued)

CCO Clinical Question	CCO Recommendation	CCO Qualifying Statements	ASCO Panel Discussion Points and 2019 Updated Recommendations
		Oncotype DX is not consistently funded by health authorities across Canada. The consensus panel agreed that the test is useful in selecting patients either with HR (ER or PR)-positive, HER2-negative, lymph node–negative cancer or with lymph node micrometastasis in whom the additional benefit of chemotherapy compared with endocrine therapy alone is unclear. Prognostic information from the US SEER cancer information database forms the core of Adjuvant! Online, which was validated by Olivotto et al.[15] Correlations generated by Adjuvant! Online are good overall, with some exceptions. In the United Kingdom validation,[16] patients did worse than predicted, a result that might relate to differences in the US and United Kingdom health systems. Adjuvant! Online and Oncotype DX produce correlations that are good in patients with midrisk of recurrence but poor at the high and low ends. Several consensus panel participants considered Adjuvant! Online a good tool to help explain risk and treatment options to patients but said that they do not use it for decision making, because it does not include other factors that must be considered, such as HER2 status. Risks depend on the comorbidities entered into the system.	Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30. ***2019 Update MammaPrint Recommendations from the ASCO Biomarkers Guideline***[14] If a patient has ER/PR–positive, HER2-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. If a patient has ER/PR–positive, HER2-negative, node-negative breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer. If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node. If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population. If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy. If a patient has ER/PR–negative and HER2-negative (triple-negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy.
3. Which patient factors should be considered in making adjuvant systemic therapy decisions?	Age Menopausal status Medical comorbidities (including validated tools used to measure health status)	The consensus panel agreed that age should not be the sole factor used in selecting patients for chemotherapy. In the absence of other comorbidities, advanced age should not be used as an independent criterion to not recommend chemotherapy. Younger age can more often be correlated with aggressive tumor biology or subtypes and can also predict response to certain treatments, but it should not be an independent factor in determining candidacy for chemotherapy. A desire to spare fertility in younger women and a desire to avoid certain adverse effects in older patients might affect selection of treatment. Age has been used as a surrogate for menopausal status in some clinical studies.	The ASCO Panel agreed with the patient factors listed by CCO that should be considered when making decisions about adjuvant systemic therapy. Panel members also felt that the preferences of the patient are an important factor in the selection of adjuvant systemic therapy. In addition, for patients with advanced age, the ASCO Panel also recommends measurement of estimated life expectancy and other factors included in validated geriatric assessments tools,[17,18] such as functional status, comorbidity, cognitive function and social support, rather than reliance solely on chronologic age when making decisions about adjuvant systemic therapy.
4. In those patients in whom chemotherapy would likely be tolerated and is acceptable to the patient, adjuvant chemotherapy should be considered for patients with which tumor characteristics?	In no particular order: Lymph node positive: one or more lymph nodes with a macrometastatic deposit (> 2 mm) ER negative with T size > 5 mm HER2-positive tumors High-risk lymph node–negative tumors with T size > 5 mm and another high-risk feature (see next recommendation, R5) Adjuvant! Online 10−year risk of death from breast cancer > 10%	Consideration of disease factors in the selection of patents to receive chemotherapy was based on a review of existing guidelines and models of risk stratification as outlined in the Introduction. The Adjuvant! Online 10-year risk of death was considered by the panel at two cutoffs: 10% and 15%. The consensus for 15% was strong; the consensus for 10% was less robust. Therefore, a 10-year risk of death judged to be either 10% or 15% using the Adjuvant! Online model is a reasonable threshold for considering chemotherapy.	The ASCO Panel suggests a slight revision to the CCO language concerning the Adjuvant! Online: a 10-year risk of death judged to be greater than 10% or 15% using the Adjuvant! Online model is a reasonable threshold for considering chemotherapy.

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TABLE 1. CCO Clinical Practice Guideline Recommendations on Patient and Disease Factors in the Selection of Adjuvant Therapy for Women With Early-Stage Breast Cancer (continued)

CCO Clinical Question	CCO Recommendation	CCO Qualifying Statements	ASCO Panel Discussion Points and 2019 Updated Recommendations
5. When considering lymph node negative tumors with T size > 5mm, what should be considered high-risk features (thus considered candidates for chemotherapy)?	Grade 3 Triple negative (ER negative, PR negative, and HER2 negative) LVI positive An Oncotype DX recurrence score that is associated with an estimated distant relapse risk of 15% or more at 10 years HER2 positive	The panel reached consensus for considering all of the specified features to be high risk; patients with tumors having these characteristics should therefore be considered for adjuvant chemotherapy. As noted earlier, these features were derived from review of existing guidelines and models of risk stratification.	The ASCO panel suggests a slight revision to the CCO language concerning the Oncotype DX threshold for this recommendation. Specifically, for lymph node–negative tumors with T > 5mm, grade 3, triple negative (ER negative, PR negative, and HER2 negative), LVI positive, Oncotype DX recurrence score associated with an estimated distant relapse risk of > 20% at 10 years, and HER2 positive should be considered high-risk features and thus considered candidates for chemotherapy.
6. Patients with which disease characteristics may not benefit from adjuvant chemotherapy?	T < 5 mm, lymph node negative and no other high-risk features (see previous recommendation)		
7. Adjuvant chemotherapy may not be required in patients with HER2-negative, strongly ER-positive and PR-positive breast cancer with any of the following additional characteristics?	Lymph node positive with micrometastasis (< 2 mm) only, *or* T < 5 mm, *or* An Oncotype DX recurrence score with an estimated distant relapse risk of less than 15% at 10 years	[Qualifying Statements for Recommendations 6 and 7] Cutoffs for the degree of ER expression do not formally exist. The generally accepted degree of strong ER positivity is more than 90%, and that level was used for the consensus question. Refer to local pathology policy with respect to degree of ER expression. Few randomized controlled trials have addressed the role of systemic chemotherapy in female patients with early-stage breast cancer having a good prognosis. In addition, available data concerning the benefit of systemic therapy in patients with lymph node-positive micrometastatic disease (< 2 mm) are limited. The International Breast Cancer Study Group 23-01 trial concluded that axillary dissection could be avoided in patients with early breast cancer and limited sentinel node involvement (micrometastasis only), thus eliminating the complications of axillary surgery with no adverse effect on survival rates.[19] In the 23-01 trial, more than 60% of patients received adjuvant endocrine treatment alone, with excellent 5-year disease-free survival and overall survival. Sentinel node micrometastases have been associated with adverse prognosis in some long-term follow up studies. Retrospective data have shown some benefit of systemic therapy in patients with micrometastatic disease. Until the results of prospective randomized, controlled trials are available, the potential role of systemic therapy should be discussed with each patient.[20] Prognostic tools such as Adjuvant! Online and Oncotype DX can be used to assist health care providers in determining the potential benefits of chemotherapy. The potential benefit of adjuvant systemic therapy is modest for patients with small (< 1 cm) node-negative breast cancer that is endocrine sensitive and HER2 negative. Such patients can be considered for endocrine therapy alone (see the guideline from the US National Comprehensive Cancer Network). Although most of the consensus group agreed that patients with lymph node–positive breast cancer with micrometastases only (< 2 mm) and no other high-risk features might not need adjuvant chemotherapy, 25% disagreed or were undecided, and consensus was not reached. However, consensus was reached about potentially omitting chemotherapy when patients are found to have lower-risk (see recommendation 7) strongly ER-positive or PR-positive disease. There was disagreement about whether lymph node micrometastasis alone is a high- or low-risk factor. Lymph node positivity with micrometastasis alone is therefore not included in the recommendation.	The ASCO Panel suggests a minor revision from the CCO "…Oncotype DX recurrence score with an estimated distant relapse risk of less than 15% at 10 years" to "an Oncotype DX recurrence score with an estimated distant relapse risk of less than 10% at 10 years."

NOTE. Adapted by permission from Multimed, Inc.[21]

Abbreviations: ASCO, American Society of Clinical Oncology; CCO, Cancer Care Ontario; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITC, isolated tumor cells; LVI, lymphovascular invasion; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; PR, progesterone receptor; TAILORx, Trial Assigning Individualized Options for Treatment.

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approved. The ASCO Clinical Practice Guidelines Committee reviewed and approved the final document. The ASCO Panel will continue to coordinate with CCO guideline development staff and breast content experts to update the endorsement as new data become available.

Guideline Disclaimer

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Guideline and Conflict 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/rwc). All members of the 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.

UPDATED RECOMMENDATIONS

Clinical Question

This update of the ASCO endorsement of the CCO recommendations focuses solely on new evidence pertaining to the question, "What risk stratification tools may be used in determining the utility of certain systemic therapies in patients with early-stage breast cancer?" In particular, the update addresses the implications of recently published results of TAILORx for treatment of patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer with intermediate Onco*type* DX recurrence scores[2]; it also adds relevant recommendations on the use of MammaPrint assay[3] from the updated ASCO guideline on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer.[14]

Onco*type* DX Updated Recommendations

All recommendations refer to patients who present with a hormone receptor–positive, HER2 not overexpressed, axillary node–negative early breast cancer.

- For patients older than age 50 years and whose tumors have Onco*type* DX recurrence scores less than 26, and for patients age 50 years or younger whose tumors have Onco*type* DX recurrence scores less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For patients age 50 years or younger with Onco*type* DX scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Patients with Onco*type* DX recurrence scores greater than 30 should be considered candidates for chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Onco*type* DX scores of 26 to 30 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review. In TAILORx, a prospective, noninferiority clinical trial, 6,711 patients with hormone receptor–positive, HER2-negative, and axillary node–negative breast

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cancer and an Onco*type* DX recurrence score between 11 and 25 were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone.[2] The primary outcome of the trial, invasive disease–free survival, was defined as freedom from invasive disease recurrence, second primary cancer, or death. Results indicated that endocrine therapy was noninferior to chemoendocrine therapy (hazard ratio, 1.08; 95% CI, 0.94 to 1.24; $P = .26$; Table 2).

However, in an exploratory subgroup analysis among women with an Onco*type* DX recurrence score who were age 50 years or younger, some benefit of chemotherapy was suggested. Table 3, adapted from Sparano et al,[2] shows the type of first invasive disease–free survival event by age and recurrence score for patients who were randomly assigned to receive endocrine therapy alone or chemoendocrine therapy. Among women age 50 years or younger with a recurrence score of 21 to 25, approximately 6.3% lower invasive disease–free survival was observed at 9 years in the cohort that received endocrine therapy alone compared with chemoendocrine therapy. For women age 50 years or younger with a recurrence score of 16 to 20, approximately 9% lower invasive disease–free survival was observed at 9 years in the cohort that received endocrine therapy alone compared with chemoendocrine therapy. Finally, there was a statistically significant interaction of chemotherapy benefit and age for invasive disease–free survival and freedom from distant or locoregional recurrence.

The Expert Panel provided separate recommendations for patients with recurrence scores of 26 to 30 and for patients with recurrence scores greater than 30 based on the results of published prospective-retrospective analyses. Onco*type* DX was developed and validated in samples obtained retrospectively from participants who enrolled in the prospective National Surgical Adjuvant Breast and Bowel Project B-14 and B-20 clinical trials.[7,23] In these studies, a recurrence score of greater than 30 was selected as the cutoff indicating that individuals are at high risk of recurrence and should be recommended chemoendocrine therapy. When TAILORx was developed, cutoffs were selected based on the distribution estimates by way of the Kaplan-Meier method and were compared using the log-rank test. Therefore, patients enrolled in TAILORx whose recurrence scores were greater than 25 were recommended chemoendocrine therapy.

In a recent exploratory reanalysis of B-20, the performance of the 21-gene assay in predicting chemotherapy benefit was assessed using the recurrence score cutoffs used in TAILORx.[24] The analysis demonstrated a statistically significant benefit from chemoendocrine therapy in women with a recurrence score greater than 25 (hazard ratio, = 0.27; 95% CI, 0.12 to 0.62; $P < .001$). Specifically, the 10-year distant recurrence–free estimate for women treated with tamoxifen alone was 62% (95% CI, 48% to 81%) compared with 88% (95% CI, 81% to 95%) in individuals treated with tamoxifen and chemotherapy. The benefit was more substantial in women age 50 years or younger.

Although there are no data from a randomized clinical trial to guide treatment of women with recurrence scores of 26 to 30, because they were not randomly assigned in TAILORx, oncologists should consider recommending chemoendocrine therapy for women meeting these criteria.

MammaPrint Assay Recommendations From the ASCO 2017 Biomarkers Guideline

- If a patient has estrogen receptor (ER)/progesterone receptor (PR)–positive, HER2-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PR–positive, HER2-negative, node-negative breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).
- If a patient has ER/PR–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

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TABLE 2. Summary of Results of TAILORx

Source	Intervention/ Comparison	Primary End Points	No. of Patients Evaluated	Survival					Freedom From Recurrence of Breast Cancer at a Distant Site			Freedom From Recurrence of Breast Cancer at a Distant or Locoregional Site	
				IDFS			OS						
				Rate at 5 Years (%)	Rate at 9 Years (%)		Rate at 5 Years (%)	Rate at 9 Years (%)	Rate at 5 Years (%)	Rate at 9 Years (%)		Rate at 5 Years (%)	Rate at 9 Years (%)
Sparano et al (2018)[2]	Recurrence score of ≤ 10, endocrine therapy	Primary: IDFS Secondary: freedom from recurrence at a distant site; OS	1,619	94.0 ± 0.6	84.0 ± 1.3		98.0 ± 0.4	93.7 ± 0.8	99.3 ± 0.2	96.8 ± 0.7		98.8 ± 0.3	95.0 ± 0.8
	Recurrence score of 11-25, endocrine therapy		3,399	92.8 ± 0.5	83.3 ± 0.9	HR, 1.08; 95% CI, 0.94 to 1.24; $P = .26$	98.0 ± 0.2	93.9 ± 0.5	98.0 ± 0.3	94.5 ± 0.5	HR, 1.10; 95% CI, 0.85 to 1.41; $P = .48$	96.9 ± 0.3	92.2 ± 0.6
	Recurrence score of 11-25, chemoendocrine therapy		3,312	93.1 ± 0.5	84.3 ± 0.8		98.1 ± 0.2	93.8 ± 0.5	98.2 ± 0.2	95.0 ± 0.5		97.0 ± 0.3	92.9 ± 0.6
	Recurrence score of ≥ 26, chemoendocrine therapy		1,389	87.6 ± 1.0	75.7 ± 2.2		95.9 ± 0.6	89.3 ± 1.4	93.0 ± 0.8	86.8 ± 1.7		91.0 ± 0.8	84.8 ± 1.7

Abbreviations: HR, hazard ratio; IDFS, invasive disease–free survival; OS, overall survival; TAILORx, Trial Assigning Individualized Options for Treatment.

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TABLE 3. Type and Number of First IDFS Events for Randomly Assigned Patients by Age, RS, and Arm

	RS 11-15		RS 16-20		RS 21-25	
Patient Group	**Arm B***	**Arm C†**	**Arm B***	**Arm C†**	**Arm B***	**Arm C†**
Age ≤ 50 years						
No. of patients	439	362	454	469	246	246
Ipsilateral breast tumor recurrence	8	7	10	4	6	1
Other locoregional recurrence (± ipsilateral breast recurrence)	3	3	8	8	8	5
Distant recurrence (± ipsilateral breast or other locoregional recurrence)	9	7	17	10	17	9
Opposite breast cancer	4	6	9	5	3	3
Other second primary cancer	16	8	16	9	5	6
Death	5	4	5	2	2	2
Total No. of events	45	35	65	38	41	26
Age 51-65 years						
No. of patients	602	648	732	693	437	433
Ipsilateral breast tumor recurrence	1	4	5	6	5	4
Other locoregional recurrence (± ipsilateral breast recurrence)	4	7	7	3	7	4
Distant recurrence (± ipsilateral breast or other locoregional recurrence)	15	8	16	20	16	20
Opposite breast cancer	4	5	8	17	8	9
Other second primary cancer	13	32	38	35	20	14
Death	11	15	7	12	8	2
Total No. of events	48	71	81	93	64	53
Age 66-75 years						
No. of patients	173	149	182	182	134	130
Ipsilateral breast tumor recurrence	0	2	3	2	0	1
Other locoregional recurrence (± ipsilateral breast recurrence)	1	0	1	1	0	0
Distant recurrence (±ipsilateral breast or other locoregional recurrence)	4	3	5	7	8	8
Opposite breast cancer	5	0	3	3	0	0
Other second primary cancer	18	15	12	14	7	13
Death	7	4	9	8	9	3
Total No. of events	35	24	33	35	24	25

NOTE. From the New England Journal of Medicine, Sparano et al, Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer, Volume 379, Page S23.[2] Copyright© 2018 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.[2]

Abbreviations: IDFS, invasive disease-free survival; RS, recurrence score.

*Patients in Arm B were randomly assigned to endocrine therapy alone.

†Patients in Arm C were randomly assigned to chemoendocrine therapy.

- If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- If a patient has ER/PR–negative and HER2-negative (triple-negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

Literature review. No new data from the MINDACT trial were reviewed for this guideline update. From Krop et al[14]: The MINDACT study was a randomized trial that included 6,693 women with histologically proven operable invasive breast cancer, zero to three positive nodes, and no distant metastases.[3] Patients were recruited from 2007 to 2011. Only patients with node-negative disease were enrolled initially, and the study was amended to include women with one to three positive nodes in 2009. Each participant's genomic risk was determined by using the MammaPrint assay, and clinical risk was determined by using a modified version of Adjuvant! Online (version 8.0 with HER2 status). Adjuvant! Online is currently unavailable

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TABLE 4. 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. From the New England Journal of Medicine, Cardoso et al, 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer, Volume 375, Page S20.[3] Copyright© 2016 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.[3]

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

for use. Clinicians can use Table 4, reprinted from Cardoso et al,[3] to help determine clinical risk. Table 4 provides a classification of patients according to clinical risk assessment by the modified version of Adjuvant! Online. Individuals with both low clinical and low genomic risk did not receive chemotherapy, but those at high clinical and high genomic risk received adjuvant chemotherapy. Those with discordant clinical and genomic risk results (high/low or low/high) were randomly assigned to chemotherapy or to no chemotherapy. Women in all groups were recommended to receive 7 years of hormonal therapy, if appropriate, on the basis of ER/PR status.

The study included additional optional random assignments. First, participants who were allocated to chemotherapy could elect to be randomly assigned to receive an anthracycline-containing regimen or a docetaxel-plus-capecitabine regimen. Second, participants with hormone receptor–positive breast cancer could be randomly assigned to a sequential regimen of tamoxifen for 2 years followed by letrozole for 5 years, or to 7 years of letrozole only. Premenopausal women who entered random assignment had to have adequate ovarian function suppression during letrozole therapy. Results from these random assignments are yet to be reported.

The primary analysis of the study, which was reported in a recent publication,[3] was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% CI for the rate of 5-year survival without distant metastasis (distant metastasis–free survival [DMFS]) was 92% or greater. A prespecified secondary analysis was to estimate the efficacy of chemotherapy in those patients with discordant clinical and genomic risk

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results who were randomly assigned to chemotherapy versus no chemotherapy, but the study was not designed to detect a significant difference. An additional secondary analysis was to determine the proportion of patients who were assigned chemotherapy according to the clinical risk compared with the genomic risk.

The study included 6,693 participants, of whom 5,914 (88.4%) had ER/PR–positive tumors, 6,043 (90.3%) had HER2-negative tumors, and 640 (9.6%) had triple-negative tumors. Of the 6,693 participants, 2,745 (41.0%) had tumors with low clinical and low genomic risks, 592 (8.8%) had tumors with low clinical risk and high genomic risk, 1,550 (23.2%) had tumors with high clinical risk and low genomic risk, and 1,806 (27.0%) had tumors with high clinical and high genomic risks. This first report included a cutoff date of March 1, 2016, which corresponded to a median follow-up time of 5.0 years. Of the 644 women who represented the primary test population (ie, those with high clinical risk and low genomic risk who did not receive chemotherapy), the DMFS at 5 years was 94.7% (95% CI, 92.5% to 96.2%), thus demonstrating a lower boundary of the 95% CI for the rate of DMFS of at least 92%. In the 749 women in the intention-to-treat population with a high clinical risk and low genomic risk who were randomly assigned to receive chemotherapy, the 5-year DMFS was 95.9% (95% CI, 94.0% to 97.2%) compared with a 5-year DMFS of 94.4% (95% CI, 92.3% to 95.9%) in women who were randomly assigned to not receive chemotherapy. The difference between these two groups was 1.5 percentage points, with an adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy of 0.78 (95% CI, 0.50 to 1.21; P = .27). In terms of other end points in this group with high clinical risk and low genomic risk who received chemotherapy per the intention-to-treat population and the per-protocol population assessments, the DMFS was 1.5% and 1.9% higher, respectively; DFS was 2.8% and 3% higher, respectively; the overall survival was 1.4% and 1.5% higher, respectively, compared with no chemotherapy. Given that a subset of the patients received a nonstandard adjuvant chemotherapy regimen of docetaxel plus capecitabine, and given that the follow-up was only 5 years in a predominantly ER/PR–positive cohort who received up to 7 years of endocrine therapy, a small chemotherapy benefit in patients with high clinical risk and low genomic risk cannot be excluded.

Patients at low clinical risk but high genomic risk who received chemotherapy had a 5-year DMFS of 95.8% (95% CI, 92.9% to 97.6%) compared with 95.0% (95% CI, 91.8% to 97.0%) among those who did not receive chemotherapy. The adjusted hazard ratio for distant metastasis or death with chemotherapy versus no chemotherapy in this group was 1.17 (95% CI, 0.59 to 2.28; P = .66). Thus, a chemotherapy benefit is unlikely in women with tumors at low clinical risk regardless of genomic subtype.

ADDITIONAL RESOURCES

More information, including slide sets and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. Patient information is available at https://www.cancer.net/.

RELATED ASCO GUIDELINES

- Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer (http://ascopubs.org/doi/10.1200/JCO.2015.65.2289)
- ACS/ASCO Breast Cancer Survivorship Care Guideline (http://ascopubs.org/doi/10.1200/JCO.2015.64.3809)
- Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer (http://ascopubs.org/doi/10.1200/JCO.2015.65.8609)
- Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2)–Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers (http://ascopubs.org/doi/10.1200/JCO.2016.67.0182)

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline update provides updated recommendations of an ASCO endorsement that was based originally on the review and analyses

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of the relevant literature in "Optimal systemic therapy for early breast cancer: A clinical practice guideline" by Eisen et al, published in 2015 in *Current Oncology*. Additional information, which may include slide sets and other clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: Update of the ASCO Endorsement of the Cancer Care Ontario Guideline

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APPENDIX

TABLE A1. Update Expert Panel Members

Name (designation)	Affiliation/Institution	Expertise
N. Lynn Henry, MD, PhD (co-chair)	University of Utah Huntsman Cancer Institute, Salt Lake City, UT	Medical oncology
Vered Stearns, MD (co-chair)	Kimmel Cancer Center at Johns Hopkins, Baltimore, MD	Medical oncology
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Abbreviation: PGIN, Practice Guideline Implementation Network.

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