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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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Abstract

Purpose—This focused update addresses the use of MammaPrint (Agendia, Irvine, CA) to guide decisions on the use of adjuvant systemic therapy.

Methods—ASCO uses a signals approach to facilitate guideline updates. For this focused update, the publication of the phase III randomized MINDACT (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) study to evaluate the MammaPrint assay in 6,693 women with early-stage breast cancer provided a signal. An expert panel reviewed the results of the MINDACT study along with other published literature on the MammaPrint assay to assess for evidence of clinical utility.

Recommendations—If a patient has hormone receptor–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 to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, the MammaPrint assay does not have clinical utility in such patients. If a patient has hormone receptor–positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node. The clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy in patients with hormone receptor–positive, HER2-negative, node-positive breast cancer at low clinical risk, nor any patient with HER2-positive or triple-negative breast cancer, because of the lack of definitive data in these populations.

Additional information can be found at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on the use of biomarkers to guide adjuvant therapy for early-stage invasive breast cancer was most recently published in February 2016.[1] ASCO Guidelines are updated at regular intervals; however, there may be new evidence that potentially changes a recommendation and becomes available between scheduled updates. ASCO uses a signals approach to facilitate guideline updates. This approach is intended to identify new, potentially practice-changing data (ie, signals) that might translate into revised practice recommendations. The approach relies on routine literature searches and the expertise of ASCO Guideline Panel members to identify signals. The Methodology Supplement (www.asco.org/breast-cancer-guidelines) provides additional information about this approach. For this focused update, the publication of the “Microarray in node-negative and one to three positive lymph node disease may avoid

chemotherapy" (MINDACT) study, a randomized controlled trial on a 70-gene assay (MammaPrint; Agendia, Irvine, CA) provided the signal.[2]

THE BOTTOM LINE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Guideline Question

For women with early-stage invasive breast cancer, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Target Population

Women with early-stage invasive breast cancer being considered for adjuvant systemic therapy

Target Audience

An Expert Panel was convened to update the clinical practice guideline recommendations based on a review of recently published literature.

Focused Update Recommendation(s)

Recommendation 1.1.1 (update of 2016 recommendation 1.7): If a patient has **ER/PgR–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; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2 (update of 2016 recommendation 1.7): If a patient**has ER/PgR–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; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2.1: (update of 2016 recommendation 1.7): If a patient has **ER/PgR–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; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.2.2: (update of 2016 recommendation 1.7): If a patient has **ER/PgR–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).

Recommendation 1.3: (update of 2016 recommendation 1.8): 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).

Recommendation 1.4: (update of 2016 recommendation 1.9): If a patient has **ER/PgR 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).

Refer to Table 1 for the full list of the original recommendations for question 1.

Additional Resources

More information, including a Methodology Supplement with information on evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki. 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.

The decision to update this aspect of the guideline was intended to convey any recommendation changes to the practicing community in a timely fashion. Although evidence on other aspects of the guideline may have become available after release of the guideline, no other strong signal likely to affect the recommendations has been identified to date. This approach acknowledges that frequent updating is not practical or necessary unless indicated by practice-changing evidence. It is important to note that new evidence, published in a peer-reviewed journal, about any ASCO guideline may be submitted at any time. Please access the ASCO Guidelines Wiki for more information on evidence submission at http://www.asco.org/guidelineswiki. All new evidence submissions are reviewed by ASCO Staff for study selection eligibility requirements and by the Expert Panel co-chairs for a content assessment. If the new evidence is determined to constitute a signal, it will prompt an expedited update on the topic.

Focused updates for Clinical Practice Guidelines are approved by the Clinical Practice Guideline Committee, and this update reflects new evidence about recommendations 1.7 to 1.9 on MammaPrint in the previous version of this guideline.[1] This focused update reviews

and analyzes new data about these recommendations while applying the same criteria of clinical utility as described in the 2016 guideline.

As stated in the 2016 guideline, a biomarker-based test is judged to have clinical utility if use of the test is associated with a favorable balance of benefits to harm compared with treatment of the patient in the absence of the biomarker test result. Benefits may include improvement in survival end points such as event-free survival (EFS), disease-free survival (DFS), progression-free survival (PFS), or overall survival (OS).[1] The Use of Biomarkers Update Committee clarified that reduction in toxicity of treatment also can be considered a benefit. For example, a biomarker test that provides evidence that a patient can be treated effectively with hormonal therapy alone provides benefit to that patient by avoiding the potential serious toxicity of chemotherapy.

GUIDELINE QUESTIONS

For women with early-stage invasive breast cancer, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy: (a) in patients with estrogen receptor (ER) and/or progesterone receptor (PgR)–positive, human epidermal growth factor receptor 2 (HER2)-negative (node-negative or node-positive) breast cancer; (b) in patients with HER2-positive breast cancer; and (c) in patients with triple-negative breast cancer?

As this focused update addresses the role of MammaPrint in early breast cancer, only the first clinical question from the original guideline is addressed here.

METHODS

This ASCO Clinical Practice Guideline focused update provides revised recommendations with a comprehensive discussion of the relevant literature for this specific biomarker identified through the methodology described above. The full guideline to which this revision applies and additional information are available at www.asco.org/breast-cancer-guidelines and www.asco.org/guidelineswiki. The complete list of recommendations, including the updated recommendation(s), is in Table 1.

Related ASCO Guidelines

- Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer[1] (http://ascopubs.org/doi/full/10.1200/JCO.2015.65.2289)
- ACS/ASCO Breast Cancer Survivorship Care Guideline[16] (http://ascopubs.org/doi/full/10.1200/JCO.2015.64.3809)
- Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision-Making for Early-Stage, Operable Breast Cancer[17] (http://ascopubs.org/doi/full/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[13] (http://ascopubs.org/doi/full/10.1200/JCO.2016.67.0182)

Guideline Disclaimer

The clinical practice guidelines and other guidance published therein are provided by ASCO to assist providers in clinical decision making. The information therein 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 reflect high, moderate or low 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” indicate 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 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/rwc). 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.

Guideline Update Process

ASCO uses a signals approach to facilitate guideline updating.[3] This approach is intended to identify new, potentially practice-changing data (ie, 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 Methodology Supplement (www.asco.org/breast-cancer-guidelines) provides additional information about the signals approach.

For this focused update, the publication of the randomized controlled trial on MammaPrint provided the signal. The full ASCO Update Committee (Appendix Table A1, online only) was then convened to review the evidence. A summary of the relevant studies on this biomarker can be found in the Data Supplement.

The Expert Panel met via conference calls to consider the evidence for each of the 2017 recommendations on MammaPrint (Appendix Table A2, online only). The guideline was circulated in draft form to the Expert Panel for review and approval. ASCO's Clinical Practice Guidelines Committee reviewed and approved the final document. Because this was a focused update based on the signal described above, only MammaPrint was reviewed by the Panel for this update.

RESULTS

Study Characteristics

The MINDACTstudy 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.[2] 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)[4,5]. The clinical risk classification criteria are included in the Data Supplement. 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/PgR 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 the recent publication,[2] 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, or 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 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/PgR–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 per-protocol population) assessment, the DMFS was 1.5% (and 1.9%) higher, respectively; DFS was 2.8% (and 3%) higher, respectively; and OS 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 that the follow-up was only 5 years in a predominantly ER/PgR–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.

GUIDELINE RECOMMENDATIONS

Clinical Question

For women with operable invasive breast cancer which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Recommendation 1.1.1 (update of Recommendation 1.7)—If a patient has **ER/PgR–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; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2 (update of Recommendation 1.7)—If a patient has **ER/PgR–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 as 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; Evidence quality: high; Strength of recommendation: strong).

Clinical interpretation of literature review: The recently published MINDACT[2] study informs the revision of the 2007 and 2016 ASCO Guidelines.[1,6] In the MINDACT study, the Mamma-Print assay was able to identify patients with node-negative, ER/PgR–positive, HER2-negative breast cancer with high clinical risk (as determined by using a modified version of Adjuvant! Online) but low genomic risk who have a favorable outcome when treated with endocrine therapy alone: the 5-year rate of DMFS was 93.9% (95% CI, 90.6% to 96.1%). This was similar to the DMFS of the women randomly assigned to receive chemotherapy: 95.5% (95% CI, 92.5% to 97.3%).[2] Additional retrospective studies of MammaPrint also support its prognostic value in ER/PgR–positive breast cancer.[7–12] Together, these data indicate that MammaPrint can provide guidance about the prognosis of women with ER/PgR–positive, HER2-negative breast cancer and a high clinical risk but low genomic risk, whose outcome is likely to be favorable even in the absence of chemotherapy. When reviewing these data with individual patients with high clinical risk and low genomic risk, the clinician should acknowledge that a small benefit from chemotherapy cannot be excluded, because the MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospectively. In addition, the clinician should consider that MINDACT included an optional random assignment to anthracycline-containing versus nonanthracycline-containing regimens, and whether the specific chemotherapy assignment affected patient outcome is not yet known. Last, the median duration of follow-up was only 5 years at the time of the 2016 publication. Additional follow-up and assessment of the clinical outcomes for key prognostic subgroups are needed.

Women with node-negative cancers and low clinical risk (as determined by using a modified version of Adjuvant! Online) had excellent outcomes regardless of genomic risk, and even those patients with high genomic risk did not appear to benefit from chemotherapy. Thus, in patients with node-negative cancers and low clinical risk, who will have an excellent outcome with endocrine therapy alone, MammaPrint does not provide significant clinical utility. Therefore, the MammaPrint assay should not be recommended to patients with low clinical risk who will receive endocrine therapy for hormone receptor–positive breast cancer.

Recommendation 1.2.1 (update of Recommendation 1.7)—If a patient has **ER/PgR–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; Evidence quality: high; Strength of recommendation: moderate).

Recommendation 1.2.2 (update of Recommendation 1.7)—If a patient has **ER/PgR–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).

Clinical interpretation of literature review: In the MIND-ACT study, 1,404 patients had node-positive breast cancers. Of these, 737 patients were categorized as high clinical risk (determined by using a modified version of Adjuvant! Online) but low genomic risk. These patients had a favorable outcome when treated with endocrine therapy alone (5-year rate of survival without distant metastasis, 95.6% [95% CI, 92.7% to 97.4%) compared with 96.3% (95% CI, 93.1% to 98.1%) among such patients randomly assigned to receive chemotherapy. On the basis of these results, the Panel felt that the MammaPrint assay may be used in patients with positive nodes and high clinical risk to identify those whose outcome is predicted to be sufficiently favorable that chemotherapy is unlikely to provide meaningful benefit. However, the Panel noted that there were several important limitations to the MINDACT data. The first is that the MINDACT study was not designed to detect a significant difference in favor of chemotherapy and is underpowered to do so retrospectively. Second, a separate outcome assessment of the subgroup of patients with ER/PgR–positive, HER2-negative, node-positive cancers was not performed. Third, only a minority (31.1%) of these patients with high clinical risk, low genomic risk, and node-positive disease had more than one node involved.[2] Fourth, no specific information is available for other key prognostic characteristics, such as tumor grade, in the node-positive subgroup. Fifth, because patients with node-positive disease were only enrolled starting in 2009, their follow-up is likely shorter than the overall 5-year median follow-up of the entire study population. Last, study participants may have received an anthracycline-containing regimen or a nonstandard regimen, and the impact of the specific chemotherapy regimen on chemotherapy benefit is unknown. Given these limitations, and the concern that patients with node-positive disease are generally at greater potential risk for undertreatment, the Panel felt that although the MammaPrint assay may be used in patients with one to three positive nodes, such patients should be informed that given the available data, a benefit from chemotherapy cannot be excluded. In addition, the assay should be used with some caution in patients with two to three positive nodes because of the relatively limited number of such patients in the MINDACT study.

The utility of the MammaPrint assay in patients with lymph node–positive disease assessed at low clinical risk per MINDACT categorization is not clear, because the number of patients was small and was not analyzed separately. It is possible that patients in this category may not benefit from chemotherapy use regardless of genomic risk. Given the limited data available at this time, the Panel does not recommend the routine use of MammaPrint in women with node-positive tumors and low clinical risk.

Recommendation 1.3 (update of Recommendation 1.8)—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).

Clinical interpretation of literature review: Currently, the standard of care for the adjuvant treatment of patients with HER2-positive tumors includes both chemotherapy and anti-HER2 agents.[13] In MINDACT, only 8% of patients (n = 124) had HER2-positive tumors with high clinical risk and low genomic risk and were randomly assigned to chemotherapy or not. In addition, results of this subgroup were not reported separately.[2] There are, therefore, insufficient data to support the use of MammaPrint in HER2-positive breast cancer. It is possible that patients with HER2-positive disease might not need chemotherapy if their prognoses are sufficiently favorable. Knauer et al[8] performed a retrospective, grade-C study to address whether the MammaPrint assay might identify such patients. This study involved 168 patients with HER2-positive tumors from a pooled database who were classified by the MammaPrint assay as having a good or a poor prognosis. Of these, 89 (53%) patients did not receive adjuvant chemotherapy or HER2-targeted therapy. With a median follow-up of 7.4 years, MammaPrint classified 22% of patients with a good prognosis as having a 10-year DMFS of 84% compared with 78% of patients with a poor prognosis as having a 10-year DMFS of 55%. The hazard ratios were 4.5 (95% CI, 1.1 to 18.7; $P = .04$) and 3.8 (95% CI, 0.9 to 15.8; $P = .07$) for DMFS and breast cancer–specific survival, respectively.[8]

Thus, the MammaPrint assay appears to have prognostic value in HER2-positive breast cancer in a retrospective study.[8] However, the Panel does not consider the data sufficiently robust or a suggestion of a 10-year distant DFS of 84%[8] sufficiently favorable to omit chemotherapy from an adjuvant regimen. Given the small HER2-positive subgroup in MINDACT and the known substantial benefit women with HER2-positive tumors derive from the addition of anti-HER2 agents to adjuvant chemotherapy, the Panel concluded that the data do not support use of the MammaPrint assay to decide whether a patient with HER2-positive breast cancer may safely forgo adjuvant chemotherapy.

Recommendation 1.4 (update of Recommendation 1.9)—If a patient has **ER/PgR–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).

Clinical interpretation of literature review: Although patients with triple-negative breast cancer were included in the prospective MINDACT study, the number of patients with this tumor subtype was small (n = 640 [9.6%]). The majority of women with this subtype (n = 566 [88%]) were classified as high clinical and high genomic risk and were not randomly assigned. Therefore, the absolute number of women with triple-negative breast cancer and a low genomic risk who did not receive chemotherapy was extremely small, and this subgroup was not analyzed separately. Given that no other therapies (eg, endocrine therapy or HER2-targeted therapy) are recommended for these patients, the Panel felt strongly that until data from larger data sets are available, the MammaPrint assay should not be used to guide clinical decisions in patients with triple-negative breast cancer.

DISCUSSION

Reduction of overtreatment in patients with early-stage breast cancer is an important goal. For several reasons, such a reduction would likely have the greatest societal and individual impact in patients with ER/PgR–positive disease. First, this is the most common type of breast cancer. Second, outcomes for this subtype generally are favorable for the majority of patients. Third, the available data suggest that only a minority of patients with ER/PgR–positive breast cancer derive significant benefit from adjuvant chemotherapy. Fortunately, it is clear from a number of biomarker studies that genomic assays that measure the expression of a relatively small number of genes in breast tumor tissue can provide important prognostic and possibly predictive information that can be used to identify patients with early-stage hormone receptor–positive breast cancer for whom chemotherapy is unlikely to be associated with a meaningful clinical benefit. Several of these genomic signatures, including Oncotype DX, EndoPredict, PAM50 risk of recurrence score, and Breast Cancer Index, were noted as having clinical utility for this purpose for patients with node-negative ER/PgR–positive cancers in a 2016 ASCO Clinical Practice Guideline.[1]

In this focused update of the 2016 ASCO Clinical Practice Guideline, we review data from the recently reported MINDACT study, which prospectively evaluated another gene expression signature, the 70-gene MammaPrint assay. In the MINDACT study, the MammaPrint assay was able to identify patients with high clinical risk but low genomic risk who had a relatively favorable prognosis in the absence of adjuvant chemotherapy. The assay had similar functionality in both node-negative and node-positive cancers. On the basis of these results, the Panel recommended that the MammaPrint assay could be used to guide decisions on withholding adjuvant systemic chemotherapy in patients with ER/PgR-positive lymph node–negative breast cancer and in select patients with lymph node–positive cancers. In both patients with node-positive and with node-negative disease, evidence of clinical utility of the MammaPrint assay was only apparent in those determined to be at high clinical risk, defined by a modified version of Adjuvant! Online. The Panel therefore did not recommend the use of the MammaPrint assay in any patient determined to be at low clinical risk. Of note, at the time of publication of this guideline update, the Adjuvant! Online website was not functional. As an alternative, clinicians can determine a patient's clinical risk status by using the printed version of the Adjuvant! Online clinical risk criteria found in the Data Supplement.

Now that there are several assays with clinical utility, particularly in patients with node-negative cancers, how does one select the assay to use for a particular patient? At this time, head-to-head comparisons of the different assays are limited. Sestak et al[14] did attempt one such comparison, but this study was limited by methodologic constraints.[15] Clearly, additional work is needed to allow clinicians to choose the optimal assay for individual patients. Panel members caution that there are no data to suggest that ordering more than one assay in an individual patient will be helpful to guide treatment decisions and do not recommend the use of more than one test. Clinicians should choose a test that they are most comfortable with to guide treatment decisions.

It should be noted that although the Panel concluded that several genomic assays have clinical utility in guiding decisions on withholding adjuvant systemic chemotherapy, none of these assays are perfect. In the available studies, some patients still developed recurrent disease despite favorable assay results, and many patients with poor-prognosis genomic scores remain disease free even in the absence of chemotherapy. Thus, improvements are needed in the assays to additionally reduce overtreatment but minimize risk of recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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. 2016; 34:1134–1150. [PubMed: 26858339]
2. 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. 2016; 375:717–729. [PubMed: 27557300]
3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007; 147:224–233. [PubMed: 17638714]
4. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol. 2001; 19:980–991. [PubMed: 11181660]
5. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol. 2005; 23:2716–2725. [PubMed: 15837986]
6. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007; 25:5287–5312. [PubMed: 17954709]
7. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J Natl Cancer Inst. 2006; 98:1183–1192. [PubMed: 16954471]
8. Knauer M, Cardoso F, Wesseling J, et al. Identification of a low-risk subgroup of HER-2-positive breast cancer by the 70-gene prognosis signature. Br J Cancer. 2010; 103:1788–1793. [PubMed: 21081926]

9. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1–3 positive lymph nodes in an independent validation study. Breast Cancer Res Treat. 2009; 116:295–302. [PubMed: 18661261]
10. Drukker CA, van Tinteren H, Schmidt MK, et al. Long-term impact of the 70-gene signature on breast cancer outcome. Breast Cancer Res Treat. 2014; 143:587–592. [PubMed: 24445566]
11. Bueno-de-Mesquita JM, Linn SC, Keijzer R, et al. Validation of 70-gene prognosis signature in node-negative breast cancer. Breast Cancer Res Treat. 2009; 117:483–495. [PubMed: 18819002]
12. Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat. 2010; 120:655–661. [PubMed: 20204499]
13. Denduluri N, Somerfield MR, Eisen A, et al. Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor Receptor 2 (HER2)–negative and adjuvant targeted therapy for HER2-positive breast cancers: An American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2016; 34:2416–2427. [PubMed: 27091714]
14. Sestak I, Buus R, Cuzick J, et al. Comprehensive comparison of prognostic signatures for breast cancer in TransATAC. Cancer Res. 2017; 77(suppl) abstr S6-05.
15. Hilsenbeck, S. Comprehensive comparison of prognostic signatures for breast cancer in TransATAC. San Antonio Breast Cancer Symposium; San Antonio, TX. December 6–10, 2016; S6-06: Discussant
16. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2016; 34:611–635. [PubMed: 26644543]
17. Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: American Society of Clinical Oncology endorsement of Cancer Care Ontario guideline recommendations. J Clin Oncol. 2016; 34:2303–2311. [PubMed: 27001586]

Appendix

Table A1

Guideline Expert Panel Membership

Name	Affiliation
Vered Stearns, MD, (co-chair)	Johns Hopkins University, Baltimore, MD
Ian Krop, MD, PhD (co-chair)	Dana-Farber Cancer Institute, Boston, MA
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William Barlow	Cancer Research and Biostatistics, Seattle, WA
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Deborah E. Collyar (patient representative)	Patient Advocates in Research, Danville, CA
Catherine Van Poznak, MD (PGIN representative)	University of Michigan, Ann Arbor, MI

NOTE. ASCO Staff: Nofisat Ismaila, MD.

Abbreviation: PGIN, Practice Guidelines Implementation Network.

Table A2

Summary of All Recommendations on MammaPrint

2016 Recommendation	Focused Update Recommendation
Recommendation 1.7: If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the 70-gene assay (MammaPrint; Agendia, Irvine, CA) to guide decisions on adjuvant systemic chemotherapy (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).	*Recommendation 1.1.1:* If a patient has **ER/PgR–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; Evidence quality: high; Strength of recommendation: strong) *Recommendation 1.1.2:* If a patient **has ER/PgR–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; Evidence quality: high; Strength of recommendation: strong). *Recommendation 1.2.1:* If a patient has **ER/PgR–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; Evidence quality: igh; Strength of recommendation: moderate). *Recommendation 1.2.2:* If a patient has **ER/PgR–positive, HER2-negative, node-positive,** breast cancer, the MammaPrint assay **should not** be used in patients with 1–3 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).
Recommendation 1.8: If a patient has HER2-positive breast cancer, the clinician should not use the 70-gene assay to guide decisions on adjuvant systemic therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).	*Recommendation 1.3*: 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).
Recommendation 1.9: If a patient has TN breast cancer, the clinician should not use the 70-gene assay to guide decisions on adjuvant systemic therapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).	No changes.

NOTE. Clinical question: For women with operable invasive breast cancer and with known ER/PgR and HER2 statuses, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy? All recommendations include original recommendations and focused update recommendations. Only recommendations 1.7 and 1.8 have been changed/modified. Bold type highlights the different patient subgroups.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; PgR, progesterone receptor; TN, triple-negative.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Table 1

Summary of Original Recommendations for Question 1 With Focused Updated Recommendations

Recommendation No.	Recommendation	Evidence Rating
1.1	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the 21-gene RS (Oncotype DX; Genomic Health, Redwood, CA) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: high Strength of recommendation: strong
1.2	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 21-gene RS (Oncotype DX; Genomic Health) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.3	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the 21-gene RS (Oncotype DX; Genomic Health) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.4	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Köln, Germany) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.5	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict; Sividon Diagnostics) to guide decisions for adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: insufficient Strength of recommendation: moderate
1.6	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use 12-gene risk score (EndoPredict; Sividon Diagnostics) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.7 Recommendation 1.1.1 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint (Agendia, Irvine, CA) 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 Evidence quality: high Strength of recommendation: strong**
1.7 Recommendation 1.1.2 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint (Agendia) 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 Evidence quality: high Strength of recommendation: strong**
1.7 Recommendation 1.2.1 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint (Agendia) 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 Evidence quality: high Strength of recommendation: moderate**
1.7 Recommendation 1.2.2 in 2017	**If a patient has ER/PgR–positive, HER2-negative, node-positive, breast cancer, the MammaPrint (Agendia) 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**
1.8 Recommendation 1.3 in 2017	**If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint (Agendia) 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 HER-2–targeted therapy.**	**Type: informal consensus Evidence quality: low Strength of recommendation: moderate**
1.9 Recommendation 1.4 in 2017	**If a patient has ER/PgR–negative and HER2-negative breast cancer (triple-negative), the clinician should not use the MammaPrint (Agendia) assay to guide decisions on adjuvant systemic chemotherapy.**	**Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong**

Recommendation No.	Recommendation	Evidence Rating
1.10	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the PAM50 ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies, Seattle, WA) in conjunction with other clinicopathologic variables to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: high Strength of recommendation: strong
1.11	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the PAM50 ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.12	If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.13	If a patient has triple-negative breast cancer, the clinician should not use the PAM50-ROR score (Prosigna Breast Cancer Prognostic Gene Signature Assay; NanoString Technologies) to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.14	If a patient has ER/PgR–positive, HER2-negative, node-negative breast cancer, the clinician may use the Breast Cancer Index (bioTheranostics, San Diego, CA) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.15	If a patient has ER/PgR–positive, HER2-negative, node-positive breast cancer, the clinician should not use the Breast Cancer Index (bioTheranostics) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.16	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the Breast Cancer Index ((bioTheranostics) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.17	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the five-protein assay Mammostrat (GE Healthcare, Aliso Viejo, CA) to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.18	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the five-protein assay Mammostrat (GE Healthcare) to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.19	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use IHC-4 to guide decisions on adjuvant systemic chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.20	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use IHC-4 to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong
1.21	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use the uPA and PAI-1 to guide decisions on adjuvant systemic therapy.	Type: Evidence based Evidence quality: high Strength of recommendation: weak
1.22	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the uPA and PAI-1 to guide decisions on adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: weak
1.23	The clinician should not use CTCs to guide decisions for adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: strong
1.24	If a patient has ER/PgR–positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use TILs to guide decisions for adjuvant systemic therapy.	Type: informal consensus Evidence quality: insufficient Strength of recommendation: strong

Recommendation No.	Recommendation	Evidence Rating
1.25	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use TILs to guide decisions on adjuvant systemic therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: strong
1.26	Ki67 labeling index by immunohistochemistry should not be used to guide the choice of adjuvant chemotherapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate
1.27	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC-4) to guide decisions on extended endocrine therapy.	Type: evidence based Evidence quality: intermediate Strength of recommendation: moderate

NOTE. Focused update recommendations are in bold. Clinical question 1 is as follows: For women with operable invasive breast cancer and with known ER/PgR and HER2 status, which other biomarkers have demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy?

Abbreviations: CTC, circulating tumor cell; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC-4, immunohistochemistry 4; MINDACT, Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy; PAI-1, plasminogen activator inhibitor type 1; PgR, progesterone receptor; ROR, risk of recurrence; RS, recurrence score; TIL, tumorinfiltrating lymphocyte; uPA, urokinase plasminogen activator.