ASCO special article

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

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abstract

PURPOSE This focused update addresses the use of Onco*type* DX in guiding decisions on the use of adjuvant systemic therapy.

METHODS ASCO uses a signals approach to facilitate guideline updating. For this focused update, the publication of the Trial Assigning Individualized Options for Treatment (TAILORx) evaluating noninferiority of endocrine therapy alone versus chemoendocrine therapy for invasive disease–free survival in women with Onco*type* DX scores provided a signal. An expert panel reviewed the results of TAILORx along with other published literature on the Onco*type* DX assay to assess for evidence of clinical utility.

UPDATED RECOMMENDATIONS For patients with hormone receptor–positive, axillary node–negative breast cancer whose tumors have Onco*type* DX recurrence scores of less than 26, there is little to no benefit from chemotherapy, especially for patients older than age 50 years. Clinicians may recommend endocrine therapy alone for women older than age 50 years. For patients 50 years of age 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 these patients with recurrence scores of 26 to 30. Additional information can be found 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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F.A. and V.S. were Expert Panel co-chairs.

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INTRODUCTION

The 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 updating. 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 Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach. For this focused update, the publication of the Trial Assigning Individualized Options for Treatment (TAILORx) evaluating noninferiority of endocrine therapy alone versus chemoendocrine therapy for invasive disease–free survival in women with intermediate Onco*type* DX (Genomic Health, Redwood City, CA) scores provided a signal.[2]

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 that was felt likely to affect the recommendations has been identified to date. This approach acknowledges that frequent updating is not practicable or necessary unless indicated by practice-changing evidence. It is important to note that new evidence, published in a peer-reviewed journal, regarding any ASCO guideline may be submitted at any time at www.asco.org/breast-cancer-guidelines. 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

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 Update—Integration of Results from TAILORx

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

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

Methods

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

Updated Recommendations

All recommendations refer to patients who present with a hormone receptor–positive, human epidermal growth factor receptor not overexpressed, axillary node–negative early breast cancer

Recommendation 1.1.1. For patients older than 50 years and whose tumors have Onco*type* DX recurrence scores of less than 26, and for patients age 50 years or younger whose tumors have Onco*type* DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.2. For patients age 50 years or younger with Onco*type* DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.1.3. Patients with Onco*type* DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.4. Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Onco*type* DX scores of 26 to 30 (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
Refer to Table 1 for the full list of the original recommendations for Question 1.

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

Additional Resources

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

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 regarding recommendations on Onco*type* DX in the previous version of this guideline.[1] This focused update reviews and analyzes new data regarding these recommendations while applying the same criteria of clinical utility as described in the 2016 guideline.

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

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: (a) in patients with estrogen receptor– and/or progesterone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative (node-negative or node-positive) breast

TABLE 1. Summary of Original Recommendations for Question 1 With Focused Updated Recommendations

Clinical Question 1: 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?

Recommendation No.	Recommendation	Evidence Rating
1.1	If a patient has ER/PgR–positive, HER2-negative (node-negative) breast cancer, the clinician may use 21-gene RS (Onco*type* DX; Genomic Health, Redwood, CA) to guide decisions for adjuvant systemic chemotherapy.	Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong
1.1.1*	For patients older than 50 years whose tumors have Onco*type* DX RSs < 26 and for patients age 50 years or younger whose tumors have Onco*type* DX RSs < 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone.	Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong
1.1.2*	For patients 50 years of age or younger with Onco*type* DX RSs of 16 to 25, clinicians may offer chemoendocrine therapy.	Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate
1.1.3*	Patients with Onco*type* DX RSs > 30 should be considered candidates for chemoendocrine therapy.	Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong
1.1.4*	Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Onco*type* DX scores of 26 to 30.	Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate
1.2	If a patient has ER/PgR–positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 21-gene RS to guide decisions for adjuvant systemic chemotherapy.	Type of recommendation: 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 (Onco*type* DX) to guide decisions for adjuvant systemic therapy.	Type of recommendation: 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 of recommendation: 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) to guide decisions for adjuvant systemic chemotherapy.	Type of recommendation: 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) to guide decisions for adjuvant systemic therapy.	Type of recommendation: 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 assay (Agendia, Irvine, CA) 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 of recommendation: 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 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 of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong

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TABLE 1. Summary of Original Recommendations for Question 1 With Focused Updated Recommendations (continued)

Clinical Question 1: 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?

Recommendation No.	Recommendation	Evidence Rating
1.7 (recommendation 1.2.1 in 2017)	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 of recommendation: 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 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 of recommendation: 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 assay to guide decisions regarding 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 of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate
1.9 (recommendation 1.4 in 2017)	If a patient has ER-negative, PgR-negative, HER2-negative breast cancer (triple negative), the clinician should not use the MammaPrint assay to guide decisions about adjuvant systemic chemotherapy.	Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong
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 about adjuvant systemic therapy.	Type of recommendation: 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) to guide decisions about adjuvant systemic therapy.	Type of recommendation: 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 to guide decisions regarding adjuvant systemic therapy.	Type of recommendation: 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 to guide decisions regarding adjuvant systemic therapy.	Type of recommendation: 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 about adjuvant systemic therapy.	Type of recommendation: 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 to guide decisions about adjuvant systemic therapy.	Type of recommendation: 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 to guide decisions about adjuvant systemic therapy.	Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong

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TABLE 1. Summary of Original Recommendations for Question 1 With Focused Updated Recommendations (continued)

Clinical Question 1: 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?

Recommendation No.	Recommendation	Evidence Rating
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 about adjuvant systemic therapy.	Type of recommendation: 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 five-protein assay Mammostrat to guide decisions about adjuvant systemic therapy.	Type of recommendation: 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 about adjuvant systemic chemotherapy.	Type of recommendation: 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 about adjuvant systemic therapy.	Type of recommendation: 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 about adjuvant systemic therapy.	Type of recommendation: 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 about adjuvant systemic therapy.	Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak
1.23	The clinician should not use circulating tumor cells to guide decisions about adjuvant systemic therapy.	Type of recommendation: 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 about adjuvant systemic therapy.	Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong
1.25	If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use TILs to guide decisions about adjuvant systemic therapy.	Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong
1.26	Ki-67 labeling index by immunohistochemistry should not be used to guide choice of adjuvant chemotherapy.	Type of recommendation: 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 about extended endocrine therapy.	Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate

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

*Updated recommendation.

cancer; (b) in patients with HER2-positive breast cancer; and (c) in patients with triple-negative breast cancer?

Because this focused update addresses the role of Onco*type* DX in early breast cancer, only the first clinical question from the original guideline is addressed here.[1]

METHODS

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. 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 earlier. The full guideline to which this revision applies and additional information are available at www.asco.org/breast-cancer-guidelines. The complete list of recommendations is provided in Table 1, including the updated recommendation(s). All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

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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;

TABLE 2. Summary of Results of the Trial Assigning Individualized Options for Treatment (TAILORx)[2]

Comparison and Intervention	No. of Patients Evaluated	Survival (± SE)				Freedom From Recurrence of Breast Cancer at a Distant Site (± SE)		Freedom From Recurrence of Breast Cancer at a Distant or Locoregional Site (± SE)	
		Invasive Disease–Free Survival		Overall Survival					
		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 (%)
Recurrence score of ≤ 10, endocrine therapy	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*	98.0 ± 0.2	93.9 ± 0.5	98.0 ± 0.3	94.5 ± 0.5†	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

NOTE. Primary end point was invasive disease–free survival; secondary outcomes were freedom from recurrence at a distant site and overall survival.
*Hazard ratio was 1.08 (95% CI, 0.94 to 1.24; $P = .26$).
†Hazard ratio was 1.10 (95% CI, 0.85 to 1.41; $P = .48$).

TABLE 3. Type of First IDFS Event in Randomly Assigned Patients by Age, RS, and Arm

	No. of Patients					
	RS 11-15		RS 16-20		RS 21-25	
Event	Arm B*	Arm C†	Arm B*	Arm C†	Arm B*	Arm C†
Patients age ≤ 50 years	439	362	454	469	246	246
Ipsilateral breast tumor recurrence	8	7	10	4	6	1
Other locoregional recurrence (with or without ipsilateral breast recurrence)	3	3	8	8	8	5
Distant recurrence (with or without 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 events	45	35	65	38	41	26
Patients age 51-65 years	602	648	732	693	437	433
Ipsilateral breast tumor recurrence	1	4	5	6	5	4
Other locoregional recurrence (with or without ipsilateral breast recurrence)	4	7	7	3	7	4
Distant recurrence (with or without 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 events	48	71	81	93	64	53
Patients age 66-75 years	173	149	182	182	134	130
Ipsilateral breast tumor recurrence	0	2	3	2	0	1
Other locoregional recurrence (with or without ipsilateral breast recurrence)	1	0	1	1	0	0
Distant recurrence (with or without 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 events	35	24	33	35	24	25

NOTE. Adapted from Sparano et al,[2] by permission.
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.

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.

UPDATE DEVELOPMENT METHODOLOGY

Guideline Update Process

ASCO uses a signals[3] approach to facilitate guideline updating. 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 Manual available at www.asco.org/guideline-methodology provides additional information about the guideline update approach.

For this focused update, the publication of the randomized controlled trial on Onco*type* DX provided the signal.[2] The full ASCO Expert Panel (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 and e-mail correspondence to consider the evidence for each of the 2017 recommendations on Onco*type* DX. 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 earlier, only Oncotype DX was reviewed by the Expert Panel for this update.

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

Recommendation 1.1.1. For patients older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26 and for patients age 50 years or younger whose tumors have Oncotype DX recurrence scores of 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).

Recommendation 1.1.2. For patients 50 years of age or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.1.3. Patients with Oncotype DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.1.4. 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).

Literature Review and Clinical Interpretation

In TAILORx, a prospective, noninferiority clinical trial, 6,711 patients with hormone receptor–positive, HER2-negative, axillary node–negative breast cancer and an Oncotype 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 Oncotype DX recurrence score of 21 to 25 who were 50 years of age 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 either endocrine therapy alone or chemoendocrine therapy. Among women age 50 years or younger with recurrence scores of 21 to 25, approximately 6.3% lower invasive disease–free survival was observed at 9 years in the cohort of patients who received endocrine therapy alone compared with those who received chemoendocrine therapy. For women 50 years of age or younger with recurrence scores of 16 to 20, approximately 9% lower invasive disease–free survival was observed at 9 years in the cohort of patients who received endocrine therapy alone compared with those who received chemoendocrine therapy. 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 of greater than 30 based on the results of published prospective-retrospective analyses. Oncotype 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.[4,5] 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 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.[6] The analysis demonstrated a statistically significant benefit from chemoendocrine therapy in women with a recurrence score of 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 50 years of age 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.

ADDITIONAL RESOURCES

Additional information, including clinical tools and resources, can be found at www.asco.org/breast-cancer-guidelines. Patient information is available there and at www.cancer.net.

RELATED ASCO GUIDELINES

- 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[1] (http://ascopubs.org/doi/10.1200/JCO.2015.65.2289)
- American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline[7] (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: American Society of Clinical Oncology Endorsement of Cancer Care Ontario Guideline Recommendations[8] (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: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline[9] (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 provides recommendations, with a comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including slide sets, clinical tools and resources, and links to patient information at www.cancer.net, 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

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

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APPENDIX

TABLE A1. Focused Update Guideline Expert Panel Membership

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Nicole M. Kuderer, MD	Advanced Cancer Research Group and University of Washington, Seattle, WA	Biostatistics, epidemiology, and health services research
Minetta C. Liu, MD	Mayo Clinic College of Medicine, Rochester, MN	Medical oncology
William Barlow, PhD	Cancer Research and Biostatistics, Seattle, WA	Biostatistics
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Abbreviation: PGIN, Practice Guidelines Implementation Network.