ASCO special articles

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Kimberly H. Allison, MD[1]; M. Elizabeth H. Hammond, MD[2]; Mitchell Dowsett, PhD[3]; Shannon E. McKernin[4]; Lisa A. Carey, MD[5]; Patrick L. Fitzgibbons, MD[6]; Daniel F. Hayes, MD[7]; Sunil R. Lakhani, MD[8,9]; Mariana Chavez-MacGregor, MSc[10]; Jane Perlmutter, PhD[11]; Charles M. Perou, PhD[5]; Meredith M. Regan, ScD[12]; David L. Rimm, MD, PhD[13]; W. Fraser Symmans, MD[10]; Emina E. Torlakovic, MD, PhD[14,15]; Leticia Varella, MD[16]; Giuseppe Viale, MD[17,18]; Tracey F. Weisberg, MD[19]; Lisa M. McShane, PhD[20]; and Antonio C. Wolff, MD[21]

abstract

PURPOSE To update key recommendations of the American Society of Clinical Oncology/College of American Pathologists estrogen (ER) and progesterone receptor (PgR) testing in breast cancer guideline.

METHODS A multidisciplinary international Expert Panel was convened to update the clinical practice guideline recommendations informed by a systematic review of the medical literature.

RECOMMENDATIONS The Expert Panel continues to recommend ER testing of invasive breast cancers by validated immunohistochemistry as the standard for predicting which patients may benefit from endocrine therapy, and no other assays are recommended for this purpose. Breast cancer samples with 1% to 100% of tumor nuclei positive should be interpreted as ER positive. However, the Expert Panel acknowledges that there are limited data on endocrine therapy benefit for cancers with 1% to 10% of cells staining ER positive. Samples with these results should be reported using a new reporting category, ER Low Positive, with a recommended comment. A sample is considered ER negative if < 1% or 0% of tumor cell nuclei are immunoreactive. Additional strategies recommended to promote optimal performance, interpretation, and reporting of cases with an initial low to no ER staining result include establishing a laboratory-specific standard operating procedure describing additional steps used by the laboratory to confirm/adjudicate results. The status of controls should be reported for cases with 0% to 10% staining. Similar principles apply to PgR testing, which is used primarily for prognostic purposes in the setting of an ER-positive cancer. Testing of ductal carcinoma in situ (DCIS) for ER is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer, while testing DCIS for PgR is considered optional. Additional information can be found at www.asco.org/breast-cancer-guidelines.

J Clin Oncol 38. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT
Appendix
Data Supplement
Author affiliations and support information (if applicable) appear at the end of this article.
Accepted on September 3, 2019 and published at jco.org on January 13, 2020: DOI https://doi.org/10.1200/JCO.19.02309
Clinical Practice Guidelines Committee approval: July 10, 2019
Reprint Requests: 2318 Mill Road, Suite 800, Alexandria, VA 22314; guidelines@asco.org.

INTRODUCTION

First released in 2010, the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) estrogen receptor (ER) and progesterone receptor (PgR) testing guideline is aimed at improving the analytic performance and diagnostic accuracy of ER and PgR testing and their clinical utility as biomarkers for the management of women with primary breast cancer.[1,2] The guideline focuses entirely on immunohistochemical testing, as this reflects the near exclusive use of this approach in contemporary practice. The Expert Panel (Appendix Table A1, online only) reconvened to consider evidence for changes in laboratory and clinical practice or the emergence of new data that might require an update in this guideline. The importance of the accurate assessment (protocols and readout) and interpretation of ER and PgR expression is emphasized by more than 1,000,000 women per year worldwide diagnosed with primary breast cancer and tested for these receptors. Studies using contemporary populations note increases in the proportion of breast cancers that are ER positive, with overall rates of between 79% and 84% of breast cancers (with higher ER-positive rates occurring in postmenopausal subpopulations).[3-9] While ER-positive rates are influenced by population-dependent variables (eg, age, race, screening, birth rate, and so on), increased analytic sensitivity of assay protocols due to adherence to previously published guidelines, newer detection methods, more sensitive primary antibodies, and protocol design changes after feedback provided by external quality assessment may also have contributed to this increase.

THE BOTTOM LINE

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Guideline Questions

1. What are the optimum quality assurance (QA), tissue handling, scoring system, and reporting for determining potential benefit from endocrine therapy?
2. What additional strategies can promote optimal performance, interpretation, and reporting of immunohistochemistry (IHC) assays, particularly in cases with low estrogen receptor (ER) expression?
3. Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?
4. Should ductal carcinoma in situ (DCIS) be routinely tested for hormone receptors?

Target Population

Patients with breast cancer.

Target Audience

Medical oncologists, pathologists, surgeons, radiation oncologists, and patients and their caregivers.

Methods

A multidisciplinary Expert Panel was convened to update the clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Recommendation 1.1*: *Optimal algorithm for ER/progesterone receptor testing. Samples with 1% to 100% of tumor nuclei positive for ER or progesterone receptor (PgR) are interpreted as positive. For reporting of ER (not PgR), if 1% to 10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment (Table 2; Fig 1). A sample is considered negative for ER or PgR if < 1% or 0% of tumor cell nuclei are immunoreactive. A sample may be deemed uninterpretable for ER or PgR if the sample is inadequate (insufficient cancer or severe artifacts present, as determined at the discretion of the pathologist), if external and internal controls (if present) do not stain appropriately, or if preanalytic variables have interfered with the assay's accuracy (Figs 1-4). Clinicians should be aware of and able to discuss with patients the limited data on ER Low Positive cases and issues with test results that are close to a positive threshold (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.2*: *Optimal testing conditions (no change). Large (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection. Accession slip and report must include guideline-detailed elements (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.3*: *Optimal tissue handling requirements (no change). Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% neutral buffered formalin (NBF) for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margin designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded. As in the American Society of Clinical Oncology/College of American Pathologists (CAP) human epidermal growth factor receptor 2 guideline, use of unstained slides cut more than 6 weeks before analysis is not recommended. Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.4*: *Optimal internal validation procedures (change anticipated). This topic is deferred to the forthcoming CAP guideline update of the principles of analytic validation of IHC assays, once available. There should be initial test validation/verification prior to reporting any clinical samples. Prior to that, previously recommended principles apply, as described by Fitzgibbons et al[12] and more recently Torlakovic[13] (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.5*: *Optimal internal QA procedures. Ongoing quality control and equipment maintenance are required. Initial and ongoing laboratory personnel training and competency assessment should be performed. Standard operating procedures (SOPs) should be used that include routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections (or other appropriate control) on each tested slide, wherever possible. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are recommended. Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[12]). Revalidation is needed whenever there is a significant change to the test system.[13] Ongoing competency assessment and education of pathologists are required (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 1.6*: *Optimal external proficiency assessment. The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.7*: *Optimal laboratory accreditation. On-site inspection every other year should be undertaken, with annual requirement for self-inspection (Type: Informal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Recommendation 2.1. Laboratories should include ongoing quality control using SOPs for test evaluation prior to scoring (readout) and interpretation of any case as defined in the checklist in Figure 1 (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.2. Interpretation of any ER result should include evaluation of the concordance with the histologic findings of each case. Clinicians should also be aware of when results are highly unusual/discordant and work with pathologists to attempt to resolve or explain atypical reported findings; Table 3 is an aid in this process (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.3. Laboratories should establish and follow an SOP stating the steps the laboratory takes to confirm or adjudicate ER results for cases with weak stain intensity or ≤ 10% of cells staining; Data Supplement 2, Figure 1 provides an example SOP (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.4. The status of internal controls should be reported for cases with 0% to 10% staining. For cases with these results without internal controls present and with positive external controls, an additional report comment is recommended (Table 2) (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 3. Validated IHC is the recommended standard test for predicting benefit from endocrine therapy. No other assay types are recommended as the primary screening test for this purpose (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 4. ER testing in cases of newly diagnosed DCIS (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. PgR testing is considered optional (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

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

Additional Resources

More information, including a supplement with evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

Utility of ER and PgR Testing and Threshold Setting

The Expert Panel acknowledged that hormone receptor testing in breast cancer currently serves other purposes beyond identification of which patients may benefit from endocrine-specific strategies for breast cancer treatment. These include the following: 1) to assist in classification of breast cancer for the most appropriate overall treatment pathway (with most treatment guidelines centered around ER-positive *v* ER-negative pathways); 2) to assist in prognostication, such as classification of breast cancer, for the most appropriate overall prognostic stage group (eg, American Joint Committee on Cancer [AJCC] eighth edition prognostic stage groupings)[10]; and 3) as a diagnostic aid in metastatic breast cancer. The Expert Panel acknowledged that a well-performed ER assay should be useful in each of these scenarios. It should be noted, however, that the specific thresholds for a positive versus a negative test result in this guideline are based on the data supporting the optimal threshold to use ER status as a predictive marker for endocrine treatment strategies in breast cancer.

There is unequivocal evidence that patients with cancers devoid of ER expression do not benefit from endocrine treatment.[11] The challenge has been and remains defining an ER expression cutoff that best segregates patients who may derive meaningful clinical benefit from endocrine therapy strategies from those who will not. The 2010 guideline recommended that invasive breast cancers be considered positive if at least 1% of cancer nuclei stain positive and that patients with such cancers be considered for endocrine therapy, while such therapy should be withheld from patients with cancers with < 1% staining. It was also noted that it is reasonable for oncologists to discuss the pros and cons of endocrine therapy with patients whose cancers contain low levels of ER by immunohistochemistry (IHC; 1%-10% weakly positive cells) and to make a decision based on the totality of information about the individual case. This recommendation is reaffirmed in this 2019 update (Clinical Question 1).

The utility of PgR testing continues to be largely prognostic in the ER-positive population, but testing using principles similar to those used in ER testing is still recommended for invasive breast cancers.

Current Status of ER and PgR Testing and Focus Areas for Improvement

The Expert Panel examined data on the quality of hormone receptor testing in breast cancer in the years since the 2010 guideline was first published to identify areas where additional guidance might be beneficial. There has been an apparent improvement in the overall quality of hormone receptor testing in breast cancer and improved monitoring of performance. While interlaboratory variability for ER and PgR results has decreased, some variability continues to exist, emphasizing the need for continued publication of antibody- and method-specific results, guidance on best practices, and continued monitoring of pathologist scoring (readout) performance to improve reproducibility and reduce interobserver variation.

Handling of Cases With Low ER Expression

Although the recent literature supports reaffirming the current guideline recommendations overall (Clinical Question 1), there has been increased concern over the proper handling of cases with low ER expression. Such cases with low levels of ER expression are included in ER-positive treatment and prognostic algorithms designed for a majority of cases, which have strong ER expression. Although uncommon (accounting for only 2%-3% of ER-positive cancers), cancers with 1% to 10% cells staining for ER present particular clinical challenges. For example, should a high-grade cancer with 1% to 10% ER expression, 0% PgR expression, and human epidermal growth factor receptor 2 (HER2) –negative results be considered for treatments designed for triple-negative cancers? One of the most common questions asked during the open comment period for the ASCO/CAP HER2 guideline update, which included a question on issues related to the 2010 ER/PgR testing guideline, was what to do clinically with ER Low Positive cancers.

Cases with weak or low ER or PgR staining are also noted to be particular challenges for test reproducibility due to a variety of factors (reproducibility of scoring close to a threshold, particular sensitivity to preanalytic [eg, cold ischemic time, fixation type and time, and so on] and analytic factors [eg, antibody used, methodology], heterogeneity of expression, and lack of standardized low ER–expressing controls). Clinical Question 2 of this update focuses on strategies to promote optimal performance, interpretation, and reporting of all cases, and new recommendations for interpreting and reporting cases with weak or ≤ 10% ER expression are provided.

Given recent advances in alternative testing strategies, the guideline update also addresses the question of whether evolving genomic/molecular and image analysis methods are ready to be incorporated into routine testing for ER and PgR (Clinical Question 3).

All the recommendations apply to patients with invasive breast cancer; however, recommendations on hormone receptor testing in ductal carcinoma in situ (DCIS) are also offered (Clinical Question 4).

GUIDELINE QUESTIONS

This update specifically addresses four clinical questions raised after the publication of the 2010 guideline:

1. What are the optimum quality assurance (QA), tissue handling, scoring system, and reporting for determining potential benefit from endocrine therapy?
2. What additional strategies can promote optimal performance, interpretation, and reporting of IHC assays, particularly in cases with low ER expression?
3. Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?
4. Should DCIS be routinely tested for hormone receptors?

METHODS

This ASCO and CAP clinical practice guideline update provides revised recommendations with a comprehensive discussion of the relevant literature for these specific recommendations. The full guideline and additional information are available at www.asco.org/breast-cancer-guidelines. The complete list of recommendations is in Table 1, including the updated recommendations.

Guideline Update Process

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guideline staff member with health research methodology expertise. PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines for the period from January 1, 2008, of the previous update through April 30, 2019. The disease and intervention search terms were those that were used for the 2010 guideline. The searches identified 4,897 abstracts, and ultimately, 87 papers met the selection criteria.[11,14-99] Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- The population included adults with a new diagnosis of breast cancer or a recurrence
- Studies of ER or PgR testing by IHC
- Primary end points considered positive and negative predictive values of assays used to accurately

TABLE 1. Summary of All Recommendations

2010 Recommendation	Updated Recommendation
Clinical Question 1. What is the optimum QA, specimen handling, positive threshold, scoring system, and reporting for determining potential benefit from endocrine therapy?	
Optimal algorithm for ER/PgR testing	**Optimal algorithm for ER/PgR testing**
Positive for ER or PgR if finding that ≥ 1% of tumor cell nuclei are immunoreactive.	Samples with 1%-100% of tumor nuclei positive for ER or PgR are interpreted as positive.
Negative for ER or PgR if finding that < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen).	For reporting of ER (not PgR), if 1%-10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment (Table 2; Fig 1).
Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.	A sample is considered negative for ER or PgR if < 1% or 0% of tumor cell nuclei are immunoreactive.
	A sample may be deemed uninterpretable for ER or PgR if the sample is inadequate (insufficient cancer or severe artifacts present, as determined at the discretion of the pathologist), if external and internal controls (if present) do not stain appropriately, or if preanalytic variables have interfered with the assay's accuracy (Figs 1 to 4).
	Clinicians should be aware of and able to discuss with patients the limited data on ER Low Positive cases and issue test results that are close to a positive threshold.
Optimal testing conditions	**Optimal testing conditions (no changes)**
Large (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection.	Large (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection.
Accession slip and report must include guideline-detailed elements.	Accession slip and report must include guideline-detailed elements.
Optimal tissue handling requirements	**Optimal tissue handling requirements (no changes)**
Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.	Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% NBF for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.
As in the ASCO/CAP HER2 guideline, use of unstained slides cut more than 6 weeks before analysis is not recommended.	As in the ASCO/CAP HER2 guideline, use of unstained slides cut more than 6 weeks before analysis is not recommended.
The time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.	The time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.
Optimal internal validation procedures	**Optimal internal validation procedures**
Internal validation must be done before test is offered; see separate article on testing validation (Fitzgibbons et al[12]).	This topic is deferred to the forthcoming CAP guideline update, Principles of Analytic Validation of IHC Assays, once available. There should be initial test validation/verification prior to reporting any clinical samples. Prior to that, previously recommended principles apply (Fitzgibbons et al[12] and more recently Torlakovic[13]).
Validation must be done using a clinically validated ER or PgR test method.	
Revalidation should be done whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems.	
Optimal internal QA procedures	**Optimal internal QA procedures**
Ongoing quality control and equipment maintenance.	Ongoing quality control and equipment maintenance are required.
Initial and ongoing laboratory personnel training and competency assessment.	Initial and ongoing laboratory personnel training and competency assessment should be performed.

(continued on following page)

TABLE 1. Summary of All Recommendations (continued)

2010 Recommendation	Updated Recommendation
Use of SOPs, including routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections on each tested slide, wherever possible.	SOPSs should be used that include routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections (or other appropriate control) on each tested slide, wherever possible. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are recommended.
Regular, ongoing assay reassessment should be done at least semiannually (as described by Fitzgibbons et al[12] and more recently Torlakovic[13]); revalidation is needed whenever there is a significant change to the test system.	Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[12]). Revalidation is needed whenever there is a significant change to the test system.[13.]
Ongoing competency assessment and education of pathologists.	Ongoing competency assessment and education of pathologists is required.
Optimal external proficiency assessment	**Optimal external proficiency assessment**
Mandatory participation in external proficiency testing program with at least two testing events (mailings) per year.	The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization.
Satisfactory performance requires at least 90% correct responses on graded challenges for either test.	
Optimal laboratory accreditation	**Optimal laboratory accreditation**
On-site inspection every other year with annual requirement for self-inspection.	On-site inspection every other year should be undertaken with annual requirement for self-inspection.
Clinical Question 2. What additional strategies can promote optimal performance, interpretation, and reporting of IHC assays, particularly in cases with low ER expression?	
No specific recommendations were specified in 2010 for low ER expression cases.	Laboratories should include ongoing quality control using SOPs for test evaluation prior to scoring (readout) and interpretation of any case, as defined in the checklist in Figure 1.
	Interpretation of any ER result should include evaluation of the concordance with the histologic findings of each case. Clinicians should also be aware of when results are highly unusual/discordant and work with pathologists to attempt to resolve or explain atypical reported findings (Table 3 is an aid in this process).
	Laboratories should establish and follow an SOP stating the steps the laboratory takes to confirm or adjudicate ER results for cases with weak stain intensity or $\leq$ 10% of cells staining (Data Supplement 2, Figure 1 provides an example SOP).
	The status of internal controls should be reported for cases with 0%-10% staining. For cases with these results without internal controls present and with positive external controls, an additional report comment is recommended (Table 2).
Clinical Question 3. Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?	
No assays other than IHC are recommended as testing platforms.	Validated IHC is the recommended standard test for predicting benefit from endocrine therapy. No other assay types are recommended as the primary screening test for this purpose.
Clinical Question 4. Should DCIS be routinely tested for hormone receptors?	
ER and PgR testing of DCIS is optional (no formal recommendation made to test or not test).	ER testing in cases of newly diagnosed DCIS (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer; PgR testing is considered optional.

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NBF, neutral buffered formalin; PgR, progesterone receptor; QA, quality assurance SOP, standard operating procedure.

determine hormone receptor status, including (but not necessarily limited to): specific assay performance, technique, standardization attempted, QA, proficiency testing, individual or institutional training, or improvement in assay results based on interventions

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language.

The Expert Panel met in person at ASCO headquarters to update the guideline. The updated ASCO/CAP guideline was circulated in draft form, reviewed, and approved by the Expert Panel. ASCO's Clinical Practice Guidelines Committee (CPGC) reviewed and approved the final document. For CAP, an independent review panel was assembled to review and approve the guideline. The independent review panel was masked to the Expert Panel and was vetted through the conflict-of-interest process. All funding for the administration of the project was provided by ASCO.

Guideline Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. ("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) as agreed upon with CAP. 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.

RECOMMENDATIONS

CLINICAL QUESTION 1

What are the optimum QA, testing conditions, tissue handling, scoring system, and reporting for determining potential benefit from endocrine therapy?

Recommendation 1.1. Optimal Algorithm for ER/PgR Testing Samples with 1% to 100% of tumor nuclei positive for ER or PgR are interpreted as positive. For reporting of ER (not PgR), if 1% to 10% of tumor cell nuclei are immunoreactive, the sample should be reported as ER Low Positive with a recommended comment (Table 2; Fig 1). A sample is considered negative for ER or PgR if < 1% or 0% of tumor cell nuclei are immunoreactive. A sample may be deemed uninterpretable for ER or PgR if the sample is inadequate (insufficient cancer or severe artifacts present, as determined at the discretion of the pathologist), if external and

TABLE 2. Additional Recommended Reporting Comments for Specific Scenarios

Result	Additional Recommended Comment
1%-10% cells staining	The cancer in this sample has a low level (1%-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1%-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers.
No internal controls and ER is 0%-10%	No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status.

Abbreviations: ER, estrogen receptor; IHC, immunohistochemistry.

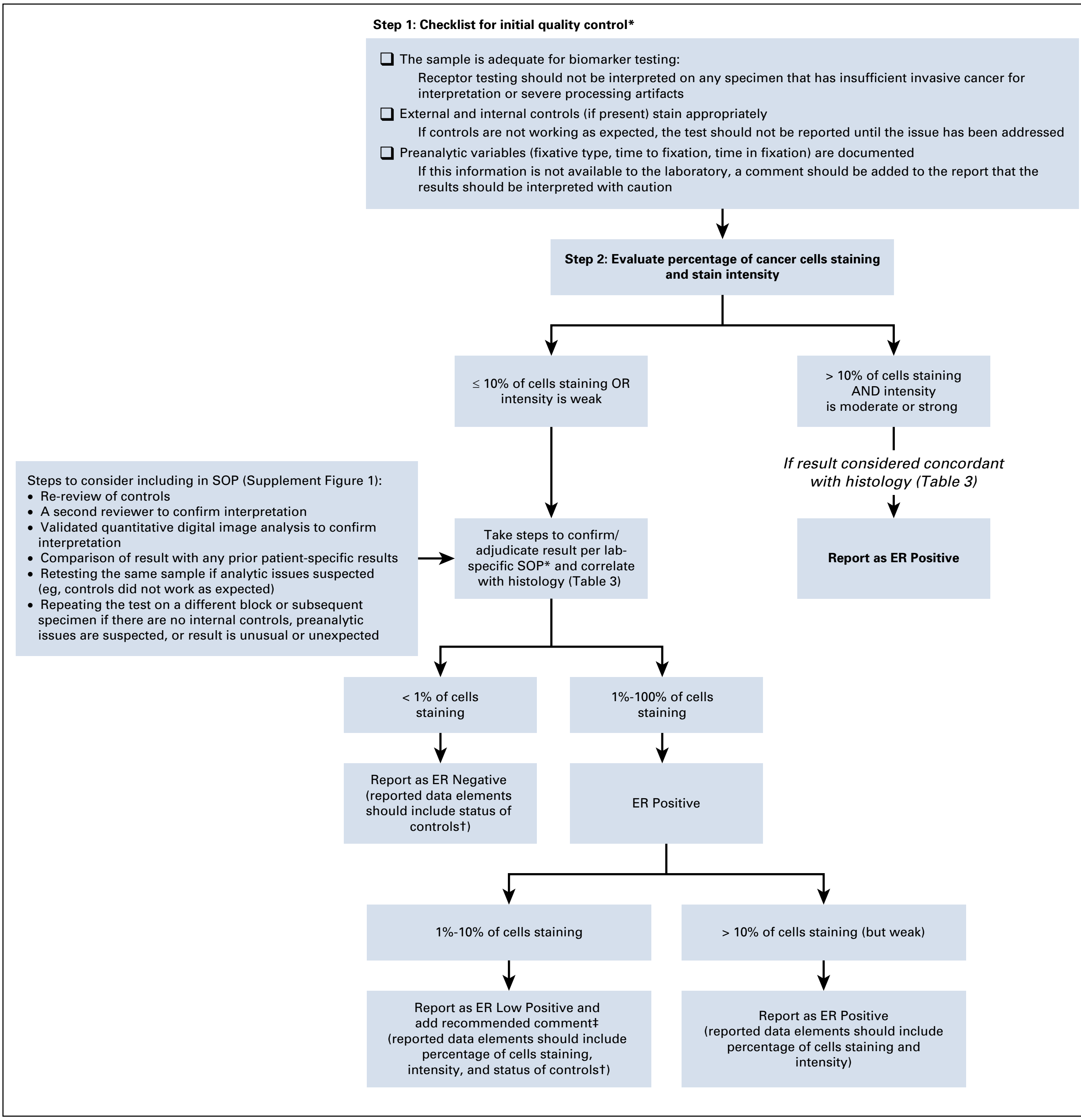

FIG 1. Recommendations for scoring (readout) and interpretation of immunohistochemistry (IHC) test to determine estrogen receptor (ER) status in breast cancers. For progesterone receptor (PgR) testing, the same overall interpretation principles apply, but the reporting elements are only recommended for ER testing. PgR should be interpreted as either positive (if 1%-100% of cells have nuclear staining) or negative (if < 1% or 0% of cells have nuclear staining), with the overall percentage and intensity of staining reported. (*) Hormone receptor testing should only be done with a validated method and with appropriate laboratory procedures, including ongoing assay monitoring and pathologist competency assessment. (†) If no internal controls are present but external controls are positive, include comment: “No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status.” (‡) For ER Low Positive results, include comment: “The cancer in this sample has a low level (1%-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with these results, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers.”

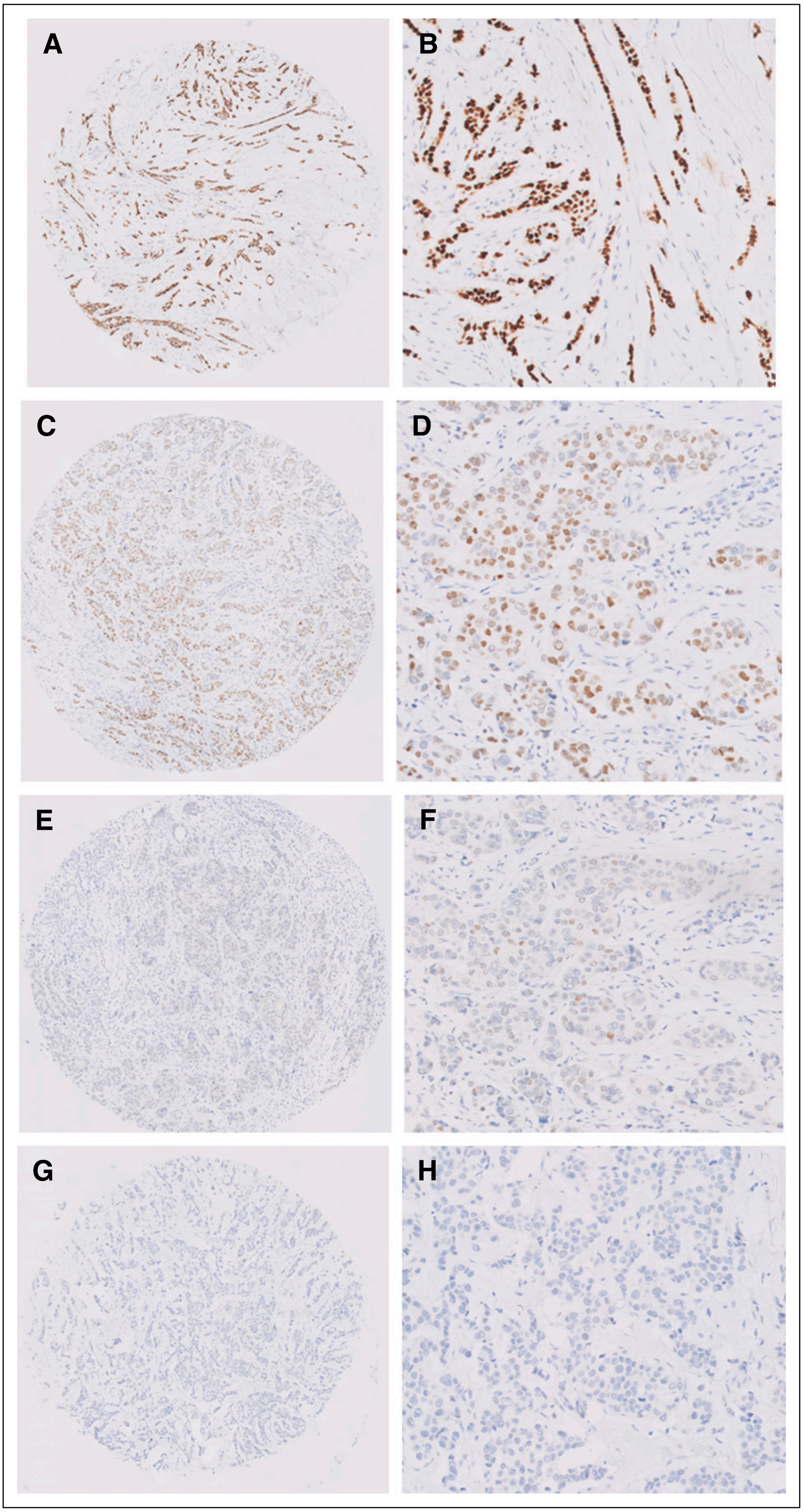

FIG 2. Case examples to illustrate stain intensity and percentage interpretation. Examples of invasive cancers with various levels of estrogen receptor (ER) expression. Magnification of slides at (A) ×50 and (B) ×200 from a case that was strongly and uniformly positive (90%-100% cells staining, strong intensity), at (C) ×50 and (D) ×200 from a case with weak-moderate intensity but almost uniform positivity (70%-80% cells staining, weak-moderate intensity), and at (E) ×50 and (F) ×200 from a case that had between 1% and 10% of cancer cells staining with weak intensity (ER Low Positive). This low level of expression is not easily seen on (E) low power but is more readily seen on (F) moderate to higher power. Magnification of slides at (G) ×50 and (H) ×200 from an invasive cancer with no ER expression (0% staining). Cases with nuclear staining in < 1% of total cells in the invasive carcinoma sample are also classified as negative.

internal controls (if present) do not stain appropriately, or if preanalytic variables have interfered with the assay's accuracy (Figs 1-4). Clinicians should be aware of and able to discuss with patients the limited data on ER Low Positive cases and issues with test results that are close to a positive threshold (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.2. Optimal Testing Conditions (no change)
Large (preferably multiple) core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection. Accession slip and report must include guideline-detailed elements (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.3. Optimal Tissue Handling Requirements (no change)
Time from tissue acquisition to fixation should be as short as possible. Samples for ER and PgR testing are fixed in 10% neutral buffered formalin (NBF) for 6 to 72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margin designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in

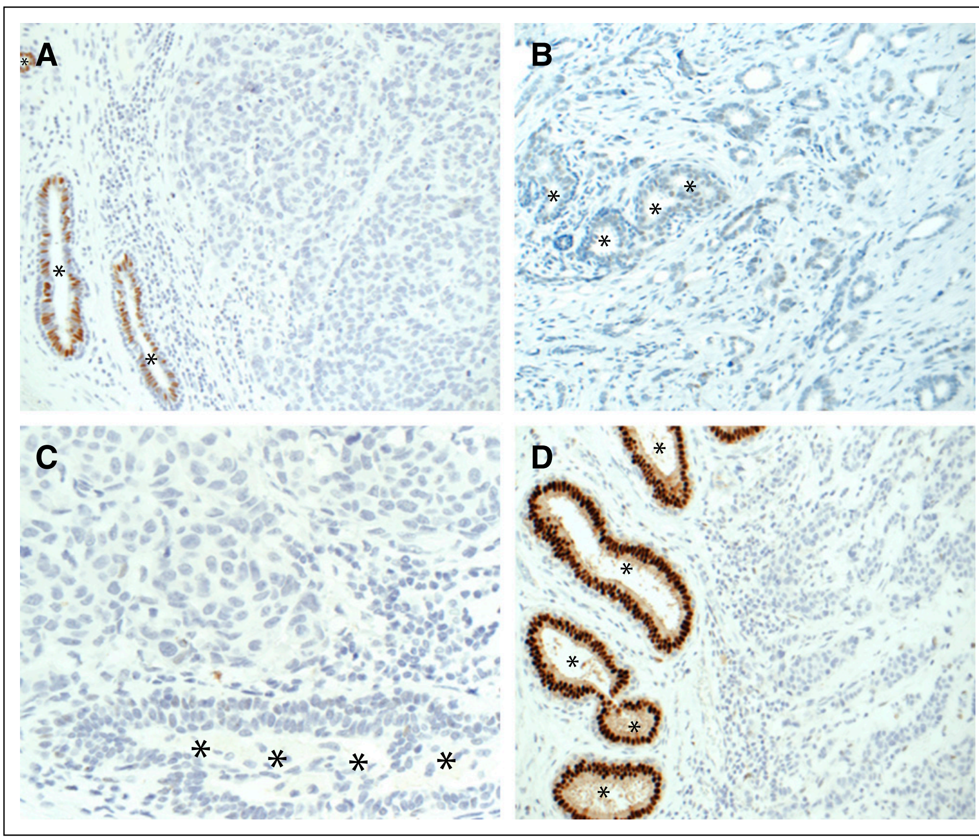

FIG 3. Internal controls. Examples of internal control analysis in estrogen receptor (ER) stains. (A) ER-negative invasive cancer (×200) with an adjacent internal normal duct control (asterisks) with optimal staining (nuclear staining varying from weak to very strong with alternating clusters of negative cells). (B) Unexpectedly weak stain result (×200) in both the grade 1 invasive cancer and normal duct internal controls (asterisks). This result, although positive, raises concern about possible preanalytic variables affecting the assay or, if these are deemed appropriate, that the level of analytic sensitivity of the assay may be` too low (especially to detect ER Low Positive results). (C) Case negative for ER expression (×400) both in the in the invasive cancer and the internal control duct (asterisks). The assay should be repeated and an investigation for potential causes of negative internal controls performed (including both preanalytic and analytic factors). If internal controls remain negative and this issue appears isolated to this sample, the test should be reported as "cannot be determined" (indeterminate; uninterpretable because of negative internal controls, possible preanalytic tissue preservation issues). (D) Invasive cancer with no ER staining (×200) and internal control columnar cell epithelium (asterisks) with uniformly strong nuclear staining (as expected). These results help support that there were no serious issues with the preanalytic or analytic phases. However, such strong positive internal controls are less optimal to evaluate how well the assay is able to detect low levels of ER expression (evaluation of noncolumnar cell, normal duct controls is more optimal, as in panel A).

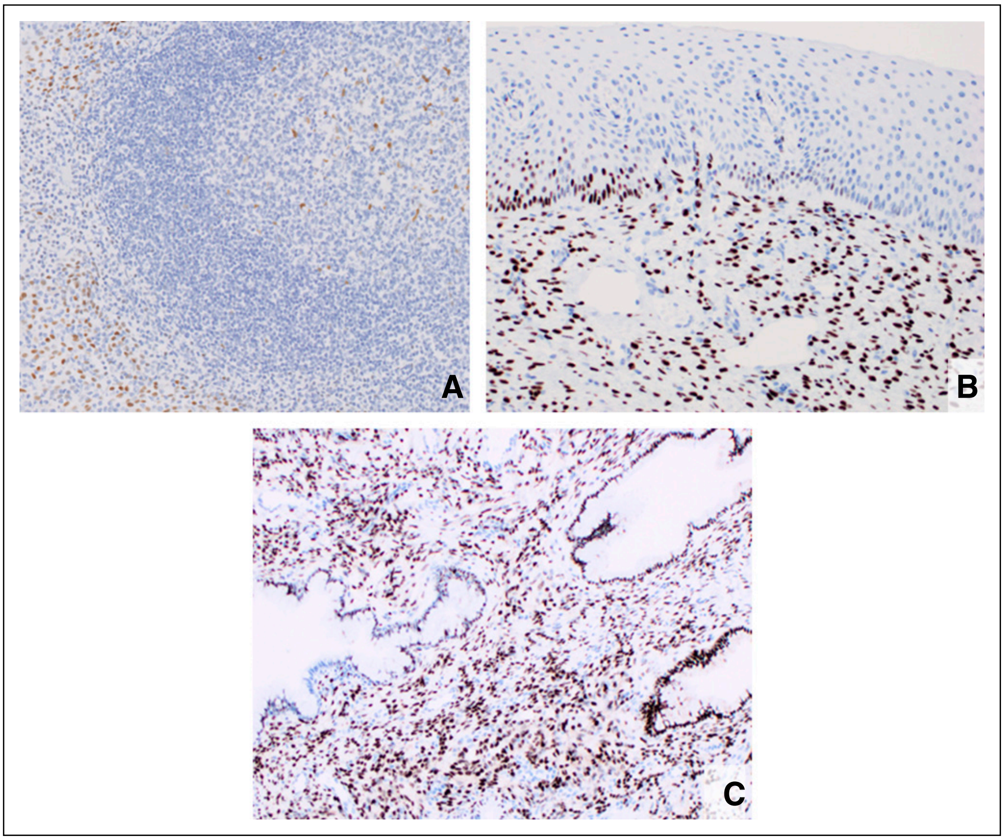

FIG 4. External controls. Optimal external (ideally on-slide) controls for both estrogen receptor (ER) and progesterone receptor (PgR) should include multiple tissues, including ones with expected strong staining, lower limit of detection levels, and negative controls; tonsil and cervix have been used to meet these criteria. (A) Tonsil tissue (×200) with optimal staining for ER to ensure an appropriate low limit of detection; dispersed germinal center cells and the squamous epithelium should be ER positive, but the B cells in the mantle zones should be ER negative. In contrast to ER, no nuclear PgR staining should be seen in tonsillar tissue. Weak-positive PgR staining in tonsil should result in workup to determine if assay drift has occurred. (B) PgR variably staining the basal layer of the squamous mucosa (×200) as expected (this staining should ensure an appropriate low limit of detection for PgR). Stromal cells stain strongly for both ER and PgR. ER should stain the squamous mucosa more uniformly (not just the basal layer), with at least moderate to strong stain intensity. (C) PgR staining (×200) should also be positive in the endocervical columnar epithelial cells (with some variability expected). ER should stain almost all endocervical columnar epithelial cells. Of note, it should be taken into consideration that hormone receptor staining of cervical tissue may be reduced in tissue from postmenopausal women.

a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded. As in the ASCO/CAP HER2 guideline, use of unstained slides cut more than 6 weeks before analysis is not recommended. Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.4. Optimal Internal Validation Procedures (change anticipated)

This topic is deferred to the forthcoming CAP guideline update of the principles of analytic validation of IHC assays, once available. There should be initial test validation/verification prior to reporting any clinical samples. Prior to that, previously recommended principles apply, as described by Fitzgibbons et al[12] and more recently Torlakovic.[13] (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.5. Optimal Internal QA Procedures

Ongoing quality control and equipment maintenance are required. Initial and ongoing laboratory personnel training and competency assessment should be performed. Standard operating procedures (SOPs) should be used that include routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections (or other appropriate control) on each tested slide, wherever possible. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are recommended.

Regular, ongoing assay reassessment should be done at least semiannually (as described by Fitzgibbons et al[12]). Revalidation is needed whenever there is a significant change to the test system.[13] Ongoing competency assessment and education of pathologists are required (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.6. Optimal External Proficiency Assessment The laboratory performing ER and PgR testing must participate in external proficiency testing or alternative performance assessment as required by its accrediting organization (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.7. Optimal Laboratory Accreditation
On-site inspection every other year should be undertaken, with annual requirement for self-inspection (Type: Informal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review and analysis. Data from proficiency testing and quality control programs indicate that an overall improvement in the quality and reproducibility of ER and PgR testing in breast cancer has occurred over time. This is likely the result of improvements in standardization of preanalytic, analytic, and postanalytic factors, as well as increases in antibody sensitivity, allowing the Expert Panel to reaffirm the original 2010 recommendations on specimen handling, optimal testing conditions, and QA.[100,101]

Much of the focus of the update review involved reexamining the data on the optimal ER positive threshold and scoring systems to determine potential benefit from endocrine therapy. There are limited new data on this threshold, as most randomized clinical trials addressing the topic took place in the 1990s. There is little argument about the potential benefit of endocrine therapy in patients with cancers with > 10% ER expression or the lack of potential benefit for cancers with < 1% ER expression. However, there are much more limited data on the 2% to 3% of cancers that are low ER expressers (most often defined as 1%-10% ER-positive cells by IHC) and their potential benefit from endocrine therapy. In 2011, a large meta-analysis was published of 20 prior clinical trials with more than 200,000 women-years of follow-up, reporting on the benefit of 5 years of tamoxifen according to ER and PgR levels as measured by ligand-binding assay (LBA).[11] More than 50,000 women-years of follow-up were available for women with tumors having < 10 fmol ER/mg protein, and no evidence of benefit was apparent. However, patients with cancers with low levels of ER (10-20 fmol ER/mg protein) had their likelihood of recurrence reduced by one third with the addition of approximately 5 years of tamoxifen (risk ratio [RR], 0.67; SE, 0.08). Of note, while benefit increased somewhat with higher ER levels, the proportional effect at the highest ER levels (> 200 fmol/mg) was only slightly better than that at weak ER levels (RR, 0.52; SE, 0.07). Although there are limited data from prospective randomized trials comparing the predictive power of LBAs with the standard IHC methods of ER assessment in routine use, multiple studies support high rates of agreement between these assays.[98,99,102-104] In most studies, a ≥ 10 fmol/mg threshold corresponded best (albeit imperfectly) with ≥ 1% of cells with nuclear ER staining by IHC, the current recommended IHC cutoff for ER positivity.[11,97,105]

Complicating the understanding of low ER–expressing cancers are data indicating that these cancers are a heterogeneous group but often have clinical outcomes and biologic/molecular profiles that are often more similar to those of ER-negative cancers.[91-97,106] However, none of these retrospective and nonrandomized studies can address the potential benefit of endocrine therapy for at least some patients in the 1% to 10% ER-positive group. The Expert Panel acknowledges the data from these studies provide support that cancers with low ER expression may be biologically distinct from high ER expressers and that the 1% threshold for ER positivity may not uniformly predict differences in prognosis, chemotherapy benefit, or regimen or define a specific molecular subtype. Most important, low ER expression status has not been validated for these purposes.

Given the relatively low toxicity of endocrine therapy, the desire to minimize false-negative results, and the available (although limited) data supporting potential benefit even in cases with as low as 1% to 10% positivity, the Expert Panel continues to recommend ≥ 1% nuclear ER staining by IHC as the threshold for reporting a positive ER result to predict potential clinical benefit from endocrine therapy treatments. However, cases with 1% to 10% staining should be reported as ER Low Positive, with a recommended comment explaining the more limited clinical data, heterogeneous behavior, and biology of this subgroup of ER-positive cancers. As in 2010, The Expert Panel recommends that oncologists discuss the pros and cons of endocrine therapy with patients whose cancers contain low levels of ER by IHC and base decisions on the totality of information available about an individual case. Laboratories should continue to report both the percentage and intensity of hormone receptor staining in addition to the test interpretation as positive, low positive, or negative. Clinical Question 2 addresses additional steps that should be taken to promote optimal performance and interpretation, especially in the weak or low ER–expressing cases.

Controls. Control tissues are essential for evaluating assay performance. External controls should include negative and positive samples as well as samples with lower percentages of ER expression (such as tonsil). On-slide controls are ideal because each slide is evaluated and the control stays with the slide. Regardless of the control type, the controls must include samples fixed under conditions similar to those of the test samples and incorporate tissues or cell lines with no ER, low ER, and high ER and be as well standardized as possible.[107-110] While newer forms of standardized controls are becoming more available, some of which are engineered tissue-like materials with defined quantities of ER or PgR included, long-standing experience has also been good for cervix (as a strong ER-positive/PgR-positive control) and tonsil (for PgR see: https://www.nordiqc.org/epitope.php?id=67 and for ER: https://www.nordiqc.org/downloads/assessments/118_2.pdf).[111-115] Tonsil has been suggested as an ideal tissue type to include in external controls to monitor the analytic sensitivity for ER and PgR (Fig 4). Dispersed germinal center cells and the squamous epithelium should be ER positive, but the B cells in the mantle zones should be ER negative. In contrast to ER, no nuclear PgR staining should be seen in tonsillar tissue. Weak positive PgR staining in tonsil should result in workup to determine if assay drift has occurred. Tumor tissues with variable levels of expression can be useful as a supplement to tonsil and control tissue with uniform ER/PgR expression (such as cervix); however, it should be noted that tumor tissue can be heterogeneous (creating different staining patterns on a given level), and expression levels may not be as well characterized. If changes in staining results over time or between runs (drift) are noted (especially the staining with low levels of ER expression), the laboratory should undertake a careful analysis of its procedures and any recent changes in test methods (eg, new lot of antibody, change in clone, or modified reagents) prior to issuing results to assess whether revalidation is required.

A guideline update dealing with IHC assay validation is under development by CAP at the time of this publication and should be deferred to once published. Prior to its publication, the Expert Panel recommends applying previously recommended validation principles (as described by Fitzgibbons et al[12] and more recently Torlakovic[13]).

Do the same principles apply to PgR testing? There is substantial evidence for higher rates of clinical response to endocrine therapy in PgR-positive tumors treated neoadjuvantly or in metastatic disease, but randomized trials in the adjuvant setting have revealed no difference in the degree of benefit from adjuvant endocrine treatment according to PgR status.[11] The Expert Panel therefore acknowledges that only ER should be used as a predictor of benefit from adjuvant endocrine therapy. Because of this, the Expert Panel discussed whether to continue to recommend routine PgR testing in invasive breast cancers. PgR levels can add prognostic information by helping to stratify outcomes in the ER-positive population, with data supporting that cases with lower or negative PgR expression may have a worse prognosis.[88-90,116] Used in combination with ER (and other markers), PgR levels by IHC have been used by various tools that estimate prognosis, such as the IHC4 score, Magee equations, nomograms that predict the 21-gene recurrence score results, AJCC eighth edition prognostic stage groupings, and various predictors of response to neoadjuvant therapy.[10,73,75,77-87]

In addition, PgR may serve as an informal control for samples that test ER negative but PgR positive (especially in the absence of normal internal controls), since there are data suggesting that this phenotype is frequently the result of technical artifact.[74] In the 2010 guideline, repeat testing in cases with initial ER-negative/PgR-positive results was suggested (not required), and the Expert Panel continues to support this recommendation (Table 1). Lastly, although controversial as a result category, confirmed ER-negative/PgR-positive samples may be a rare biologic phenotype that may be offered endocrine therapies, although due to the rarity of this result group, there are limited data to support this.[70,71,76]

Given the utility of PgR testing for the above reasons, we continue to recommend routine PgR testing of invasive breast cancers. Many thresholds have been used to differentiate cancers on the basis of PgR expression for prognostic purposes. This may reflect that PgR acts as a more continuous variable for prognosis,[72] and in the absence of data consistently supporting alternative thresholds or standards for PgR testing, we recommend using 1% as a positivity threshold for PgR in invasive breast cancers but also continue to recommend reporting the percentage and intensity of cells staining. However, the low positive reporting category and comment recommendation for samples with 1% to 10% ER expression does not apply to PgR. Otherwise, the same general recommendations that apply to ER testing should also apply to PgR testing, including participation in external proficiency testing by the laboratory's accrediting organization. However, laboratory accreditation should primarily be dependent on a passing grade for ER proficiency testing.

CLINICAL QUESTION 2

What additional strategies can promote optimal performance, interpretation, and reporting of IHC assays, particularly in cases with low to negative ER expression?

Recommendation 2.1

Laboratories should include ongoing quality control using SOPs for test evaluation prior to scoring (readout) and interpretation of any case as defined in the checklist in Figure 1 (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.2

Interpretation of any ER result should include evaluation of the concordance with the histologic findings of each case. Clinicians should also be aware of when results are highly unusual/discordant and work with pathologists to attempt to resolve or explain atypical reported findings; Table 3 is an aid in this process. (Type: Informal

TABLE 3. Invasive Breast Cancer Histopathologic Concordance With ER Staining

Highly Unusual ER-Negative Results	Highly Unusual ER-Positive Results
Low-grade invasive carcinomas of no special type (also known as invasive ductal carcinoma)	Metaplastic carcinomas of all subtypes
Lobular carcinomas (classic type)	Adenoid cystic carcinomas and other salivary gland–like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Carcinomas with apocrine differentiation

NOTE. If a result is considered highly unusual/discordant, additional steps should be taken to check the accuracy of the histologic type or grade as well as the preanalytic and analytic testing factors. This workup may include second reviews and repeat testing. If all results appear valid, the result can be reported with a comment noting that the findings are highly unusual and testing of additional samples may be of value to confirm the findings.

Abbreviation: ER, estrogen receptor.

consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.3

Laboratories should establish and follow an SOP stating the steps the laboratory takes to confirm or adjudicate ER results for cases with weak stain intensity or ≤ 10% of cells staining; Data Supplement 2, Figure 1 provides an example SOP. (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Recommendation 2.4

The status of internal controls should be reported for cases with 0% to 10% staining. For cases with these results without internal controls present and with positive external controls, an additional report comment is recommended (Table 2) (Type: Informal consensus; Evidence quality: High; Strength of recommendation: Strong).

Literature review and analysis. Recommendations 2.1 and 2.2 re-emphasize elements of the original 2010 guideline. Recommendation 2.3 is a new focus of this update because of concerns about test validity and reproducibility for cases with weak-intensity, low-level, or negative ER staining. The updated recommendations focus on increased standardization in the workup of these weak, low, or negative ER cases with the development of a specific SOP to confirm or adjudicate the result (Fig 1). This is noted to be already standard best practice in many laboratories.

Figure 1 reviews initial steps in the evaluation of any ER IHC and includes the quality control checklist. Cases with moderate-strong stain intensity and > 10% of cells staining are considered to have robust, reportable results as long as they are considered concordant with histology (Table 3) and no checklist issues are identified. For cases with weak stain intensity or ≤ 10% of nuclei staining, additional steps should be taken to confirm or adjudicate the validity of the results, and correlation with histology should be performed. Steps to consider including in an SOP are shown in Figure 1, and an example of a more detailed SOP for these purposes is available as Data Supplement Figure 1. Because of previously identified factors involved in false-negative results such as negative or absent internal controls, evaluation of controls is considered an essential part of this process.[118] If internal controls are negative, or there are no internal controls and the external positive controls do not have appropriate staining, the assay has failed and needs to be troubleshot. In addition, correlation with any prior patient-specific ER results on a breast cancer would be considered relevant. There are data to support that second reviews and digital quantitative image analysis reads can be used to improve reproducibility and accuracy in a pathologist's scoring (readout) and interpretation, so these can be useful components of an SOP for these cases; however, the Expert Panel acknowledges that current data on these topics are not specific enough to distinguish ER Low Positive from ER-negative cases.[61-69,119-121] Additional comments to include in reports for samples of invasive carcinoma that are ER Low Positive (1%-10%) or cancers (either invasive or DCIS) with ≤ 10% staining without internal controls present (but positive external controls) are listed in Table 2.

CLINICAL QUESTION 3

Are other ER expression assays acceptable for identifying patients likely to benefit from endocrine therapy?

Recommendation 3

Validated IHC is the recommended standard test for predicting benefit from endocrine therapy. No other assay types are recommended as the primary screening test for this purpose (Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong).

Literature review and analysis. The Expert Panel reviewed the existing evidence and concluded that data are insufficient at this time to recommend newer methods of ER testing as alternatives to IHC for the purposes of determining ER status or selecting which patients are likely to benefit from endocrine therapy. One issue that was apparent was the lack of data from randomized clinical trials using these assays and platforms to select patients for treatment with endocrine therapy versus observation. However, the Expert Panel recognizes that there are limited avenues for validation of new assays and platforms, as these types of prospective clinical trials are not likely to be conducted. While there are multiple studies that compare messenger RNA (mRNA) with IHC with relatively good agreement, the Expert Panel agreed that this was insufficient to recommend the assays.

Some panel-based gene-expression assays, like Oncotype DX (Genomic Health, Redwood City, CA), have already been incorporated into standard treatment algorithms for IHC ER-positive cancers as a tool to assess the likelihood of clinical benefit offered by chemotherapy when added to endocrine therapy.[122-125] Assays like Oncotype DX, Mammaprint (Agendia, Irvine, CA), the Prosignia Breast Cancer Prognostic Gene Signature Assay (PAM-50; Prosignia NanoString Technologies, Seattle, WA), EndoPredict (Myriad Genetics, Salt Lake City, UT), and the Breast Cancer Index (Biotheranostics, San Diego, CA) also offer prognostic information regarding the risk of recurrence in patients treated with endocrine therapy, and they have improved the ability to understand the biologic behavior of ER-positive breast cancer as defined by standard IHC measures. In most cases, studies of these new assays established their clinical validity regarding their prognostic utility (outcome after a therapy) but were limited in their predictive utility in identifying patients expected to benefit specifically from endocrine treatment.[126,127]

Some of the limited data on benefit from endocrine treatment in relation to ER mRNA expression come from a retrospective study of the NSABP B-14 trial of tamoxifen versus no endocrine therapy. This study showed that in a selected population of patients who were ER positive by LBA, higher *ESR1* expression by the Oncotype DX assay was the strongest linear predictor of tamoxifen benefit, with a significant interaction with treatment.[60] However, specific ER mRNA expression thresholds to predict potential benefit from endocrine therapy as a screening test for all breast cancers were not developed in this study, since ER-negative cases by LBA were not enrolled in NSABP B-14.

Therefore, while new methods of ER testing may offer some advantages over IHC methods (such as producing a quantitative, highly reproducible result), data on their ability to predict endocrine therapy benefit for all cancers as an initial screening test are limited. In addition, a disadvantage of most current mRNA-based methods is that intermixed noncancer tissues can contribute to test results, which may particularly affect cases close to the positive threshold (eg, an IHC ER Low Positive result testing ER negative by quantitative mRNA due to dilution by intermixed noncancer ER-negative tissue). There are very limited data on patients with tumors that are deemed ER Low Positive by IHC and tested with newer alternative assays. Test comparison studies suggest that cases that have low levels of ER expression by IHC (but $\geq 1\%$) are more frequently deemed ER negative by mRNA assays and have variable *ESR1* expression across IHC categories (in one study, 24% of cases were considered ER positive by mRNA expression if IHC 1%-9% and 92% if IHC $> 10\%$).[59,106] Therefore, ER expression of $\geq 1\%$ by IHC remains the current standard to identify patients who could benefit from endocrine therapy in breast cancer, and a negative quantitative mRNA ER result (eg, on Oncotype DX testing) should not negate an IHC-positive result.

CLINICAL QUESTION 4

Should DCIS be routinely tested for hormone receptors?

Recommendation 4

ER testing in cases of newly diagnosed DCIS (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. PgR testing is considered optional (Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Literature review and analysis. In 2010, the Expert Panel acknowledged that newly diagnosed DCIS cases (in the absence of invasion) were commonly being tested for ER and PgR based largely on early but unpublished results from the NSABP B-24 trial.[128] Because of the limited data available at the time, the Expert Panel did not make a formal recommendation, leaving it up to patients and their physicians to decide on testing. Subsequently, in 2012, the subset analysis of the NSABP B-24 clinical trial was published comparing tamoxifen versus placebo after lumpectomy and radiation therapy; these trial data showed a significant reduction in relative risk of subsequent breast cancer restricted to patients with ER-positive DCIS at 10 years of follow-up (hazard ratio [HR], 0.49; $P = .001$).[58] In the UK/ANZ randomized clinical trial examining endocrine therapy in DCIS (*v* no endocrine therapy), long-term follow-up data showed that tamoxifen reduced the incidence of all new breast events in excised DCIS treated with radiation therapy. However, these cases were untested for ER.[57,129] In another phase III clinical trial, women with intraepithelial neoplasia, including ER-positive DCIS, were randomly assigned to receive low-dose tamoxifen or placebo. After a median follow-up of 5.1 years, tamoxifen reduced the incidence of new DCIS or invasive breast cancer (HR, 0.48; 95% CI, 0.26 to 0.92).[130] Retrospective data from single-institution studies also appear to support a higher risk of recurrence in patients with ER-positive DCIS who were not treated with endocrine therapy.[55,56] However, it should be acknowledged that there are currently no data indicating that endocrine-based therapy in the setting of newly diagnosed DCIS has a significant impact on overall survival. Therefore, the decision to use endocrine therapy will depend on individual patient goals and discussion with their clinical care team, but patients should be aware of primary risk reduction options based on the ER status of their DCIS.

Based on the current evidence, the Expert Panel now recommends ER testing in DCIS to guide discussions about adjuvant endocrine therapy. The ER status of newly diagnosed DCIS should be reported when no invasive cancer is present.

Data on whether PgR testing in DCIS adds predictive or prognostic value beyond that of ER alone are currently lacking. In the NSAPB B-24 trial, ER alone was more predictive than combined ER and PgR statuses or PgR status of DCIS for tamoxifen benefit, as patients with ER-positive/PgR-negative DCIS still received benefit, although subsets were small. However, contrary to the prognostic value seen for PgR testing in invasive cancers, studies have not shown significant differences in outcome between ER-positive/PgR-positive and ER-positive/PgR-negative statuses in patients with DCIS.[55,56] Given that there are no data currently supporting the prognostic or predictive value of PgR testing in DCIS independent of ER, the Expert Panel considers PgR testing of DCIS to be optional.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from April 15 through April 29, 2019. Response categories of “Agree” and “Disagree” were captured for every proposed recommendation, with 163 written comments received.

More than 80% of the 163 respondents agreed to eight of the 10 questions pertaining to the recommendations and two questions fell below an 80% agreement rate. Expert Panel members reviewed comments from all sources and determined to revise the recommendations for clarity that did not receive at least 80% agreement. All changes were incorporated prior to ASCO CPGC and CAP review and approval.

ADDITIONAL RESOURCES

More information, including a supplement with evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update[131] (http://ascopubs.org/doi/10.1200/JCO.2018.77.8738)
- 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[125] (http://ascopubs.org/doi/10.1200/JCO.19.00945)
- Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update[132] (http://ascopubs.org/doi/10.1200/JCO.18.01160)
- Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update[133] (http://ascopubs.org/doi/10.1200/JCO.2018.79.2697)

AFFILIATIONS

[1]Stanford University School of Medicine, Stanford, CA
[2]Intermountain Healthcare, Salt Lake City, UT
[3]Royal Marsden Hospital, London, United Kingdom
[4]American Society of Clinical Oncology, Alexandria, VA
[5]University of North Carolina, Chapel Hill, NC
[6]St Jude Medical Center, Fullerton, CA
[7]University of Michigan, Ann Arbor, MI
[8]University of Queensland, Brisbane, Queensland, Australia
[9]Pathology Queensland, Brisbane, Queensland, Australia
[10]MD Anderson Cancer Center, Houston, TX
[11]Gemini Group, Ann Arbor, MI
[12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[13]Yale Cancer Center, New Haven, CT
[14]Saskatchewan Health Authority, Saskatoon, Saskatchewan, Canada
[15]University of Saskatchewan, Saskatoon, Saskatchewan, Canada
[16]Weill Cornell Medicine, New York, NY
[17]IEO, European Institute of Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy
[18]University of Milan, Milan, Italy
[19]Maine Center for Cancer Medicine, Scarborough, ME
[20]National Cancer Institute, Rockville, MD
[21]Johns Hopkins University, Baltimore, MD

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EQUAL CONTRIBUTION

K.H.A. and A.C.W. were Expert Panel co-chairs, M.E.H.H., M.D., and L.M.M. were members of the Steering Group with the co-chairs.

EDITOR’S NOTE

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

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the College of American Pathologists and has been published jointly by inivitation and consent in both *Journal of Clinical Oncology* and *Archives of Pathology & Laboratory Medicine*.

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

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02309.

AUTHOR CONTRIBUTIONS

Conception and design: Kimberly H. Allison, M. Elizabeth H. Hammond, Mitchell Dowsett, Lisa A. Carey, Daniel F. Hayes, David L. Rimm, W. Fraser Symmans, Leticia Varella, Giuseppe Viale, Tracey F. Weisberg, Lisa M. McShane, Antonio C. Wolff

Administrative support: Shannon E. McKernin, Antonio C. Wolff

Collection and assembly of data: Kimberly H. Allison, M. Elizabeth H. Hammond, Shannon E. McKernin, Sunil R. Lakhani, Charles M. Perou, Meredith M. Regan, David L. Rimm, Leticia Varella, Tracey F. Weisberg, Lisa M. McShane, Antonio C. Wolff

Data analysis and interpretation: Kimberly H. Allison, M. Elizabeth H. Hammond, Mitchell Dowsett, Shannon E. McKernin, Lisa A. Carey, Patrick L. Fitzgibbons, Sunil R. Lakhani, Mariana Chavez-MacGregor, Jane Perlmutter, Charles M. Perou, Meredith M. Regan, David L. Rimm, Emina E. Torlakovic, Leticia Varella, Lisa M. McShane, Antonio C. Wolff

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Carey Anders, MD, Zeina Nahleh, MD, the CAP Independent Review Panel, and the ASCO Clinical Practice Guidelines Committee for their thoughtful reviews and insightful comments on this guideline.

REFERENCES

1. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med 134:e48-e72, 2010
2. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784-2795, 2010
3. Hwang KT, Kim J, Jung J, et al: Impact of breast cancer subtypes on prognosis of women with operable invasive breast cancer: A population-based study using SEER database. Clin Cancer Res 25:1970-1979, 2019
4. Dodson A, Parry S, Ibrahim M, et al: Breast cancer biomarkers in clinical testing: analysis of a UK national external quality assessment scheme for immunocytochemistry and in situ hybridisation database containing results from 199 300 patients. J Pathol Clin Res 4:262-273, 2018
5. Anderson WF, Katki HA, Rosenberg PS: Incidence of breast cancer in the United States: Current and future trends. J Natl Cancer Inst 103:1397-1402, 2011
6. Sharpe KH, McClements P, Clark DI, et al: Reduced risk of oestrogen receptor positive breast cancer among peri- and post-menopausal women in Scotland following a striking decrease in use of hormone replacement therapy. Eur J Cancer 46:937-943, 2010
7. Anderson WF, Rosenberg PS, Petito L, et al: Divergent estrogen receptor-positive and -negative breast cancer trends and etiologic heterogeneity in Denmark. Int J Cancer 133:2201-2206, 2013
8. Mullooly M, Murphy J, Gierach GL, et al: Divergent oestrogen receptor-specific breast cancer trends in Ireland (2004-2013): Amassing data from independent Western populations provide etiologic clues. Eur J Cancer 86:326-333, 2017
9. Rosenberg PS, Barker KA, Anderson WF: Estrogen receptor status and the future burden of invasive and in situ breast cancers in the United States. J Natl Cancer Inst 107:djv159, 2015
10. Hortobagyi GN, Connolly JL, D'Orsi CJ, et al: Breast, in Amin MB, Edge S, Greene F, et al (eds): AJCC Cancer Staging Manual, 8th ed. Chicago, IL, American College of Surgeons, 2018, pp 589-637
11. Davies C, Godwin J, Gray R, et al: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. Lancet 378:771-784, 2011
12. Fitzgibbons PL, Murphy DA, Hammond ME, et al: Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. Arch Pathol Lab Med 134:930-935, 2010
13. Torlakovic EE, Cheung CC, D'Arrigo C, et al: Evolution of quality assurance for clinical immunohistochemistry in the era of precision medicine. Part 3: Technical validation of immunohistochemistry (IHC) assays in clinical IHC laboratories. Appl Immunohistochem Mol Morphol 25:151-159, 2017
14. Ravaioli S, Tumedei MM, Foca F, et al: Androgen and oestrogen receptors as potential prognostic markers for patients with ductal carcinoma in situ treated with surgery and radiotherapy. Int J Exp Pathol 98:289-295, 2017
15. Lin Y, Hatem J, Wang J, et al: Tissue microarray-based immunohistochemical study can significantly underestimate the expression of HER2 and progesterone receptor in ductal carcinoma in situ of the breast. Biotech Histochem 86:345-350, 2011
16. Aitken SJ, Thomas JS, Langdon SP, et al: Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. Ann Oncol 21:1254-1261, 2010
17. Tuominen VJ, Ruotoistenmäki S, Viitanen A, et al: ImmunoRatio: A publicly available Web application for quantitative image analysis of estrogen receptor (ER), progesterone receptor (PR), and Ki-67. Breast Cancer Res 12:R56, 2010
18. Słodkowska J, Filas V, Buszkiewicz E, et al: Study on breast carcinoma Her2/neu and hormonal receptors status assessed by automated images analysis systems: ACIS III (Dako) and ScanScope (Aperio). Folia Histochem Cytobiol 48:19-25, 2010
19. Nassar A, Cohen C, Agersborg SS, et al: A multisite performance study comparing the reading of immunohistochemical slides on a computer monitor with conventional manual microscopy for estrogen and progesterone receptor analysis. Am J Clin Pathol 135:461-467, 2011
20. Ali HR, Irwin M, Morris L, et al: Astronomical algorithms for automated analysis of tissue protein expression in breast cancer. Br J Cancer 108:602-612, 2013
21. Stålhammar G, Fuentes Martinez N, Lippert M, et al: Digital image analysis outperforms manual biomarker assessment in breast cancer. Mod Pathol 29:318-329, 2016
22. Liu WL, Wang LW, Chen JM, et al: Application of multispectral imaging in quantitative immunohistochemistry study of breast cancer: A comparative study. Tumour Biol 37:5013-5024, 2016
23. Gertych A, Mohan S, Maclary S, et al: Effects of tissue decalcification on the quantification of breast cancer biomarkers by digital image analysis. Diagn Pathol 9:213, 2014
24. Nielsen TO, Parker JS, Leung S, et al: A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. Clin Cancer Res 16:5222-5232, 2010

25. Müller BM, Kronenwett R, Hennig G, et al: Quantitative determination of estrogen receptor, progesterone receptor, and HER2 mRNA in formalin-fixed paraffin-embedded tissue: A new option for predictive biomarker assessment in breast cancer. Diagn Mol Pathol 20:1-10, 2011
26. Maeda I, Kubota M, Ohta J, et al: Effectiveness of computer-aided diagnosis (CADx) of breast pathology using immunohistochemistry results of core needle biopsy samples for synaptophysin, oestrogen receptor and CK14/p63 for classification of epithelial proliferative lesions of the breast. J Clin Pathol 70: 1057-1062, 2017
27. Tramm T, Hennig G, Kyndi M, et al: Reliable PCR quantitation of estrogen, progesterone and ERBB2 receptor mRNA from formalin-fixed, paraffin-embedded tissue is independent of prior macro-dissection. Virchows Arch 463:775-786, 2013
28. Cheang MC, Martin M, Nielsen TO, et al: Defining breast cancer intrinsic subtypes by quantitative receptor expression. Oncologist 20:474-482, 2015
29. Bastien RR, Rodríguez-Lescure Á, Ebbert MT, et al: PAM50 breast cancer subtyping by RT-qPCR and concordance with standard clinical molecular markers. BMC Med Genomics 5:44, 2012
30. Wirtz RM, Sihto H, Isola J, et al: Biological subtyping of early breast cancer: A study comparing RT-qPCR with immunohistochemistry. Breast Cancer Res Treat 157:437-446, 2016
31. Sheffield BS, Kos Z, Asleh-Aburaya K, et al: Molecular subtype profiling of invasive breast cancers weakly positive for estrogen receptor. Breast Cancer Res Treat 155:483-490, 2016
32. Laible M, Schlombs K, Kaiser K, et al: Technical validation of an RT-qPCR in vitro diagnostic test system for the determination of breast cancer molecular subtypes by quantification of ERBB2, ESR1, PGR and MKI67 mRNA levels from formalin-fixed paraffin-embedded breast tumor specimens. BMC Cancer 16: 398, 2016
33. Wu NC, Wong W, Ho KE, et al: Comparison of central laboratory assessments of ER, PR, HER2, and Ki67 by IHC/FISH and the corresponding mRNAs (ESR1, PGR, ERBB2, and MKi67) by RT-qPCR on an automated, broadly deployed diagnostic platform. Breast Cancer Res Treat 172:327-338, 2018
34. Varga Z, Lebeau A, Bu H, et al: An international reproducibility study validating quantitative determination of ERBB2, ESR1, PGR, and MKI67 mRNA in breast cancer using MammaTyper. Breast Cancer Res 19:55, 2017
35. Hyeon J, Cho SY, Hong ME, et al: NanoString nCounter approach in breast cancer: A comparative analysis with quantitative real-time polymerase chain reaction, in situ hybridization, and immunohistochemistry. J Breast Cancer 20:286-296, 2017
36. Cai H, Guo W, Zhang S, et al: A qualitative transcriptional signature to reclassify estrogen receptor status of breast cancer patients. Breast Cancer Res Treat 170:271-277, 2018
37. Wilson TR, Xiao Y, Spoerke JM, et al: Development of a robust RNA-based classifier to accurately determine ER, PR, and HER2 status in breast cancer clinical samples. Breast Cancer Res Treat 148:315-325, 2014
38. Welsh AW, Moeder CB, Kumar S, et al: Standardization of estrogen receptor measurement in breast cancer suggests false-negative results are a function of threshold intensity rather than percentage of positive cells. J Clin Oncol 29:2978-2984, 2011
39. Karn T, Metzler D, Ruckhäberle E, et al: Data-driven derivation of cutoffs from a pool of 3,030 Affymetrix arrays to stratify distinct clinical types of breast cancer. Breast Cancer Res Treat 120:567-579, 2010
40. Bordeaux JM, Cheng H, Welsh AW, et al: Quantitative in situ measurement of estrogen receptor mRNA predicts response to tamoxifen. PLoS One 7:e36559, 2012
41. Wesseling J, Tinterri C, Sapino A, et al: An international study comparing conventional versus mRNA level testing (TargetPrint) for ER, PR, and HER2 status of breast cancer. Virchows Arch 469:297-304, 2016
42. Viale G, Slaets L, Bogaerts J, et al: High concordance of protein (by IHC), gene (by FISH; HER2 only), and microarray readout (by TargetPrint) of ER, PgR, and HER2: Results from the EORTC 10041/BIG 03-04 MINDACT trial. Ann Oncol 25:816-823, 2014
43. Dekker TJ, ter Borg S, Hooijer GK, et al: Quality assessment of estrogen receptor and progesterone receptor testing in breast cancer using a tissue microarray-based approach. Breast Cancer Res Treat 152:247-252, 2015 [erratum: Breast Cancer Res Treat 152:253, 2015]
44. Zarrella ER, Coulter M, Welsh AW, et al: Automated measurement of estrogen receptor in breast cancer: A comparison of fluorescent and chromogenic methods of measurement. Lab Invest 96:1016-1025, 2016
45. Viale G, Slaets L, de Snoo FA, et al: Discordant assessment of tumor biomarkers by histopathological and molecular assays in the EORTC randomized controlled 10041/BIG 03-04 MINDACT trial breast cancer: Intratumoral heterogeneity and DCIS or normal tissue components are unlikely to be the cause of discordance. Breast Cancer Res Treat 155:463-469, 2016
46. Viale G, de Snoo FA, Slaets L, et al: Immunohistochemical versus molecular (BluePrint and MammaPrint) subtyping of breast carcinoma: Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial. Breast Cancer Res Treat 167:123-131, 2018
47. Reisenbichler ES, Lester SC, Richardson AL, et al: Interobserver concordance in implementing the 2010 ASCO/CAP recommendations for reporting ER in breast carcinomas: A demonstration of the difficulties of consistently reporting low levels of ER expression by manual quantification. Am J Clin Pathol 140: 487-494, 2013
48. Cserni G, Francz M, Kálmán E, et al: Estrogen receptor negative and progesterone receptor positive breast carcinomas: How frequent are they? Pathol Oncol Res 17:663-668, 2011
49. Bae SY, Kim S, Lee JH, et al: Poor prognosis of single hormone receptor-positive breast cancer: Similar outcome as triple-negative breast cancer. BMC Cancer 15:138, 2015
50. Zhang Z, Wang J, Skinner KA, et al: Pathological features and clinical outcomes of breast cancer according to levels of oestrogen receptor expression. Histopathology 65:508-516, 2014
51. Landmann A, Farrugia DJ, Zhu L, et al: Low estrogen receptor (ER)-positive breast cancer and neoadjuvant systemic chemotherapy: Is response similar to typical ER-positive or ER-negative disease? Am J Clin Pathol 150:34-42, 2018
52. Spring LM, Gupta A, Reynolds KL, et al: Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: A systematic review and meta-analysis. JAMA Oncol 2:1477-1486, 2016
53. Ejlertsen B, Aldridge J, Nielsen KV, et al: Prognostic and predictive role of ESR1 status for postmenopausal patients with endocrine-responsive early breast cancer in the Danish cohort of the BIG 1-98 trial. Ann Oncol 23:1138-1144, 2012
54. Bui MM, Riben MW, Allison KH, et al: Quantitative image analysis of human epidermal growth factor receptor 2 immunohistochemistry for breast cancer: Guideline from the College of American Pathologists. Arch Pathol Lab Med 143:1180-1195, 2019
55. Hwang KT, Kim EK, Jung SH, et al: Tamoxifen therapy improves overall survival in luminal A subtype of ductal carcinoma in situ: A study based on nationwide Korean Breast Cancer Registry database. Breast Cancer Res Treat 169:311-322, 2018
56. Chaudhary LN, Jawa Z, Hanif A, et al: Does progesterone receptor matter in the risk of recurrence for patients with ductal carcinoma in situ? WMJ 117:62-67, 2018
57. Cuzick J, Sestak I, Pinder SE, et al: Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: Long-term results from the UK/ANZ DCIS trial. Lancet Oncol 12:21-29, 2011

58. Allred DC, Anderson SJ, Paik S, et al: Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor–positive ductal carcinoma in situ: A study based on NSABP protocol B-24. J Clin Oncol 30:1268-1273, 2012
59. Kraus JA, Dabbs DJ, Beriwal S, et al: Semi-quantitative immunohistochemical assay versus oncotype DX qRT-PCR assay for estrogen and progesterone receptors: An independent quality assurance study. Mod Pathol 25:869-876, 2012
60. Kim C, Tang G, Pogue-Geile KL, et al: Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor–positive breast cancer. J Clin Oncol 29:4160-4167, 2011
61. Rimm DL, Leung SCY, McShane LM, et al: An international multicenter study to evaluate reproducibility of automated scoring for assessment of Ki67 in breast cancer. Mod Pathol 32:59-69, 2019
62. Jorns JM, Healy P, Zhao L: Review of estrogen receptor, progesterone receptor, and HER-2/neu immunohistochemistry impacts on treatment for a small subset of breast cancer patients transferring care to another institution. Arch Pathol Lab Med 137:1660-1663, 2013
63. Engelberg JA, Retallack H, Balassanian R, et al: "Score the Core" Web-based pathologist training tool improves the accuracy of breast cancer IHC4 scoring. Hum Pathol 46:1694-1704, 2015
64. Elmore JG, Tosteson AN, Pepe MS, et al: Evaluation of 12 strategies for obtaining second opinions to improve interpretation of breast histopathology: Simulation study. BMJ 353:i3069, 2016
65. Tosteson ANA, Yang Q, Nelson HD, et al: Second opinion strategies in breast pathology: A decision analysis addressing over-treatment, under-treatment, and care costs. Breast Cancer Res Treat 167:195-203, 2018
66. Lloyd MC, Allam-Nandyala P, Purohit CN, et al: Using image analysis as a tool for assessment of prognostic and predictive biomarkers for breast cancer: How reliable is it? J Pathol Inform 1:29, 2010
67. Barnes M, Srinivas C, Bai I, et al: Whole tumor section quantitative image analysis maximizes between-pathologists' reproducibility for clinical immunohistochemistry-based biomarkers. Lab Invest 97:1508-1515, 2017
68. Ahern TP, Beck AH, Rosner BA, et al: Continuous measurement of breast tumour hormone receptor expression: A comparison of two computational pathology platforms. J Clin Pathol 70:428-434, 2017
69. Peck M, Moffat D, Latham B, et al: Review of diagnostic error in anatomical pathology and the role and value of second opinions in error prevention. J Clin Pathol 71:995-1000, 2018
70. Kuroda H, Muroi N, Hayashi M, et al: Oestrogen receptor-negative/progesterone receptor-positive phenotype of invasive breast carcinoma in Japan: Re-evaluated using immunohistochemical staining. Breast Cancer 26:249-254, 2019
71. Knoop AS, Lænkholm AV, Jensen MB, et al: Estrogen receptor, progesterone receptor, HER2 status and Ki67 index and responsiveness to adjuvant tamoxifen in postmenopausal high-risk breast cancer patients enrolled in the DBCG 77C trial. Eur J Cancer 50:1412-1421, 2014
72. Dowsett M, Allred C, Knox J, et al: Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. J Clin Oncol 26:1059-1065, 2008
73. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al: Validation study of the American Joint Committee on Cancer Eighth Edition prognostic stage compared with the anatomic stage in breast cancer. JAMA Oncol 4:203-209, 2018
74. Foley NM, Coll JM, Lowery AJ, et al: Re-appraisal of estrogen receptor negative/progesterone receptor positive (ER-/PR+) breast cancer phenotype: True subtype or technical artefact? Pathol Oncol Res 24:881-884, 2018
75. Allison KH, Kandalaft PL, Sitlani CM, et al: Routine pathologic parameters can predict Oncotype DX recurrence scores in subsets of ER positive patients: Who does not always need testing? Breast Cancer Res Treat 131:413-424, 2012
76. Ahmed SS, Thike AA, Zhang K, et al: Clinicopathological characteristics of oestrogen receptor negative, progesterone receptor positive breast cancers: Re-evaluating subsets within this group. J Clin Pathol 70:320-326, 2017
77. Turner BM, Skinner KA, Tang P, et al: Use of modified Magee equations and histologic criteria to predict the Oncotype DX recurrence score. Mod Pathol 28: 921-931, 2015
78. Klein ME, Dabbs DJ, Shuai Y, et al: Prediction of the Oncotype DX recurrence score: Use of pathology-generated equations derived by linear regression analysis. Mod Pathol 26:658-664, 2013
79. Farrugia DJ, Landmann A, Zhu L, et al: Magee equation 3 predicts pathologic response to neoadjuvant systemic chemotherapy in estrogen receptor positive, HER2 negative/equivocal breast tumors. Mod Pathol 30:1078-1085, 2017
80. Bhargava R, Clark BZ, Dabbs DJ: Breast cancers with Magee equation score of less than 18, or 18-25 and mitosis score of 1, do not require Oncotype DX testing: A value study. Am J Clin Pathol 151:316-323, 2019
81. Yeo B, Zabaglo L, Hills M, et al: Clinical utility of the IHC4+C score in oestrogen receptor-positive early breast cancer: A prospective decision impact study. Br J Cancer 113:390-395, 2015
82. Lee SB, Kim J, Sohn G, et al: A nomogram for predicting the Oncotype DX recurrence score in women with T1-3N0-1miM0 hormone receptor–positive, human epidermal growth factor 2 (HER2)–negative breast cancer. Cancer Res Treat 51:1073-1085, 2019
83. Cuzick J, Dowsett M, Pineda S, et al: Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol 29:4273-4278, 2011
84. Tan W, Luo W, Jia W, et al: A combination of Nottingham prognostic index and IHC4 score predicts pathological complete response of neoadjuvant chemotherapy in estrogen receptor positive breast cancer. Oncotarget 7:87312-87322, 2016
85. Sheri A, Smith IE, Hills M, et al: Relationship between IHC4 score and response to neo-adjuvant chemotherapy in estrogen receptor-positive breast cancer. Breast Cancer Res Treat 164:395-400, 2017
86. Lakhanpal R, Sestak I, Shadbolt B, et al: IHC4 score plus clinical treatment score predicts locoregional recurrence in early breast cancer. Breast 29:147-152, 2016
87. Kim HS, Umbricht CB, Illei PB, et al: Optimizing the use of gene expression profiling in early-stage breast cancer. J Clin Oncol 34:4390-4397, 2016
88. Regan MM, Francis PA, Pagani O, et al: Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor–positive, human epidermal growth factor receptor 2–negative early breast cancer: TEXT and SOFT trials. J Clin Oncol 34:2221-2231, 2016
89. Albert JM, Gonzalez-Angulo AM, Guray M, et al: Patients with only 1 positive hormone receptor have increased locoregional recurrence compared with patients with estrogen receptor-positive progesterone receptor-positive disease in very early stage breast cancer. Cancer 117:1595-1601, 2011
90. Ahn SG, Yoon CI, Lee JH, et al: Low PR in ER(+)/HER2(-) breast cancer: High rates of TP53 mutation and high SUV. Endocr Relat Cancer doi: 10.1530/ERC-18-0281 [epub ahead of print on November 1, 2018]
91. Raghav KP, Hernandez-Aya LF, Lei X, et al: Impact of low estrogen/progesterone receptor expression on survival outcomes in breast cancers previously classified as triple negative breast cancers. Cancer 118:1498-1506, 2012

92. Honma N, Horii R, Iwase T, et al: Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy. Breast 23:754-762, 2014
93. Chen T, Zhang N, Moran MS, et al: Borderline ER-positive primary breast cancer gains no significant survival benefit from endocrine therapy: A systematic review and meta-analysis. Clin Breast Cancer 18:1-8, 2018
94. Balduzzi A, Bagnardi V, Rotmensz N, et al: Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression. Clin Breast Cancer 14:258-264, 2014
95. Gloyeske NC, Dabbs DJ, Bhargava R: Low ER+ breast cancer: Is this a distinct group? Am J Clin Pathol 141:697-701, 2014
96. Deyarmin B, Kane JL, Valente AL, et al: Effect of ASCO/CAP guidelines for determining ER status on molecular subtype. Ann Surg Oncol 20:87-93, 2013
97. Yi M, Huo L, Koenig KB, et al: Which threshold for ER positivity? A retrospective study based on 9639 patients. Ann Oncol 25:1004-1011, 2014
98. Khoshnoud MR, Löfdahl B, Fohlin H, et al: Immunohistochemistry compared to cytosol assays for determination of estrogen receptor and prediction of the long-term effect of adjuvant tamoxifen. Breast Cancer Res Treat 126:421-430, 2011
99. Badve SS, Baehner FL, Gray RP, et al: Estrogen- and progesterone-receptor status in ECOG 2197: Comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. J Clin Oncol 26:2473-2481, 2008 [Erratum: J Clin Oncol 26:3472, 2008]
100. Cheang MC, Treaba DO, Speers CH, et al: Immunohistochemical detection using the new rabbit monoclonal antibody SP1 of estrogen receptor in breast cancer is superior to mouse monoclonal antibody 1D5 in predicting survival. J Clin Oncol 24:5637-5644, 2006
101. Dowsett M: Estrogen receptor: Methodology matters. J Clin Oncol 24:5626-5628, 2006
102. Harvey JM, Clark GM, Osborne CK, et al: Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol 17:1474-1481, 1999
103. Fisher ER, Anderson S, Dean S, et al: Solving the dilemma of the immunohistochemical and other methods used for scoring estrogen receptor and progesterone receptor in patients with invasive breast carcinoma. Cancer 103:164-173, 2005
104. Molino A, Micciolo R, Turazza M, et al: Prognostic significance of estrogen receptors in 405 primary breast cancers: A comparison of immunohistochemical and biochemical methods. Breast Cancer Res Treat 45:241-249, 1997
105. Bouchard-Fortier A, Provencher L, Blanchette C, et al: Prognostic and predictive value of low estrogen receptor expression in breast cancer. Curr Oncol 24: e106-e114, 2017
106. Iwamoto T, Booser D, Valero V, et al: Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. J Clin Oncol 30:729-734, 2012
107. Pérez T, Makrestsov N, Garatt J, et al: Modeling Canadian quality control test program for steroid hormone receptors in breast cancer: Diagnostic accuracy study. Appl Immunohistochem Mol Morphol 24:679-687, 2016
108. Torlakovic EE, Nielsen S, Vyberg M, et al: Getting controls under control: The time is now for immunohistochemistry. J Clin Pathol 68:879-882, 2015
109. Torlakovic EE, Nielsen S, Francis G, et al: Standardization of positive controls in diagnostic immunohistochemistry: Recommendations from the International Ad Hoc Expert Committee. Appl Immunohistochem Mol Morphol 23:1-18, 2015
110. Cheung CC, Taylor CR, Torlakovic EE: An audit of failed immunohistochemical slides in a clinical laboratory: The role of on-slide controls. Appl Immunohistochem Mol Morphol 25:308-312, 2017
111. Bogen SA: A root cause analysis into the high error rate in clinical immunohistochemistry. Appl Immunohistochem Mol Morphol 27:329-338, 2019
112. Vani K, Sompuram SR, Schaedle AK, et al: The importance of epitope density in selecting a sensitive positive IHC control. J Histochem Cytochem 65:463-477, 2017
113. Sompuram SR, Vani K, Tracey B, et al: Standardizing immunohistochemistry: A new reference control for detecting staining problems. J Histochem Cytochem 63:681-690, 2015
114. Vani K, Sompuram SR, Naber SP, et al: Levey-Jennings analysis uncovers unsuspected causes of immunohistochemistry stain variability. Appl Immunohistochem Mol Morphol 24:688-694, 2016
115. Sompuram SR, Vani K, Schaedle AK, et al: Selecting an optimal positive IHC control for verifying antigen retrieval. J Histochem Cytochem 67:275-289, 2019
116. Prat A, Cheang MC, Martín M, et al: Prognostic significance of progesterone receptor–positive tumor cells within immunohistochemically defined luminal A breast cancer. J Clin Oncol 31:203-209, 2013
117. Reference deleted
118. Cameron MA: Commission of Inquiry on Hormone Receptor Testing. St John's, Newfoundland, Canada, Government of Newfoundland and Labrador, 2009
119. Aeffner F, Wilson K, Martin NT, et al: The gold standard paradox in digital image analysis: Manual versus automated scoring as ground truth. Arch Pathol Lab Med 141:1267-1275, 2017
120. Khazai L, Middleton LP, Goktepe N, et al: Breast pathology second review identifies clinically significant discrepancies in over 10% of patients. J Surg Oncol 111:192-197, 2015
121. Allen TC: Second opinions: Pathologists' preventive medicine. Arch Pathol Lab Med 137:310-311, 2013
122. Sparano JA, Gray RJ, Makower DF, et al: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111-121, 2018
123. Sparano JA, Gray RJ, Makower DF, et al: Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 373:2005-2014, 2015
124. Dowsett M, Turner N: Estimating risk of recurrence for early breast cancer: Integrating clinical and genomic risk. J Clin Oncol 37:689-692, 2019
125. Andre F, Ismaila N, Henry NL, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline update—Integration of results from TAILORx. J Clin Oncol 37:1956-1964, 2019
126. Krop I, Ismaila N, Andre F, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol 35:2838-2847, 2017
127. Harris LN, Ismaila N, McShane LM, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:1134-1150, 2016
128. Allred DC, Bryant J, Land S, et al: Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24. Breast Cancer Res Treat 76:S36, 2002
129. Houghton J, George WD, Cuzick J, et al: Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomised controlled trial. Lancet 362:95-102, 2003
130. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al: Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol 37:1629-1637, 2019

131. Wolff AC, Hammond MEH, Allison KH, et al: Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Arch Pathol Lab Med 142:1364-1382, 2018

132. Burstein HJ, Lacchetti C, Anderson H, et al: Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. J Clin Oncol 37:423-438, 2019

133. Giordano SH, Temin S, Chandarlapaty S, et al: Systemic therapy for patients with advanced human epidermal growth factor receptor 2–positive breast cancer: ASCO clinical practice guideline update. J Clin Oncol 36:2736-2740, 2018

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Kimberly H. Allison
Honoraria: Genentech
Consulting or Advisory Role: Mammotome
Expert Testimony: Kaiser Permanente

Mitchell Dowsett
Honoraria: Myriad Genetics
Consulting or Advisory Role: GTx, Radius Health, Orion Pharma GmbH
Research Funding: Pfizer (Inst), Radius Health (Inst)
Travel, Accommodations, Expenses: Pfizer, Myriad Genetics
Other Relationship: Institute of Cancer Research

Lisa A. Carey
Research Funding: Innocrin Pharma (Inst), Syndax (Inst), Immunomedics (Inst), Novartis (Inst)
Patents, Royalties, Other Intellectual Property: Royalty-sharing agreement, investorship interest in licensed intellectual property to startup company, Falcon Therapeutics, which is designing neural stem cell–based therapy for glioblastoma multiforme (I)

Patrick L. Fitzgibbons
Stock and Other Ownership Interests: Johnson & Johnson, Pfizer, Medtronic, Merck

Daniel F. Hayes
Stock and Other Ownership Interests: OncImmune, InBiomotion
Consulting or Advisory Role: Cepheid, Freenome, Cellworks
Consulting or Advisory Role: CVS Caremark Breast Cancer Expert Panel, Agendia
Research Funding: AstraZeneca (Inst), Pfizer (Inst), Merrimack (Inst), Menarini Silicon Biosystems (Inst)
Patents, Royalties, Other Intellectual Property: Royalties from licensed technology; Diagnosis and treatment of breast cancer, patent No. US 8,790,878 B2, date of patent July 29, 2014, applicant proprietor University of Michigan, Daniel F. Hayes designated as inventor/co-inventor; circulating tumor cell capturing techniques and devices, patent No. US 8,951,484 B2, date of patent February 10, 2015, applicant proprietor University of Michigan, Daniel F. Hayes designated as inventor/co-inventor; method for predicting progression-free and overall survival at each follow-up time point during therapy of metastatic breast cancer patients using circulating tumor cells, patent No. 05725638.0-1223-US2005008602
Travel, Accommodations, Expenses: Menarini Silicon Biosystems
Other Relationship: Menarini

Sunil R. Lakhani
Consulting or Advisory Role: Suburban Hospital (Inst)
Travel, Accommodations, Expenses: Ventana Medical Systems

Mariana Chavez-MacGregor
Employment: MD Anderson Physician's Network
Honoraria: Pfizer, Eisai
Consulting or Advisory Role: Roche/Genentech
Research Funding: Novartis (Inst)
Expert Testimony: Abbott Laboratories, Pfizer
Travel, Accommodations, Expenses: Pfizer

Charles M. Perou
Leadership: GeneCentric
Stock and Other Ownership Interests: Bioclassifier, GeneCentric
Consulting or Advisory Role: Bioclassifier, GeneCentric, G1 Therapeutics, Ions Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Royalties from PAM50 breast cancer gene patent application and from lung gene signature patent
Travel, Accommodations, Expenses: Takeda, Chugai Pharma

Meredith M. Regan
Consulting or Advisory Role: Ipsen (Inst)
Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Roche (Inst), Astellas Pharma (Inst), Medivation (Inst), Janssen (Inst), Millennium Pharmaceuticals (Inst), Sanofi (Inst), Sotio (Inst), Dendreon (Inst), TerSera (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

David L. Rimm
Stock and Other Ownership Interests: Pixel Gear
Honoraria: Amgen, Bristol-Myers Squibb, Ventana Medical Systems
Consulting or Advisory Role: Biocept, Perkin Elmer, Bristol-Myers Squibb, AstraZeneca, Agendia, Ultivue, Merck, Daiichi Sankyo, GlaxoSmithKline, Konica Minolta, NanoString Technologies, NextCure, Cell Signaling Technology, Roche, Paige AI, Cepheid
Research Funding: Cepheid (Inst), Perkin Elmer (Inst), AstraZeneca/MedImmune (Inst), NextCure (Inst), Lilly (Inst), NanoString Technologies (Inst), Navigate Biopharma (Inst), Ultivue (Inst)
Patents, Royalties, Other Intellectual Property: Rarecyte circulating tumor cells; quantitative immunofluorescence (AQUA) (Inst)
Travel, Accommodations, Expenses: Ventana Medical Systems, Genentech, NextCure

W. Fraser Symmans
Stock and Other Ownership Interests: ISIS Pharmaceuticals, Nuvera Biosciences, Delphi Diagnostics
Consulting or Advisory Role: Merck, Almac Diagnostics
Travel, Accommodations, Expenses: Luminex, Merck

Emina E. Torlakovic
Honoraria: Janssen Latin America Oncology, Leica Biosystems, Janssen
Consulting or Advisory Role: Merck, Pfizer, Millipore, Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Janssen Oncology, Roche
Research Funding: AstraZeneca (Inst), Roche (Inst), Bristol-Myers Squibb, Merck, Pfizer (Inst)

Giuseppe Viale
Honoraria: MSD Oncology, Pfizer
Consulting or Advisory Role: Dako, Roche/Genentech, Astellas Pharma, Novartis, Bayer
Speakers; Bureau: Roche/Genentech
Research Funding: Roche/Genentech, Ventana Medical Systems (Inst), Dako/Agilent Technologies (Inst)
Travel, Accommodations, Expenses: Roche, Celgene

Tracey F. Weisberg
Honoraria: Invitae
Research Funding: NanoString Technologies (Inst)

Antonio C. Wolff
Consulting or Advisory Role: Ionis Pharmaceuticals
Research Funding: Myriad Genetics (Inst), Pfizer (Inst), Biomarin (Inst), Celldex (Inst)
Patents, Royalties, Other Intellectual Property: Antonio Wolff has been named as inventor on one or more issued patents or pending patent applications relating to methylation in breast cancer and has assigned his rights to Johns Hopkins University (JHU) and participates in a royalty-sharing agreement with JHU

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Clinical Practice Guideline Update Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Kimberly H. Allison, co-chair	Stanford University School of Medicine, Stanford, CA	Pathology
Antonio C. Wolff, co-chair	Johns Hopkins University, Baltimore, MD	Medical oncology
M. Elizabeth H. Hammond, steering group member	Intermountain Healthcare, Salt Lake City, UT	Pathology
Mitchell Dowsett, steering group member	Royal Marsden Hospital, London, United Kingdom	Clinical scientist
Lisa M. McShane, steering group member	National Cancer Institute, Rockville, MD	Statistician
Lisa A. Carey	University of North Carolina, Chapel Hill, NC	Medical oncology
Patrick L. Fitzgibbons	St Jude Medical Center, Fullerton, CA	Pathology
Daniel F. Hayes	University of Michigan, Ann Arbor, MI	Medical oncology
Sunil R. Lakhani	University of Queensland and Pathology Queensland, Brisbane, Queensland, Australia	Pathology
Mariana Chavez-MacGregor	MD Anderson Cancer Center, Houston, TX	Medical oncology
Jane Perlmutter	Gemini Group, Ann Arbor, MI	Patient representative
Charles M. Perou	University of North Carolina, Chapel Hill, NC	Pathology
Meredith M. Regan	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Statistician
David L. Rimm	Yale Cancer Center, New Haven, CT	Pathology
W. Fraser Symmans	MD Anderson Cancer Center, Houston, TX	Pathology
Emina E. Torlakovic	Saskatchewan Health Authority and University of Saskatchewan, Saskatoon, Saskatchewan, Canada	Pathology
Leticia Varella	Weill Cornell Medicine, New York, NY	Medical oncology
Giuseppe Viale	IEO, European Institute of Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, and University of Milan, Italy	Pathology
Tracey F. Weisberg, PGIN representative	Maine Center for Cancer Medicine, Scarborough, ME	Medical oncology
Shannon E. McKernin	American Society of Clinical Oncology, Alexandria, VA	Practice guidelines staff (health research methods)

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; PGIN, Practice Guidelines Implementation Network.