# **Management of Male Breast Cancer: ASCO Guideline**

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2 **PURPOSE** To develop recommendations concerning the management of male breast cancer.

METHODS ASCO convened an Expert Panel to develop recommendations based on a systematic review and a formal consensus process.

bstract **RESULTS** Twenty-six descriptive reports or observational studies met eligibility criteria and formed the evidentiary basis for the recommendations.

RECOMMENDATIONS Many of the management approaches used for men with breast cancer are like those used for women. Men with hormone receptor-positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen for an initial duration of five years; those with a contraindication to tamoxifen may be offered a gonadotropin-releasing hormone agonist/antagonist plus aromatase inhibitor. Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence may be offered an additional five years of therapy. Men with early-stage disease should not be treated with bone-modifying agents to prevent recurrence, but could still receive these agents to prevent or treat osteoporosis. Men with advanced or metastatic disease should be offered endocrine therapy as first-line therapy, except in cases of visceral crisis or rapidly progressive disease. Targeted systemic therapy may be used to treat advanced or metastatic cancer using the same indications and combinations offered to women. Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy regardless of genetic predisposition; contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation. Breast magnetic resonance imaging is not recommended routinely. Genetic counseling and germline genetic testing of cancer predisposition genes should be offered to all men with breast cancer.

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#### INTRODUCTION

Male breast cancer is a rare disease representing < 1% of all breast carcinomas diagnosed in the United States each year. In 2019. an estimated 2.670 new cases of breast cancer were expected to be diagnosed among men in the United States, and about 500 men were expected to die as a result of breast cancer.<sup>1</sup> The lifetime risk of breast cancer is about 1:1,000 for a man, whereas it is approximately 1:8 for a woman. Breast cancer incidence rates rise steadily with age in men as they do in women; however, the average age of a new breast cancer diagnosis is five years older for men (67 years) than for women (62 years). Other risk factors for male breast cancer include a family history of breast cancer; black ethnicity; exposure to radiation to the breast or chest; carrying a predisposition germline genetic mutation (eg, BRCA2, BRCA1, CHEK2, PALB2); use of exogenous estrogen; and diseases associated with hyperestrogenism (eg, Klinefelter's syndrome).<sup>2</sup>

There are substantial knowledge gaps concerning the optimal management of breast cancer in men. To date, approaches to treating men with breast cancer have been extrapolated largely from research conducted in women with breast cancer. Planned or ongoing treatment trials that focus on men should eventually inform the standard of care, but they are years from completion and will not address all important questions for male breast cancer. This American Society of Clinical Oncology (ASCO) guideline offers recommendations on several key aspects of the management of male breast cancer.

ASSOCIATED CONTENT Appendix

# **Data Supplement**

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

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#### THE BOTTOM LINE

## Management of Male Breast Cancer: ASCO Guideline

#### Guideline Question

What is the optimal management for men with breast cancer including use of adjuvant endocrine therapy, use of endocrine therapy for advanced or metastatic disease, targeted therapies, management of treatment-related adverse effects, genetic testing, and post-treatment surveillance?

## **Target Population**

Men diagnosed with invasive breast cancer.

#### Target Audience

Medical oncologists, radiologists, radiation oncologists, surgical oncologists, endocrinologists, oncology nurses, patients/ caregivers/advocates, oncology advanced practice providers, genetic counselors.

#### Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature. Guideline development involved a formal consensus process.

## Results of Phase I—The Breast Cancer Advisory Group Guideline Survey

The Advisory Group reported high-level consensus that the following components of management were largely the same for men and women: (1) use of gene expression profile testing to guide adjuvant treatment decision making (eg, Oncotype DX and prognostic tests), (2) primary surgery, (3) adjuvant chemotherapy, (4) adjuvant radiation therapy, and (5) chemotherapy for advanced/metastatic disease.

Based on these findings, the Expert Panel recommends that, for men with breast cancer, the approach to the use of gene expression profile testing to guideline adjuvant treatment decision making, to primary surgery, to adjuvant chemotherapy, to adjuvant radiation therapy, and to chemotherapy for advanced/metastatic disease should be the same as the approach used for women.

## Results of Phase II—The Expert Panel Consensus Development Process

The Consensus Development Process focused on topics for which the Advisory Group and Expert Panel did not believe there was already widespread agreement that the management of men and women was largely the same: (1) endocrine therapy in the adjuvant setting, (2) endocrine therapy in the metastatic setting, (3) management of adverse effects from endocrine therapy, (4) germline genetic testing, (5) survivorship care, and (6) the use of targeted therapies for advanced/metastatic disease. Over two rounds of ratings, 12 recommendations pertaining to 10 clinical questions derived from these six topics satisfied the required 75% consensus agreement threshold.

## Recommendations

**Recommendation 1.1.** Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

**Recommendation 1.2.** Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy but have a contraindication to tamoxifen may be offered gonadotropin-releasing hormone agonist/antagonist and an aromatase inhibitor (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 2.1.** Men who are treated with adjuvant endocrine therapy should be treated for an initial duration of five years (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

**Recommendation 2.2.** Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence may be offered an additional five years of tamoxifen therapy (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

**Recommendation 3.** Men with early-stage breast cancer should not be treated with bone-modifying agents to prevent recurrence but could still receive these agents to prevent or treat osteoporosis (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 4.1.** Men with advanced or metastatic, hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer should be offered endocrine therapy as first-line therapy except in cases of visceral crisis or rapidly progressive disease. Options include tamoxifen, an aromatase inhibitor with a gonadotropin-releasing hormone agent, and fulvestrant. Cyclin-dependent kinase 4/6 inhibitors can be used in men as they are used in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

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#### THE BOTTOM LINE (CONTINUED)

**Recommendation 4.2.** Men who develop recurrent metastatic, hormone receptor–positive, HER2-negative breast cancer while receiving adjuvant endocrine therapy should be offered an alternative endocrine therapy except in cases of visceral crisis or rapidly progressive disease (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

**Recommendation 4.3.** Endocrine therapy for men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer may be sequenced as in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 5.** Targeted therapy guided by HER2, programmed death ligand 1, PIK3CA, and germline *BRCA* mutation status may be used in the treatment of advanced or metastatic male breast cancer using the same indications and combinations that are offered to women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong). (Targeted therapy based on hormone receptor status is addressed in Recommendations 4.1 to 4.3.)

**Recommendation 6.1.** Management of endocrine therapy toxicity is similar to the approach used for women (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 6.2.** Testosterone/androgen supplementation should not be used by men with breast cancer (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 7.** Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches. The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for patients with breast cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 8.** Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy, if technically feasible, regardless of genetic predisposition (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

**Recommendation 9.1.** Contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 9.2.** Breast magnetic resonance imaging is not recommended routinely in men with a history of breast cancer (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

**Recommendation 10.** Male patients with breast cancer should be offered genetic counseling and genetic testing for germline mutations (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

#### Draft Recommendations That Did Not Reach the Required 75% Consensus Threshold

Two draft recommendations did not exceed the required 75% consensus agreement threshold: (1) contralateral annual mammography in men without a predisposing genetic mutation and (2) chemoprevention. In accordance with the modified Delphi approach used by ASCO, the Expert Panel could not issue formal consensus recommendations for these clinical questions.

#### Additional Resources

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

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.

## **SCOPE OF THE GUIDELINE**

In foundational work, the Expert Panel (Appendix Table A1, online only) identified 14 core management components for male breast cancer and chose to develop the guideline using a two-phase consensus development process. In phase I, the Expert Panel identified aspects of breast cancer care for which treatment of men and women was likely to be the same, using a survey of content experts from ASCO's Breast Cancer Guideline Advisory Group. The survey asked two questions regarding each management component. First, how strongly do you agree that the approach to care is largely the same for men and women (using a 5-point scale from "strongly agree" to "strongly disagree")? Second, would it be important to address this component of management in a male breast cancer guideline ("yes" v "no")?

Detailed findings of the Breast Cancer Advisory Group survey are presented in the Results section. Briefly, the Breast Cancer Advisory Group reported high-level consensus that the following components of management were largely the same for men and women: (1) use of gene expression profile testing to guide adjuvant treatment decision making (eg, Oncotype DX and prognostic tests), (2) primary surgery, (3) adjuvant chemotherapy, (4) adjuvant radiation therapy, and (5) chemotherapy for advanced/ metastatic disease. For these aspects of management, ASCO recommends that the approach used for men should be the same as the approach used for women.

The Breast Cancer Advisory Group did not identify consensus that treatment of men and women should be the same for five components of management: (1) endocrine therapy in the adjuvant setting, (2) endocrine therapy in the metastatic setting, (3) management of adverse effects from endocrine therapy, (4) germline genetic testing, and (5) survivorship care. These five topics, combined with an additional topic identified by the Expert Panel, became the focus of phase II of the consensus development process, in which a dedicated Expert Panel used the modified Delphi method to develop guideline recommendations.

## **GUIDELINE QUESTIONS**

This clinical practice guideline addresses 10 clinical questions, which were derived from the six components of management described previously: (1) Which adjuvant endocrine therapy should be offered to men with earlystage, hormone receptor-positive breast cancer? (2) What is the optimal duration of adjuvant endocrine treatment of men with early-stage, hormone receptor-positive breast cancer? (3) What is the role of bone-modifying agents in men with early-stage, hormone receptor-positive breast cancer? (4) Which endocrine therapies should be offered to men with advanced or metastatic, hormone receptorpositive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer? (5) What is the role of cyclin-dependent kinase (CDK) inhibitors and mammalian target of rapamycin inhibitors in the treatment of men with advanced or metastatic breast cancer? (6) What is the optimal approach to managing toxicity of endocrine therapy in men with breast cancer? (7) What guidance around follow-up and management should be available to men who have been previously treated for breast cancer? (8) What testing is recommended for the detection of breast cancer after curative-intent primary therapy for patients who are not germline mutation carriers of breast cancer susceptibility genes? (9) How should post-treatment surveillance recommendations differ for men with breast cancer who carry predisposing germline mutations in breast cancer susceptibility genes? (10) Should referral for genetic counseling and genetic testing for germline mutations be recommended for newly diagnosed male patients with breast cancer?

## **METHODS**

#### **Guideline Development Process**

This systematic review–based, formal consensus guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise.

The Expert Panel met in person and via teleconference and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of two weeks allowing the public to review and comment on the recommendations after they submitted a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to Journal of Clinical Oncology for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed based on a systematic review of the literature and clinical experience. The literature review involved a search of PubMed for the period of January 1, 1998, through September 20, 2019. The search string was adopted from the literature search that informed the National Cancer Institute's Physician Data Query cancer information summary about male breast cancer treatment. The search was broad and included clinical trials; systematic reviews and meta-analyses; casecontrol studies; case series; cohort studies; and a wide range of outcomes including survival, toxicity, and patientreported outcomes. Genetic mutation and "BRCA" search terms were also included.

Articles from the search were included if they reported data on outcomes of endocrine therapy in men with breast cancer; on the prevalence and/or management of endocrine therapy adverse effects in men treated for breast cancer; on clinical, pathologic, or prognostic features of breast cancer in men; on the risk of subsequent cancers among men diagnosed with a first primary breast cancer; or on the frequency of germline genetic mutations in men with breast cancer. Reports of case series were included if the series included  $\geq$  20 patients treated in the adjuvant setting or  $\geq$  10 patients treated in the metastatic setting. Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peerreviewed journals; (2) single case studies; (3) editorials, commentaries, letters, news articles, narrative reviews; or (4) published in a non-English language. A guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice.

Because of the limited evidence available for most of the clinical questions, recommendations were developed using the ASCO modified Delphi formal consensus methodology.<sup>3</sup> This process involved the drafting of recommendations by

a subgroup of the Expert Panel using clinical expertise and the available evidence. The Expert Panel (n = 13) met in person to review and refine the recommendations. The Expert Panel was then supplemented by additional experts (n = 21), who were recruited to rate their agreement with the recommendations. The entire membership of 34 experts is referred to as the Consensus Panel. Each recommendation had to be agreed to by at least 75% of Consensus Panel respondents to be accepted. Ratings for the type and strength of recommendation and quality of evidence are provided with each recommendation. A "strong" rating was assigned when the observed consensus agreement was between 90% and 100%; otherwise, a "moderate" rating was assigned. This methodology is described in further detail elsewhere (www.asco.org/ guideline-methodology).

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

## **Guideline Disclaimer**

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## **Guideline and Conflicts of Interest**

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

# RESULTS

## Results of Breast Cancer Guidelines Advisory Group Survey

The goal of the ASCO Breast Cancer Guidelines Advisory Group Survey was to distinguish between components of management for which there was widespread consensus that the approach for men and women was largely the same versus those for which widespread consensus did not exist. with the intention that the Guideline Panel would focus its work on the latter topics. Using data from the survey of the ASCO Breast Cancer Guidelines Advisory Group, the Expert Panel used the following thresholds to identify components of management for which there was not widespread agreement: (1) at least 25% of respondents disagreed with the statement that the management of men and women with breast cancer was largely the same, and (2) at least 25% of respondents reported that addressing the component of management in the male breast cancer guideline was important (Table 1).

The survey asked respondents to comment on 14 components of management. The Breast Cancer Guideline Advisory Group reported high-level consensus that five components of management were largely the same for men and women: (1) use of gene expression profile testing to guide adjuvant treatment decision making (eg, Oncotype DX and prognostic tests),<sup>4</sup> (2) primary surgery, (3) adjuvant chemotherapy, (4) adjuvant radiation therapy, and (5) chemotherapy for advanced/metastatic disease. Consequently, these components of care were not further

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**TABLE 1.** Survey of ASCO Breast Cancer Guidelines Advisory Group Members to Identify Areas of Pre-Existing Consensus and Refine Topics to be Addressed

 by the Expert Panel

	-	Guideline to Address this Topic (%)
High-level agreement		
Gene expression profile testing (eg, Oncotype DX, MammaPrint)	100	NR
Adjuvant chemotherapy	91	58
Chemotherapy for advanced/metastatic disease	91	42
Adjuvant radiation therapy	84	42
Primary surgery	75	58
Lower-level agreement and high-level importance		
Hormone therapy for advanced/metastatic disease	45	83
Post-treatment surveillance	42	67
Adjuvant hormone therapy	27	100
Management of adverse effects from endocrine therapy	25	75
Genetic testing	0	100
Lower-level agreement and lower-level importance		
Neoadjuvant chemotherapy	50	NR
Psychosocial support	24	58
Neoadjuvant hormone therapy	8	NR
Breast reconstruction	8	8

NOTE. Bold highlights aspects of breast cancer management on which the Expert Panel focused. Abbreviation: NR, not reported due to low response rate in the survey.

addressed by the Expert Panel. The Breast Cancer Guideline Advisory Group reported a lack of consensus with and a high degree of importance to address five components of management: (1) endocrine therapy in the adjuvant setting, (2) endocrine therapy in the metastatic setting, (3) management of adverse effects from endocrine therapy, (4) germline genetic testing, and (5) survivorship care. These components formed the foundation of the Expert Panel's work.

The Breast Cancer Guideline Advisory Group and Expert Panel identified four components of management rated as having a low level of importance for inclusion in the male breast cancer guideline: (1) neoadjuvant chemotherapy, (2) neoadjuvant endocrine therapy, (3) breast reconstruction, and (4) psychosocial support. These components were not addressed in the guideline. Last, the Expert Panel elected to address the use of targeted chemotherapy for advanced/metastatic disease. While the Guideline Advisory Group reported a high level of consensus that chemotherapy use was substantially similar for men and women, the Expert Panel judged that the relative novelty and high cost associated with targeted treatments warranted their inclusion.

## Literature Review Results

A total of 26 descriptive reports or observational studies met the eligibility criteria and form the evidentiary basis for the guideline recommendations. The studies included in the review are summarized in the Data Supplement Tables 1-5 (online only). Twelve studies addressed endocrine treatment in men with breast cancer<sup>5-16</sup>; four addressed the prevalence and/or management of endocrine therapy adverse effects<sup>17-20</sup>; six reported on clinical, pathologic, and prognostic features of breast cancer in men<sup>21-26</sup>; two addressed the risk of second breast cancers in men<sup>27,28</sup>; and two addressed the frequency of germline pathogenic and likely pathogenic variants (ie, mutations) in hereditary cancer predisposition genes, such as *BRCA1* and *BRCA2*, in men with breast cancer.<sup>29,30</sup>

# **Results of the Formal Consensus Development Process**

As mentioned, because of the limitations of the available evidence, the guideline relied on a formal consensus development process to generate practice recommendations. During an in-person meeting, the Expert Panel drafted 19 recommendations pertaining to 10 clinical questions. Then, the full Consensus Panel conducted two rounds of voting. During the first round, agreement with the individual recommendations ranged from 50% to 100% (N = 34 respondents).

Only two of the 19 recommendations did not reach the required 75% agreement threshold, and another two achieved a marginal level of agreement at 75%. All four of these recommendations were revised based on comments from the Consensus Panel's first round of voting. These four revised recommendations underwent a second round of voting with the full Consensus Panel. A recommendation pertaining to genetic counseling and testing had in-advertently been omitted from round 1 of voting, so it was reviewed with the four revised guideline recommendations in round 2.

Agreement with the recommendations in round 2 ranged from 58.07% to 96.77% (n= 31 respondents). Results for each of the recommendations and each round of voting are provided in the Data Supplement. Two recommendations did not exceed the required 75% threshold: (1) contralateral annual mammography and (2) chemoprevention. Consequently, these two recommendations were excluded from the practice recommendations that follow, although the topics are addressed in the Discussion.

#### FORMAL CONSENSUS RECOMMENDATIONS

#### **CLINICAL QUESTION 1**

Which adjuvant endocrine therapy should be offered to men with early-stage, hormone receptor-positive breast cancer?

## Recommendation 1.1

Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

## Recommendation 1.2

Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy but have a contraindication to tamoxifen may be offered gonadotropinreleasing hormone (GnRH) agonist/antagonist and an aromatase inhibitor (AI; Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

*Literature review and analysis.* Most male breast cancers are hormone receptor positive; about 99% are estrogen receptor positive and about 81% are progesterone receptor positive.<sup>26</sup> Adjuvant endocrine therapy is thus the mainstay of systemic treatment in men with early-stage breast cancer. Tamoxifen is the preferred adjuvant endocrine therapy based on observational studies that have suggested a survival benefit.<sup>12,24,25</sup>

Data on the use of AIs in the treatment of men with earlystage breast cancer are sparse. Population-based series comparing AI and tamoxifen have reported inferior survival among men with breast cancer who were treated with an AI.<sup>9,10,24</sup> For this reason, treatment of men with an AI alone is generally not preferred. However, use of an AI in combination with a GnRH analog is an acceptable alternative, especially for men who have a contraindication to tamoxifen (eg, a history of thrombosis).<sup>17</sup> Adding the GnRH analog may help overcome the lack of complete estradiol suppression sometimes seen in men treated with an AI alone.<sup>2</sup> Some have argued in favor of using an AI alone in selected patients, such as those who are unlikely to tolerate combined therapy, although concerns about the efficacy of this approach persist.

## **CLINICAL QUESTION 2**

What is the optimal duration of adjuvant endocrine treatment of men with early-stage, hormone receptor–positive breast cancer?

## Recommendation 2.1

Men who are treated with adjuvant endocrine therapy should be treated for an initial duration of five years (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

## **Recommendation 2.2**

Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence based on considerations of recurrence risk using established prognostic factors (eg, nodal status, tumor size and grade)<sup>31</sup> may be offered an additional five years of tamoxifen therapy (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

*Literature review and analysis.* There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the duration of adjuvant endocrine therapy. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of male breast cancer and extrapolation from studies conducted in women with early-stage breast cancer.<sup>31,32</sup> Of note, tamoxifen use in men with breast cancer can be associated with treatment-limiting adverse effects,<sup>33</sup> which can lead to low adherence, treatment discontinuation,<sup>18</sup> and a greater risk of recurrence and death.<sup>20</sup> Additional research on the effects of long-term tamoxifen use in men with breast cancer is warranted.

# CLINICAL QUESTION 3

What is the role of bone-modifying agents in preventing recurrence in men with early-stage, hormone receptor-positive breast cancer?

## Recommendation 3

Men with early-stage breast cancer should not be treated with bone-modifying agents to prevent recurrence but could still receive these agents to prevent or treat osteoporosis . (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the use of bone-modifying agents to prevent breast cancer recurrence. The Expert Panel based its recommendation on the following considerations: (1) studies of bone-modifying agents among women have demonstrated somewhat inconsistent findings; (2) there is as yet no Food and Drug Administration (FDA) indication for bone-modifying agents among women in this clinical setting; (3) the benefit of bone-modifying agents in women appears to be most prominent among those who are postmenopausal and receiving Als<sup>34</sup>; and (4) most men receive tamoxifen. This recommendation represents the best clinical opinion of the Expert Panel based on personal experience in the management of male breast cancer and extrapolation from studies in women. Preservation of bone health remains a long-term clinical challenge in patients with breast cancer. Additional research is needed to establish any potential benefits before recommending the use of bone-modifying agents to prevent the recurrence of early breast cancer.

# **CLINICAL QUESTION 4**

Which endocrine therapies should be offered to men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer?

#### Recommendation 4.1

Men with advanced or metastatic, hormone receptorpositive, HER2-negative breast cancer should be offered endocrine therapy as first-line therapy except in cases of visceral crisis or rapidly progressive disease. Options include tamoxifen, an AI with a GnRH agent, and fulvestrant. CDK 4/6 inhibitors can be used in men as they are used in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

#### **Recommendation 4.2**

Men who develop recurrent metastatic, hormone receptorpositive, HER2-negative breast cancer while receiving adjuvant endocrine therapy should be offered an alternative endocrine therapy except in cases of visceral crisis or rapidly progressive disease (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

#### **Recommendation 4.3**

Endocrine therapy for men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer may be sequenced as in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

*Literature review and analysis.* Metastatic breast cancer in men is treated with the same endocrine therapies used to treat metastatic breast cancer in women. Endocrine treatment options include tamoxifen, an AI with a GnRH agent, and fulvestrant. There is no evidence from clinical trials in men with advanced or metastatic breast cancer to

inform clinical questions regarding the optimal sequencing of endocrine therapies. In general, the Expert Panel recommends using the therapies in the order listed above. The recommendations offered here reflect the best clinical opinion of the Expert Panel members based on their personal clinical experience managing male breast cancer, and based on extrapolation from studies of endocrine therapy conducted in women with advanced breast cancer.<sup>35</sup> As with women, men experiencing visceral crisis and/ or rapidly progressive disease should consider chemotherapy as an initial treatment option.

Available data from case reports and small case series do not support strong conclusions about the use of monotherapy versus combination endocrine therapy in men with metastatic breast cancer, but some studies<sup>7,8</sup> have reported greater responses when an AI is combined with a GnRH analog. Based on this information, the Expert Panel suggests combining AIs with GnRH analogs but acknowledges that single-agent AIs may be reasonable for patients unlikely to tolerate combined therapy who have unmeasurable estrogen levels. A pooled analysis of case reports and case series conducted by Zagouri et al<sup>15</sup> suggests a promising role for fulvestrant.

Among women with hormone receptor–positive metastatic breast cancer, endocrine therapy is often combined with CDK inhibitor therapy, because multiple studies have demonstrated that this treatment increases the response rate and prolongs progression-free survival.<sup>36,37</sup> Data regarding the benefits and adverse effects of CDK4/6 inhibitors in men with metastatic breast cancer are sparse, but selected trials of these targeted agents have included men and small case series have been reported. Consequently, the FDA granted approval for the use of one CDK4/ 6 inhibitor in men with metastatic hormone receptor– positive breast cancer (https://www.ascopost.com/News/ 59909). The Expert Panel suggests that it would be reasonable to use CDK4/6 inhibitors in men as they are used in women.

#### **CLINICAL QUESTION 5**

What is the role of targeted therapy in the treatment of men with advanced or metastatic breast cancer? Note that "targeted therapy" refers to treatments that target HER2-positive tumors, PD-L1–positive tumors, and patients carrying pathogenic germline *BRCA 1/2* mutations; endocrine therapies are addressed elsewhere in the guideline.

#### Recommendation 5

Targeted therapy guided by hormone receptor (HR), HER2, programmed death ligand 1 (PDL-1), PIK3CA, and germline *BRCA* mutation status may be used in the treatment of advanced or metastatic male breast cancer using the same indications and combinations that are offered to women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong). (Targeted

therapy based on hormone receptor status is addressed in Recommendations 4.1 to 4.3.)

*Literature review and analysis.* There is no evidence from randomized clinical trials in men with breast cancer to inform clinical questions regarding the use of targeted systemic therapy in combination with endocrine therapy in the treatment of advanced or metastatic male breast cancer. Other targeted nonendocrine therapies have recently been approved (eg, alpelisib), and the Panel believes they are likely to be similarly effective in men as in women. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of male breast cancer and extrapolation from studies conducted in women.<sup>38-41</sup>

# **CLINICAL QUESTION 6**

What is the optimal approach to managing the toxicity of endocrine therapy in men with breast cancer?

# **Recommendation 6.1**

Management of endocrine therapy toxicity is similar to the approach used for women (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

## Recommendation 6.2

Testosterone/androgen supplementation should not be used by men with breast cancer (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

*Literature review and analysis.* There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the optimal management of endocrine therapy toxicity in men. The recommendations offered represent the best clinical opinion of the Expert Panel members based on personal experience in the management of male breast cancer, and, for management of adverse effects such as hot flashes that are commonly experienced by both men and women being treated for breast cancer, based on extrapolation from studies of women and a study of men being treated for prostate cancer.<sup>42</sup>

The systematic review conducted for this consensus guideline identified four studies that addressed the prevalence and/or management of endocrine therapy adverse effects.<sup>17-20</sup> These studies found an increased incidence of thrombotic events in men treated with tamoxifen. more than 80% of which occurred in the first 18 months after the start of treatment<sup>17</sup>; a high rate of treatment discontinuation due to adverse effects (eg, hot flashes, weight gain, sexual dysfunction) among men with breast cancer who received tamoxifen<sup>18</sup>; a substantial prevalence of sexual dysfunction and hormonal symptoms among male breast cancer survivors<sup>19</sup>; and a greater risk of cancer recurrence and death among men with breast cancer who were less adherent to tamoxifen treatment.<sup>20</sup> With respect to the management of hot flashes in men, venlafaxine has been shown to be an effective treatment of hot flashes in men with prostate cancer who were receiving GnRH analogs.<sup>42</sup> This drug may

be effective in reducing hot flashes in men with breast cancer treated with tamoxifen or GnRH analogs. With respect to testosterone, its conversion to estrogen by aromatase raises concern about its use among men with hormone receptor–positive breast cancer. Use of exogenous testosterone for hypogonadism among men with a history of hormone receptor–positive breast cancer should follow an informed discussion about the potential benefits and risks of this treatment, considering the patient's residual risk of breast cancer recurrence.

#### **CLINICAL QUESTION 7**

What guidance around follow-up and management should be available to men who have been previously treated for breast cancer?

#### Recommendation 7

Physicians should counsel patients about the symptoms of recurrence, including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches. The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for patients with breast cancer is recommended and should be performed by a physician experienced in the surveillance of patients with cancer and in breast examination, including the examination of irradiated breasts<sup>43</sup> (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. Recommendation 7 is adapted from the guideline for women: "Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update."43 There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the optimal post-treatment surveillance and management after primary treatment. The recommendations offered represent the best clinical opinion of the Expert Panel members based on personal experience in the management of male breast cancer. Follow-up care for men who are treated for breast cancer should generally be similar to care provided for women with breast cancer. As noted previously, there is no clear role for the use of bone-modifying agents to prevent recurrence in men with breast cancer. However, men who are receiving a GnRH analog and an AI are at increased risk of bone loss; thus, monitoring bone mineral density in this group is warranted.44

#### **CLINICAL QUESTION 8**

What testing is recommended for the detection of breast cancer after curative-intent primary therapy for patients who are not germline mutation carriers of breast cancer susceptibility genes?

#### **Recommendation 8**

Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy, if technically feasible, regardless of genetic predisposition (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

*Literature review and analysis.* There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the usefulness or necessity of ipsilateral mammography in men with a history of breast cancer that was treated with lumpectomy. The recommendation offered represents the best clinical opinion of the Expert Panel members based on personal experience in the management of male breast cancer. Use of contralateral annual mammography for men with a history of breast cancer is discussed in the section Draft Recommendations That Did Not Reach the Required 75% Consensus Threshold, because the Expert Panel did not reach consensus on this topic.

## **CLINICAL QUESTION 9**

How should post-treatment surveillance recommendations differ for men with breast cancer who carry predisposing germline mutations in breast cancer susceptibility genes?

#### **Recommendation 9.1**

Contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

#### **Recommendation 9.2**

Breast magnetic resonance imaging is not recommended routinely in men with a history of breast cancer (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

*Literature review and analysis.* Among men carrying *BRCA1* and *BRCA2* mutations, the cumulative risk of breast cancer by age 70 years was 1.2% and 6.8%, respectively.<sup>45</sup> These values are lower than the risks experienced by women carrying *BRCA1* and *BRCA2* mutations but are still substantially elevated over the average man's risk. Consequently, the Expert Panel recommended that contralateral mammography may be offered. The recommendation against routine breast magnetic resonance imaging was based in part on (1) the relatively small amount of breast tissue present in most men, (2) the lack of data demonstrating an improvement in survival for this screening test among women, and (3) the potential for false positives.

#### **CLINICAL QUESTION 10**

Should referral for genetic counseling and genetic testing for germline mutations be recommended for male patients with breast cancer?

#### **Recommendation 10**

Male patients with breast cancer should be offered genetic counseling and genetic testing for germline mutations

(Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

Literature review and analysis. Previous population-based studies have found that 0% to 4% of men with breast cancer have mutations of the BRCA1 gene, and 4% to 16% have mutations of the BRCA2 gene.<sup>46-48</sup> In contrast, mutations of the BRCA1 and BRCA2 tumor-suppressor genes have been identified in 5% to 10% of women with breast cancer.<sup>49</sup> Mutations in other genes, such as CHEK2, PALB2, and PTEN, are less common but also appear to confer elevated breast cancer risk among men.<sup>50-52</sup> When considering all these genes, > 20% of male patients with breast cancer may carry an identifiable inherited risk factor for breast cancer. Consequently, the Expert Panel recommends genetic counseling and consideration of genetic testing for all male patients with breast cancer. Identification of an inherited risk factor could (1) influence screening recommendations for other types of cancer, (2) lead to testing of family members for inherited risk factors, and (3) identify treatment opportunities for patients with metastatic breast cancer (eg, poly-ADP ribose polymerase inhibitors).<sup>39,40</sup>

## DRAFT RECOMMENDATIONS THAT DID NOT REACH THE REQUIRED 75% CONSENSUS THRESHOLD

Two draft recommendations did not exceed the 75% consensus agreement threshold required for adoption into the formal guideline statement: (1) contralateral annual mammography in men without a predisposing genetic mutation and (2) chemoprevention. In accordance with the modified Delphi approach used by ASCO,<sup>3</sup> the Expert Panel could not issue formal consensus recommendations for these clinical questions. Regarding the draft recommendation pertaining to the routine use of contralateral annual mammography, panel members and reviewers expressed mixed views. The discussion centered around the perceived incidence of contralateral second primary breast cancer relative to the perceived burden of mammography. Prior studies have suggested that the lifetime risk of a second primary breast cancer among men is approximately 2%.<sup>27,53</sup> While this is higher than the risk of breast cancer among the general population of men, it is lower than the risk of breast cancer among the general population of women. Gao et al<sup>54</sup> reported a similar cancer detection rate when screening high-risk men and average-risk women, but the population of screened men was likely not representative of all men with a history of breast cancer, and the study was a single-institution retrospective study from a tertiary-care academic medical center. In addition, the study did not evaluate the impact of screening on survival, so the benefit of such screening remains uncertain.

Regarding the draft recommendation for the use of chemoprevention in men with (1) noninvasive breast cancer, (2) invasive breast cancer for whom adjuvant therapy is not otherwise indicated, and (3) no history of breast cancer who have a germline pathogenic or likely pathogenic variant (mutation) in a *BRCA 1/2* gene, the level of agreement was 74%. Comments from the Consensus Panel suggested that the wording of the draft guideline was confusing and that consensus regarding the use of chemoprevention in this setting did not exist.

## SUMMARY AND DIRECTIONS FOR FUTURE RESEARCH

This formal consensus ASCO guideline provides practice recommendations on a range of aspects related to the management of male breast cancer, including endocrine therapy, targeted therapy, genetic testing, management of treatment-related adverse effects, and post-treatment surveillance. A multidisciplinary Consensus Panel, composed of 13 members from an ASCO Expert Panel and an additional 21 content experts, rated its agreement with a series of 18 recommendations. Most of the draft guide-lines were endorsed by the Consensus Panel during the first round of voting. Only four draft guidelines were reviewed during the second round of voting, and of these, only two did not reach or exceed the a priori–defined 75% agreement threshold.

To date, recommendations for the treatment of male breast cancer have been extrapolated from the results of clinical trials that enrolled only women,<sup>2,55</sup> from small case series, or from personal clinical experience in treating men with breast cancer.<sup>56</sup> This ASCO formal consensus guideline is no exception. Clearly, additional research is needed on a broad array of topics concerning the management of male breast cancer,<sup>57</sup> even those for which agreement on the treatment approach was high. Fortunately, several current treatment trials are enrolling both women and men, after many years of encouragement from both patient organizations (see https://malebreastcancercoalition.org) and the International Male Breast Cancer Program. In that regard, the FDA recently issued draft guidance for industry encouraging the inclusion of men in clinical trials studying treatments for breast cancer. The FDA recommended that, "when males have not been included...in clinical trials for a specific breast cancer drug: it may be possible to extrapolate findings to include patients with the FDAapproved indication for the drug where no difference in efficacy or safety is anticipated between males and females based on the mechanism of action of a drug" (https:// www.fda.gov/regulatory-information/search-fda-guidancedocuments/male-breast-cancer-developing-drugs-treatment). Concern for differential efficacy in males versus females is greatest with endocrine therapies, making the inclusion of men in clinical trials of endocrine treatments particularly important.

## PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patientclinician communication, see the ASCO Consensus Guideline on Patient-Clinician Communication.<sup>58</sup> This ASCO guideline offers a series of recommendations on core skills and tasks to improve communication and suggests a number of concrete implementation strategies. One recommendation that is particularly relevant to clinical encounters with male patients with breast cancer is the need for clinicians to "Remain aware that members of...marginalized populations have an increased likelihood of having had negative past health care experiences, including feeling...alienated...."<sup>58(p3628)</sup>

The literature on male breast cancer survivorship is sparse<sup>59-64</sup>; however, several qualitative studies have suggested that feelings of emasculation associated with having a "woman's disease,"65 sexual stigmatization, and ignorance of the disease<sup>65</sup> are common among men with breast cancer.<sup>60,63</sup> The lack of male-specific educational information<sup>59</sup> and limited opportunities for men with breast cancer to talk with other men with breast cancer likely contribute to their sense of isolation and cancer-related distress.<sup>62</sup> Fortunately, some of these problems can be ameliorated in relatively straightforward ways. Brain et al<sup>59</sup> and Williams et al<sup>62</sup> have suggested several practical solutions: (1) inclusion of booklets or leaflets on male breast cancer to improve information and awareness, (2) providing male patients a photograph of a male mastectomy to show men what they will look like after the surgery, (3) telephone help-lines and referrals to other sources of support, and (4) efforts to increase public awareness of male breast cancer.

#### **HEALTH DISPARITIES**

ASCO clinical practice guidelines represent expert recommendations for best practices in disease management. However, it is important to note that many patients have limited access to medical care, and that racial and ethnic disparities contribute significantly to this problem in the United States and around the world. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from inferior outcomes, experience more obstacles to receiving optimal care, are more likely to be uninsured or underinsured, and are at greater risk of receiving care of poor quality. Geographic location (ie, a long distance from appropriate treatment facilities) may also impair access to optimal care. Most of the studies that have identified disparities in the care provided to and outcomes experienced by patients with breast cancer have focused on women.

The electronic literature search conducted to inform this section of the male breast cancer guideline identified eight articles (from a total of 88 abstracts) on the topic of health disparities. Studies of disparities among male patients with breast cancer have yielded inconsistent results.<sup>66-68</sup> However, the small sample sizes and inherent selection bias associated with these observational studies of patients with male breast cancer are substantial limitations for these studies. The Expert Panel believes that disparities are just

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as likely to occur in men as in women, and therefore recommends: (1) awareness of the disparities and barriers to accessing care when considering this clinical practice guideline, and (2) that health care providers should strive to deliver the highest level of cancer care to all populations, including those that are more vulnerable. The Expert Panel also notes that transgender individuals have not been evaluated in most prior studies of breast cancer disparities and believes that these individuals may also be at risk of experiencing disparities. Recent studies have begun to explore the risk of developing breast cancer among trans women and trans men.<sup>69</sup> The Expert Panel believes that the treatment of breast cancer should be the same for transgender women, with the notable exception that exogenous estrogen is not recommended for patients with a history of breast cancer.

#### **MULTIPLE CHRONIC CONDITIONS**

Creating evidence-based recommendations to inform the oncology care of patients with multiple chronic conditions (MCCs)—where patients have two or more serious noncancer conditions—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all the possible permutations and to develop specific recommendations for cancer care. In addition, the best available evidence for treating cancer often comes from clinical trials that exclude patients with MCCs. This is done to avoid potential interaction effects and confounding of results, but it limits the ability to generalize outcomes data from these studies to patients with MCCs and constrains expert groups' efforts to make recommendations for this heterogeneous patient population. The Expert Panel believes that any treatment plan should consider the complexity and uncertainty created by the presence of MCCs and highlights the importance of shared decision making that incorporates the goals of the patient as well as the input of the specialists treating the patient's other chronic conditions. The need for clinicians to consider all relevant chronic conditions when formulating a treatment and follow-up plan for a new breast cancer diagnosis is the same whether the patient is male or female. That having been said, the Expert Panel believes it is important to note that the average age of a new breast cancer diagnosis is five years older for men (67 years) than for women (62 years). Consequently, clinicians should expect a higher comorbidity burden due to age among men with breast cancer.

# **COST IMPLICATIONS**

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance. Higher patient out-of-pocket costs are a barrier to initiating and adhering to recommended cancer treatments. Discussion of cost can be an important part of shared decision making. Clinicians should discuss with patients the use of less expensive alternatives Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary among different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.

Providers treating male patients with breast cancer should be aware that men could be at greater risk of being denied coverage for some expensive breast cancer treatments, because coverage determinations focused only on women, and appeals of coverage denials may be more common.

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are costeffectiveness analyses that lack contemporary cost data; agents that are not currently available in either the United States or Canada; and/or studies that are industry sponsored. No cost-effectiveness analyses were identified to inform the topic.

## EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from September 3, 2019, through September 17, 2019. Response categories of "Agree as written", "Agree with suggested modifications", and "Disagree. See comments" were captured for every proposed recommendation, with 15 written comments received. Respondents either agreed or agreed with slight modifications with 13 of the 16 recommendations; one respondent disagreed with three of the recommendations; another respondent disagreed with a single recommendation. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

#### **GUIDELINE IMPLEMENTATION**

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

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

## **ADDITIONAL RESOURCES**

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources,

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#### **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 is available at www.asco.org/breast-cancer-guidelines. Patient information is available at www.cancer.net.

#### **RELATED ASCO GUIDELINES**

- Patient-Clinician Communication<sup>58</sup> (http:// ascopubs.org/doi/10.1200/JC0.2017.75.2311)
- Prostate Cancer Survivorship Care<sup>70</sup> (https:// ascopubs.org/doi/10.1200/JCO.2014.60.2557)
- Breast Cancer Follow-Up and Management After Primary Treatment<sup>43</sup> (http://ascopubs.org/doi/ 10.1200/JC0.2012.45.9859)
- Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer<sup>38</sup> (http://ascopubs.org/ doi/10.1200/JCO.2018.79.2697)

www.cancer.net, is available at www.asco.org/breast-cancerguidelines.

# 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/JC0.19.03120.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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