Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline

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ABSTRACT

PURPOSE To develop recommendations for germline mutation testing for patients with breast cancer.

METHODS An ASCO–Society of Surgical Oncology (SSO) panel convened to develop recommendations based on a systematic review and formal consensus process.

RESULTS Forty-seven articles met eligibility criteria for the germline mutation testing recommendations; 18 for the genetic counseling recommendations.

RECOMMENDATIONS *BRCA1/2* mutation testing should be offered to all newly diagnosed patients with breast cancer ≤65 years and select patients >65 years based on personal history, family history, ancestry, or eligibility for poly(ADP-ribose) polymerase (PARP) inhibitor therapy. All patients with recurrent breast cancer who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing, regardless of family history. *BRCA1/2* testing should be offered to women who develop a second primary cancer in the ipsilateral or contralateral breast. For patients with prior history of breast cancer and without active disease, testing should be offered to patients diagnosed ≤65 years and selectively in patients diagnosed after 65 years, if it will inform personal and family risk. Testing for high-penetrance cancer susceptibility genes beyond *BRCA1/2* should be offered to those with supportive family histories; testing for moderate-penetrance genes may be offered if necessary to inform personal and family cancer risk. Patients should be provided enough pretest information for informed consent; those with pathogenic variants should receive individualized post-test counseling. Variants of uncertain significance should not impact management, and patients with such variants should be followed for reclassification. Referral to providers experienced in clinical cancer genetics may help facilitate patient selection and interpretation of expanded testing, and provide counseling of individuals without pathogenic germline variants but with significant family history.

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

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

ASCO has a long history of offering guidance on germline genetic testing, beginning in 1996 with its statement on genetic testing for cancer susceptibility.[1] This ASCO statement was updated in 2003[2] and 2010[3] in response to developments in cancer predisposition testing, and again in 2015, to address opportunities and challenges arising from the application of next-generation sequencing to cancer susceptibility testing.[4] In 2014, ASCO also published a statement on the collection and use of a family cancer history.[5]

ASCO, with the Society of Surgical Oncology (SSO), remains attuned to the issues surrounding the appropriate use of germline genetic testing in patients with breast cancer. Until broad multigene panels became more widely available and affordable, testing for germline mutations in breast cancer susceptibility genes was limited to patients with a strong

THE BOTTOM LINE

Germline Testing in Patients with Breast Cancer: ASCO-SSO Guideline

Guideline Question

Which patients with breast cancer should have germline genetic testing for pathogenic variants in cancer susceptibility genes?

Target Population

Patients with breast cancer and their families.

Target Audience

Medical oncologists, radiation oncologists, surgical oncologists, medical geneticists, oncology nurses, patients, caregivers, oncology advanced practice providers, and genetic counselors.

Methods

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

Recommendations

Recommendation 1.1

All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are 65 years or younger at diagnosis should be offered *BRCA1/2* testing (Type: Formal Consensus; Agreement: 87.50%).

Recommendation 1.2

All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are older than age 65 should be offered *BRCA1/2* testing if:

- they are candidates for poly(ADP–ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease,
- they have triple-negative breast cancer,
- their personal or family history suggests the possibility of a pathogenic variant,
- they were assigned male sex at birth,
- they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (Type: Formal Consensus; Agreement: 92.50%).

Recommendation 1.3

Patients undergoing *BRCA1/2* testing should also be offered testing for other cancer predisposition genes as suggested by their personal or family history. Consultation with a provider experienced in clinical cancer genetics can help guide this decision-making and should be made available to patients when possible (Type: Formal Consensus; Agreement: 90%).

Recommendation 2.1

All patients with recurrent breast cancer (local or metastatic) who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing regardless of family history (Type: Formal Consensus; Agreement: 97.50%).

Qualifying statement. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in women with metastatic breast cancer and germline pathogenic variants in *PALB2*.

Recommendation 2.2

BRCA1/2 testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast (Type: Formal Consensus; Agreement: 89.74%).

Recommendation 3.1

All patients with a personal history of breast cancer diagnosed ≤65 years who are without active disease should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment (Type: Formal Consensus; Agreement: 90%).

Recommendation 3.2

All patients with a personal history of breast cancer diagnosed over age 65 with no active disease, who meet one of the following criteria, should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment:

- their personal or family history suggests the possibility of a pathogenic variant,

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- they were assigned male sex at birth,
- they had triple-negative breast cancer,
- they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (Type: Formal Consensus; Agreement: 94.87%)

Recommendation 4.1

Testing for high penetrance genes beyond *BRCA1/2*, including *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients (Type: Formal Consensus; Agreement: 92.31%).

Recommendation 4.2

Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing *BRCA1/2* testing (Type: Formal Consensus; Agreement: 87.50%).

Recommendation 4.3

If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. Consultation with a provider experienced in clinical cancer genetics can be helpful in selecting a specific multi-gene panel or interpreting its results and should be made available to patients when possible (Type: Formal Consensus; Agreement: 91.43%).

Recommendation 5.1

Patients undergoing genetic testing should be given sufficient information before testing to provide informed consent (Type: Formal Consensus; Agreement: 94.87%).

Recommendation 5.2

Patients with pathogenic variants should be provided with individualized post-test genetic counseling and offered referral to a provider experienced in clinical cancer genetics (Type: Formal Consensus; Agreement: 95%).

Recommendation 5.3

Variants of uncertain significance should not alter management. Patients should be made aware that variants of uncertain significance may be reclassified as being pathogenic, and they should understand that periodic follow up is necessary. Consultation with a provider experienced in clinical cancer genetics can be helpful and should be made available to patients when possible (Type: Formal Consensus; Agreement: 88.57%).

Recommendation 5.4

Patients without a pathogenic variant on genetic testing may still benefit from counseling, if there is a significant family history of cancer, and referral to a provider experienced in clinical cancer genetics is recommended (Type: Formal Consensus; Agreement: 90%).

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. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

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

family history of cancer or other high-risk factors such as young age at the time of a breast cancer diagnosis.[6] In other words, whether germline testing for pathogenic variants (PVs) was performed depended in large part on the likely prevalence of the PV in the population of interest.[6] This testing involved a relatively small number of genes known to have strong associations with breast cancer such as *BRCA1* and *BRCA2* (*BRCA1/2*), *PALB2*, *PTEN*, *TP53*, *STK11*, and *CDH1*.[7] The breast cancer risk is lower for other genes such as *ATM*, *CHEK2*, *BARD1*, *NF*, *RAD51C*, and *RAD51D*, and incorporation of testing for these genes has been a more recent development.

The advent of next-generation sequencing and multigene panel testing has changed the landscape of germline mutation testing with valuable implications for both prevention (particularly surgical) and treatment. For patients with germline

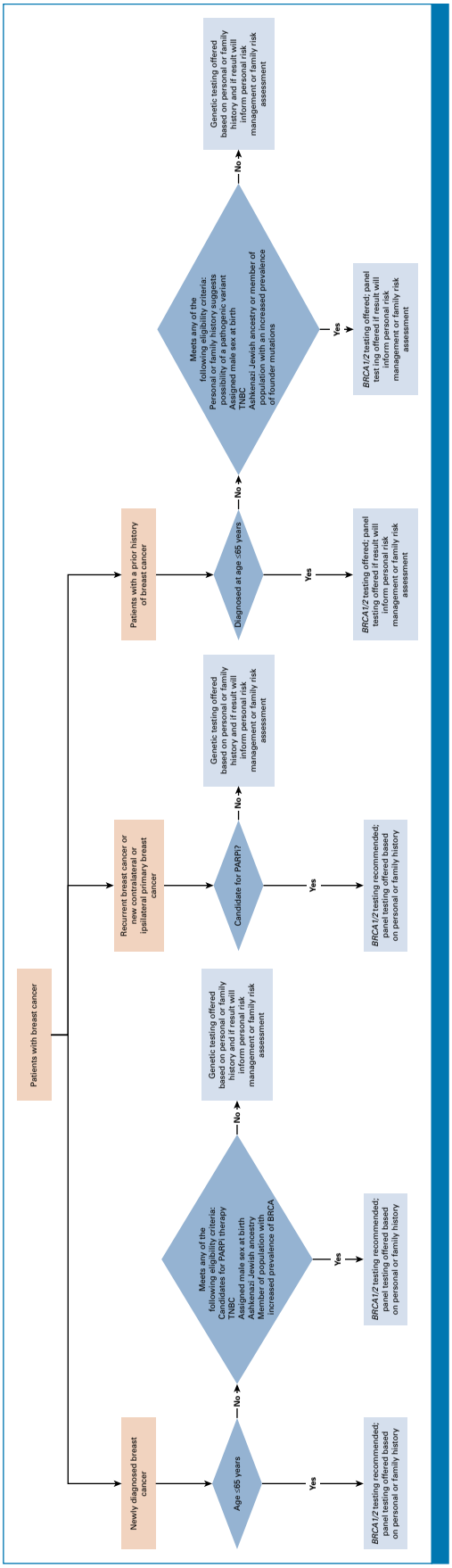

FIG 1. Algorithm for Germline Testing in Patients with Breast Cancer Abbreviations. PARPi, poly(ADP-ribose) polymerase inhibitors; TNBC, triple-negative breast cancer.

BRCA1/2 pathogenic or likely PVs, olaparib and talazoparib have become established as standards of care in both early-stage and metastatic breast cancer.[8] Similarly, in patients with germline *PALB2* PVs, one small, phase II study has suggested that olaparib is highly active in the metastatic setting.[9] However, the advent of expanded testing also presents challenges as the ease with which genes can be sequenced has outpaced the understanding of the clinical implications of the germline findings. For many genes other than *BRCA1/2*, there is less information about the normal range of genetic variation, which leads to the identification of a large number of variants of unknown significance, particularly in patients of non-European ancestry. The inclusion of moderate-risk genes such as *ATM* and *CHEK2* in panel testing, for instance, has led to more patients with cancer being found to have PVs of uncertain clinical consequence; and the management implications for unaffected family members who are found to share these moderate-penetrance PVs are also less clear than for high-penetrance genes.[10] Thus, many oncology professionals may not feel well equipped to provide guidance on the rapidly expanding breadth of testing and/or the nuances of the data associated with cancer risk to inform patients accordingly.[11]

Although the rapid expansion of genetic testing and the complexities of test interpretation have increased the imperative for appropriate patient education, the traditional pre- and post-test counseling model clearly is not sustainable, given the substantial number of patients that will qualify for testing and the shortage in genetics counselors nationally. Other health care providers are going to be increasingly asked to order genetic testing panels and it is thus more important than ever that they understand which tests to send and when. There is a paucity of consistent guidance for clinicians on whom to test and/or which genes to include in germline genetic testing panels for PVs. This ASCO-SSO clinical practice guideline provides clinicians and other health care practitioners, nurses and social workers, patients, genetic counselors, and caregivers with formal consensus-based recommendations regarding the role of germline mutation testing in patients with breast cancer based on the best available evidence (Fig 1).

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions:

1. Should clinicians offer *BRCA1/2* testing to all patients with newly diagnosed breast cancer?
2. Should all people with recurrent disease, local or metastatic, or with second breast primary, be offered *BRCA1/2* testing?
3. Should people with a personal history of breast cancer (and no active disease) be offered *BRCA1/2* testing?
4. What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than *BRCA1/2*?
5. How should patients with breast cancer considering genetic testing be counseled?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary, joint ASCO-SSO Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The Expert Panel met via web conference and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to provide ongoing input on the quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met routinely with the expert panel co-chairs and corresponded with the panel via e-mail to coordinate the process to completion. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. 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 the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee (EBMC) before publication. All funding for the administration of the project was provided by ASCO. The joint guideline manuscript was reviewed by SSO's Breast Cancer Disease Site Work Group and approved by the SSO Quality Committee and Executive Committee.

The recommendations were developed by using a systematic review of the literature, expert consensus, and clinical experience. The literature review involved searches of PubMed for the period from September 20, 2012, through January 12, 2023. The mutation testing searches were broad and included a combination of treatment, genetic mutation, and breast cancer search terms (see the Data Supplement, Supplement 1 [online only] for more details of the literature searches). A targeted search was conducted to address the question of whether people with local recurrence, contralateral breast cancer, or metastatic disease should be offered *BRCA1/2* testing. Finally, two broad searches of PubMed spanning the period from February 7, 2018, to February 7, 2023, were conducted to inform the cancer genetic counseling–related clinical questions addressed in the guideline. These two searches were limited to practice guidelines, policy statements, and frameworks for communication regarding (1) informed decision-making around genetic testing, and (2) patient counseling and education concerning variants of uncertain significance (VUS). The VUS search excluded articles that addressed only the prevalence of VUS or the prevalence of variant reclassification, as well as articles on the clinical management of individuals with VUS. Each of the electronic searches was supplemented by articles identified

by Expert Panel members and by reviews of the bibliographies of relevant articles.

Articles from the mutation testing search were included if they reported data on the prevalence of pathogenic variants and/or the risk of breast cancer conferred by these pathogenic variants. An article was excluded from the literature search if (1) it reported on a single case; (2) it reported on a study with a variant that was not pathogenic or likely pathogenic (eg, single nucleotide polymorphisms, or variant overexpression in the tumor); (3) it was a meeting abstract not subsequently published in a peer-reviewed journal; or (4) it was reported in a non–English-language journal.

Because of the limited high-quality evidence available to inform the clinical questions, recommendations were developed using the ASCO-modified Delphi formal consensus methodology.[12] This process involved the drafting of recommendations by a subgroup of the joint ASCO-SSO Expert Panel using clinical expertise and the available evidence. The Expert Panel (N = 18) met via web conference to review and refine the recommendations. The Expert Panel was then supplemented by additional experts (n = 22), who were recruited to rate their agreement with the recommendations. The entire membership of 40 experts is referred to as the Consensus Panel (Appendix Table A2). Each recommendation had to be agreed to by at least 75% of the Consensus Panel respondents to be accepted. This methodology is described in further detail elsewhere (www.asco.org/guideline-methodology).

A guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type of recommendation and percent agreement are provided for each recommendation. The ASCO Expert Panel and guidelines staff will work with the Expert Panel 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

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 herein 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 specify the level of 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" indicates 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 does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, expressed 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/guideline-methodology). 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

A total of 47 articles satisfied the inclusion criteria for the germline mutation testing–related recommendations (Recommendations 1.1 through 4.3) and these articles, in combination with expert opinion, form the evidence base for the corresponding guideline recommendations. The two broad searches conducted to inform the recommendations pertaining to how patients with breast cancer considering genetic testing should be counseled (Recommendations 5.1 through 5.4) yielded 10 and eight articles, respectively. The

latter search results reflect a representative, not exhaustive set of articles on the key elements of cancer genetic counseling and informed consent, and on patient counseling and education concerning VUS.

As mentioned, because of the limitations of the available evidence, the guideline relied on a formal consensus development process to generate practice recommendations. The Expert Panel drafted guideline recommendations during a web conference. Then, the full Consensus Panel conducted three rounds of voting (Data Supplement, Supplement 3). During the first round, agreement with the individual recommendations ranged from 70.00% to 97.50%, with an average agreement rating of 87.78%. The number of respondents across recommendations ranged from 39 to 40 of the 40 Consensus Panel members.

Only two of the 19 recommendations did not reach the required 75% agreement threshold in round 1. These two recommendations were revised based on comments from the Consensus Panel's first round of voting and the revised recommendations underwent a second round of voting with the full Consensus Panel. Agreement with the recommendations in round 2 ranged from 80% to 95% (N = 40 respondents). Although all three of the revised recommendations exceeded the required 75% agreement threshold in round 2, the Panel Co-Chairs chose to submit two of the three Round 2 recommendations to a third round of voting after revising the recommendations based on Consensus Group members' comments. Agreement with these two recommendations after round 3 was 91.43% and 88.57%, respectively (N = 36 respondents). Consensus rating results for all the recommendations, by round, are provided in the Data Supplement.

RECOMMENDATIONS

Clinical Question 1

Should clinicians offer *BRCA1/2* testing to all patients with newly diagnosed breast cancer?

Recommendation 1.1

All patients newly diagnosed with breast cancer stage I-III or de novo stage IV/metastatic disease who are 65 years or younger at diagnosis should be offered *BRCA1/2* testing (Type: Formal Consensus; Agreement: 87.50%).

Recommendation 1.2

All patients newly diagnosed with breast cancer with stage I-III or de novo stage IV/metastatic disease who are older than age 65 should be offered *BRCA1/2* testing if:

- they are candidates for poly(ADP–ribose) polymerase (PARP) inhibitor therapy for early-stage or metastatic disease,
- they have triple-negative breast cancer,
- their personal or family history suggests the possibility of a pathogenic variant,
- they were assigned male sex at birth,
- they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (Type: Formal Consensus; Agreement: 92.50%).

Recommendation 1.3

Patients undergoing *BRCA1/2* testing should also be offered testing for other cancer predisposition genes as suggested by their personal or family history. Consultation with a provider experienced in clinical cancer genetics can help guide this decision-making and should be made available to patients when possible (Type: Formal Consensus; Agreement: 90%).

Literature Review and Analysis

Studies of germline *BRCA1/2* mutations and PARP inhibitor therapy in patients with breast cancer. The systematic literature review identified five studies that inform the question of the role of *BRCA1/2* testing to guide the use of PARP inhibitors in the treatment of patients with human epidermal growth factor receptor 2 (HER2)–negative breast cancer.[13-17] In the observational, cross-sectional BREAKOUT study,[17] the prevalence of germline *BRCA1/2* mutations in a cohort of 341 patients with HER2-negative metastatic breast cancer (MBC) was 9.7%; the prevalence was 5.8% among patients without a traditional risk factor for a germline *BRCA1/2* mutation. The mutation frequency for *BRCA1/2* was 5% among patients with MBC in the German prospective, multicentric breast cancer registry study, PRAEGNANT, conducted by Fasching et al.[16]

Three of the articles identified by the literature search investigated the efficacy of PARP inhibitors in phase III randomized controlled trials (RCTs) among patients with PVs of *BRCA1/2*. Robson et al[14] compared the efficacy and safety of the PARP inhibitor, olaparib (n = 205), with the efficacy and safety of standard therapy with single-agent chemotherapy (capecitabine, eribulin mesylate, or vinorelbine; n = 91) in women with HER2-negative MBC and a germline *BRCA1/2* mutation. The primary end point was progression-free survival (PFS). Median PFS was significantly longer in the group that received olaparib monotherapy than in the group that received standard chemotherapy (7 months *v* 4.2 months; hazard ratio [HR] for disease progression or death, 0.58 [95% CI, 0.43 to 0.80]; $P < .001$). The relative risk of disease progression or death in the olaparib group was 42% lower than in the standard therapy group, and the response rate was almost two times the response rate in the standard therapy group (59.9% *v* 28.8%). The rate of grade 3 or higher adverse events in patients who received olaparib was 36.6%; it was 50.5% in the group that received standard chemotherapy. Health-related quality of life measures were also superior with olaparib than with chemotherapy: treatment with olaparib led to improvements in the functioning,

symptoms, and health-related quality of life. One exception was the nausea and vomiting symptom score, which was worse among patients who received olaparib.

In 2019, Robson et al reported the results of the prespecified final analysis of overall survival (OS) in the OlympiAD study (at 64% data maturity) and on the long-term tolerability of olaparib. Analyses showed that, compared with chemotherapy treatment of physician's choice (TPC), there was no statistically significant improvement in OS with olaparib: median OS was 19.3 months with olaparib compared to 17.1 months with TPC (HR, 0.90 [95% CI, 0.66 to 1.23]; $P = .513$).

Litton et al[13] reported the results of an open-label, phase III RCT (EMBRACA) that compared the efficacy and safety of the PARP inhibitor, talazoparib (n = 287), with standard single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine; n = 144) for the treatment of advanced breast cancer in women with a germline *BRCA1/2* mutation. Median PFS in the talazoparib group was significantly longer than in the standard chemotherapy group (8.6 months *v* 5.6 months; HR for disease progression or death, 0.54 [95% CI, 0.41 to 0.71]; $P < .001$). Benefits were seen in patients with either triple-negative or estrogen receptor (ER)–positive breast cancer. There were also differences in the patient-reported outcomes (PROs) of global health status, quality of life, and breast symptoms. Compared with standard chemotherapy, talazoparib treatment resulted in a significant delay in the onset of clinically meaningful deterioration; in significant improvement in global health status/quality of life; and in improvement in the breast symptom scale score from baseline.

In a final analysis of OS, Litton et al found that talazoparib did not significantly improve OS over standard, physician's choice of single-agent chemotherapy (HR, 0.848 [95% CI, 0.670 to 1.073]; $P = .17$). Median OS was 19.3 months with talazoparib (95% CI, 16.6 to 22.5) compared to 19.5 months (95% CI, 17.4 to 22.4) with chemotherapy, although these results were confounded by significant cross-over following progression from placebo to PARP inhibitor. Analyses of PROs demonstrated a positive risk-benefit profile of talazoparib.

Taken together, these efficacy data from OlympiAD and EMBRACA support a recommendation in favor of routine testing for mutations in this HER2-negative MBC population to determine treatment eligibility for PARP inhibitors.[18] Elsewhere,[19,20] ASCO has addressed the use of biomarker results to inform the use of PARP inhibitors in patients with *PALB2* PVs and hormone receptor–positive, HER2-negative MBC. Those ASCO panels concluded that there was insufficient evidence to support a recommendation either for or against testing for a germline *PALB2* PV to determine eligibility for treatment with PARP inhibitor therapy in the metastatic setting. The Panel acknowledged that the data from Tung et al,[9] although from a single-arm, phase II trial, were quite striking in patients with germline *PALB2* PVs, with 10 of 11 patients having at least some tumor shrinkage and one patient with no change in tumor size.

The OlympiA phase III, double-blind, randomized trial evaluated the efficacy of adjuvant PARP inhibitor therapy with olaparib in patients with early-stage, HER2-negative breast cancer with high risk of recurrence and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants. Tutt et al[15] reported that, compared with placebo, 1 year of olaparib following completion of local treatment and (neo) adjuvant chemotherapy was associated with significantly longer survival free of invasive or distant disease (interim analysis, median follow-up of 2.5 years). Patients had completed at least six cycles of neoadjuvant or adjuvant chemotherapy; 95% of patients in the trial received anthracycline and taxane-based chemotherapy. In the olaparib group, the 3-year invasive disease-free survival (DFS) was 85.9%; it was 77.1% in the placebo group (HR, 0.58 [99.5% CI, 0.41 to 0.82]; $P < .001$). In the olaparib group, the 3-year distant DFS was 87.5% versus 80.4% in the placebo group (HR, 0.57 [99.5% CI, 0.39 to 0.83]; $P < .001$). The occurrence of serious adverse events, including myelodysplastic syndrome and acute leukemia, was not more frequent in the olaparib arm versus placebo.

Studies of the prevalence of *BRCA1/2* mutations in patients with breast cancer and age-at-diagnosis cutoffs for *BRCA1/2* testing. The systematic review conducted for this guideline identified 11 studies pertinent to the question of whether all patients with newly diagnosed breast cancer should be offered *BRCA1/2* mutation testing. Five of these studies provide data on the frequency of *BRCA1/2* pathogenic variants among patients with breast cancer.[21–25] These data reveal consistent support for *BRCA1/2* testing based on sufficiently high mutation prevalence[6,26] coupled with data from RCTs demonstrating the efficacy of PARP inhibitors in *BRCA1/2* mutation carriers.[13–15] However, the question of which patients with breast cancer to test routinely for *BRCA1/2* pathogenic variants persists. Age at breast cancer diagnosis—≤65 years of age versus >65 years of age—is a key consideration in this regard and a source of ongoing debate.[27] Data from six studies[6,27–31] identified by the systematic review, combined with the best clinical opinion and experience of the Expert Panel members, provide the basis for the age-based *BRCA1/2* testing recommendations offered here.

Yadav et al[27] compared the sensitivity and specificity of the National Comprehensive Cancer Networks (NCCN)[32] and American Society of Breast Surgeons (ASBrS)[33] genetic testing criteria for the detection of germline pathogenic variants in nine breast cancer predisposition genes among 3,907 women with ductal carcinoma in situ (16%) or invasive breast cancer (84%) enrolled in the Mayo Clinic prospective breast cancer registry. Women who met NCCN criteria for genetic testing were more likely to carry a pathogenic variant in the nine genes (9.0%) than women who did not meet the

NCCN criteria (3.5%; $P < .001$). Analyses conducted for six high-risk risk genes (5.7% *v* 1.4%; $P < .001$) and for *BRCA1* or *BRCA2* only (5.0% *v* 0.7%) yielded similar results for patients who met or did not meet NCCN criteria, respectively. Notably, 29.9% (72 of 241) of women with pathogenic variants in the nine predisposition genes did not qualify for genetic testing according to NCCN criteria; 20.9% (28 of 134) of women with pathogenic variants in the six high-risk genes did not qualify; and 13.1% (14 of 107) of women with pathogenic variants in *BRCA1* or *BRCA2* did not qualify. By expanding the NCCN criteria to include all women ≤65 years of age, Yadav et al improved the sensitivity of the criteria. For the nine predisposition genes and the six high-risk genes, the sensitivity of the selection criteria achieved was >90%; for *BRCA1* or *BRCA2*, the sensitivity improved to 98% with the expanded criteria.

Based on an updated analysis of the Mayo Clinic Registry data, Desai et al[30] argued for further lowering the age of breast cancer diagnosis cutoff for genetic testing from 65 to 60 years of age. This would preserve the >90% sensitivity achieved with the hybrid approach evaluated by Yadav et al[27] for detecting a pathogenic variant; however, the lower cutoff could spare an additional 10% of patients from unnecessary genetic testing.

Three studies examined the prevalence of *BRCA1/2* mutations in patients with triple-negative breast cancer. The observed rates of *BRCA1/2* pathogenic variants among patients ≥60 years old across these studies were 2.3%,[29] 3.1%,[28] and 4.9%.[31]

The retrospective analysis of cancer susceptibility genes conducted by Pritzlaff et al[25] supports the recommendation for testing newly diagnosed patients 65 years of age or older who were assigned male sex at birth for *BRCA1/2* pathogenic variants. Among the male patients with breast cancer who had undergone analysis of cancer susceptibility genes, *BRCA2* was the most frequently mutated gene. Pathogenic variants in *BRCA2* were identified in 53 of 480 patients (11.0%) who had no prior *BRCA 1/2* testing.

Studies of testing for non-*BRCA1/2* pathogenic variants among patients undergoing *BRCA1/2* testing. Two studies from the systematic review inform the recommendation that patients undergoing *BRCA1/2* testing should also be offered testing for other cancer predisposition genes as suggested by their personal or family history.[34,35] In a study of the prevalence of mutations in 22 cancer susceptibility genes among *BRCA1/2*-negative patients with breast cancer diagnosed before 40 years of age, Maxwell et al[34] found that 31% of patients had a clinically reportable variant. Eleven percent, or 31 of 278 patients, had at least one deleterious or possibly deleterious non-*BRCA1/2* variant. In the subgroup of patients without a *BRCA1* or *BRCA2* mutation in their sample of breast cancer–affected women and cancer-free women, Thompson et al[35] reported an overall sensitivity of 4% (95% CI, 3.2 to 4.9) for detection of an actionable mutation (78 variants in 1,994 cancer cases and 33 variants in 1,984 cancer-free controls). Among the 16 non-*BRCA1/2* breast cancer predisposition genes on the multigene panel, *TP53* (five cases, zero controls) and *PALB2* (26 cases, four controls) were the greatest contributors to the mutation detection rate.

Clinical interpretation. PVs in *BRCA1* and *BRCA2* in women with newly diagnosed breast cancer are associated with significantly increased risks of synchronous or metachronous disease, especially in premenopausal patients. For this reason, newly diagnosed women may benefit from knowing their *BRCA1/2* status to plan their surgical approach in the most informed way. In addition, the OlympiA study has shown that knowledge of *BRCA1/2* status can impact adjuvant therapy decisions in a way that can improve OS in women at higher risk of recurrence. Furthermore, women with *BRCA1/2* PVs are at increased risk for ovarian cancer and may be at increased risk for pancreatic cancer. Risk-reducing salpingo-oophorectomy at an appropriate age is recommended to manage ovarian cancer risk and screening for pancreatic cancer is under active study. Lastly, the finding of a *BRCA1/2* PV has significant implications for family members and may help them plan their own preventive care.

In two large population-based case-control studies composed of 48,826 and 32,247 women with breast cancer, the prevalence of PVs in *BRCA1* and *BRCA2* was 2.6% and 2.1%, respectively.[7,26] Some studies have shown that guideline-based testing is incompletely sensitive for detecting these alterations, which has led to calls for universal testing of all patients with breast cancer. Personal and family history–based guidelines, such as those provided by the NCCN, are nonspecific, with 1,872 of 3,907 (48%) unselected women with breast cancer meeting these criteria in a recent series.[27] Sensitivity of the NCCN criteria in that series was 87% for *BRCA1/2* PV, but only 70% for a panel of nine breast cancer predisposition genes and <60% for genes other than *BRCA1/2*.[27] Extending the NCCN criteria to include all women with triple-negative breast cancer, as in the most recent version of the guideline, likely improves sensitivity for *BRCA1/2* mutations, but not for other genes. Other guideline criteria have not been rigorously evaluated for sensitivity and specificity.

Given the relevance of *BRCA1/2* status for determining benefit of systemic therapy in the form of PARP inhibitors, and in appropriate risk management of second primary cancer, optimizing sensitivity is clearly desirable. Testing all women would of course provide perfect sensitivity (within the limits of the test itself), but would require testing approximately twice the number of women than would be tested using NCCN criteria. Sensitivity would be improved to 98% by extending testing to all women 65 or younger, and older women who had personal or family history suggesting an alteration, and would require testing approximately 80% of all women. Sensitivity for the nine breast cancer predisposition genes would improve to 92%. Since the incidence of

breast cancer rises sharply after age 60-65, and yet the prevalence of *BRCA1/2* PVs is very low beyond age 65 in the absence of suggestive criteria, the Expert Panel concluded that the ideal balance of sensitivity and specificity was reached at a testing age threshold of 65, although testing could still be appropriate for older women under specific circumstances.

Clinical Question 2

Should all patients with recurrent disease, local or metastatic, or with second breast primary, be offered *BRCA1/2* testing?

Recommendation 2.1

All patients with recurrent breast cancer (local or metastatic) who are candidates for PARP inhibitor therapy should be offered *BRCA1/2* testing regardless of family history (Type: Formal Consensus; Agreement: 97.50%).

Qualifying statement. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in women with metastatic breast cancer and germline pathogenic variants in *PALB2*.

Recommendation 2.2

BRCA1/2 testing should be offered to patients with a second primary cancer either in the contralateral or ipsilateral breast (Type: Formal Consensus; Agreement: 89.74%).

Literature Review and Analysis

Studies of germline *BRCA1/2* pathogenic variants and PARP inhibitor therapy in patients with breast cancer. Five studies from the systematic review inform the question of the role of *BRCA1/2* testing to guide the use of PARP inhibitors in the treatment of patients with HER2-negative breast cancer.[13-17] These studies were reviewed earlier (see Recommendation 1.2).

Clinical interpretation. PARP inhibitors (olaparib and talazoparib) have been shown to improve PFS in women with metastatic HER2-negative breast cancer and germline PVs in *BRCA1/2* and were approved by the US Food and Drug Administration on this basis even though there was no statistically significant improvement in OS with either agent compared to treatment of physician's choice.[36] Despite the lack of survival benefit, these agents are still widely used clinically in patients with PV in *BRCA1/2*. Olaparib has been shown to improve OS in high-risk women with early-stage breast cancer due to a germline PV in *BRCA1/2*. Given the direct treatment implications, the Expert Panel concluded that women who meet the clinical criteria for PARP inhibitor treatment should be offered testing regardless of other characteristics.

Literature Review and Analysis

Studies of germline *BRCA1/2* pathogenic variants and contralateral breast cancer risk. The systematic review of the literature identified 15 articles (13 studies[37-49] and two meta-analyses[50,51]) that inform the question of whether all patients with local recurrence or contralateral primary breast cancer should be offered *BRCA1/2* testing. With the exception of one study that provides direct evidence,[38] the studies identified constitute indirect evidence in support of the recommendation that *BRCA1/2* testing should be offered to patients with contralateral breast cancer or ipsilateral second breast primary. These studies provide consistent evidence that women with germline *BRCA1/2* PVs are at higher risk for a second cancer. As an exemplar, Kuchenbaecker et al estimated the age-specific risk of asynchronous contralateral breast cancer among *BRCA1* and *BRCA2* mutation carriers in a large prospective cohort study. Among the 2213 women eligible for the contralateral breast cancer analysis, 245 were diagnosed during follow up as having contralateral breast cancer (173 *BRCA1* mutation carriers and 72 *BRCA2* carriers). The cumulative risk for contralateral breast cancer 20 years after a breast cancer diagnosis for *BRCA1* carriers was 40% (95% CI, 35 to 45) and 26% for *BRCA2* carriers (95% CI, 20 to 3). As reported in other studies,[42,44,45,47,50] younger age at first breast cancer diagnosis was associated with a significantly higher risk of contralateral breast cancer among *BRCA1/2* mutation carriers. The approximately three-fold increased risk of contralateral breast cancer in *BRCA1/2* carriers was confirmed in a recent population-based study[39] that did not select women by age at diagnosis or family history.

A study by Yao et al[38] investigated the prevalence of *BRCA1/2* PVs in women who presented with contralateral breast cancer or a second breast cancer, and provides direct evidence to inform the question of whether all patients with local recurrence or contralateral primary breast cancer should be offered *BRCA1/2* testing. In a retrospective analysis, Yao et al compared the frequency of pathogenic and likely pathogenic variants in *BRCA1* and *BRCA2* (among other clinically actionable genes) between women with a primary breast cancer (n = 75,550) and women with a second breast cancer (n = 7,728) who were referred for genetic testing. Results indicated that women who presented with a second breast primary were significantly more likely to harbor *BRCA1/2* pathogenic or likely pathogenic variants than women with primary breast cancer. This finding was observed most robustly in Caucasian and African American patients. Among Hispanic patients, there was a significant increase in prevalence of *BRCA1* in women with second breast cancer as compared to those with only a primary event; however, no *BRCA2* carriers were identified in this population. Within the subset of Asian patients, a nearly two-fold increase in prevalence of a germline *BRCA1* PV was observed, although this did not reach statistical significance (odds ratio, 1.8; 95% CI, 0.82 to 3.50), likely due to small sample size and,

again, no *BRCA2* mutation carriers were observed. Similarly, no statistically significant differences in prevalence of *BRCA* germline mutations were noted between Ashkenazi Jewish patients with primary versus second breast cancer, again likely due to relatively small numbers of such patients. Other germline mutations that were noted to be significantly enriched in patients with second breast cancer included *CHEK2* in Caucasian women, and *PALB2* and *TP53* in African American women.

Clinical interpretation. The increased risk of second breast cancer among *BRCA1/2* pathogenic and likely pathogenic carriers has been well established and best characterized by risk of contralateral breast primary. Given this association, it has been assumed that patients who present with a second breast primary are more likely to harbor pathogenic or likely pathogenic germline mutations compared to women without such a subsequent event. Recent data from Yao et al[38] provide direct evidence in support of this assumption, demonstrating that a detection of a *BRCA1/2* pathogenic or likely pathogenic variant is more likely in the secondary setting as compared to a primary diagnosis. These data confirm the importance of testing for germline *BRCA1/2* mutations in women with a second breast cancer. The data also suggested differences in which germline PVs were most prevalent across race and ethnicity; however, these patient subsets were generally small. Therefore, for women presenting with a second breast cancer, testing for a relatively broad panel of actionable genes is appropriate.

Although these data are readily applicable to those with a new contralateral breast cancer, their relevance to those with a second ipsilateral event is less clear, given the difficulty in distinguishing between a local recurrence and a second breast primary within the ipsilateral breast. In the paper by Yao et al,[38] no distinction was made between local recurrence and ipsilateral second primary, and all patients with ipsilateral second breast cancer (10% of the study group) as reported by the ordering clinicians were included in the analysis. Given the implications of finding a germline *BRCA1/2* PV, in cases where a local recurrence cannot be readily excluded, assumption of second breast primary and subsequent germline testing would be reasonable.

Clinical Question 3

Should patients with a personal history of breast cancer, and no active disease, be offered *BRCA1/2* testing?

Recommendation 3.1

All patients with a personal history of breast cancer diagnosed at age ≤65 years who are without active disease should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment (Type: Formal Consensus; Agreement: 90%).

Recommendation 3.2

All patients with a personal history of breast cancer diagnosed over age 65 with no active disease, who meet one of the following criteria, should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment:

- their personal or family history suggests the possibility of a pathogenic variant,
- they were assigned male sex at birth,
- they had triple-negative breast cancer,
- they are of Ashkenazi Jewish ancestry or are members of a population with an increased prevalence of founder mutations (Type: Formal Consensus; Agreement: 94.87%).

Literature Review and Analysis

The findings of eight studies identified by the systematic review,[6,25,52-57] combined with the best clinical opinion and experience of the Expert Panel members, inform the question of whether people with a personal history of breast cancer (and no active disease) should be offered *BRCA1/2* testing. The studies offer empirical support for the Panel's recommendation that all patients with a personal history of breast cancer diagnosed at age ≤65[6] as well as those diagnosed over age 65 years, and those who are assigned male at birth[25] or who had triple-negative breast cancer[52,53,55-57] should be offered *BRCA1/2* testing if the result will inform personal risk management or family risk assessment.

Clinical interpretation. The considerations of testing women with a personal history of breast cancer who are not undergoing active treatment are similar to those of testing newly diagnosed women except that decisions regarding primary surgical treatment and systemic therapy have already been made. The rationale for testing such women is to inform strategies to reduce the risks posed by second primary malignancies and to inform family members about risks. The specificity and sensitivity considerations described in Recommendations 1.1 and 1.2 pertain to women with a personal history of breast cancer and the Expert Panel considered that an age threshold of 65 years at the time of a breast cancer diagnosis was again appropriate. Importantly, as there are no direct therapeutic implications, personal utility is crucial in women who have completed active treatment and testing, while it may be offered, should not be mandated. For instance, women with no family members at risk and who have completed surgical risk reduction would not clearly benefit from testing and may not wish to pursue it.

Clinical Question 4

What is the value of testing patients with a diagnosis of breast cancer for breast cancer predisposition genes other than *BRCA1/2*?

Recommendation 4.1

Testing for high penetrance genes beyond *BRCA1/2*, including *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*, could inform medical therapy, influence surgical decision making, refine estimates of risks of second primary cancer, and inform family risk assessment, and thus should be offered to appropriate patients (Type: Formal Consensus; Agreement: 92.31%).

Recommendation 4.2

Testing for moderate penetrance breast cancer genes currently offers no benefits for treatment of the index breast cancer but may inform risks of second primary cancer or family risk assessment, and thus may be offered to appropriate patients who are undergoing *BRCA1/2* testing (Type: Formal Consensus; Agreement: 87.50%).

Recommendation 4.3

If a multi-gene panel is ordered, the specific panel chosen should take into account the patient's personal and family history. Consultation with a provider experienced in clinical cancer genetics can be helpful in selecting a specific multigene panel or interpreting its results and should be made available to patients when possible (Type: Formal Consensus; Agreement: 91.43%).

Literature Review and Analysis

Studies reporting on the frequency of germline mutations in moderate-penetrance and non-*BRCA1/2* high-penetrance genes. The systematic review identified 10 studies that reported data on the prevalence of pathogenic or likely pathogenic variants in moderate-penetrance and non-*BRCA1/2* high-penetrance genes in patients with breast cancer.[16,21-24,27,28,34,58,59] For the moderate-penetrance genes evaluated in these studies, pathogenic or likely pathogenic variants were detected most frequently in *CHEK2* and *ATM*. For example, in an analysis of germline DNA from a prospective cohort of patients with metastatic breast cancer, Fasching et al[16] found that 57 of 2,595 patients (2.2%) had a mutation in *CHEK2* and 23 (0.9%) patients had a mutation in *ATM*. Similar mutation prevalence estimates of roughly 2% and 1% for *CHEK2* and *ATM*, respectively, were observed across studies.[21,23,24,27] Pathogenic variants in non-*BRCA1/2* high-penetrance genes detected in the mutation prevalence studies identified by the review were *PALB2*,[16,21-23,28,58] *TP53*,[22,24,34] *PTEN*,[21,24] and *CDH1*.[22,24]

Studies reporting on the association of germline mutations in moderate- or non-*BRCA1/2* high-penetrance genes and breast cancer risk. Eight studies identified by the systematic review provided data on the risk of breast cancer associated with pathogenic or likely pathogenic variants in moderate-penetrance or non-*BRCA1/2* high-penetrance genes.[7,39,56,60-64] This research has demonstrated that germline PVs in selected moderate- and high-penetrance genes are associated with an increased risk of breast cancer. There is evidence from several additional studies of an association between *PALB2* PVs and increased breast cancer risk.[7,60-62] Additional studies have consistently reported significant associations of increased breast cancer risk and PVs in other moderate-penetrance genes, including *ATM*,[7,61,62] *CHEK2*, and *BARD1*[7,61]; and other non-*BRCA* high-penetrance genes, including *TP53*[7,62] and *CDH1*.[57] Yadav et al[39] reported recently that a subset of women diagnosed with breast cancer who are germline *PALB2* or *CHEK2* mutation carriers are at increased risk of second breast cancer. Two additional studies[63,64] showed that *CHEK2* mutations were associated with a higher rate of contralateral breast cancer. Large population-based, case-control studies have identified a few other genes in which PVs confer modestly increased risk.[7,26] Taken together, these data underscore the Panel's recommendation in support of testing for moderate- and non-*BRCA1/2* high penetrance breast cancer genes to inform on risks of second primary cancer among women with a first breast cancer and/or to inform on risk of primary breast cancer among the proband's relatives.

Clinical interpretation. *BRCA1/2* PVs are clearly actionable for both the person tested and their family members. Other genes responsible for autosomal dominant predisposition syndromes (eg, *PTEN*, *TP53*, *STK11*, *CDH1*) are similarly actionable for risk management, although not for treatment as PARP inhibitors are not currently approved for the treatment of individuals with germline PVs in any of these genes, recognizing that breast cancers associated with *PALB2* PVs may respond.[9] It is, however, unusual to identify PVs in these high-penetrance genes unless suggested by a personal or family history. The appropriate management of PVs in *CDH1* remains unclear outside of the context of a family history suggesting hereditary diffuse gastric cancer, and in particular, the value of prophylactic total gastrectomy in this circumstance is a topic of some controversy. Similarly, *TP53* PVs may be identified in the absence of a family history, suggesting Li-Fraumeni Syndrome, but a meaningful proportion of these are likely post-zygotic (mosaic) and appear to arise de novo in the family. High-penetrance genes are almost always included on breast cancer susceptibility gene panels despite these considerations.

Other breast cancer susceptibility genes are often considered for testing. The particular genes included on breast cancer susceptibility gene panels varies between testing laboratories. Almost all include *ATM*, *CHEK2*, and *PALB2*. These genes do not currently have direct relevance for treatment of patients newly diagnosed with breast cancer as PARP inhibitors are not approved for treatment of individuals with germline PVs in any of these genes, and contralateral risks are modest at best.[39] Affected women with PVs in these genes may be at sufficient risk to benefit from breast magnetic resonance imaging (MRI) screening and *PALB2* is linked to an increased risk of ovarian cancer that may warrant post-menopausal

salpingo-oophorectomy. The major benefit of testing for these genes, however, is to inform risk assessment of family members.

Many genes other than breast cancer predisposition genes may be included on different multigene panels offered by diagnostic testing laboratories. These genes may be of clear clinical validity (association with the presenting disease) but uncertain clinical utility for a patient with breast cancer, and thus PVs would not change management. Other genes may be of clear clinical validity (and sometimes utility) for conditions other than those suggested by the personal and/or family history of the patient (for instance, Lynch syndrome genes in women with breast cancer). Finally, some genes included on panels may be of uncertain association with any disease, or be of such low penetrance as to be meaningless clinically. Evaluating these genes in patients with breast cancer is similar to population testing and should be approached as such. Testing with an extensive panel that is not clearly indicated by the personal or family history of the patient is not obligatory. Consultation with a provider experienced in clinical cancer genetics is recommended if the ordering provider is uncertain about what genes would be appropriate to test. A provider experienced in clinical cancer genetics may also be helpful in the interpretation of PV results in genes that are unfamiliar to the ordering provider, as well as unexpected PV results in genes that are not usually considered to be associated with the patient's personal or family history. Experienced providers can also be helpful in the interpretation of VUS in any gene.

Clinical Question 5

How should patients with breast cancer considering genetic testing be counseled?

Recommendation 5.1

Patients undergoing genetic testing should be given sufficient information before testing to provide informed consent (Type: Formal Consensus; Agreement: 94.87%).

Recommendation 5.2

Patients with pathogenic variants should be provided with individualized posttest genetic counseling and offered referral to a provider experienced in clinical cancer genetics (Type: Formal Consensus; Agreement: 95.00%).

Recommendation 5.3

Variants of uncertain significance should not alter management. Patients should be made aware that variants of uncertain significance may be reclassified as being pathogenic, and they should understand that periodic follow up is necessary. Consultation with a provider experienced in clinical cancer genetics can be helpful and should be made available to patients when possible (Type: Formal Consensus; Agreement: 88.57%).

Recommendation 5.4

Patients without a pathogenic variant on genetic testing may still benefit from counseling, if there is a significant family history of cancer, and referral to a provider experienced in clinical cancer genetics is recommended (Type: Formal Consensus; Agreement: 90%).

Literature Review and Analysis

Articles that addressed informed consent and genetic counseling. The systematic review identified 10 articles.[4,65-72] These articles, combined with the best clinical opinion and experience of the Expert Panel members, inform the question of how patients with breast cancer considering genetic testing should be counseled.

The search identified two systematic reviews on, respectively, outcomes studies in genetic counseling[68] and information needs of individuals from families harboring *BRCA1/2* pathogenic variants.[69] Based on a systematic review of 23 articles (13 or 57% conducted in a cancer setting), Madlensky et al[68] reported that genetic counseling could lead to increased perceived personal control, knowledge, and positive health behaviors; and to decreased decisional conflict, cancer-related worry, and anxiety. From a content analysis of narrative data from 18 studies, Park et al[69] identified nine categories of information needs among individuals from families that harbored *BRCA* pathogenic variants. The most frequently reported information needs concerned risk-reducing strategies (94.4%), personalized risk assessment (66.7%), family implications of hereditary cancers (55.6%), and decision-making for risk-reducing options (44.4%).

The search yield comprised several practice guidelines, recommendation statements, and position statements. These include cancer genetic counseling recommendations that define essential elements of genetic cancer risk assessment, counseling, and testing[65]; a national recommendation statement on genetic counseling and genetic testing for *BRCA1/2*-related cancer[66]; a comprehensive guideline on genetic/familial high-risk assessment that addresses cancer risk assessment and counseling[67]; a consensus guideline on genetic testing to assess hereditary risk for breast cancer[33]; and a policy statement published by ASCO on genetic and genomic testing for cancer susceptibility that summarizes the components of informed consent and pretest education in clinical cancer genetics.[4]

Two workgroup reports offered genetic evaluation frameworks. Giri et al,[70] employing a formal consensus development approach, developed a prostate cancer conceptual framework for genetic evaluation and management that included, among other topics, optimal pretest informed consent

TABLE 1. Critical Elements of Pre- and Post-test Counseling in Clinical Cancer Genetics

Pretest Counseling	
Traditional Pretest Counseling for Susceptibility Testing (purpose of testing)	**Pretest Counseling for Multigene Panel Testing (same general components as traditional counseling, with the following special considerations)**
Information on specific genetic mutation(s) or genomic variant(s) being tested, including whether range of risk associated with variant will affect medical care	Discussions of specific genes may need to be batched, because it may not be feasible to review each gene individually; high-penetrance syndromes being evaluated should be described (eg, hereditary breast-ovary, Lynch, hereditary diffuse gastric, Li-Fraumeni); patients should be aware of possible detection of high-penetrance mutations not suggested by personal or family history; genes of uncertain clinical utility may need to be described more generally
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and in findings of mutations in genes associated with syndromes not suggested by personal or family history
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance
Risk that children and/or other family members may have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (eg, *ATM*, Fanconi's [eg, *BRCA2*, *PALB2*], *NBN*, *BLM*)
Fees involved in testing and counseling; for DTC testing, whether counselor is employed by testing company	
Psychological implications of test results (benefits and risks)	
Risks and protections against genetic discrimination by employers or insurers	
Confidentiality issues, including DTC testing companies and policies related to privacy and data security	
Possible use of DNA samples for future research	
Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing	
Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information	
Plans for disclosing test results and providing follow-up	
Posttest Counseling	
Discussion of results and associated medical risks	
Interpretation of results in context of personal and family history of cancer	
Discussion of recommended medical management options, including discussion of therapeutic implications by a qualified health care provider if positive	
Discussion of the importance of notifying family members and offering materials/resources for informing and testing family members who also have increased risk	
Discussion of available resources such as high-risk clinics, disease-specific support groups, and research studies	

NOTE. Adapted from Robson et al[4] and adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.2.2024.[73] 2023 National Comprehensive Cancer Network, Inc All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.

and post-test discussion. Hallquist et al[71] reported on a framework designed to guide genetic testing communication. A third workgroup defined critical elements of informed consent for genetic testing using an expert consensus process.[72]

The various guidelines and frameworks that highlight the most critical elements of informed consent and counseling for germline cancer genetic testing share many features in common. However, the extent of pretest genetic counseling needed to provide informed consent may vary by indication. Studies have shown that in oncology settings where genetic testing may impact treatment decisions, streamlined approaches that incorporate education tools and/or facilitation of testing by the oncologist or oncology staff increase completion of genetic testing. Hallquist et al[71] propose that the necessary level of detail for providing informed consent for cancer genetic testing can be achieved with a targeted discussion and with education materials. Education about germline genetic testing should address, among other issues, the purpose of germline testing; the genes being tested; the possible results of germline genetic testing (pathogenic

or likely pathogenic variants, negative, VUS); what the results may mean for medical management; to whom the test results will be returned; the implications of testing for family members; and legal and confidentiality concerns, including discrimination by health insurers or employers. Table 1 provides exemplars from this literature of the most critical components of pretest (informed consent) and posttest (disclosure of results) strategies for germline mutation testing in clinical cancer genetics from ASCO[4] and NCCN,[73] respectively.

Clinical interpretation. There has been a broad consensus since the advent of genetic testing for cancer susceptibility that individuals undergoing germline testing should be active participants in the decision to be tested and should provide consent for such testing. For patients who are uncertain about the decision, referral to a provider experienced in clinical cancer genetics is encouraged. There is awareness of a need to minimize barriers to genetic testing, particularly when this information will impact treatment decisions. However, those undergoing testing should still understand why they are being tested and what they are being tested for, the possible results of such testing (positive, negative, uncertain), the implications and actions to be considered with each type of result, and the potential harms including distress to the patient or their family and societal harms such as stigmatization and discrimination.

Unlike other types of diagnostic testing, those being tested should also clearly understand that their testing has potential implications for family members. Indeed, in some circumstances, the main reason for testing is to inform family members, and the person being tested should agree that this is a worthwhile goal and be prepared to communicate findings to at-risk relatives. In some larger practices and often academic settings, this information has traditionally been communicated in a formal genetic counseling session with a provider specifically trained in genetic counseling. This may not always be possible due to a need for rapid diagnostic testing or due to barriers to obtaining genetic counseling. A number of alternative approaches have been employed to deliver the necessary information to a person considering testing (or being recommended such). The most common approaches include telehealth and clinician-ordered testing. It is beyond the scope of this guideline to recommend a specific process for pre-test education.

The Expert Panel did strongly endorse that the traditional elements of informed consent should be provided by whatever means, and that results should be delivered in a manner that allowed the person being tested to understand clearly the meaning of their results (associated risks along with the degree of confidence in those estimates), options for management of those risks, and the need to inform family members of potential risks in carriers. In the event the ordering provider is unfamiliar with the implications of the results, a provider experienced in clinical cancer genetics should be engaged. In addition, clinical cancer genetics providers may be instrumental in counseling other family members and in the interpretation and follow-up of uncertain results.

Articles that addressed counseling and education of patients regarding the interpretation and clinical management of VUS. The systematic review identified eight relevant articles.[67,74-80] In combination with the best clinical opinion and experience of the Expert Panel members, these articles form the basis for the Panel's recommendations.

Four studies provide data on patient experiences around the receipt of VUS results. In a study of psychological reactions to panel gene testing, Lumish et al[79] found, compared to patients with negative genetic testing results, the distress, intrusive thoughts, and avoidance scores were elevated in the small (n = 20) group of patients with a family history but no personal history of cancer, who had received a VUS result. Halverson et al[77] reported that most participants in their study did not express distress, diminished trust, or doubt regarding their genetic evaluation in response to VUS reclassification; however, levels of understanding and retention of the information in the updated VUS reports were low (all study participants had received pre- and post-test genetic counseling). Data from a study by Solomon et al[81] of patients who received a VUS for Lynch syndrome mismatch repair genes similarly show that a VUS may be difficult for patients to understand fully.

Patel et al[76] compared outcomes of patients who were referred to genetic counseling for VUS (n = 5) to those of patients not referred to genetic counseling for VUS (n = 11). Patients referred to counseling reported less disappointment, less confusion, and more confidence in understanding their VUS than patients not referred for counseling. Culver et al[78] conducted a case-control study to compare reports of cancer distress between patients with *BRCA1/2* VUS results (n = 71) and patients with *BRCA* uninformative negative results (n = 714), all of whom had undergone genetic counseling. Among the patients with uninformative negative results, 36% indicated a reduction in the frequency of their concerning thoughts about cancer (cancer distress) compared to 23% of patients in the VUS group as a result of genetic counseling based on risk management guidelines ($P = .043$).

In a related vein, a study of genetic health professionals[75] reported that a proportion of these professionals found it difficult to convey VUS information and expressed concerns around patients' understanding of such information. In their analysis of genomic sequencing consent forms from 40 separate clinics or laboratories, Vears et al[74] found marked variation across consent forms in VUS terms and definitions, VUS reporting practices, and policies for variant reinterpretation and patient recontact. Of the 58 consent forms analyzed, 20 (34%) did not mention VUS in any way; and just half of the consent forms that mentioned VUS offered a description of VUS. Reinterpretation of variants as a possible outcome was explicitly stated in only a third of the 58

TABLE 2. National Comprehensive Cancer Network Principles of Cancer Risk Assessment: Variants of Uncertain Significance

VUS
VUS are alterations in the genetic code for which the impact on protein function is uncertain
VUS are common, particularly with the use of large multi-gene panels. The more genes that are included on a genetic testing panel, the more likely a VUS will be identified
VUS are more commonly found during genetic testing of racial and ethnic minorities compared with non-Hispanic Whites
In VUS that are reclassified, approximately 80%-90% are reclassified to likely benign or benign and 10%-20% to P/LP
There are discordant variant interpretations across labs, requiring careful counseling and skilled interpretation. Resources are available to review the available data supporting pathogenic consequences of specific variants and identify discrepant results (eg, ClinVar[82]; BRCA Exchange Mobile App[83]; CanVIG-UK[84])
VUS should not be used to alter medical management. In the event additional discussion is needed for classification and management, additional genetic expertise is recommended. Screening and risk reduction strategies should be recommended on the basis of personal and family history
RNA studies (when appropriate) may be a consideration to further define functional impact of variants
Testing family members for a VUS should not be done for clinical purposes, unless there are data to support discrepancy in interpretation of results. Consider a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries

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Abbreviations: P, pathogenic; LP, likely pathogenic; VUS, variants of uncertain significance.

consent forms, and just 23 of the 58 (40%) forms mentioned recontact for clinical (*v* research) purposes.

Two articles identified by the review provide guidelines for the management of VUS.[67,80] In the guideline proposed by Chiang et al,[80] management is based on the patient's personal and family history and the interpretation of the variant (suspicious VUS, clinically relevant VUS, or nonclinically relevant VUS). The frequency of VUS follow-up is based on the particular VUS subgroup. Thus, the guideline recommends follow-up every 2 years for patients with suspicious or clinically relevant VUS; patients with nonclinically relevant VUS may not require active follow-up and would be recalled only in the event of variant reclassification. The NCCN guideline[73] offers a concise description and definition of VUS and recommendations for clinical practice. These are listed in Table 2. The NCCN guideline highlights two key points: (1) VUS should not be used to change medical management; and (2) among VUS carriers, family history should guide risk reduction and screening strategies.

Clinical interpretation. VUS are generally missense variants whose impact on the function of a particular gene is undefined. Different laboratories employ the American College of Medical Genetics and Genomics (ACMG) Variant Classification framework[85] to determine the functional significance of a particular variant; but some place different emphasis on various components, such as functional assays or internal family history data, and discordance among laboratories is not uncommon. Unless a specific variant is conclusively characterized as pathogenic or likely pathogenic, it should not be incorporated into clinical decision making and recommendations should be based exclusively on a personal and/or family history. It is important to remember that sharing of a variant among a small number of affected close relatives does not constitute strong evidence of pathogenicity.

Many VUS are unique to the family being tested and may not be resolvable as definitively pathogenic or benign without a validated functional assay. Other variants may be reclassified through various other means. The legal responsibility for communicating variant reclassification, particularly reclassification to pathogenic or likely pathogenic, has not been clearly delineated. Many ordering providers are unfamiliar with the ways in which they may learn whether a particular variant has been reclassified and laboratory communication may be unreliable for various reasons (eg, different providers, relocation). Providers should develop their own procedures for follow-up of those they test who have VUS. Engagement of providers experienced in clinical cancer genetics who have their own procedures may be helpful and systems-level solutions should be considered to ensure systematic implantation across a given practice. Absent data on the optimal interval, yearly follow up seems reasonable.

GAPS IN THE LITERATURE AND FUTURE RESEARCH DIRECTIONS

The sequencing of the *BRCA1* and *BRCA2* genes in the 1990s was a pivotal moment in the understanding of the genetics of breast cancer. Research involving cohorts of carriers of PVs has provided an invaluable understanding of breast cancer risk and has opened doors to new therapeutic strategies. The expansion to extended panel testing carries with it the potential to build on these advances. However, a full realization of this potential is contingent on addressing several gaps in the field.

A primary challenge in genetics is that the ease with which genes can be sequenced has outpaced our ability to understand the significance of the finding. For many genes other than *BRCA1*/2, there is less information about the normal range of genetic variation which leads to the identification of a large number of variants of unknown significance, particularly in groups of patients other than European ancestry. Even for germline alterations which are classified as

pathogenic or likely pathogenic, the understanding of associated risks is incomplete, limiting the ability for appropriate risk counseling for both primary and metachronous cancers. Particularly troubling is the evidence that moderate-penetrance breast cancer predisposition is more subject to modification by factors such as traditional reproductive factors, polygenic risk, and mammographic density. For instance, after adjustment for proposed polygenic risks scores, which are still under investigation, a substantial proportion of unaffected women with PVs in *CHEK2* or *ATM* have a cumulative lifetime risk below the 20% threshold that is used to indicate breast MRI surveillance in the United States. Approaches to more precise individual risk prediction must be developed, as a one-size-fits-all approach is clearly inadequate; it risks either overtreatment or, less likely, undertreatment.

The field also needs to be deliberate in researching risks for subsequent cancers. One area of particular interest is the degree to which the primary manifestation of the predisposition influences the risk of metachronous cancers. For instance, in germline *BRCA1/2* PV carriers presenting with ovarian cancer as their first manifestation of the variant, the risk of metachronous breast cancer appears to be substantially lower than reported for unaffected *BRCA1/2* PV carriers,[86] although this may also be impacted by the competing mortality associated with a diagnosis of ovarian cancer. Such patterns may also be true for variants in other genes and should be the focus of future research.

Further adding to the complexity of the science in this area is the limited understanding of how family history may influence the penetrance and expression pattern of germline findings. As panel testing is widely adopted, often in the absence of a family history, clinicians need to be careful in interpretation of risks conferred by germline findings. In patients noted to have *TP53* germline PV detected incidentally on panel testing, the patterns of disease may appear different when compared to classic Li-Fraumeni families.[87] In addition to family history, age can also mitigate risks associated with a given germline PV.[88] The phenotype conferred by a finding of a germline PV will likely need to be considered in the context of family history, when known, and age. As data on non-*BRCA1/2* germline mutation carriers mature, addressing these questions to provide a more nuanced understanding of the clinical impact of germline PVs represents a key area of research need. Indeed, the simple question of which genes should be included on a panel is a topic of active discussion, with some viewing testing for breast cancer susceptibility as an entry point for wider genomic screening and others advocating for a more targeted approach.

As the indications for genetic testing expand, there are significant questions about how to implement broader testing. The traditional pre- and post-test counseling model clearly is not sustainable if one is to test all patients with breast cancer under age 65; however, this begs the question of how that counseling and/or testing should be delivered. While extensive pre-test counseling for written informed consent is no longer necessary, post-test counseling that accounts for the complexities of result interpretation after multigene panel testing is still a challenge that many clinicians have difficulty meeting. Developing a larger cadre of providers experienced in clinical cancer genetics remains crucial, and implementation science research is needed to develop posttest pathways that ensure that people are adequately and correctly informed about the meaning of their results and the options available for management. In addition, effective familial testing approaches need to be developed to ensure that the entire family benefits from the proband's test result.[89] Both posttest education and cascade testing approaches must be developed so that they can be deployed in lower-resource environments, such as rural and underserved urban settings.

Along these lines, given the persistence in health disparities, driven in part by disparities in access to care, research needs to continue to investigate how to best reach and test minority and under-represented populations. Understanding the association between germline PVs and race and ethnicity is critical to resolving the disproportionate rate of VUS in these populations and cannot be accomplished without addressing the current disparities in genetic testing.[90,91]

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[92] Communication topics of particular relevance to germline mutation testing were addressed in the Literature review and analysis section of Clinical Question 5, addressing discussion of informed consent and counseling. ASCO has long underscored the primacy of informed consent for germline genetic testing.[1,3,5] The most critical aspects of pretest genetic counseling (informed consent) and posttest genetic counseling (disclosure of results) are listed in Table 1. Table 2, adapted from NCCN's genetic/familial high-risk assessment guideline, highlights key communication strategies and recommendations for patients with VUS. The results of testing can occasion or exacerbate a range of feelings among patients and family members, including anxiety, distress about the future, guilt, fear, anxiety, and worry,[93] which clinicians should acknowledge and respond to empathically in the context of a shared decision-making approach.[92,94] Communication around VUS should emphasize that VUS are increasingly common with the advent of multi-gene panels; may require follow up; and may later be reclassified.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in

health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Recent studies have also noted disparities in the collection of family history information necessary for determining testing eligibility.[95,96]

A unique challenge in germline genetic testing is the unequal distribution of VUS. These ambiguous results are more frequent among racial and ethnic groups who have received less testing of a particular gene or genes, and for whom the normal range of genetic variability is less well mapped.[90,97] Essentially, a testing access disparity perpetuates a disparity in the clarity of genetic information. Population-based studies have documented a widening racial and ethnic gap in VUS results, which has been exacerbated by the trend toward sequencing many more genes.[58,91] Efforts to expand genetic testing access among clinically indicated patients are crucial to reduce the unequal burden of uncertain results on non-White patients. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

EXTERNAL REVIEW AND OPEN COMMENT

The draft, revised recommendations were released to the public for open comment from December 7, 2022 to December 21, 2022. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for each proposed recommendation. Seventy-two individuals completed the survey. Agreement (either "Agree as written" or "Agree with suggested modifications") ranged from 87.14% to 98.595%; disagreement ranged from 1.41% to 12.86%. In addition, members of the ASCO Breast Cancer Guideline Advisory Group reviewed the full guideline. The Expert Panel Co-Chairs reviewed comments from all sources and determined whether to maintain the original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to EBMC review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline panel includes a member from ASCO's Practice Guideline Implementation Network (PGIN). The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation a reader should consider. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line 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 website and most often published in the *JCO*.

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

RELATED ASCO GUIDELINES

- Patient-Clinician Communication (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer (https://ascopubs.org/doi/full/10.1200/JCO.19.02960)
- Biomarkers for Systemic Therapy in Metastatic Breast Cancer (https://ascopubs.org/doi/full/10.1200/JCO.22.01063)
- Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer (https://ascopubs.org/doi/full/10.1200/JCO.21.01392)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[98] Transgender and non-binary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[99–102] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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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 (via www.cancer.net), is available at www.asco.org/breast-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Germline Testing in Patients with Breast Cancer: ASCO–Society of Surgical Oncology Guideline

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Germline Testing in Patients with Breast Cancer Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Isabelle Bedrosian, MD (Co-Chair)	The University of Texas MD Anderson Cancer Center, Houston, TX	Surgical Oncology
Mark E. Robson, MD (Co-Chair)	Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology/Cancer Genetics
Maria Isabel Achatz, MD, PhD[a]	Centro de Oncologia, Hospital Sírio-Libanês, São Paulo, Brazil	Medical Oncology
Judy C. Boughey, MD	Mayo Clinic, Rochester, MN	Surgical Oncology
Giuseppe Curigliano, MD, PhD	University of Milan, Italy, European Institute of Oncology, IRCCS, Milano, Italy	Medical Oncology
Sue Friedman, DVM	FORCE (Facing Our Risk of Cancer Empowered), Tampa, FL	Patient Advocacy
Wendy K. Kohlmann, MS	University of Utah Huntsman Cancer Institute, Salt Lake City, UT	Genetic Counseling
Allison W. Kurian, MD, MSc	Stanford University School of Medicine, Stanford, CA	Medical Oncology/Cancer Genetics
Christine Laronga, MD	Moffitt Cancer Center, Tampa, FL	Surgical Oncology
Filipa Lynce, MD	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Barbara S. Norquist, MD	University of Washington Medical Center, Seattle, WA	Gynecologic Oncology
Jennifer K. Plichta, MD, MS	Duke University Medical Center, Department of Surgery, Durham, NC	Surgical Oncology
Patricia Rodriguez, MD	Hereditary Cancer Risk Assessment Program, Virginia Cancer Specialists, Arlington, VA	Practice Guideline Implementation Network/Community Oncology
Payal D. Shah, MD	Basser Center for BRCA & Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA	Medical Oncology
Marc Tischkowitz, MD, PhD	Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Center, University of Cambridge, Cambridge, UK	Medical Genetics
Marie Wood, MD	University of Colorado, Denver, CO	Medical Oncology
Siddhartha Yadav, MD	Mayo Clinic, Rochester, MN	Medical Oncology
Katherine Yao, MD	Division of Surgical Oncology at NorthShore University Health System Evanston, IL	Surgical Oncology
Mark R. Somerfield, PhD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guidelines Staff (Health Research Methods)

[a]Member of the ASCO–Society of Surgical Oncology Expert Panel.

TABLE A2. Germline Testing in Patients with Breast Guideline Consensus Panel Membership

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Isabelle Bedrosian, MD[a]	The University of Texas MD Anderson Cancer Center, Houston, TX
Judy C. Boughey, MD[a]	Mayo Clinic, Rochester, MN
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Allison W. Kurian, MD, MSc[a]	Stanford University School of Medicine
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Barbara S. Norquist, MD[a]	University of Washington Medical Center, Seattle, WA
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Jennifer Plichta, MD, MS[a]	Duke University Medical Center, Department of Surgery, Durham, NC
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Marie Wood, MD[a]	University of Colorado, Denver, CO
Siddhartha Yadav, MD[a]	Mayo Clinic, Rochester, MN
Katherine Yao, MD[a]	Division of Surgical Oncology at NorthShore University Health System Evanston, IL

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