ASCO special articles

Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline

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abstract

PURPOSE To develop recommendations for management of patients with breast cancer (BC) with germline mutations in BC susceptibility genes.

METHODS The American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology convened an Expert Panel to develop recommendations based on a systematic review of the literature and a formal consensus process.

RESULTS Fifty-eight articles met eligibility criteria and formed the evidentiary basis for the local therapy recommendations; six randomized controlled trials of systemic therapy met eligibility criteria.

RECOMMENDATIONS Patients with newly diagnosed BC and *BRCA1/2* mutations may be considered for breast-conserving therapy (BCT), with local control of the index cancer similar to that of noncarriers. The significant risk of a contralateral BC (CBC), especially in young women, and the higher risk of new cancers in the ipsilateral breast warrant discussion of bilateral mastectomy. Patients with mutations in moderate-risk genes should be offered BCT. For women with mutations in *BRCA1/2* or moderate-penetrance genes who are eligible for mastectomy, nipple-sparing mastectomy is a reasonable approach. There is no evidence of increased toxicity or CBC events from radiation exposure in *BRCA1/2* carriers. Radiation therapy should not be withheld in *ATM* carriers. For patients with germline *TP53* mutations, mastectomy is advised; radiation therapy is contraindicated except in those with significant risk of locoregional recurrence. Platinum agents are recommended versus taxanes to treat advanced BC in *BRCA* carriers. In the adjuvant/neoadjuvant setting, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. Poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) are preferable to nonplatinum single-agent chemotherapy for treatment of advanced BC in *BRCA1/2* carriers. Data are insufficient to recommend PARP inhibitor use in the early setting or in moderate-penetrance carriers. Additional information available at www.asco.org/breast-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

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

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INTRODUCTION

The integration of genomics into the care of oncology patients has led to an increasing population of patients with breast cancer identified with germline (ie, inherited) mutations in breast cancer susceptibility genes, requiring physicians to integrate this information into treatment decision making. Available practice guidelines have addressed managing future cancer risk associated with germline mutations and focused on surveillance and prevention strategies. However, guidelines for managing mutation carriers with newly diagnosed breast cancer are lacking. Therefore, many physicians are uncertain about the optimal surgical, radiation, and systemic therapies for patients with breast cancer with germline mutations in breast cancer susceptibility genes.

Pathogenic or likely pathogenic variants (commonly referred to as mutations) in high-penetrance breast cancer susceptibility genes increase the risk of breast cancer more than fourfold. Germline mutations in *BRCA1* or *BRCA2* (*BRCA1/2*) are found in 3% to 4% of all women with breast cancer,[1,2] including 10% to 20% of those with triple-negative breast cancer (TNBC)[3-6] and 10% to 15% of Jewish women with breast cancer.[7] The lifetime risk of breast cancer for a *BRCA* mutation carrier is approximately 70%,[8,9] but risk estimates from 50% to 90% have been reported,[10-12] with variability based on

THE BOTTOM LINE

Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline

Guideline Question

What is the optimal management of patients with breast cancer with germline mutations in breast cancer susceptibility genes?

Target Population

Women with hereditary breast cancer with germline mutations, advanced or early stage. The approach to management of hereditary breast cancer should be largely the same for men and women.

Target Audience

Medical oncologists, radiation oncologists, surgical oncologists, 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

Providers caring for patients with breast cancer with germline BRCA1/2 mutations should discuss treatment options related to the index cancer and the increased risk of contralateral breast cancer (CBC) and new ipsilateral breast cancer.

Recommendation 1.1

Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for breast-conserving therapy (BCT) from receiving BCT (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.2

Surgical management of the index malignancy (BCT *v* ipsilateral therapeutic and contralateral risk-reducing mastectomy [CRRM]) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3

The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers: age at diagnosis (the strongest predictor of future CBC; Table 1), family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian), ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI]), comorbidities, and life expectancy (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.4

BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.1

For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.2

In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT should be offered to those for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.3

The evidence regarding CBC risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data on *CHEK2* 1100delC. Information about the specific gene and what is known about the risk of CBC should be discussed in the context of shared decision making (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

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Recommendation 2.4

Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.1

For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in *BRCA1/2*, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2

For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in a moderate-penetrance gene, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.1

For women with breast cancer who have a *BRCA1/2* mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be offered. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy: age at diagnosis (the strongest predictor of future CBC), family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian), ability of patient to undergo appropriate breast surveillance (MRI), comorbidities, and life expectancy (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.2

For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding CRRM should not be based predominantly on mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 5.1

For patients with breast cancer with a deleterious germline *BRCA1/2* mutation interested in CRRM, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.2

For patients with breast cancer with a mutation in a moderate-penetrance gene who are interested in CRRM, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.1

For women with breast cancer who are treated with BCT or with mastectomy for whom postmastectomy radiation therapy (RT) is considered, RT should not be withheld because of mutation status, except for mutations in *TP53* (see Recommendation 6.3). There is no evidence of a significant increase in toxicity or CBC related to radiation exposure among patients with a mutation in a *BRCA1/2* or a moderate-penetrance gene (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.2

For women with breast cancer who are carriers of an *ATM* mutation, RT should be offered when clinically indicated. Data regarding rates of toxicity between *ATM* mutation carriers and noncarriers are limited and inconsistent. Potential absolute risks seem to be small; however, more research is needed. Discussion with *ATM* carriers interested in BCT is encouraged (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.3

For women with breast cancer who are carriers of a germline *TP53* mutation, irradiation of the intact breast is contraindicated. Mastectomy is the recommended therapeutic option. Postmastectomy RT should only be considered in patients with

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significant risk of locoregional recurrence (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 7

When offering chemotherapy for germline *BRCA* mutation carriers with metastatic breast cancer, platinum chemotherapy is preferred to taxane therapy for patients who have not previously received platinum. There are no data to address platinum efficacy in other germline mutation carriers (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 8

For germline *BRCA* mutation carriers with breast cancer treated with (neo)adjuvant therapy, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. While single-agent platinum has demonstrated activity in the neoadjuvant setting, there are no data yet comparing it with standard chemotherapy. There are no data to address platinum efficacy in other germline mutation carriers (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 9.1

For *BRCA1/2* mutation carriers with metastatic human epidermal growth factor receptor 2 (HER2) –negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line settings. For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, there are no data directly comparing efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors with platinum chemotherapy (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 9.2

For patients with breast cancer with mutations in moderate-penetrance genes, there are currently no robust data to support the use of PARP inhibitors (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Recommendation 10

For germline *BRCA* mutation carriers, there are insufficient data at this time to recommend a PARP inhibitor for patients with nonmetastatic breast cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

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

Additional Resources

More information, including a supplement with 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.

population studied, gene, study design, and method of analysis. Other high-penetrance breast cancer susceptibility genes include *PTEN* (Cowden's syndrome), *TP53* (Li-Fraumeni syndrome), *STK11* (Peutz-Jeghers syndrome), and *CDH1* (hereditary invasive lobular breast-diffuse gastric cancer).

Mutations in other genes are associated with breast cancer, but with lower lifetime risk than with *BRCA1* and *BRCA2* mutations. The lifetime risk of breast cancer associated with a mutation in *PALB2* is approximately 35% to 60%,[13] whereas with *ATM* and truncating *CHEK2* mutations, the lifetime risk is 25% to 30%, although genetic and non-genetic modifiers can greatly affect risk estimates.[14,15] Mutations in these more moderate-penetrance genes such as *PALB2*, *CHEK2*, and *ATM* occur in 4% to 6% of patients with breast cancer.[2,16,17] The list of genes with sufficient clinical validity to be considered breast cancer susceptibility genes is continuously evolving.

There are data to support consideration of different local management choices (eg, surgery, radiation therapy [RT]) for certain mutation carriers.[18,19] In addition, there is a growing body of evidence that certain systemic therapies are more effective in breast cancer patients with germline mutations in breast cancer risk genes than in those without mutations.[20-22] This joint American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) guideline offers recommendations for the management of breast cancer in patients with germline mutations in *BRCA1/2*, *PALB2*, *CHEK2*, and *ATM*.

GUIDELINE QUESTIONS

This clinical practice guideline addresses 10 clinical questions:

1. What is the appropriate surgical management of the index malignancy for women with newly diagnosed nonmetastatic breast cancer who have a *BRCA1/2* mutation?
2. What is the appropriate surgical management of the index malignancy for women with newly diagnosed nonmetastatic breast cancer who have a selected moderate-penetrance mutation?
3. Among women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance non-*BRCA1/2* germline mutation who are undergoing therapeutic mastectomy, what is the role of nipple-sparing mastectomy?
4. What is the role of contralateral prophylactic mastectomy for women with breast cancer who have a *BRCA1/2* mutation or a selected moderate-penetrance gene mutation?
5. Among women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance mutation who are undergoing contralateral risk-reducing mastectomy (CRRM), what is the role of nipple-sparing mastectomy?
6. What is the role of RT in women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance non-*BRCA1/2* germline mutation?
7. What is the role of platinum chemotherapy in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and advanced breast cancer?
8. What is the role of (neo)adjuvant platinum chemotherapy in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and breast cancer?
9. What is the role of poly (ADP-ribose) polymerase (PARP) inhibitors in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and advanced breast cancer?
10. What is the role of PARP inhibitors in women who have a *BRCA1/2* mutation or selected moderate-penetrance mutation and nonmetastatic breast cancer?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary, joint ASCO-ASTRO-SSO Expert Panel (Appendix Table A1, online only), which included a patient representative and an ASCO guidelines staff with health research methodology expertise. The Expert Panel met in person and via Webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of 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 Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO. The joint guideline manuscript was reviewed by ASTRO's Guidelines Subcommittee and approved by the ASTRO Board of Directors; the guideline was reviewed by SSO's Breast Cancer Disease Site Work Group and approved by the SSO Quality Committee and Executive Council.

The recommendations for the local therapy clinical questions were developed by using a systematic review of the literature and clinical experience. The literature review involved searches of PubMed for the period from January 1, 2010, through September 26, 2019 (surgery search), or January 1, 1999, through September 26, 2019 (RT search). The searches were broad and included a combination of treatment, genetic mutation, and breast cancer search terms (see Data Supplement [online only] 1 for more details of the literature search).

Articles from the search were included if they reported data on outcomes of local therapy (therapeutic or prophylactic mastectomy, nipple-sparing mastectomy, RT) among women with newly diagnosed nonmetastatic or advanced breast cancer and a high- or moderate-penetrance germline mutation. Disease outcomes considered in the studies included in the literature were ipsilateral events, including true recurrences and new primary tumors, survival, cosmesis, contralateral breast cancer (CBC), and treatment toxicity/complications. An article was excluded from the local therapy literature review if (1) it was a narrative (*v* systematic) review of the literature, (2) it reported on a single case, (3) 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), (4) it was a meeting abstract not subsequently published in peer-reviewed journal, or (5) it reported exclusively on a study of a group of women who received postmastectomy RT versus breast-conserving surgery (BCS) plus RT.

Because of the limited high-quality evidence available for the local therapy clinical questions, recommendations were developed using the ASCO modified Delphi formal consensus methodology.[23] This process involved the drafting of recommendations by a subgroup of the joint ASCO-ASTRO-SSO Expert Panel using clinical expertise and the available evidence. The Expert Panel (N = 18) met in person to review and refine the recommendations. The Expert Panel was then supplemented by additional experts (N = 37),

who were recruited to rate their agreement with the recommendations. The entire membership of 52 experts is referred to as the Consensus Panel (Data Supplement 6). Each recommendation had to be agreed upon by at least 75% of Consensus Panel respondents to be accepted. This methodology is described in further detail elsewhere (www.asco.org/guideline-methodology).

The recommendations for the systemic therapy questions were developed based on a systematic review of phase II or phase III randomized controlled trials (RCTs) for the period from January 1, 2005, through September 26, 2019, and on clinical experience. Articles were selected for inclusion in the systematic review if they reported data on outcomes of systemic therapy (platinum-based chemotherapy, targeted therapy with PARP inhibitors) among women with newly diagnosed nonmetastatic or advanced breast cancer and a high- or moderate-penetrance germline mutation. Disease outcomes considered in the studies included in the literature were pathologic complete response (pCR), response rate, survival, health-related quality of life, and safety and treatment toxicity. Articles were excluded from the systemic therapy literature review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language.

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 and strength of recommendation and quality of evidence are provided with 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

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; 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 58 articles satisfied the inclusion criteria for the local therapy clinical questions and form the evidentiary basis for the corresponding guideline recommendations. The studies included in the review are summarized in Data Supplement Tables 1-13. Three studies addressed the role of breast-conserving therapy (BCT; BCS/RT) versus unilateral mastectomy for the index tumor in women with breast cancer who have a germline mutation,[24-26] four addressed the role of nipple-sparing surgery among *BRCA* mutation carriers undergoing mastectomy,[27-30] 17 reported on the role of contralateral prophylactic mastectomy for women

with breast cancer who have a germline mutation,[18,31-46] and 28 addressed the role of RT in women with breast cancer who have a germline mutation.[19,25,26,32,40,47-69] The search identified six guidelines or systematic reviews and meta-analyses[70-75] that provided confirmatory, supplementary evidence (Data Supplement Table 15).

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 an in-person meeting. Then, the full Consensus Panel conducted two rounds of voting (Data Supplement 5). During the first round, agreement with the individual recommendations ranged from 72% to 98%, with an average agreement rating of 90%. The number of respondents across recommendations ranged from 47 to 49.

Just one of the 17 recommendations did not reach the required 75% agreement threshold ("For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, CRRM can be offered. The impact of CRRM on decreasing risk of CBC is dependent on the individual gene"). This recommendation was revised based on comments from the Consensus Panel's first round of voting, and the revised recommendation underwent a second round of voting with the full Consensus Panel. Agreement with the recommendation in round 2 was 90% (n = 50 respondents). Consensus results for all of the recommendations, by round, are provided in the Data Supplement.

Six articles satisfied the inclusion criteria for the review conducted to address the systemic therapy clinical questions.[20-22,76-78] The studies included in the review are summarized in Data Supplement Table 14. The identified RCTs were published between 2017 and 2018. Study quality was formally assessed for the six RCTs identified (Data Supplement 3). Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Refer to the Methodology Manual for definitions of ratings for overall potential risk of bias (www.asco.org/guideline-methodology).

Table 2 lists the local and systemic hereditary breast cancer management guideline recommendations by *BRCA1/2* versus moderate-penetrance genes.

RECOMMENDATIONS

CLINICAL QUESTION 1

Providers caring for patients with breast cancer with germline *BRCA1/2* mutations should discuss treatment options related to the index cancer and the increased risk of CBC and new ipsilateral breast cancer.

What is the appropriate surgical management of the index malignancy for women with newly diagnosed nonmetastatic breast cancer who have a *BRCA1/2* mutation?

Recommendation 1.1

Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for BCT from receiving BCT (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.2

Surgical management of the index malignancy (BCT v ipsilateral therapeutic and CRRM) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 1.3

The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy in *BRCA1/2* mutation carriers: age at diagnosis (the strongest predictor of future contralateral breast cancer; Table 1), family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian), ability of patient to undergo appropriate breast surveillance (magnetic resonance imaging [MRI]), comorbidities, and life expectancy (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 1.4

BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. The systematic review identified three studies that bear on the question of the appropriate surgical management for women with newly diagnosed nonmetastatic breast cancer who have a *BRCA1/2* mutation (Data Supplement Tables 1 and 2). Nilsson et al[24] compared local recurrence (LR) rates and survival between *BRCA1/2* mutation carriers treated with BCT and those treated with mastectomy. In this cohort study, *BRCA1/2* carriers treated with BCT versus mastectomy had a higher risk of LR as first recurrence, although many of the LRs in the BCT group were likely new primary breast cancers. Nilsson et al found no significant differences in death resulting from breast cancer, distant recurrence, or overall survival (OS) between the BCT group and the mastectomy group.

Pierce et al[25] compared clinical outcomes (local failure as first failure, development of CBC, and survival) of women with *BRCA1/2* mutations who were treated for stage I to III

breast cancer between those with BCT and those treated with mastectomy. Local failure as first event was significantly more likely among women treated with BCT compared with women treated with mastectomy (cumulative estimated risk at 15 years, 23.5% *v* 5.5%, respectively), although most of these events (70%) seemed to be second primary cancers versus true recurrences. The lower rate of local failure with mastectomy included women who received postmastectomy RT because of a significant risk of locoregional recurrence. The risk of CBC was high regardless of treatment (BCT or mastectomy). There were no significant differences observed between the two treatment groups in breast cancer–specific survival or OS.

Finally, van den Broek et al[26] studied the effects of BCT versus mastectomy in *BRCA1/2* mutation carriers compared with noncarriers on a range of clinical outcomes (OS, breast cancer–specific survival, metastasis-free survival, breast cancer disease-free survival [DFS], LR, and ipsilateral breast cancer risk). In both noncarriers and *BRCA1* mutation carriers, patients treated with BCT had similar OS compared with patients treated with mastectomy (Data Supplement Table 2). Similarly, the LR rate after BCT was not different between *BRCA1* carriers (10-year LR risk, 7.3%) and noncarriers (10-year LR risk, 7.9%). Numbers for *BRCA2* carriers were insufficient to draw conclusions.

Considering the published literature, these studies suggest that BCT is a safe surgical option for management of the index breast cancer in *BRCA1/2* carriers, although it is important to counsel patients regarding the elevated risk of ipsilateral second primary breast cancer and CBC. The studies to date include relatively small numbers of patients, limiting subgroup analysis and evaluation of potential modifying factors. All of the studies are observational studies and therefore at risk for selection bias, and follow-up is too short to evaluate lifetime risk.

CLINICAL QUESTION 2

What is the appropriate surgical management of the index malignancy for women with newly diagnosed nonmetastatic breast cancer who have a selected moderate-penetrance mutation?

Recommendation 2.1

For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.2

In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT should be offered to patients for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.3

The evidence regarding CBC risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data for *CHEK2* 1100delC. Information about the specific gene and what is known about the risk of CBC should be discussed in the context of shared decision making (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 2.4

Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. There is no evidence from studies of women with newly diagnosed nonmetastatic breast cancer who have a selected moderate-penetrance mutation to inform clinical questions regarding the appropriate surgical management of these patients. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of women with newly diagnosed nonmetastatic breast cancer who have a selected moderate-penetrance mutation and on extrapolation from studies on surgical management conducted in women with newly diagnosed nonmetastatic breast cancer who have a *BRCA1/2* mutation.

CLINICAL QUESTION 3

Among women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance non-*BRCA1/2* germline mutations who are undergoing therapeutic mastectomy, what is the role of nipple-sparing mastectomy?

Recommendation 3.1

For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in *BRCA1/2*, nipple-sparing mastectomy can be offered to patients for whom nipple-sparing mastectomy is an appropriate oncologic treatment option (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2

For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in a moderate-penetrance gene, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. BRCA1/2 mutation carriers. There are limited published data specific to nipple-sparing mastectomy in women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in *BRCA1/2*. Two studies have addressed this question (Data Supplement Table 3). Manning et al[29] evaluated clinical outcomes among 26 *BRCA1/2* mutation carriers who underwent nipple-sparing mastectomy for the treatment of early-stage breast cancer (mean tumor size, 1.4 cm; range, 0.1-3.5 cm) and contralateral prophylactic mastectomy. At a median follow-up of 2.34 years, there were no cases of LR or regional recurrence in this group and an acceptable complication rate. Nipple-areolar or flap necrosis was the most common surgical complication (7.3% of 89 total patients, including the 63 patients who underwent prophylactic nipple-sparing mastectomy). There were seven cases of infection (4% of 89 patients). There were two deaths in the therapeutic mastectomy group. One patient died as a result of distant metastases 2 years after nipple-sparing mastectomy for stage IIA breast, and one patient died as a result of metastatic ovarian cancer.

Yao et al[30] studied 51 *BRCA1/2* mutation carriers who underwent therapeutic nipple-sparing mastectomy for breast cancer. After a mean follow-up period of 32.6 months, there were three cancer events: one LR and distant recurrence 11 months after the original therapeutic nipple-sparing mastectomy, and two axillary recurrences. None of the patients with breast cancer treated with nipple-sparing mastectomy had a recurrence at the nipple-areolar complex.

These studies suggest that nipple-sparing mastectomy in appropriately selected *BRCA1/2* carriers is associated with low rates of locoregional recurrence and low complication rates; however, larger series and longer follow-up are needed. In women with *BRCA1/2* mutations with breast cancer, nipple-sparing mastectomy can be considered in those who otherwise, based on patient and tumor factors, would be considered for nipple-sparing mastectomy. Tumor size, location, nodal status, and breast size should be taken into consideration in the decision-making process for nipple-sparing mastectomy.

Literature review and analysis. **Women with a moderate-penetrance germline mutation.** There is no evidence from studies of women with newly diagnosed breast cancer who have a deleterious moderate-penetrance germline mutation and are undergoing therapeutic mastectomy to inform the clinical question regarding the role of nipple-sparing surgery in these patients. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of women with newly diagnosed breast cancer who have a selected moderate-penetrance mutation and on extrapolation from the limited research on nipple-sparing surgery conducted in women with newly diagnosed breast cancer who have a *BRCA1/2* mutation.[29,30]

CLINICAL QUESTION 4

What is the role of contralateral prophylactic mastectomy for women with breast cancer who have a *BRCA1/2* mutation or a selected moderate-penetrance gene mutation?

Recommendation 4.1

For women with breast cancer who have a *BRCA1/2* mutation and who have been treated or are being treated with unilateral mastectomy, CRRM should be offered. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and role of risk-reducing mastectomy: age at diagnosis (the strongest predictor of future contralateral breast cancer), family history of breast cancer, overall prognosis from this or other cancers (eg, ovarian), ability of patient to undergo appropriate breast surveillance (MRI), comorbidities, and life expectancy (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.2

For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding CRRM should not be based predominantly on mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. BRCA1/2 **mutation carriers.** The systematic review identified seven studies that inform the question of the role of contralateral prophylactic mastectomy for women with breast cancer who have a *BRCA1/2* mutation (Data Supplement Tables 4 and 5). A study by Kaas et al[38] evaluated events in the contralateral breast in a consecutive series of *BRCA1/2* mutation carriers with breast cancer who had contralateral prophylactic mastectomy. After 580 follow-up years (mean, 5.4 years), just one incident invasive breast cancer was detected.

Six studies evaluated the efficacy of contralateral prophylactic mastectomy on OS outcomes in *BRCA1/2* mutation carriers with breast cancer.[18,36,41,43-45] Evans et al[36] investigated whether contralateral risk-reducing mastectomy improved survival in a series of women with unilateral breast cancer and *BRCA1/2* mutations. In women (n = 105) who elected to have CRRM, the 10-year OS was 89%; in the group (n = 593) of women who did not undergo CRRM, the 10-year OS was 71% ($P < .001$). In a separate

matched case-control analysis designed to control for potential confounding factors (the effect of bilateral risk-reducing salpingo-oophorectomy [RRSO], stage at diagnosis, and tumor characteristics), survival in the 105 CRRM cases was 89% versus 73% in 105 controls who did not have risk-reducing surgery (hazard ratio [HR], 0.37; 95% CI, 0.17 to 0.80; $P = .008$).

Heemskerk-Gerritsen et al[18] studied the efficacy of CRRM with regard to OS in 583 *BRCA1/2* mutation carriers with a history of primary breast cancer. In the group of women who elected to have CRRM (n = 242), mortality was lower than in the group of 341 women who chose surveillance (21.6 *v* 9.6 per 1,000 person-years of observation; HR, 0.49; 95% CI, 0.29 to 0.82). Exploratory analyses revealed that the survival benefit after CRRM was particularly evident in patients age < 40 years, in patients who were not treated with adjuvant chemotherapy, and in patients having a primary breast cancer with grade 1/2 differentiation and/or no triple-negative phenotype.

In a retrospective analysis of *BRCA1/2* mutation carriers with stage I or II breast cancer, Metcalfe et al[41] compared breast cancer–specific survival outcomes of women treated with unilateral mastectomy (n = 209) with those of women treated with bilateral mastectomy (n = 181). The survival rate at 20 years for women who had contralateral mastectomy was 88% (95% CI, 83% to 93%); the survival rate for women who had unilateral mastectomy was 66% (95% CI, 59% to 73%). Women treated with bilateral mastectomy were 48% less likely to die as a result of breast cancer than women treated with unilateral mastectomy within 20 years of their breast cancer diagnosis (adjusted HR, 0.52; 95% CI, 0.29 to 0.93; $P = .03$).

Three additional studies have reported data on the efficacy of contralateral prophylactic mastectomy with regard to survival outcomes in *BRCA1/2* mutation carriers with nonmetastatic breast cancer. Soenderstrup et al[44] found that CRRM was associated with a significantly reduced risk of death (adjusted OS HR, 0.42; 95% CI, 0.21 to 0.84; $P = .01$) but not with DFS in 237 patients with a *BRCA1/2* mutation (*BRCA1*, n = 141; *BRCA2*, n = 96); Schmidt et al[43] observed a protective effect of CRRM on OS in *BRCA1* mutation carriers diagnosed with breast cancer before 50 years of age, but not in noncarriers; and van Sprundel et al[45] reported that, in *BRCA* mutation carriers with unilateral invasive breast cancer, OS was 94% in the contralateral prophylactic mastectomy group versus 77% in the surveillance group ($P = .03$), although this effect was no longer statistically significant after adjusting for bilateral prophylactic oophorectomy (BPO). van Sprundel et al observed that, independent of the effect of BPO, contralateral prophylactic mastectomy did reduce the relative risk of CBC by 91% in this population of *BRCA1/2* carriers with unilateral breast cancer.

While multiple studies have shown that CRRM improves survival, controlling for confounding factors often demonstrated no survival advantage from CRRM. These studies have significant selection bias,[71] with healthier, younger patients undergoing CRRM potentially accounting for the improved outcomes seen. In addition, outcomes after CRRM were not compared with outcomes with currently recommended breast cancer surveillance strategies, namely annual breast MRI plus annual mammography. Overall, there is insufficient evidence that CRRM does or does not improve survival to require CRRM in this situation. However, while the survival benefit of CRRM remains unclear, the benefit of CRRM to decrease subsequent CBC in *BRCA* mutation carriers is clear.

Literature review and analysis. **Moderate-penetrance germline mutation carriers.** There is no evidence from studies of women with newly diagnosed nonmetastatic breast cancer who have a selected moderate-penetrance mutation to inform the clinical question regarding the role of contralateral prophylactic mastectomy in these patients. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of women with newly diagnosed nonmetastatic breast cancer who have selected moderate-penetrance mutations, on extrapolation from studies on CRRM conducted in women with newly diagnosed nonmetastatic breast cancer who have a *BRCA* mutation, and on the limited literature concerning the risk of CBC among women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene.[31,33,35,37,39,46]

CLINICAL QUESTION 5

Among women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance mutation who are undergoing CRRM, what is the role of nipple-sparing mastectomy?

Recommendation 5.1

For patients with breast cancer with a deleterious germline *BRCA1/2* mutation interested in CRRM, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.2

For patients with breast cancer with a mutation in a moderate-penetrance gene who are interested in CRRM, physicians should discuss nipple-sparing mastectomy as a reasonable oncologic option (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. Women with a deleterious BRCA1/2 mutation. Jakub et al[28] reported on the oncologic safety of nipple-sparing mastectomy among 346 women with *BRCA1* (n = 201) or *BRCA2* (n = 145) mutations, 144

of which were contralateral risk-reducing nipple-sparing mastectomies and 202 of which were bilateral risk-reducing nipple-sparing mastectomies (Data Supplement Table 7). The primary outcome was the development of a new breast cancer (invasive breast cancer or ductal carcinoma in situ) in the chest wall or regional nodes after undergoing nipple-sparing mastectomy. With a median follow-up of 34 months, no new breast cancers occurred in any of the women undergoing nipple-sparing mastectomy. With short term follow-up, nipple-sparing mastectomy is a reasonable approach for risk-reducing mastectomy in patients with *BRCA1/2* mutations.

Literature review and analysis. Women with a moderate-penetrance germline mutation. There is no evidence from studies of women with newly diagnosed nonmetastatic breast cancer who have selected moderate-penetrance mutations to inform the clinical question regarding the role of nipple-sparing contralateral prophylactic mastectomy in these patients. These recommendations represent the best clinical opinion of the Expert Panel based on personal experience in the management of women with newly diagnosed nonmetastatic breast cancer who have selected moderate-penetrance mutations and on extrapolation from studies on nipple-sparing contralateral prophylactic mastectomy conducted in women with newly diagnosed nonmetastatic breast cancer who have a *BRCA* mutation.

CLINICAL QUESTION 6

What is the role of RT in women with breast cancer who have a *BRCA1/2* germline mutation or selected moderate-penetrance non-*BRCA1/2* germline mutation?

Recommendation 6.1

For women with breast cancer who are treated with BCT or with mastectomy for whom postmastectomy RT is considered, RT should not be withheld because of mutation status alone, except for mutations in *TP53* (see Recommendation 6.3). There is no evidence of a significant increase in toxicity or CBC events related to radiation exposure among patients with a mutation in a *BRCA1/2* or moderate-penetrance gene (Type: formal consensus; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.2

For women with breast cancer who are carriers of an ATM mutation, RT should be offered when clinically indicated. Data regarding rates of toxicity between *ATM* mutation carriers and noncarriers are limited and inconsistent. Potential absolute risks seem to be small; however, more research is needed. Discussion with *ATM* carriers interested in BCT is encouraged (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 6.3

For women with breast cancer who are carriers of a germline *TP53* mutation, irradiation of the intact breast is contraindicated. Mastectomy is the recommended therapeutic option. Postmastectomy RT should only be considered in patients with significant risk of locoregional recurrence (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis. RT in women with breast cancer who have a BRCA1/2 mutation versus noncarriers. The systematic review identified 10 studies that addressed the role of RT after BCS in women with breast cancer who have a *BRCA1/2* mutation. In a retrospective cohort study of 305 women of Ashkenazi Jewish descent, Robson et al[63] evaluated the importance of *BRCA1/2* mutation status in determining outcomes (including CBC incidence, distant DFS, and breast cancer–specific survival) after BCT. The authors reported that, after BCT, women with *BRCA1/2* mutations (n = 28) were at elevated risk for breast cancer–related events; they were also more likely to develop CBC, and their distant DFS and breast cancer–specific survival were shorter compared with women without mutations (n = 277; Data Supplement Table 10).

Haffty et al[54] compared the risk of ipsilateral and contralateral breast events in patients with breast cancer and *BRCA1/2* germline mutations (n = 22) with the risk in women who had sporadic breast cancer (n = 105). All patients had early-onset disease (average age at diagnosis, 37 years; range, 25-42 years) and underwent BCS and received RT. The results revealed that, after 12 years of follow-up, the group with *BRCA* mutations had significantly higher rates of both ipsilateral (49% *v* 21%; $P = .007$) and contralateral events (42% *v* 9%; $P = .001$) than the group with sporadic cancer. Looking at the outcomes in the *BRCA1/2* carriers only, these data demonstrated similar rates of ipsilateral and contralateral events at 10 to 15 years after initial diagnosis.

In a study of ipsilateral breast tumor recurrence (IBTR)/events after BCT, Seynaeve et al[64] found that hereditary breast cancer (including 26 patients with *BRCA1/2* mutations) was associated with a greater frequency of early recurrences (2-5 years after initial treatment) and late LRs (> 5 years after initial treatment). Pierce et al[19] compared 10-year rates of IBTR/events after BCS and RT among *BRCA1/2* mutation carriers and women with sporadic breast cancer and found no statistically significant difference. However, when carriers who underwent oophorectomy were excluded from analysis, the incidence of in-breast events was significantly greater for carriers than controls. CBCs were significantly more frequent in carriers compared with controls; use of tamoxifen significantly reduced the risk of CBC events.

Brekelmans et al[68] compared rates of ipsilateral recurrence, CBC, and survival outcomes observed among

women with sporadic breast cancer (n = 759) with rates of these outcomes observed in three cohorts of patients with hereditary breast cancer—103 cases from families with an identified *BRCA2* mutation, 223 cases from families with an identified *BRCA1* mutation, and 311 cases from families testing negative for *BRCA1/2* mutations. The incidence of CBC in *BRCA2*-associated breast cancer was identical to the rate seen in the *BRCA1*-associated breast cancer group; however, it was significantly higher than the rates seen in the non-*BRCA1/2* and sporadic breast cancer subgroups. The authors did not, however, observe differences in ipsilateral breast event rates between the groups.

Three other studies investigated the outcome of BCT in *BRCA* mutation carriers after BCS and RT. With > 13-year overall median follow-up, Kirova et al[57] found no significant difference in rates of ipsilateral cancer between mutation carriers (n = 27), familial cases found to be noncarriers (n = 104), and controls with sporadic disease (n = 261) in a matched retrospective case-control study. However, the CBC rate was significantly higher in familial cases, with rates of 40.7% in mutation carriers, 20%, in familial noncarriers, and 11% in controls. Garcia-Etienne et al[53] reported that, after BCS and RT, both the 10-year cumulative incidence of ipsilateral breast tumor recurrence/events and 10-year incidence of CBC were increased among *BRCA1/2* mutation carriers (n = 54) versus matched patients with sporadic breast cancer (n = 162). In contrast, in a study of *BRCA1/2* mutation carriers compared with noncarriers, van den Broek et al[26] found that, after BCS and RT, the risk of LR/events seemed to be similar between noncarriers and *BRCA1* mutation carriers and somewhat higher for *BRCA2* carriers, but patient numbers in the analyses were limited. Cao et al[69] reported risks of ipsilateral events in 103 *BRCA1/2* carriers and 1,844 noncarriers in China treated with BCS and RT. With 6.7-year median follow-up, there was no significant difference between the two groups.

Three studies that investigated RT-related toxicity in patients with breast cancer with *BRCA1/2* mutations showed that rates of radiation-associated complications in women with *BRCA1/2* mutations were comparable to rates observed in women with sporadic breast cancer.[61,62,65] Pierce et al[62] reported that there were no significant differences in the rate of chronic skin, subcutaneous tissue, lung, or bone complications between the genetic (n = 71 women with *BRCA1/2* mutations) and sporadic cohorts (n = 213) of patients with stage I or II breast cancer who were treated with BCS including RT. Shanley et al[65] similarly found comparable acute and late radiation effects in the treated breast in women with *BRCA1/2* mutations (n = 55) and in women with sporadic breast cancer (n = 55) who were evaluated in a matched case-control study of patients treated with RT. Finally, Park et al[61] observed no increased risk in acute skin toxicity in nonwhite women with breast cancer and *BRCA1/2* mutations (n = 46) who underwent BCT using RT compared with women with sporadic breast cancer. Among *BRCA1/2* mutation carriers, there was no enhancement in radiation sensitivity relative to controls.

Five studies evaluated the association between RT for primary breast cancer and risk of CBC in women with a *BRCA1/2* mutation. Broeks et al[51] conducted a case-only study to investigate the association between radiation-induced CBC and germline mutations in DNA damage repair pathway (DDRP) genes, including *BRCA1* (n = 27) and *BRCA2* (n = 5). The authors evaluated 247 consecutive patients with CBC, 169 of whom received RT and 78 of whom did not receive RT. Analyses revealed that, compared with noncarriers, carriers of a germline mutation in a DDRP gene had an increased risk of developing a radiation-associated CBC. Frequencies of CBCs in *BRCA1* and *BRCA2* carriers were individually reported, however, and were not increased when compared with rates in noncarriers.

A study of women with stage I to III breast cancer and a *BRCA1/2* mutation, treated with either BCS with breast RT or mastectomy with or without postmastectomy RT, reported by Pierce et al[25] (reviewed above) found that CBC was common (> 40%) in all carriers independent of whether they received RT. Metcalfe et al[67] studied the extent to which cancer treatment–related factors modified the risk of CBC in *BRCA1/2* carriers and reported that RT was not associated with an increase in CBC risk.

Bernstein et al[49] conducted a population-based nested case-control study (the WECARE Study) to investigate if the risk of CBC associated with RT for breast cancer was higher among germline *BRCA1/2* mutation carriers than among nonmutation carriers. The authors concluded based on their findings that there was not a clear indication that *BRCA1/2* mutation carriers were more susceptible to radiation-induced CBC than noncarriers; there was no statistically significant incremental increase in the risk of CBC that was associated with radiation dose among carriers.

Lastly, in a retrospective cohort study, Drooger et al[52] found no association between RT for primary breast cancer and the risk of CBC in *BRCA1/2* mutation carriers. This was the case even in patients who received RT before the age of 40 years.

Literature review and analysis. RT in women with breast cancer who are carriers of an ATM mutation. Seven studies identified by the systematic review addressed RT after BCT among women with breast cancer who are *ATM* mutation carriers. Meyer et al[60] evaluated survival outcomes in a cohort of 138 patients with early-stage breast cancer treated with BCS followed by RT, of whom 20 were found to carry either an *ATM* truncating or missense variant. Actuarial rates of local relapse-free survival at 7 years between carriers and noncarriers did not significantly differ. Su

et al[66] reported no excess of CBC or treatment-related toxicity in the *ATM* mutation carriers with stage I or II breast cancer whom they studied, 14 of whom had received adjuvant RT.

Iannuzzi et al[56] studied radiation-induced complications among *ATM* mutation carriers (n = 6) with early-stage breast cancer who received adjuvant RT after BCS. There was a significant correlation between *ATM* mutation status and the occurrence of grade 3 to 4 subcutaneous late effects after RT for breast cancer. By contrast, Bremer et al[50] found no evidence of increased radiation-related acute or late skin or subcutaneous adverse effects in the 10 *ATM* mutation carriers who received at least one course of adjuvant RT.

Three studies provide data on the risk of CBC after BCT and adjuvant RT among *ATM* mutation carriers. Su et al,[66] as mentioned above, found no excess of CBC in the 14 patients whom they evaluated. Broeks et al,[51] in a case-only study that examined the association between radiation-induced CBC and germline mutations in DDRP genes, identified four carriers with pathogenic truncating *ATM* mutations from among all patients with CBC tested. A statistically significant increase in *ATM* carriers among CBC cases identified after RT was not demonstrated. Lastly, in a population-based case-control study, Bernstein et al[48] found that women with breast cancer who carried a rare *ATM* deleterious missense variant (defined as occurring in < 1% of the study population) who were exposed to scatter RT (median exposure, 1.2 Gy) were at a significantly higher risk of CBC compared with unexposed women with wild-type *ATM* (risk ratio [RR], 2.8; 95% CI, 1.2 to 6.5) or unexposed women who carried the same predicted deleterious missense variant (RR, 5.3; 95% CI, 1.6 to 17.3).

Literature review and analysis. RT in women with breast cancer who are carriers of a TP53 mutation. The *p53* gene is perhaps the most critical tumor suppressor gene in preventing the development of cancer. It plays an important role in cell cycle control and apoptosis in that it provides the cell with the ability to respond to and repair DNA damage after cellular stress by triggering multiple downstream repair pathways. Thus, carriers of a *TP53* mutation would be expected to be unable to repair tissue damage from DNA-damaging RT and be at risk for significant RT-associated sequelae. For these reasons, there is limited evidence to inform the clinical question of the role of RT in women who are carriers of a *TP53* mutation. The recommendation offered by the Expert Panel therefore represents the best clinical opinion of the Expert Panel. A single case series has bearing on the clinical question. Heymann et al[55] studied the clinical outcomes of six patients with germline *TP53* mutations who had received RT after breast cancer surgery. In this group of six women, there were three contralateral breast cancers, three ipsilateral breast recurrences, two RT-induced cancers, and three new primary cancers. There was, by contrast, just one event, a CBC, among patients who had not received postoperative RT. Outcomes reported in published case reports support this recommendation against RT in women with breast cancer who are carriers of a *TP53* mutation.[79-83]

CLINICAL QUESTION 7

What is the role of platinum in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and advanced breast cancer?

Recommendation 7

When offering chemotherapy for germline *BRCA* mutation carriers with metastatic breast cancer, platinum chemotherapy is preferred to taxane therapy for patients who did not previously received platinum. There are no data to address platinum efficacy in other germline mutation carriers (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. The systematic review identified one prospective RCT that addressed the role of platinum in women with a *BRCA1/2* mutation and advanced breast cancer (Data Supplement Table 14). The Triple Negative Breast Cancer Trial (TNT) compared the efficacy of single-agent carboplatin with that of docetaxel in patients with metastatic TNBC.[22] The primary end point was objective response; progression-free survival (PFS) was one of several secondary end points. In the subset of 43 patients with *BRCA1/2* breast cancer (TNBC, n = 32; estrogen receptor (ER) –positive breast cancer, n = 11), the 25 women who received carboplatin had a greater objective response rate (ORR) and longer PFS than the 18 women who received docetaxel (carboplatin: ORR, 68%; PFS, 6.8 months; docetaxel: ORR, 33.3%; PFS = 4.4 months). There was no difference in the ORR observed between the carboplatin (ORR, 31.4%) and docetaxel (ORR, 34.0%) groups in the unselected population (n = 376 patients). The authors concluded that patients with metastatic breast cancer who harbor *BRCA1/2* mutations benefit from platinum chemotherapy.

CLINICAL QUESTION 8

What is the role of (neo)adjuvant platinum in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and breast cancer?

Recommendation 8

For germline BRCA mutation carriers with breast cancer treated with (neo)adjuvant therapy, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. While single-agent platinum has demonstrated activity in the neoadjuvant setting, there are no data yet comparing it with standard chemotherapy. There are no data to address platinum efficacy in other germline mutation carriers (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. Two studies addressed the efficacy of neoadjuvant platinum in women who have a *BRCA1/2* mutation (Data Supplement Table 14). Hahnen et al[76] reported on the results of a secondary analysis of data from the GeparSixto trial,[84] which evaluated whether *BRCA1/2* mutation status affected the response (pCR and DFS) to carboplatin or noncarboplatin therapy in 291 patients with TNBC. In this analysis, the pCR rate was 66.7% for patients with *BRCA* mutations and 36.4% for patients without *BRCA* mutations (odds ratio, 3.50; 95% CI, 1.39 to 8.84; $P = .008$). The high pCR rate seen in patients with *BRCA* mutations was not further increased, however, with the addition of carboplatin. By contrast, patients without *BRCA* mutations benefited from the addition of carboplatin. Results of the post hoc exploratory subgroup analyses for *BRCA* germline mutation status from the BrighTNess trial by Loibl et al[78] that compared pCR response between patients in the paclitaxel plus carboplatin group versus those patients who received paclitaxel alone are consistent with this lack of additive benefit of platinum in women with a *BRCA1/2* mutation (Fig 3C by Loibl et al).

CLINICAL QUESTION 9

What is the role of PARP inhibitors in women who have a *BRCA1/2* mutation or selected moderate-penetrance germline mutation and advanced breast cancer?

Recommendation 9.1

For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line settings. For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, there are no data directly comparing efficacy of PARP inhibitors with platinum chemotherapy (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 9.2

For patients with breast cancer with germline mutations in moderate-penetrance genes, there are currently no robust data to support the use of PARP inhibitors (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Literature review and analysis. Two large-scale RCTs addressed the role of PARP inhibitors in women who have a *BRCA1/2* mutation and advanced breast cancer (Data Supplement Table 14). In an open-label phase III RCT (OlympiAD), Robson et al[21] 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 metastatic breast cancer and a germline *BRCA* mutation. Median PFS, the primary trial end point, was significantly longer in the group receiving olaparib monotherapy than in the group receiving standard chemotherapy (7.0 *v* 4.2 months; HR for disease progression or death, 0.58; 95% CI, 0.43 to 0.80). In the olaparib group, the risk of disease progression or death 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 adverse events in patients who received olaparib was 36.6%; it was 50.5% in the group receiving standard chemotherapy. Health-related quality of life measures were also superior with olaparib than with chemotherapy.

Litton et al[20] 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. In the talazoparib group, median PFS was significantly longer than in the standard chemotherapy group (8.6 *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 TNBC or ER-positive breast cancer. There were also differences in the patient-reported outcomes of global health status quality-of-life and breast symptoms. As compared with standard chemotherapy, talazoparib treatment resulted in a significant delay in the onset of clinically meaningful deterioration, significant improvement in global health status quality of life, and improvement in breast symptom scale score from baseline.

The guideline systematic review identified a single study that provides data on the question of combining a PARP inhibitor and chemotherapy in germline *BRCA* mutation carriers with advanced breast cancer (Data Supplement Table 14). Han et al[77] reported the results of a randomized phase II clinical trial (BROCADE) that compared efficacy and safety of intermittent veliparib plus temozolomide (n = 94) or veliparib plus carboplatin/paclitaxel (VCP; n = 97) versus placebo plus carboplatin/paclitaxel (PCP; n = 99) in women with *BRCA1/2*-mutated locally recurrent or metastatic breast cancer. There were no statistically significant differences between the treatment groups in the primary trial end point of PFS. ORR, a secondary trial end point, was significantly improved with VCP (VCP: 78% [56 of 72]; PCP: 61.3% [49 of 80]; $P = .027$).

Finally, there are insufficient data to inform the use of PARP inhibitors in patients with moderate-penetrance germline mutations. The Expert Panel's recommendation against the current use of PARP inhibitors in this population represents the best clinical opinion of the Expert Panel members based on informal consensus.

CLINICAL QUESTION 10

What is the role of PARP inhibitors in women who have a *BRCA1/2* mutation or selected moderate-penetrance mutation and nonmetastatic breast cancer?

Recommendation 10

For germline *BRCA* mutation carriers, there are insufficient data at this time to recommend a PARP inhibitor for patients with nonmetastatic breast cancer (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. One study (BrighTNess) addressed the role of PARP inhibitors in women who have a *BRCA1/2* germline mutation and nonmetastatic breast cancer. Loibl et al[78] reported on a prespecified subgroup analysis of *BRCA* status (*BRCA1* or *BRCA2* mutation or both) that compared the proportion of patients who achieved pCR between the paclitaxel plus carboplatin plus veliparib group versus the paclitaxel plus carboplatin group. There was no evidence of an additive effect of veliparib in this subgroup analysis for *BRCA* mutation carriers with nonmetastatic breast cancer; the frequency of pCR did not differ between patients who received paclitaxel plus carboplatin plus veliparib (57%) and patients who received paclitaxel plus carboplatin (50%; risk difference, 6.5; 95% CI, −18.1 to 31.1).

DISCUSSION

Locoregional Management of Hereditary Breast Cancer

BRCA *mutation carriers.* The recommendations provided for locoregional management of nonmetastatic hereditary breast cancer are based on Expert Panel consensus because data from RCTs are lacking; most of the available data are derived from observational studies. Despite this relative lack of existing high-quality evidence, the Consensus Panel of > 50 experts reached or exceeded the 75% agreement threshold for all of the practice recommendations.

The preponderance of data demonstrates that, compared with nonmutation carriers, there is no significant increase in LR after BCT and RT for *BRCA1/2* mutation carriers with newly diagnosed breast cancer (Data Supplement Table 1). Local control of the index breast cancer is similar after BCT for *BRCA1/2* mutation carriers and noncarriers. Most ipsilateral breast events represent new primary breast cancers.[85] In addition, there are no data to support that local toxicity or the risk of contralateral breast cancer is increased for *BRCA* mutation carriers who receive breast irradiation (Data Supplement Tables 9, 10, and 12). Therefore, for mutation carriers who desire breast conservation, BCT should be offered if clinically appropriate. However, many *BRCA1/2* mutation carriers with breast cancer elect bilateral mastectomy because of both the increased rate of second primaries and the increased rate of CBC.

The risk of CBC is significantly higher for *BRCA* mutation carriers than for noncarriers. Several observational retrospective analyses reported a survival advantage for carriers who had contralateral prophylactic mastectomies (Data Supplement Table 4). However, these studies are limited by confounding factors, including patient selection; patients who chose prophylactic mastectomy were younger and healthier and more often had RRSO. In addition, by allowing inclusion of carriers who opted for CRRM many years after initial breast cancer diagnosis, these retrospective studies introduced potential survivor bias for those carriers who lived long enough to opt for CRRM. In addition, outcomes for *BRCA1/2* mutation carriers who opted for CRRM were not compared with those of carriers who underwent annual breast MRI in addition to mammography, the current surveillance recommendation for mutation carriers. The addition of breast MRI to mammography in this population allowed the detection of breast cancer at a lower stage with excellent survival outcomes in one study.[86] Currently, data are insufficient to conclude that there is a survival benefit with prophylactic mastectomy for *BRCA* carriers with breast cancer. More prospective studies of outcomes after prophylactic mastectomy in *BRCA* mutation carriers that control for confounding factors and that require surveillance with breast MRI and mammogram for those who choose BCT are needed.

Therefore, the benefit of prophylactic mastectomy for *BRCA1/2* mutation carriers is primarily to prevent a future breast cancer and allow patients to avoid annual breast MRI and mammography. Prophylactic mastectomy reduces the relative risk of breast cancer by 90% to 95%.[87,88] When discussing contralateral prophylactic mastectomy with *BRCA1/2* mutation carriers, it is essential to provide patients with their absolute risk of CBC. The younger the age at first breast cancer diagnosis, the higher the absolute risk of subsequent CBC.[8,89] For example, at 25 years, the absolute risk of CBC for *BRCA2* carriers diagnosed before age 40 years is 68% versus 20% if diagnosed at age > 50 years (refer to Table 1, reprinted from Kuchenbaecker et al[8]). Charts for determining cumulative risk of a CBC based on age at diagnosis of initial breast cancer, *BRCA1* versus *BRCA2* mutation, and interval since diagnosis have been published.[8,89] Consideration of interventions that may decrease CBC risk in *BRCA1/2* mutation carriers (eg, salpingo-oophorectomy)[90,91] should also be discussed, as should the decreased risk of CBC that results from some of the systemic therapies recommended to treat their index breast cancer (endocrine therapy and chemotherapy). Expert Panel members underscore that several other factors are important when considering prophylactic mastectomy for *BRCA* mutation carriers with breast cancer, including the prognosis of the current breast cancer or other cancers (eg, ovarian), the ability and willingness of the patient to undergo appropriate breast surveillance (MRI), the ability of the patient to tolerate treatment of a subsequent breast cancer, and comorbidities and life expectancy.

Expert Panel members support offering nipple-sparing mastectomy to *BRCA* mutation carriers with breast cancer (depending on tumor size and location and patient

TABLE 1. Contralateral Breast Cancer Incidence Rates per 1,000 Person-Years and Kaplan-Meier Estimates of the Cumulative Risks of CBC by Time Since First Breast Cancer, Overall and Stratified by Age at First Breast Cancer

Years Since First Breast Cancer Diagnosis	No. of Women Contributing in Category	No. of Person-Years	No. of Events	Incidence Rate per 1,000 Person-Years (95% CI)	Cumulative Risk (%; 95% CI)
BRCA1					
1≤ 5	827	2,107	60	28.5 (22.1 to 36.7)	13 (10 to 16)
> 5-10	618	2,071	53	25.6 (19.6 to 33.5)	23 (20 to 27)
> 10-15	435	1,438	33	22.9 (16.3 to 32.3)	32 (28 to 36)
> 15-20	236	675	17	25.2 (15.7 to 40.5)	40 (35 to 45)
> 20-45	132	661	10	15.1 (8.1 to 28.1)	53 (44 to 62)
First breast cancer diagnosis at age < 40 years					
≤ 5	370	920	31	33.7 (23.7 to 47.9)	15 (11 to 21)
> 5-10	278	945	28	29.6 (20.5 to 42.9)	27 (21 to 33)
> 10-15	217	739	20	27.1 (17.5 to 41.9)	36 (30 to 43)
> 15-20	129	378	8	21.2 (10.6 to 42.3)	43 (36 to 50)
> 20-45	70	343	6	17.5 (7.9 to 38.9)	60 (46 to 74)
First breast cancer diagnosis at age ≥ 40-50 years					
≤ 5	283	725	15	20.7 (12.5 to 34.3)	10 (6 to 16)
> 5-10	225	718	19	26.5 (16.9 to 41.5)	21 (15 to 28)
> 10-15	152	480	11	22.9 (12.7 to 41.4)	30 (23 to 38)
> 15-20	74	222	6	27.0 (12.1 to 60.2)	39 (30 to 49)
> 20-39	52	280	4	14.3 (5.4 to 38.1)	49 (37 to 62)
First breast cancer diagnosis at age ≥ 50 years					
≤ 5	174	462	14	30.3 (17.9 to 51.2)	14 (8 to 22)
> 5-10	115	408	6	14.7 (6.6 to 32.7)	20 (14 to 30)
> 10-15	66	219	2	9.1 (2.3 to 36.5)	24 (16 to 35)
> 15-20	33	75	3	40.0 (12.9 to 124.0)	38 (24 to 57)
> 20-27	10	38	0	0.0	38 (24 to 57)
BRCA2					
≤ 5	565	1,468	27	18.4 (12.6 to 26.8)	8 (6 to 12)
> 5-10	476	1,543	26	16.9 (11.5 to 24.8)	16 (12 to 21)
> 10-15	285	880	11	12.5 (6.9 to 22.6)	21 (17 to 26)
> 15-20	138	355	5	14.1 (5.9 to 33.8)	26 (20 to 33)
> 20-43	68	290	3	10.3 (3.3 to 32.1)	65 (25 to 98)
First breast cancer diagnosis at age < 40 years					
≤ 5	180	485	11	22.7 (12.6 to 41.0)	9 (5 to 17)
> 5-10	163	542	9	16.6 (8.6 to 31.9)	17 (11 to 25)
> 10-15	104	314	5	15.9 (6.6 to 38.2)	23 (16 to 32)
> 15-20	58	149	4	26.9 (10.1 to 71.5)	31 (22 to 43)
> 20-43	29	127	2	15.8 (3.9 to 63.0)	68 (29 to 98)

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TABLE 1. Contralateral Breast Cancer Incidence Rates per 1,000 Person-Years and Kaplan-Meier Estimates of the Cumulative Risks of CBC by Time Since First Breast Cancer, Overall and Stratified by Age at First Breast Cancer (continued)

Years Since First Breast Cancer Diagnosis	No. of Women Contributing in Category	No. of Person-Years	No. of Events	Incidence Rate per 1,000 Person-Years (95% CI)	Cumulative Risk (%; 95% CI)
First breast cancer diagnosis at age ≥ 40-50 years					
5≤ 5	206	550	7	12.7 (6.1 to 26.7)	6 (3 to 14)
> 5-10	181	554	9	16.3 (8.5 to 31.2)	14 (8 to 22)
> 10-15	107	322	5	15.5 (6.5 to 37.3)	20 (13 to 29)
> 15-20	52	143	1	7.0 (1.0 to 49.6)	23 (15 to 35)
> 20-37	29	123	1	8.1 (1.2 to 57.7)	28 (17 to 44)
First breast cancer diagnosis at age ≥ 50 years					
≤ 5	179	433	9	20.8 (10.8 to 40.0)	9 (5 to 17)
> 5-10	132	447	8	17.9 (9.0 to 35.8)	17 (11 to 27)
> 10-15	74	244	1	4.1 (0.6 to 29.1)	20 (13 to 30)
> 15-20	28	63	0	0.0	20 (13 to 30)
> 20-30	10	40	0	0.0	20 (13 to 30)

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Abbreviation: CBC, contralateral breast cancer.

breast size) based on existing data (Data Supplement Table 7). Larger series with longer follow-up that confirm the safety of this approach in mutation carriers will be important. Surveillance after nipple sparing mastectomy is the same as after a skin-sparing mastectomy or a total mastectomy with clinical examination, but there is no need for routine breast imaging.

PALB2, CHEK2, and ATM mutation carriers. Given the limited data on patients with breast cancer with mutations in more moderate-penetrance breast cancer susceptibility genes, locoregional management for patients with breast cancer with germline mutations in *PALB2*, *ATM*, and *CHEK2* genes should be the same as for patients with breast cancer without these inherited mutations. It is important for clinicians not to extrapolate risks associated with *BRCA1/2* mutations when caring for these patients.

It is not yet clear to what extent cancer risks are variant specific. For example, the risk of developing an initial breast cancer is approximately threefold higher for women with the inherited *CHEK2* frameshift mutation 1100delC, but only 1.5-fold higher for those with the *CHEK2* missense mutation I157T.[14,92] Whether the relative risks of CBC are also variant specific is unknown.

Similarly, while *ATM* mutation carriers have an approximately threefold increased risk of an initial breast cancer, some missense *ATM* variants are associated with much higher risks. For example, *ATM* c.7271T>G is associated with an 11-fold increased risk of breast cancer.[14,93] Most *ATM* variants are missense, and there is a lack of consensus regarding which variants are pathogenic (ie, mutations). This confounds interpretation of studies, including those that assess risks of RT in patients with breast cancer with germline *ATM* variants.

Data about the risk of CBC that are needed to make informed surgical decisions are lacking for mutations in breast cancer genes other than *BRCA1/2*. Some data exist about CBC risk for patients with the *CHEK2* 1100delC mutation. This frameshift mutation confers an approximately threefold increased risk of CBC, conferring a 10% to 12% absolute risk of CBC at 10 years.[39,46] More data are needed to assess accurate risks of CBC among patients with *CHEK2*, *ATM*, and *PALB2* mutations as well as the factors that modify these risks. Because these mutations confer more moderate breast cancer risks than *BRCA1/2* mutations, other hormonal, environmental, and genetic factors (eg, polygenic risk score) may affect CBC risk even more than for *BRCA1/2* carriers. Large prospective registry studies are needed.

One area that needs higher-quality data relates to concern about the risk of RT in patients with breast cancer with a germline *ATM* mutation. Patients with ataxia telangiectasia (ie, inheritance of biallelic *ATM* mutations) have an increased sensitivity to ionizing radiation, with preclinical data confirming reduced ability of skin cells to replicate after x-ray exposure. Case reports of radiation toxicity in heterozygous *ATM* mutation carriers exist, but whether the incidence is higher than in other breast cancer populations is unclear. One study reviewed by the Expert Panel[48] did report an increased risk of CBC for patients with breast cancer with rare *ATM* variants predicted to be deleterious who received

TABLE 2. Management of Hereditary Breast Cancer in *BRCA1/2* Versus Moderate-Penetrance Genes

Women with breast cancer who have a *BRCA1/2* mutation	
Local therapy recommendations	
Index/current cancer	Germline *BRCA* status should not preclude a patient with newly diagnosed breast cancer otherwise eligible for BCT from receiving BCT.
	Surgical management of the index malignancy (BCT *v* ipsilateral therapeutic and CRRM) in *BRCA1/2* mutation carriers should be discussed, considering the increased risk of CBC and possible increased risk of an ipsilateral new primary breast cancer compared with noncarriers.
	For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in *BRCA1/2*, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients.
	For women with breast cancer who are treated with BCT or with mastectomy for whom postmastectomy RT is considered, RT should not be withheld because of mutation status, except for mutations in *TP53* (see Recommendation 6.3, which states that irradiation of the intact breast is contraindicated in *TP53* carriers). There is no evidence of a significant increase in toxicity or CBC related to radiation exposure among patients with a mutation in a *BRCA1/2*
Contralateral risk-reducing mastectomy (CRRM)	For women with breast cancer who have a BRCA1/2 mutation, CRRM should be discussed. CRRM is associated with a decreased risk of CBC; there is insufficient evidence for improved survival. The following factors should be considered for assessing risk of CBC and the role of risk-reducing mastectomy: -Age at diagnosis (the strongest predictor of future contralateral breast cancer) -Family history of breast cancer -Overall prognosis from this or other cancers (eg, ovarian) -Ability of patient to undergo appropriate breast surveillance (MRI) -Comorbidities -Life expectancy
	For patients with breast cancer with a deleterious germline *BRCA1/2* mutation interested in risk-reducing contralateral mastectomy, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option.
	BRCA1/2 mutation carriers who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI.
Systemic therapy recommendations	When offering chemotherapy for germline *BRCA* mutation carriers with metastatic breast cancer, platinum chemotherapy is preferred to taxane therapy for patients who have not previously received platinum.
	For germline *BRCA* mutation carriers with breast cancer treated with (neo)adjuvant therapy, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy. While single-agent platinum has demonstrated activity in the neoadjuvant setting, there are no data yet comparing it with standard chemotherapy.
	For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line settings. For *BRCA1/2* mutation carriers with metastatic HER2-negative breast cancer, there are no data directly comparing efficacy of PARP inhibitors with platinum chemotherapy.
	For germline *BRCA* mutation carriers, there are insufficient data at this time to recommend a PARP inhibitor for patients with nonmetastatic breast cancer.

(continued on following page)

TABLE 2. Management of Hereditary Breast Cancer in *BRCA1/2* Versus Moderate-Penetrance Genes (continued)

Women with breast cancer who have a mutation in a moderate-penetrance gene	
Local therapy recommendations	
Index/current cancer	For women with newly diagnosed breast cancer who have a mutation in a moderate-penetrance breast cancer susceptibility gene, mutation status alone should not determine local therapy decisions for the index tumor or CRRM.
	In patients with breast cancer with a mutation in a moderate-penetrance breast cancer susceptibility gene, BCT should be offered to patients for whom BCT is an appropriate treatment option. There is a lack of data regarding ipsilateral breast cancer events after BCT among patients with moderate-risk mutations.
	For women with newly diagnosed breast cancer undergoing mastectomy who have a deleterious mutation in a moderate-penetrance gene, nipple-sparing mastectomy is a reasonable oncologic approach to consider in appropriately selected patients.
	For women with breast cancer who are carriers of an ATM mutation, RT should be offered when clinically indicated. Data regarding rates of toxicity between *ATM* mutation carriers and noncarriers are limited and inconsistent. Potential absolute risks seem to be small; however, more research is needed. Discussion with *ATM* carriers interested in BCT is encouraged.
Contralateral risk-reducing mastectomy (CRRM)	For women with breast cancer who have a mutation in a moderate-penetrance breast cancer predisposition gene and who have been treated or are being treated with unilateral mastectomy, the decision regarding CRRM should not be based predominantly on the mutation status. Additional factors that predict CBC such as age at diagnosis and family history should be considered, as they are in all cases. The impact of CRRM on decreasing risk of CBC is dependent on the risk of CBC for each individual gene. Data regarding the risk of CBC resulting from moderate-penetrance genes are limited.
	The evidence regarding CBC risk is limited for mutations in moderate-penetrance breast cancer genes, aside from some data on *CHEK2* 1100delC. Information about the specific gene and what is known about the risk of CBC should be discussed in the context of shared decision making.
	For patients with breast cancer with a mutation in a moderate-penetrance gene who are interested in risk-reducing mastectomy, physicians should discuss the option of nipple-sparing mastectomy as a reasonable oncologic option.
	Patients with mutations in moderate-penetrance genes who do not have bilateral mastectomy should undergo high-risk breast screening of remaining breast tissue with annual mammogram and MRI.
Systemic therapy recommendations	For patients with breast cancer with mutations in moderate-penetrance genes, there are currently no robust data to support the use of PARP inhibitors.There are no data to address platinum efficacy in patients with breast cancer with germline mutations in moderate-risk genes.

Abbreviations: BCT, breast-conserving therapy; CBC, contralateral breast cancer; CRRM, contralateral risk-reducing mastectomy; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PARP, poly (ADP-ribose) polymerase.

RT compared with *ATM* mutation carriers who did not receive RT. However, this finding is not consistent among studies,[32] and questions remain about which *ATM* variants included in the study are indeed pathogenic. Until there are more consistent data demonstrating increased toxicity, RT should not be avoided in patients with breast cancer with heterozygous mutations in *ATM* or any breast cancer gene, other than *TP53*. Clinicians are encouraged to discuss the data about *ATM* mutations and impact of radiation with patients.

For patients with hereditary breast cancer, breast surveillance with an annual breast MRI in addition to annual mammogram is recommended. Common practice is to alternate mammogram with breast MRI every 6 months so that remaining breast tissue is imaged every 6 months, although there are no data to mandate this surveillance schedule. Studies have shown that MRI use detects breast cancers at an earlier stage in *BRCA1/2* mutation carriers.[94] Studies evaluating survival of *BRCA1/2* mutation carriers who are monitored with MRI are scarce, but in one recent report, with a median of 8.1 years of follow-up, the survival outcomes in such patients were excellent.[86] Of 380 *BRCA* mutation carriers previously unaffected with cancer, 28 were diagnosed with invasive cancer, and only one *BRCA1* mutation carrier died after relapse of a node-positive breast cancer diagnosed on her first screen at age 48 years. Data are lacking for benefit of breast MRI in patients with breast cancer with mutations in moderate-penetrance genes; however, 88% of the Consensus Panel members favored this surveillance practice. Factors regarding the risk of CBC associated with a specific gene variant, comorbidities and life expectancy should be considered in shared decision making about breast MRI use.

Systemic Management of Hereditary Breast Cancer

***BRCA* mutation carriers. Platinum chemotherapy.** In the metastatic setting, platinum chemotherapy is preferred to a taxane agent, based on the TNT trial, which showed a significantly higher response to carboplatin than docetaxel.[22] One limitation of this study is that only 11 *BRCA* carriers with ER-positive breast cancer were included, so caution is needed when extrapolating results to carriers with ER-positive disease. In addition, patients in TNT had not previously received platinum. Of note, the ORR to docetaxel was the same among *BRCA1/2* mutation carriers and noncarriers; thus, there was no evidence for taxane resistance among *BRCA* carriers in TNT. Rather, the ORR to carboplatin was superior among *BRCA* carriers than noncarriers.

However, in contrast to noncarriers, platinum does not meaningfully increase the pCR rate among *BRCA1/2* mutation carriers when added to anthracycline- and taxane-based neoadjuvant chemotherapy.[76,78] These results were unexpected given the increased sensitivity to platinum among *BRCA1/2* mutation carriers with metastatic breast cancer in the TNT trial. Whether these seemingly contradictory results reflect increased sensitivity of *BRCA*-related breast cancer to anthracycline-based chemotherapy is not clear. Nevertheless, there does not seem to be an added benefit of platinum after combination anthracycline and taxane chemotherapy. Ongoing randomized trials that compare breast cancer response to platinum- and anthracycline-based chemotherapy in *BRCA* mutation carriers may help clarify the role of platinum in treating mutation carriers with breast cancer (https://clinicaltrials.gov/ct2/show/NCT01670500).

***BRCA* mutation carriers. PARP inhibitors.** For germline *BRCA* mutation carriers with metastatic HER2-negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first- to third-line metastatic settings, based on the two large randomized trials OlympiAD and EMBRACA, respectively (Data Supplement Table 14). There are no data directly comparing efficacy of a PARP inhibitor with platinum chemotherapy.

Combining PARP inhibitors with chemotherapy is challenging because of myelosuppression. The results of BROCADE-3 were recently presented, but were not yet published at the time that guideline writing was completed. This phase III trial evaluated the combination of carboplatin and paclitaxel with or without veliparib in *BRCA1/2* mutation carriers with locally advanced or metastatic breast cancer. It has been reported that the addition of veliparib resulted in a 2-month improvement in median PFS (14.5 *v* 12.6 months; HR, 0.71; 95% CI, 0.57 to 0.88; $P = .002$). ORR and clinical benefit rate were similar in both arms. OS was 33.5 months with veliparib and 28.2 months without the PARP inhibitor, but this was not statistically significant. It is not clear how the results of this trial will be incorporated into clinical practice, in light of the efficacy and improved quality of life demonstrated with monotherapy olaparib or talazoparib compared with nonplatinum single-agent chemotherapy.[20,21]

Combinations of PARP inhibitors with other novel agents, including immune therapy, are being evaluated in the hope of improving the response rate or duration of response to PARP inhibitors for *BRCA* carriers with breast cancer (https://clinicaltrials.gov/ct2/show/NCT02849496, https://clinicaltrials.gov/ct2/show/NCT03330405, https://clinicaltrials.gov/ct2/show/NCT03330847). Preclinical studies have shown a synergy between these agents and form the basis of future research.

PARP inhibitors have not been approved for treatment of early-stage breast cancer in *BRCA* mutation carriers. The results of ongoing trials, such as the adjuvant OlympiA[95] study, are awaited. Activity of single-agent talazoparib in the neoadjuvant setting has been reported in a small study primarily in *BRCA1* mutation carriers with TNBC[96]; ongoing studies are needed to confirm the high pCR rate observed (53%; https://clinicaltrials.gov/ct2/show/NCT03499353). The addition of veliparib to platinum-based chemotherapy in early-stage breast cancer did not improve pCR rates among *BRCA* carriers.[78] Other neoadjuvant trials assessing the benefit of adding a PARP inhibitor to platinum-based chemotherapy are ongoing.[97,98]

Of note, there are no data addressing the efficacy of PARP inhibitors in patients with breast cancer with a tumor-identified (ie, somatic) *BRCA* mutation in the absence of a germline mutation. Patients are encouraged to participate in ongoing research trials addressing this question.

PALB2, CHEK2, *and* ATM *mutation carriers.* Although *PALB2*, *ATM*, and *CHEK2* are in the DNA damage response pathway for double-strand DNA break repair with *BRCA1* and *BRCA2*, there are currently insufficient data to show that systemic therapies effective in treating *BRCA*-related breast cancer are effective to treat breast cancers that develop in other gene mutation carriers. Ongoing trials will help clarify the role of PARP inhibitors to treat breast cancer in patients with mutations in genes other than *BRCA1/2* (https://clinicaltrials.gov/ct2/show/NCT01670500, https://clinicaltrials.gov/ct2/show/NCT02401347).

PATIENT AND CLINICIAN COMMUNICATION

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[99] Communication topics of particular relevance to the management of hereditary breast cancer are briefly discussed below.

Prognosis and Breast Cancer Phenotype

When counseling a *BRCA* mutation carrier with breast cancer about whether to have a prophylactic risk-reducing

mastectomy, the prognosis and phenotype of subsequent breast cancers likely to develop are relevant. While studies regarding the prognosis of breast cancer for *BRCA1/2* mutation carriers compared with noncarriers have yielded inconsistent results, the weight of evidence suggests that, after adjusting for known prognostic factors, prognosis is the same for carriers and noncarriers.[68,100,101] A British prospective study of approximately 2,700 women diagnosed with young-onset breast cancer, including 388 *BRCA1/2* carriers, found that survival among *BRCA* mutation carriers was the same at 2, 5, and 10 years.[102] More data are needed about the prognosis of the breast cancers that develop in carriers of more moderate-risk mutations. Some studies have reported worse outcomes for patients with breast cancer with the germline *CHEK2* 1100delC mutation.[39,42,46,103]

Approximately 70% of breast cancers that develop in *BRCA1* carriers are TNBCs, whereas approximately 75% in *BRCA2* carriers are ER-positive cancers.[4,104] ER-positive breast cancers that develop in *BRCA* carriers are more often luminal B and have higher histologic grade and Onco*type* recurrence score than sporadic ER-positive breast cancers.[104,105] The breast cancers that develop in *CHEK2*[42] and *ATM*[106-108] mutation carriers are usually ER positive. While TNBC is enriched in patients with breast cancer with germline *PALB* mutations, a majority of breast cancers that develop are ER positive.[13,35,109] Additional studies are needed to better define the phenotype of breast cancers associated with mutations in moderate-penetrance breast cancer susceptibility genes. Understanding the phenotype will help inform decisions regarding optimal therapy and risk reduction.

Patient Satisfaction With Prophylactic Mastectomies

Decisions regarding risk-reducing mastectomy (bilateral or contralateral) are highly personal and must be individualized for every patient. Studies show that women who opt for prophylactic mastectomy report positive outcomes, including decreased concern about developing breast cancer. This benefit must be weighed against possible problems with implants or reconstructive therapy and potential adverse feelings related to body image, femininity, and sexuality. Most patients who opt for prophylactic mastectomy demonstrate satisfaction with their decision.[110-112]

Other Cancer Risks

This guideline does not address management of other cancer risks that patients with hereditary breast cancer may face. The cancer risks associate with germline mutations in *BRCA1/2* and other high-penetrance cancer susceptibility genes are generally well known and covered elsewhere.[113] Most importantly, RRSO has been shown to decrease ovarian and breast cancer risk and improve overall survival among *BRCA* mutation carriers[90,114,115]; in the 2019 National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment: Breast and Ovarian Guideline (version 3), RRSO is recommended between ages 35 and 40 years, when childbearing is completed, but may be delayed to age 45 years for *BRCA2* carriers if necessary.

The clinical spectrum and risk estimates of other cancers associated with inherited mutations in *PALB2*, *CHEK2*, and *ATM* are still being clarified. *CHEK2* mutations may confer an increased risk of colorectal cancer, and surveillance guidelines exist. Data to support an increased risk of other cancers with *CHEK2* mutations are insufficient at this time. *PALB2* and *ATM* mutations have been associated with an increased risk of pancreatic adenocarcinoma[116-119]; surveillance should be limited to mutation carriers with at least one relative affected with pancreatic cancer.[120-122] Data are inconsistent whether *PALB2* mutations confer an increased risk of ovarian cancer; most studies have not found a significantly increased risk,[13,123,124] while two studies have.[125,126] Some studies have reported a significantly increased risk of ovarian cancer with *ATM* mutations, although others have not.[123,125-127] Appropriate surveillance strategies for individual patients should be based on existing data about the specific gene mutation as well as family history.

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/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. 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.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials, the study selection criteria of which

may exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[128,129] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[130,131]

Discussion of cost can be an important part of shared decision making.[132] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[132]

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[132]

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from October 3, 2019, through October 17, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for 22 proposed recommendations, with 68 written comments received across survey questions. A total of 71% of the 17 respondents either agreed or agreed with slight modifications to the recommendations and 29% (five of 17) of the respondents disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes (n = 1), or consider major recommendation revisions. All changes were incorporated before Clinical Practice Guidelines Committee review and approval.

The draft was submitted to three additional external reviewers identified by ASTRO with content expertise. The comments received were reviewed by the Expert Panel.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. 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 Web site and most often published in the *Journal of Clinical (JCO) Oncology* and the *JCO Oncology Practice*.

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

ADDITIONAL RESOURCES

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

RELATED ASCO GUIDELINE

- Patient-Clinician Communication (https://ascopubs.org/doi/10.1200/JCO.2017.75.2311).

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EDITOR's NOTE

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

EQUAL CONTRIBUTION

N.M.T. and D.Z. were Expert Panel co-chairs.

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

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.00299.

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APPENDIX

TABLE A1. Guideline Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
Nadine M. Tung, MD (co-chair)	Beth Israel Deaconess Medical Center, Boston, MA	Medical oncology
Dana Zakalik, MD (co-chair)	Beaumont Health, Royal Oak, MI	Medical oncology
Judy C. Boughey, MD	Mayo Clinic, Rochester, MN	Surgical oncology
Lori J. Pierce, MD	Rogel Cancer Center, University of Michigan, Ann Arbor, MI	Radiation oncology
Mark E. Robson, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Isabelle Bedrosian, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Surgical oncology
Jill R. Dietz, MD	Case Western Reserve University School of Medicine and University Hospitals, Cleveland, OH	Surgical oncology
Anthony Dragun, MD	MD Anderson-Cooper University Hospital, Camden, NJ	Radiation oncology
Judith Balmana Gelpi, MD, PhD	Vall d'Hebron University Hospital, Barcelona, Spain	Medical oncology
Erin W. Hofstatter, MD	Yale Cancer Center, New Haven, CT	Medical oncology
Claudine J. Isaacs, MD	Georgetown University, Washington, DC	Medical oncology
Ismail Jatoi, MD, PhD	University of Texas Health Science Center at San Antonio, San Antonio, TX	Surgical oncology
Elaine Kennedy	FORCE, Washington, DC	Patient representative
Jennifer K. Litton, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology
Nina A. Mayr, MD	University of Washington, Seattle, WA	Radiation oncology
Rubina D. Qamar, MD (PGIN representative)	Advocate Aurora Health, Milwaukee, WI	Medical oncology
Mark G. Trombetta, MD	Allegheny Health Network, Pittsburgh, PA	Radiation oncology
Brittany E. Harvey, BS	ASCO, Alexandria, VA	ASCO practice guidelines staff (health research methods)
Mark R. Somerfield, PhD	ASCO, Alexandria, VA	ASCO practice guidelines staff (health research methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.