ABSTRACT

Purpose
To update the 1999 American Society of Clinical Oncology (ASCO) guideline on breast cancer follow-up and management in the adjuvant setting.

Methods
An ASCO Expert Panel reviewed pertinent information from the literature through March 2006. More weight was given to studies that tested a hypothesis directly relating testing to one of the primary outcomes in a randomized design.

Results
The evidence supports regular history, physical examination, and mammography as the cornerstone of appropriate breast cancer follow-up. All patients should have a careful history and physical examination performed by a physician experienced in the surveillance of cancer patients and in breast examination. Examinations should be performed every 3 to 6 months for the first 3 years, every 6 to 12 months for years 4 and 5, and annually thereafter. For those who have undergone breast-conserving surgery, a post-treatment mammogram should be obtained 1 year after the initial mammogram and at least 6 months after completion of radiation therapy. Thereafter, unless otherwise indicated, a yearly mammographic evaluation should be performed. Patients at high risk for familial breast cancer syndromes should be referred for genetic counseling. The use of CBCs, chemistry panels, bone scans, chest radiographs, liver ultrasounds, computed tomography scans, [18F]fluorodeoxyglucose–positron emission tomography scanning, magnetic resonance imaging, or tumor markers (carcinoembryonic antigen, CA 15-3, and CA 27.29) is not recommended for routine breast cancer follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination.

Conclusion
Careful history taking, physical examination, and regular mammography are recommended for appropriate detection of breast cancer recurrence.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) published its first evidence-based clinical practice guidelines on postoperative surveillance for the detection of recurrent breast cancer in 1997. Since the last update in 1998, there has been an increase in the availability of diagnostic testing for breast cancer patients. A review of the available data is necessary to formulate an up-to-date, evidence-based strategy for breast cancer follow-up and management in asymptomatic patients after primary, curative therapy. A summary of the 2006 recommendations is provided in Table 1. 

In 1996, ASCO published a list of clinical outcomes that justify the use of a technology or drugs in the guideline development process. The clinical outcomes include the following: improvements in overall or disease-free survival; improvement in quality of life, as shown by a valid measure of global health outcomes; reduced toxicity; and improved cost effectiveness. The ASCO Panel was guided by these criteria and recommended tests if they demonstrated a positive impact on these important clinical outcomes. Although published guidelines alone may not alter individual practice patterns, it is hoped that these guidelines will serve as a foundation for internal guideline development within institutions and practices.

Historically, breast cancer follow-up has used a conservative approach based on clinical examination and mammography, but variations in practice
patterns exist and have significant cost implications. Mille et al. at Centre Regional Leon Berard studied the impact of clinical practice guidelines on follow-up of patients with localized breast cancer. Follow-up that was not guideline compliant cost 2.2 to 3.6 times more than guideline-compliant follow-up as a result of nonmammographic examinations performed in the absence of any warning signs or symptoms of recurrence. After the introduction of surveillance guidelines in 1994, there was a one-third decrease in expenditures per patient, with no change in health outcomes expected. Although guideline compliance saves limited health care resources, patients also understand the limitations of diagnostic tests and accept limited testing from their physicians when recommended.3,4

Table 1. Summary of 2006 Guideline Recommendations for Breast Cancer Surveillance

<table>
<thead>
<tr>
<th>Mode of Surveillance</th>
<th>Summary of Recommendations</th>
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<tr>
<td>Recommended breast cancer surveillance</td>
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<tr>
<td>History/physical examination</td>
<td>Every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually</td>
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<td>Patient education regarding symptoms of recurrence</td>
<td>Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, abdominal pain, dyspnea or persistent headaches; helpful websites for patient education include <a href="http://www.plwc.org">www.plwc.org</a> and <a href="http://www.cancer.org">www.cancer.org</a></td>
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<td>Referral for genetic counseling</td>
<td>Criteria include: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative</td>
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<tr>
<td>Breast self-examination</td>
<td>First post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis but no earlier than 6 months after definitive radiation therapy; subsequent mammograms should be obtained as indicated for surveillance of abnormalities</td>
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<tr>
<td>Mammography</td>
<td>All women should be counseled to perform monthly breast self-examination</td>
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<td>Coordination of care</td>
<td>Continuity of care for breast cancer patients is encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination, including the examination of irradiated breasts; if follow-up is transferred to a PCP, the PCP and the patient should be informed of the long-term options regarding adjuvant hormonal therapy for the particular patient; this may necessitate rereferral for oncology assessment at an interval consistent with guidelines for adjuvant hormonal therapy</td>
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<tr>
<td>Pelvic examination</td>
<td>Regular gynecologic follow-up is recommended for all women; patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians</td>
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<td>Breast cancer surveillance testing: not recommended</td>
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<td>Routine blood tests</td>
<td>CBCs and liver function tests are not recommended</td>
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<td>Imaging studies</td>
<td>Chest x-ray, bone scans, liver ultrasound, computed tomography scans, FDG-PET scans, and breast MRI are not recommended</td>
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<tr>
<td>Tumor markers</td>
<td>CA 15-3, CA 27.29, and carcinoembryonic antigen are not recommended</td>
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<tr>
<td>FDG-PET</td>
<td>FDG-PET scanning is not recommended for routine breast cancer surveillance</td>
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<tr>
<td>Breast MRI</td>
<td>Breast MRI is not recommended for routine breast cancer surveillance</td>
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</table>

Abbreviations: PCP, primary care physician; FDG-PET, [18F]fluorodeoxyglucose–positron emission tomography; MRI, magnetic resonance imaging.

SUMMARY OF KEY LITERATURE REVIEW RESULTS

For the 2006 update, the Expert Panel completed the review and analysis of data published since 1998. Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature from 1999 to March 2006 combined the terms “breast neoplasms” with the MeSH term “follow-up studies” and the text words “surveillance” and “follow-up.” The set of articles yielded from this initial search was supplemented by articles identified from searches on each of the tests or procedures addressed in the original guideline (eg, history and physical examination, carcinoembryonic antigen) in combination with “surveillance,” “follow-up studies,” and “follow-up.” The searches were limited to human-only studies and to specific study design or publication type, such as randomized clinical trial, meta-analysis, practice guideline, systematic overview, or systematic review. The literature review centered on randomized clinical trials and meta-analyses of data from randomized clinical trials.

The Expert Panel did not complete an independent meta-analysis of the data from available randomized clinical trials given the availability of a high-quality and recent meta-analysis and a high-quality systematic literature review identified through the literature search.4,5 ASCO guideline recommendations for breast cancer surveillance are consistent with other thorough evidence-based reviews that have examined the available clinical and scientific data. Rojas et al. in a Cochrane Collaboration review of four randomized, controlled clinical trials involving 3,055 women with breast cancer,3,6-8 found no difference in overall survival or disease-free survival between patients observed with intensive radiologic and laboratory testing and those observed with clinical visits and mammography. In addition, the 2005 clinical practice guideline update for breast cancer surveillance after primary therapy published by Health Canada’s Canadian Breast Cancer Initiative9 recommends regular clinical visits and mammography as surveillance for breast cancer recurrence; routine laboratory and other radiologic testing are not recommended. Likewise, the ASCO breast cancer follow-up and management guideline recommends regular clinical
evaluation in conjunction with mammography as the foundation on which breast cancer follow-up should be based.

It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result.

Accordingly, ASCO considers adherence to this guideline assessment to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient’s individual circumstances. In addition, this guideline describes the use of procedures and therapies in clinical practice; it cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions and settings for further research.

### History, Physical Examination, and Patient Education Regarding Symptoms of Recurrence

**2006 recommendation.** All women should have a careful history and physical examination every 3 to 6 months for the first 3 years after primary therapy, then every 6 to 12 months for the next 2 years, and then annually. Physicians should counsel patients about the symptoms of recurrence including new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headaches. Helpful Web sites for patient education include www.plwc.org and www.cancer.org.

Women at high risk for familial breast cancer syndromes should be referred for genetic counseling in accordance with clinical guidelines recommended by the US Preventive Services Task Force. Criteria to recommend referral include the following: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative.

**Literature update and discussion.** The Panel acknowledges that there have been no recent prospective studies evaluating alternative clinical follow-up schedules for surveillance. The current recommendations are the same as the original 1997 guidelines that, in part, based its recommendations on two well-designed prospective studies evaluating surveillance with regular clinical visits and mammography (standard follow-up) versus the same surveillance program plus scheduled laboratory and other imaging studies (intensive surveillance). Since that time, a validated risk assessment tool (http://www.adjuvantageonline.com) has been developed to estimate the 10-year risk of breast cancer recurrence and death based on readily available pathologic data. No studies have evaluated the benefit of more frequent clinical visits in patients with known high-risk versus low-risk disease. In addition, more than half of breast cancer recurrences are asymptomatic and found between scheduled follow-up visits. A recent meta-analysis of 12 studies involving 5,045 patients found that 40% (95% CI, 35% to 45%) of patients with locoregional recurrences were diagnosed during routine clinic visits or routine testing, whereas the remainder (approximately 60%) developed symptomatic recurrences before their scheduled clinical visits. Conclusions could not be drawn regarding survival and cost due to the overall quality of the studies analyzed and the relatively low incidence of locoregional recurrence. Nonetheless, the study emphasizes the importance of patient education regarding the symptoms of recurrence in the interest of a timely diagnosis. There are no changes to the previous recommendation.

The previous guideline did not address the need for genetic counseling referral in patients at increased risk for familial breast cancer syndromes. The US Preventive Services Task Force recently released clinical guidelines recommending referral in certain at-risk women but specifically applied the guidelines only to women who have not received a diagnosis of breast or ovarian cancer. The Panel felt that the available data were sufficient to render an expert opinion on the matter of referral for genetic counseling in women diagnosed with breast cancer with certain personal or familial clinical characteristics. Criteria to recommend referral include the following: Ashkenazi Jewish heritage; history of ovarian cancer at any age in the patient or any first- or second-degree relatives; any first-degree relative with a history of breast cancer diagnosed before the age of 50 years; two or more first- or second-degree relatives diagnosed with breast cancer at any age; patient or relative with diagnosis of bilateral breast cancer; and history of breast cancer in a male relative.

### Breast Self-Examination

**2006 recommendation.** All women should be counseled to perform monthly breast self-examination (BSE).

**Literature update and discussion.** A large study of more than 260,000 Chinese women evaluating the efficacy of BSE alone failed to show a survival benefit in the group of women assigned to regular BSE. The cumulative breast cancer mortality rates through 10 years of follow-up were similar between the BSE and control groups (risk ratio = 1.04; 95% CI, 0.82 to 1.33; P = .72), and more benign breast lesions were diagnosed in the BSE group compared with the control group. Routine screening mammography was not available to the participants in the study. Women who perform regular BSE may be at increased risk of undergoing invasive procedures to diagnose benign breast lesions, but there are no randomized data examining the effect of BSE in conjunction with regular screening mammograms for women who have been treated for breast cancer. In the absence of such data, it is recommended that women be counseled to perform monthly BSE. Women should be made aware that monthly BSE does not replace mammography as a breast cancer screening tool.

### Mammography

**2006 recommendation.** Women treated with breast-conserving therapy should have their first post-treatment mammogram no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained every 6 to 12 months for surveillance of abnormalities. Mammography should be performed yearly if stability of mammographic findings is achieved after completion of locoregional therapy.

**Literature update and discussion.** Grunfeld et al documented the lack of high-level evidence supporting current practice of mammography surveillance. Although there is a lack of randomized controlled trial data, observational studies suggest that the method of detection (physical examination or mammography), when reported,
did not seem to influence survival. The Panel acknowledges the barriers to designing a prospective randomized trial to answer such a question. Thus, routine mammography continues to be recommended for breast cancer surveillance.

**Coordination of Care**

**2006 recommendation.** The risk of breast cancer recurrence continues through 15 years after primary treatment and beyond. Continuity of care for breast cancer patients is recommended and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination, including the examination of irradiated breasts.

Follow-up by a primary care physician (PCP) seems to lead to the same health outcomes as specialist follow-up with good patient satisfaction. If a patient with early-stage breast cancer (tumor < 5 cm and ≤ four positive nodes) desires follow-up exclusively by a PCP, care may be transferred to the PCP approximately 1 year after diagnosis. If care is transferred to a PCP, both the PCP and the patient should be informed of the appropriate follow-up and management strategy. This approach will necessitate referral for oncology assessment if a patient is receiving adjuvant endocrine therapy.

**Literature update and discussion.** Follow-up of a patient by multiple specialists after initial therapy is costly, has not been shown to improve outcomes, and may represent duplication of effort. One randomized clinical trial, included in the 1998 update, was designed specifically to evaluate whether PCPs, instead of specialist cancer physicians, can safely provide breast cancer surveillance. This well-designed, randomized clinical trial involved 296 women receiving follow-up for breast cancer in specialist oncology and surgical clinics in Great Britain. Patients were randomly assigned to continued specialist follow-up (control group) or to follow-up from their own general practitioner. This study found that primary care follow-up of women with breast cancer in remission is not associated with increase in time to diagnosis of recurrence, increase in anxiety, or deterioration in health-related quality of life, which were the outcomes selected for evaluation. The study also found that 69% of recurrences presented between follow-up visits, and almost half of the patients experiencing recurrence in the specialist group presented first to the general practitioner. Patient satisfaction was found to be greater among those treated by general practitioners. Follow-up by a PCP led to the same health outcomes as follow-up by a specialist physician, better patient satisfaction, and lower health service and patient costs. This study has been replicated in Canada involving 968 early-stage breast cancer patients (tumor < 5 cm and ≤ four positive axillary lymph nodes) observed for a median of 4.3 years from diagnosis. The Canadian study also found that follow-up by a PCP led to the same health outcomes as measured by the rate of recurrence-related serious clinical events and quality of life. This study was conducted before the widespread use of aromatase inhibitors adjunctively; approximately 50% of the patients in each arm of the study received tamoxifen as adjuvant endocrine therapy. Another randomized trial in Great Britain showed that twice as many patients preferred simpler, less frequent follow-up. Similarly rigorous evaluations of this same surveillance question (ie, PCP vs specialist physician follow-up) for breast cancer patients in the United States are not currently available. There is no a priori reason to expect that patients in the United States would want different follow-up schedules, and the demand for medically inappro-
surveillance group for overall survival (hazard ratio = 0.96; 95% CI, 0.80 to 1.15) or disease-free survival (hazard ratio = 0.84; 95% CI, 0.71 to 1.00). There was also no significant difference in 5-year mortality between the regular and intensive surveillance groups with respect to age, tumor size, or nodal status. In one trial, a higher percentage of asymptomatic metastases was found in the intensive surveillance group compared with the control group (31% vs 21%, respectively), but this did not translate into an improvement in survival.

Joseph et al\textsuperscript{23} retrospectively identified 129 patients with recurrent breast cancer from an institutional database. Patients were divided into minimalist (history, physical examination, and mammography) or intensive surveillance (serial chemistry panels, tumor markers, chest radiographs, computed tomography [CT] scans, and bone scans) groups according to the method of disease detection. No significant differences in time to detection of recurrence were found ($P = .95$) between the groups, and the method of detection did not significantly affect survival ($P = .18$). It is speculated that a small percentage (1% to 3%) of patients with limited metastatic disease may survive their disease when treated with multimodality therapy with curative and not palliative intent.\textsuperscript{23} This hypothesis must first be confirmed by prospective randomized trials before intensive surveillance monitoring is justified. Thus, there are no changes to the 1998 guideline for testing that is not recommended.

**CBC**

2006 **recommendation.** CBC testing is not recommended for routine breast cancer surveillance.

**Automated Chemistry Studies**

2006 **recommendation.** Automated chemistry studies are not recommended for routine breast cancer surveillance.

**Chest X-Rays**

2006 **recommendation.** Chest x-rays are not recommended for routine breast cancer surveillance.

**Bone Scan**

2006 **recommendation.** Bone scans are not recommended for routine breast cancer surveillance.

**Ultrasound of the Liver**

2006 **recommendation.** Liver ultrasound is not recommended for routine breast cancer surveillance.

**CT**

2006 **recommendation.** CT is not recommended for routine breast cancer surveillance.

2006 **literature update and discussion.** One study published since the 1998 update\textsuperscript{24} retrospectively evaluated 6,628 CT scans of the pelvis in 2,426 patients with breast cancer over a 9-year period. Pelvic metastases were the only site of metastases in 13 patients (0.5%) but led to over 200 additional radiographic examinations and 50 surgical procedures; 84% of the additional procedures (radiographic and surgical) yielded benign or negative results. Another recently published retrospective study\textsuperscript{25} evaluated 250 patients with early-stage breast cancer over a 2-year period. All patients had chest radiographs (74%) or CT scans (26%) for screening purposes or to evaluate symptoms. Of the 10 patients (4%) who developed metastatic disease, only two (0.8%) had metastatic disease diagnosed by chest radiograph. No patients were found to have metastatic disease by routine chest CT scanning. There have been no other published studies that demonstrate a clinical benefit to routine CT scanning in the detection of breast cancer recurrence. There are no changes to the previous recommendation.

**[18F]Fluorodeoxyglucose–Positron Emission Tomography Scanning**

2006 **recommendation.** [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is not recommended for routine breast cancer surveillance.

2006 **literature update and discussion.** This category is new since the 1998 update. We reviewed several recent studies that pertain to surveillance issues in breast cancer patients. Available data on FDG-PET scanning in breast cancer surveillance come from retrospective cohort studies; there are no prospective randomized trial data. Although FDG-PET scanning may demonstrate more sensitivity than conventional imaging in diagnosing recurrent disease, there is no evidence that there is an impact on survival, quality of life, or cost effectiveness.

One cohort study\textsuperscript{26} of 61 patients compared FDG-PET scanning to conventional imaging for detecting residual or recurrent breast cancer. Sensitivity of FDG-PET versus conventional imaging was slightly improved (93% vs 79%, respectively; $P < .05$), but there was no difference in positive predictive value or specificity. The negative predictive value of FDG-PET compared with conventional imaging was also improved (84% vs 59%, respectively; $P < .05$), but the impact of these results on survival, quality of life, and cost was not evaluated. Another study\textsuperscript{27} evaluated the efficacy of whole-body FDG-PET scanning in 60 women with clinical or radiographic suspicion of recurrent breast cancer. Forty women had histologically proven relapsed disease. PET scanning was sensitive and specific for locoregional and distant relapse and seemed to be more sensitive than tumor marker CA 15-3 for detecting recurrence. Patients enrolled onto this nonrandomized study already had evidence of recurrence (clinically or by conventional radiologic testing); thus, no conclusions can be drawn with regard to survival or other benefits from FDG-PET scanning. A meta-analysis\textsuperscript{28} of 16 studies comprising 808 patients demonstrated a median sensitivity and specificity of 92.7% and 81.6%, respectively, for FDG-PET scanning. The pooled sensitivity was 90% (95% CI, 86.8% to 93.2%), and the pooled false-positive rate was 11% (95% CI, 86.0% to 90.6%). Thus, although FDG-PET scanning seems to be a useful tool to diagnose suspected breast cancer recurrence, there are no data to support its role in routine breast cancer surveillance in asymptomatic patients.

**Breast Magnetic Resonance Imaging**

2006 **recommendation.** Breast magnetic resonance imaging (MRI) is not recommended for routine breast cancer surveillance.

2006 **literature update and discussion.** This category is new since the 1998 update. We reviewed several recent studies of breast MRI screening in patients at high familial risk for breast cancer. A cohort study\textsuperscript{29} of 529 women at high risk for breast cancer based on family history found that MRI offered higher sensitivity than mammography (91% vs 33%, respectively) at detecting breast cancer, whereas specificity was similar (97.2% vs 96.8%, respectively). Another cohort study\textsuperscript{30} in the United Kingdom of 649 women at high familial risk for breast cancer demonstrated similar results in sensitivity (MRI: 77%; 95% CI, 60% to 90%; mammography: 40%; 95% CI, 24% to 58%) and specificity (MRI: 81%; 95% CI, 80% to 83%; mammography: 93%; 95% CI, 92% to 95%) for detecting breast cancer.
Although screening breast MRI seems to be more sensitive than conventional imaging at detecting breast cancer in high-risk women, there is no evidence that breast MRI improves outcomes when used as a breast cancer surveillance tool during routine follow-up in asymptomatic patients. The decision to use breast MRI in high-risk patients should be made on an individual basis depending on the complexity of the clinical scenario.

**Breast Cancer Tumor Markers CA 15-3 and CA 27.29**

2006 recommendation. The use of the CA 15-3 or CA 27.29 is not recommended for routine surveillance of breast cancer patients after primary therapy. The ASCO Breast Cancer Tumor Markers Panel will publish guideline recommendations for selected tumor markers.

**Breast Cancer Tumor Marker Carcinoembryonic Antigen**

2006 recommendation. Carcinoembryonic antigen testing is not recommended for routine surveillance of breast cancer patients after primary therapy. The ASCO Breast Cancer Tumor Markers Panel will publish guideline recommendations for selected tumor markers.

### REFERENCES


### Acknowledgment

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Appendix. Panelist Members and Institutions

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<thead>
<tr>
<th>Panelist</th>
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<tr>
<td>Nancy E. Davidson, MD, Co-Chair</td>
<td>Johns Hopkins Hospital, Sidney Kimmel Cancer Center</td>
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<td>Laura Esserman, MD</td>
<td>University of California, San Francisco</td>
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<td>Eva Grunfeld, MD, DPhil</td>
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<td>University of Vermont</td>
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Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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