

Clinical practice guidelines in breast cancer

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ABSTRACT

Background A number of clinical practice guidelines (CPGs) concerning breast cancer (BCa) screening and management are available. Here, we review the strengths and weaknesses of CPGs from various professional organizations and consensus groups with respect to their methodologic quality, recommendations, and implementability.

Methods Guidelines from four groups were reviewed with respect to two clinical scenarios: adjuvant ovarian function suppression (OFS) in premenopausal women with early-stage estrogen receptor-positive BCa, and use of sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NAC) for locally advanced BCa. Guidelines from the American Society of Clinical Oncology (ASCO); Cancer Care Ontario's Program in Evidence Based Care (CCO's PEBC); the U.S. National Comprehensive Cancer Network (NCCN); and the St. Gallen International Breast Cancer Consensus Conference were reviewed by two independent assessors. Guideline methodology and applicability were evaluated using the AGREE II tool.

Results The quality of the CPGs was greatest for the guidelines developed by ASCO and CCO's PEBC. The NCCN and St. Gallen guidelines were found to have lower scores for methodologic rigour. All guidelines scored poorly for applicability. The recommendations for OFS were similar in three guidelines. Recommendations by the various organizations for the use of SLNB after NAC were contradictory.

Conclusions Our review demonstrated that CPGs can be heterogeneous in methodologic quality. Low-quality CPG implementation strategies contribute to low uptake of, and adherence to, BCa CPGs. Further research examining the barriers to recommendations—such as intrinsic guideline characteristics and the needs of end users—is required. The use of BCa CPGs can improve the knowledge-to-practice gap and patient outcomes.

Key Words Breast cancer, clinical practice guidelines, AGREE II

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INTRODUCTION

Despite significant progress in screening, treatment, and survivorship, breast cancer (BCa) remains the 2nd leading cause of cancer death in Canadian women. In 2017, BCa accounted for 25% of new cancer diagnoses and 13% of cancer deaths in women¹. The rapid pace of scientific discovery and the sheer volume of the evolving medical literature, as well as the varied level of expertise in critically appraising or systematically integrating the literature, can pose challenges for busy clinicians aiming to provide optimal and current care for patients. Clinical practice guidelines (CPGs) have become an essential tool to aid health care practitioners in synthesizing and summarizing available evidence to help improve patient management². The use of oncology CPGs in clinical practice has been shown to

improve recurrence-free survival and overall survival³⁻⁵. In addition, CPGs identify gaps in evidence and highlight opportunities for further research⁶. They can also guide health care policy development and support allocation of health care funding and health care structure⁶.

Several professional organizations and consensus groups have developed BCa CPGs with the overarching goal of translating evidence into recommendations for best patient care. A search for BCa guidelines published in the last 5 years, using the Guidelines International Network, the National Guideline Clearinghouse, the Standards and Guidelines Evidence Database (maintained by the Canadian Partnership Against Cancer), and PubMed (search terms in Table 1) yielded 232 guidelines. The sheer volume of BCa CPGs could cause confusion for health care practitioners, especially if recommendations conflict.

TABLE I The PubMed search

“breast neoplasms”[MeSH Terms] OR (“breast”[All Fields] AND “neoplasms”[All Fields]) OR “breast neoplasms”[All Fields] OR (“breast”[All Fields] AND “cancer”[All Fields]) OR “breast cancer”[All Fields] AND (“practice guideline”[Publication Type] OR “practice guidelines as topic”[MeSH Terms] OR “clinical practice guidelines”[All Fields]) AND (Review[ptyp] AND “2013/02/07”[PDat]: “2018/01/14”[PDat] AND English[lang])

Despite the myriad of bca guidelines, guideline uptake has been varied. Wockel *et al.*⁴ demonstrated 51.9% adherence to guideline recommendations for complete treatment of bca patients. Simos *et al.*⁷ showed that 65.0% of oncologists did not follow the American Society of Clinical Oncology (ASCO) and Choosing Wisely guidelines related to diagnostic imaging for stage I and II bca surveillance.

Barriers to guideline uptake are complex. One systematic review⁸ identified 3 categories of barriers for guideline use:

- Personal barriers such as physician knowledge, including lack of awareness and lack of familiarity with CPGs
- Barriers that influence the physician’s attitude toward change in practice
- External barriers related to the guideline, patients, and environment

Many practitioners might not use guidelines because of concerns about data or methodologic quality⁸. The definition of a high-quality CPG varies, and quality assessment of CPGs can be complicated. The U.S. Institute of Medicine defined “high quality” CPGs as “statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”². That definition focuses on methodologic rigour as a standard for high quality. However, consensus statements and expert opinions developed from meeting proceedings might not include a robust systematic review of the literature, but might still be an effective tool in patient care. Alternatively, the AGREE (Appraisal of Guidelines for Research and Evaluation) collaboration defines guideline quality as “the confidence that the potential biases of guidelines have been addressed adequately and that the recommendations are both internally and externally valid and are feasible for practice”⁹. That definition includes the guideline methodology and recommendations, and guideline applicability, as required components of high-quality CPGs. The collaboration has developed the AGREE II instrument as a framework for quality assessment and provides a methodology checklist for high-quality guideline development and reporting^{9,10}. The AGREE II instrument is a 23-item tool with 6 quality domains that are rated using a 7-point Likert scale (Table I)⁹. Although several other instruments have been developed for guideline assessment, a systematic review evaluating 40 guideline appraisal tools ranked the AGREE II tool the highest for comprehensive guideline evaluation¹¹.

TABLE II Quality domains in AGREE I and AGREE II^a

Scope and purpose
Stakeholder involvement
Rigour of development
Clarity of presentation
Applicability
Editorial independence

^a Adapted from Brouwers *et al.*, 2010¹⁰.

Synthesis and reporting of the medical literature is only one aspect of a CPG. Clinicians also rely on CPGs to provide high-quality recommendations. Recommendations can be evaluated by instruments such as the Grading of Recommendations Assessment, Development and Evaluation¹². Although AGREE II is a comprehensive tool, it does not evaluate the validity or clinical appropriateness of recommendations¹⁰. The AGREE-REX project is developing a tool to address that gap¹³.

Simple publication of a CPG does not ensure that the guideline will be used. Effective implementation strategies are also necessary. The implementability of a guideline refers to guideline characteristics that predict its implementation or uptake into clinical practice^{14,15}. Tools such as the Guideline Implementability Appraisal¹⁴, ADAPTE¹⁶, and FORM¹⁷ are used to assess CPG implementability in both the guideline development phase and the evaluation phase. More recently, a realist review using a multidisciplinary approach demonstrated that guideline uptake was influenced by 6 implementability domains, including stakeholder involvement, evidence synthesis, considered judgment (clinical relevance), implementation feasibility, message, and the format of the CPG¹⁸.

Overall, evaluating a CPG requires a comprehensive review of the CPG’s development, including data selection and content quality, linkage of the data to the final recommendations, and implementability of the recommendations in clinical practice. Furthermore, clinicians have indicated a preference for simple, patient-specific, and user-friendly guidelines^{19–21}.

Here, we evaluate the strengths and weaknesses of bca CPGs based on two clinical scenarios. Using the AGREE II instrument, we demonstrate differences in the methodology and quality of the guidelines and their recommendations. Issues with respect to guideline applicability and implementability are reviewed. For bca CPGs to make sense to clinicians for everyday use, the guidelines have to be high-quality, relevant, and applicable to patients.

METHODS

We selected four guideline-developing organizations: ASCO, Cancer Care Ontario’s Program in Evidence Based Care (CCO’s PEBC), the U.S. National Comprehensive Cancer Network (NCCN), and the St. Gallen Consensus Conference. We acknowledge that this list of organizations is limited and that many other reputable guideline developers operate internationally. However, for the present work, those four organizations were chosen to highlight

similarities and differences in guideline development methods, guideline recommendations, and presentation of recommendations.

Guidelines relating to two representative clinical scenarios encountered by oncologists treating early-stage bca and covered by all four guideline groups in cpgs during the last 5 years were selected:

- When should adjuvant ovarian function suppression (ofs) be given to premenopausal women with early-stage estrogen receptor–positive (ER+) bca?
- After neoadjuvant chemotherapy (nac) for locally advanced bca (LABC), when is a sentinel lymph node biopsy (SLNB), compared with a complete axillary lymph node dissection, recommended for axillary staging?

Two reviewers (NKT and SDT) independently examined and evaluated the most recent version of each guideline. Descriptive comparisons of guideline recommendations from the four organizations are reported. The AGREE II tool was used to evaluate the quality of each guideline according to the tool's user manual. The AGREE II domain scores are calculated by summing the scores for the individual items in the domain and then scaling the total as a percentage⁹. Domain scores exceeding 60% were defined as good quality. That definition is consistent with scoring by agencies such as the Canadian Partnership Against Cancer guideline database assessment²². Brouwers *et al.*¹⁰ found that high-quality guidelines have an average score of 78% in the rigour domain and that low-quality guidelines have an average score of 55%. Guidelines were evaluated using the online tool My AGREE II Plus²³.

RESULTS

Many differences between the guidelines were noted for multiple areas such as guideline format and presentation, methodologic rigour, and recommendations.

Guideline Presentation

The ASCO^{24,25} and PEBBC^{26,27} guidelines are similarly presented. They are expansive documents that consist of multiple components. The ASCO guidelines consist of a full guideline, with additional data and methodology supplements^{24,25}. A patient supplement is also available, together with pocket resource guides²⁸. The PEBBC guidelines often include a summary statement, an evidentiary base or systematic review, and a methodology statement of guideline development and external review^{26,27}. Details of the panel's votes on recommendations are also readily available and included in supporting documents^{26,27}.

The NCCN guidelines follow an algorithmic approach with succinct recommendations²⁹. Details about the evidence supporting the recommendations can be found in a separate "Discussion" document³⁰. A St. Gallen consensus is presented both as a summary³¹ and as a full statement³². The recommendations about ofs were limited to one paragraph in the full statement, and only supportive evidence was provided. A discussion of the evidence and voting results were not published within the consensus document, but are available online in supplementary files³².

Guideline Methodology

Table III highlights differences in guideline methodology between the four guideline developers. Although a multidisciplinary panel consisting of bca experts and researchers is found in each group, the ASCO and PEBBC guideline teams also include methodology expertise for conducting a systematic review of the literature related to a specific clinical question^{33,34}. Both ASCO and the PEBBC provide detailed search criteria, critical analyses of the studies found, and a detailed explanation accounting for the inclusion and exclusion of studies in their analysis and recommendations^{33,34}. Neither the NCCN nor St. Gallen report on the methodology used for their literature review or critical evaluation of the evidence^{30,32}. Moreover, they do not report the studies reviewed and excluded in the discussions leading to their recommendations^{30,32}. St. Gallen does publish information about the extent of the consensus achieved on the various statements included in its guideline³².

Guideline Recommendation Ratings

All four guideline organizations use different tools and rating systems to evaluate their recommendations. The ASCO rating system ranges from "insufficient" to "high," based on confidence in the available evidence³³. Unlike ASCO, the PEBBC does not rate its guideline recommendations; instead, a qualifying statement is provided^{26,27}. The NCCN guidelines provide a category of recommendations in the range 1–3²⁹. All recommendations are category 2A unless specifically noted to be different²⁹. A category 2A recommendation is based on lower-level evidence, together with uniform NCCN consensus (>90%) that the intervention is appropriate²⁹. St. Gallen does not rate its recommendations; however, the strength of a recommendation can be reflected in the choice of phrasing (that is, "strongly recommended," "clearly recommends")^{31,32}.

Guideline Review

Table IV summarizes the various guidelines and their recommendations.

Clinical Scenario 1

- When should adjuvant ofs be given to premenopausal women with early-stage ER+ bca?

Three of the four guidelines recommended ofs in addition to endocrine therapy for premenopausal women with ER+ bca^{24,30–32}.

The ASCO guideline on ofs was a focused guideline update dedicated to the topic²⁴, and ASCO endorsed ofs in addition to endocrine therapy for women with stages II and III bca. In women with stage I bca having a high risk of recurrence, for whom chemotherapy would be advised, the ASCO guideline recommended ofs with endocrine therapy²⁴. For women with stage I bca not requiring chemotherapy, ASCO recommended endocrine therapy alone. Ovarian function suppression was recommended in combination with tamoxifen or an aromatase inhibitor, and only for 5 years. The recommendation strength was moderate and was based on large clinical trials^{35–37}.

The NCCN guideline for ofs was presented in one section of a large, comprehensive statement about the

TABLE III Characteristics of the clinical practice guidelines

Characteristic	Organization			
	ASCO ³³	PEBC ³⁴	NCCN ^{29,30}	St. Gallen ^{31,32}
Panel composition				
Multidisciplinary	Yes	Yes	Yes	Yes
Methodology experts	Yes	Yes	No	No
Evidentiary review	Systematic review by health research methodologist	Systematic review by health research methodologist	Critical review by clinical experts	Literature review by members of the committee
Explicit search strategy	Yes	Yes	No	No
Criteria for evidence inclusion provided	Yes	Yes	No	No
Grading of evidence	Yes	No	Yes	No
		Narrative description with qualifying statements	NCCN category 1–3	Narrative description

ASCO = American Society of Clinical Oncology; PEBC = Cancer Care Ontario’s Program in Evidence-Based Care; NCCN = U.S. National Comprehensive Cancer Network.

TABLE IV Summary of guideline recommendations

Scenario	Guideline organization
1. Ovarian function suppression in premenopausal women with early-stage estrogen receptor–positive breast cancer	
	American Society for Clinical Oncology
<i>Guideline:</i>	Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer—update on ovarian function suppression ²⁴
<i>Recommendation:</i>	Recommend ovarian function suppression for premenopausal women with estrogen receptor–positive breast cancer: <ul style="list-style-type: none"> ■ Women with stage I, II or stage III breast cancer who received chemotherapy ■ Higher-risk woman (younger age, larger tumour, node-positive, or higher grade) Ovarian function suppression can be paired with either aromatase inhibitor or tamoxifen.
	Cancer Care Ontario, Program in Evidence-Based Care
<i>Guideline:</i>	Optimal Systemic Therapy for Early Stage Breast Cancer ²⁶
<i>Recommendation:</i>	Recommendation 19-21: <ul style="list-style-type: none"> ■ For premenopausal women with an estrogen receptor–positive tumour, ovarian function suppression with or without aromatase inhibitor or tamoxifen is not recommended. ■ Ovarian function suppression is a reasonable treatment option for women who refuse or who are not candidates for other systemic treatment.
	U.S. National Comprehensive Cancer Network
<i>Guideline:</i>	Breast Cancer, vers. 3.2017 BINV-J ³⁰
<i>Recommendation:</i>	Recommend ovarian function suppression for women at higher risk of recurrence if young age, high-grade tumour, or lymph node involvement. <p>Ovarian function suppression in addition to either aromatase inhibitor or tamoxifen.</p>
	St. Gallen International Breast Cancer Conference
<i>Guideline:</i>	De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer ^{31,32}
<i>Recommendation:</i>	Adjuvant endocrine therapy in premenopausal women <p>Recommend ovarian function suppression for women</p> <ul style="list-style-type: none"> ■ if less than 35 years of age, ■ if 4 or more lymph nodes are positive, or ■ if chemotherapy was required. Ovarian function suppression can be paired with either aromatase inhibitor or tamoxifen.

TABLE IV Continued

Scenario	Guideline organization
2. Sentinel lymph node biopsy after neoadjuvant chemotherapy	
American Society for Clinical Oncology	
<i>Guideline:</i>	Sentinel Lymph Node Biopsy for Patients with Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update ²⁵
<i>Recommendation:</i>	Sentinel lymph node biopsy could be recommended to patients receiving neoadjuvant systemic treatment. Do not recommend sentinel lymph node biopsy in T3/4 tumours.
Cancer Care Ontario, Program in Evidence-Based Care	
<i>Guideline:</i>	Locoregional Therapy of Locally Advanced Breast Cancer (LABC) ²⁷
<i>Recommendation:</i>	Recommendation 3-1: Do not recommend sentinel lymph node biopsy. It is recommended that axillary dissection remain the standard of care for axillary staging in LABC, with the judicious use of sentinel lymph node biopsy in patients who are advised of the limitations of current data.
U.S. National Comprehensive Cancer Network	
<i>Guideline:</i>	Breast Cancer, ver. 3.2017 BINV-11 ³⁰
<i>Recommendation:</i>	Sentinel lymph node biopsy adequate if <ul style="list-style-type: none"> ■ ipsilateral axillary lymph node evaluation is negative, or ■ ipsilateral axillary lymph node is initially positive, and after neoadjuvant chemotherapy, it is clinically negative. Sentinel lymph node biopsy inadequate if axillary lymph node is positive before and after neoadjuvant chemotherapy.
St. Gallen International Breast Cancer Conference	
<i>Guideline:</i>	De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer ^{31,32}
<i>Recommendation:</i>	Axillary surgery after neoadjuvant therapy Sentinel lymph node biopsy adequate if <ul style="list-style-type: none"> ■ clinically negative axilla at diagnosis, or ■ clinically negative axilla after neoadjuvant chemotherapy, and if at least 3 sentinel lymph nodes were biopsied and were negative. Sentinel lymph node biopsy inadequate if <ul style="list-style-type: none"> ■ clinically node positive, or ■ sentinel lymph node biopsy shows node-positive with macrometastatic disease.

treatment of bca³⁰. Specific guideline recommendations for OFS were therefore brief. Guideline recommendation BINV-J states that OFS, in addition to either tamoxifen or an aromatase inhibitor, should be recommended to patients with a higher risk of recurrence after a balanced discussion about the risks and benefits³⁰. Patients are considered higher risk if they are diagnosed at a younger age (not defined), if evidence of lymph node involvement is present, or if the tumour is high grade. References for OFS were limited to the SOFT and TEXT trials^{35,36}. Notably absent from the discussion was the ABCSG (Austrian Breast and Colorectal Cancer Study Group) 12 trial, which was referenced in the other three guidelines³⁷. The NCCN did reference ABCSG-12 with respect to its adjuvant bisphosphonate recommendations³⁰.

Like the NCCN guideline, the St. Gallen consensus sets out broad guidelines for all aspects of treatment in early-stage bca, with OFS being one topic discussed at the consensus conference^{31,32}. The recommendations from

the consensus meeting strongly advised OFS in addition to endocrine therapy for women at high risk of recurrence. Specifically, the St. Gallen consensus developers defined women with a high risk of recurrence as those diagnosed at less than 35 years of age, having 4 or more involved lymph nodes, or requiring chemotherapy^{31,32}. The evidentiary base for the recommendations lists the SOFT, TEXT, and ABCSG-12 trials³⁵⁻³⁷.

The PEBC guideline recommendations for OFS differed from those given in the other three guidelines. This specific clinical scenario forms part of a larger and comprehensive CPG focused on all aspects of adjuvant therapy²⁶. Recommendation 1-21 states that CCO does not recommend OFS in addition to endocrine therapy for any premenopausal woman with an ER+ tumour. A recommendation for OFS alone was given for patients in whom other systematic therapy was not advised²⁶. Published in 2014, the PEBC guideline acknowledged new data emerging from the SOFT³⁵ and TEXT³⁶ trials, but indicated that the applicability of

the evidence in clinical practice was unclear at the time²⁶. That evaluation was reflected in a qualifying statement²⁶:

Clinicians were unsure how to incorporate into their clinical practice.... 83.3% of participants agreed that the addition of [ovarian ablation] or suppression to tamoxifen in premenopausal patients is not standard of care; however, 16.7% of participants disagreed or were undecided given the existence of data that suggests a benefit in female patients aged < 40 years. There was significant discussion and divergent opinions on this issue. Pending upcoming data, the addition of ovarian ablation or suppression to tamoxifen in premenopausal patients it is not standard of care.

Clinical Scenario 2

- After NAC for LABC, when is a SLNB, compared with a complete axillary lymph node dissection, recommended for axillary staging?

The 2017 ASCO guideline was a focused update to a 2014 guideline on SLNB in early-stage bca²⁵. The guideline expert panel, after a systematic review, concluded that no new evidence had emerged to warrant a change to the 2014 guideline recommendations³⁸. The ASCO guideline recommendations conclude that clinicians could offer SLNB to patients who have received NAC²⁵. The evidence quality was judged to be intermediate, and the overall strength of the recommendation was moderate²⁵. However, given insufficient evidence (quality was poor, and overall strength of the evidence was weak)²⁵, ASCO did not recommend SLNB for larger tumours—T3 (>5 cm) or T4 (with direct extension to skin or chest wall)³⁹—or for inflammatory bca. The cco guidelines, published in 2014, also state that lack of evidence led to a recommendation against the routine use of SLNB after the administration of NAC for LABC²⁷. Studies included in the ASCO and cco guidelines were similar^{40–42}.

In contrast, NCCN and St. Gallen identified specific scenarios in which a SLNB could be considered (Table IV). The NCCN guideline recommendation BINV-11 states that if the lymph node evaluation before NAC is clinically negative, then SLNB can be recommended³⁰. A SLNB can also be recommended if axillary lymph nodes that are positive before NAC are found to be clinically negative after treatment³⁰. The recommendation was given a category 2B rating³⁰. That rating was based on lower-level evidence and a NCCN consensus in the 75%–90% range²⁹. The recommendation also states that the false-negative rate of 10% after SLNB should be discussed with patients³⁰. A SLNB was not recommended if a lymph node that was positive before NAC remains positive after treatment³⁰. The specific studies supporting the NCCN recommendations for clinical scenario 2 were not discussed³⁰.

St. Gallen recommended SLNB for women with lymph nodes that are initially clinically positive, with subsequent downstaging to a negative axilla after NAC^{31,32}. If the axilla remains clinically positive after NAC, then SLNB is appropriate if at least 3 negative lymph nodes are found^{31,32}. A SLNB would not be sufficient if, after NAC, macrometastatic nodal disease were to be observed^{31,32}. The studies justifying those

recommendations were similar to those considered by ASCO and the PEBC^{40–42} as well as by others^{43,44}. The St. Gallen consensus states that a SLNB is appropriate for a woman with clinically and radiologically negative axilla before NAC^{31,32}. The recommendation was strongly supported, with 95.7% consensus³².

AGREE II Evaluation of Guidelines

Tables v and VI present the results of the AGREE II evaluations of the guidelines for the two scenarios. All guidelines scored highest on clarity and presentation. All guidelines scored poorly on applicability. The ASCO and PEBC guidelines met all minimum quality thresholds in each domain for scenario 1, but not for scenario 2. The NCCN and St. Gallen guidelines scored poorly on rigour of development. The NCCN and St. Gallen guidelines scored well on clarity of presentation.

DISCUSSION

Research suggests that end users of cpgs value guidelines with an easy-to-use format, evidence validity, expert guidance for applying recommendations to individual patients, and engagement of patients in shared decision-making^{19,20,45}. Using two clinical scenarios in bca treatment, we applied the AGREE II tool to evaluate the quality of guidelines from four different organizations. Distinct guidelines were available from ASCO and the PEBC for each of the two clinical scenarios; the NCCN and St. Gallen covered the two scenarios within a single larger guideline.

Rigorous and clear methodologic support for guideline recommendations was found to vary between the guideline organizations. The ASCO and PEBC guideline panels included identified methodologists^{33,34}, and not surprisingly, their guidelines, compared with those from the NCCN and the St. Gallen Consensus Conference, scored higher in the domains of rigour of development^{30–32}. However, the quality support from methodologists did not translate into improved applicability; all the guidelines scored low on the applicability domain.

Despite differences in methodologic rigour, each of the organizations used similar evidence to reach fairly consistent recommendations for clinical scenario 1^{35–37}. That observation might be explained by the topic's available evidentiary base. The PEBC recommendations for OFS were completed in September 2014 and must be interpreted with care given the emergence of more recent and mature data considered by the other three guideline organizations, all of whom published their recommendations more recently.

For scenario 2, recommendations were more contradictory and confusing. The ASCO and PEBC panels were unable to recommend SLNB because of a paucity of evidence relating to SLNB after NAC. However, the NCCN and St. Gallen groups relied on expert opinion and consensus to make recommendations in the absence of high-level studies. In this particular scenario, the issues with respect to the quality of the data content and the lack of high-level evidence, coupled with a very specific clinical question, could have adversely affected the applicability of the guideline recommendations, thus resulting in low AGREE II scores.

TABLE V AGREE II scores^a of guidelines used for clinical scenario 1, ovarian function suppression

Guideline	Score (%)					
	Scope and purpose	Stakeholder involvement	Rigour	Clarity of presentation	Applicability	Editorial independence
ASCO ²⁴	75	78	66	72	63	71
PEBC ²⁶	83	67	72	72	60	71
NCCN ³⁰	61	72	34	69	19	42
St. Gallen ^{31,32}	56	42	29	69	19	33

^a Calculation⁹:

Maximum possible score = 7 (strongly agree) × 3 (items) × 2 (appraisers)

Minimum possible score = 1 (strongly disagree) × 3 (items) × 2 (appraisers)

Score in percentage = (obtained score – minimum possible score) / (maximum possible score – minimum possible score).

ASCO = American Society of Clinical Oncology; PEBC = Cancer Care Ontario's Program in Evidence-Based Care; NCCN = U.S. National Comprehensive Cancer Network; St. Gallen = St. Gallen International Breast Cancer Conference.

TABLE VI AGREE II scores^a of guidelines for clinical scenario 2, sentinel lymph node biopsy

Guideline	Score (%)					
	Scope and purpose	Stakeholder involvement	Rigour	Clarity of presentation	Applicability	Editorial independence
ASCO ²⁵	52	78	52	78	27	75
PEBC ²⁷	72	53	72	78	50	79
NCCN ³⁰	61	72	34	69	19	42
St. Gallen ^{31,32}	56	42	29	69	19	33

^a Calculation⁹:

Maximum possible score = 7 (strongly agree) × 3 (items) × 2 (appraisers)

Minimum possible score = 1 (strongly disagree) × 3 (items) × 2 (appraisers)

Score in percentage = (obtained score – minimum possible score) / (maximum possible score – minimum possible score).

ASCO = American Society of Clinical Oncology; PEBC = Cancer Care Ontario's Program in Evidence-Based Care; NCCN = U.S. National Comprehensive Cancer Network; St. Gallen = St. Gallen International Breast Cancer Conference.

The AGREE II evaluation performed for the present study has limitations. First, the evaluation was performed by 2 reviewers. The AGREE consortium recommends at least 2 reviewers, but more reviewers will increase the reliability of the assessment⁹. Another limitation was that guideline implementability was not further assessed using tools such as the Guideline Implementability Appraisal¹⁴; CAN-IMPLEMENT⁴⁶; Grading of Recommendations Assessment, Development and Evaluation¹²; and ADAPTE¹⁶.

Our results are similar to those emerging from other studies evaluating bca guidelines. Hogeveen *et al.*⁴⁷ used the AGREE instrument to evaluate the quality of bca CPGs developed by three international organizations. They found variability in guideline quality within and between organizations. They also showed that, for all bca guidelines, the lowest score on the AGREE instrument occurred in the domain of applicability⁴⁷. The applicability domain in the AGREE II tool evaluates whether the CPG identifies facilitators to help end users of the guideline apply the guideline recommendations, and assesses whether barriers impeding the implementation process were identified and whether solutions were provided⁹.

The applicability of CPGs has been problematic in several other studies, including an evaluation of surgical guidelines for bca treatment⁴⁸ and a systematic review of

bca guidelines and their sensitivity to differing resources around the globe⁴⁹. The latter finding was important, given that oncology CPGs from ASCO and the NCCN are used internationally^{50,51}. A low score in the domain of applicability for bca guidelines evaluated using either AGREE OF AGREE II identifies a weakness in most guidelines⁵².

The uptake of oncology guideline recommendations in clinical practice is challenging to ascertain. In 2013, the NCCN recorded 4.9 million PDF downloads of their guidelines⁵¹. However, guideline downloads do not necessarily translate into guideline use or adherence. An international survey conducted in 2012 of 691 oncologists practicing internationally found that 83.1% of respondents used ASCO guidelines, followed by St. Gallen and NCCN guidelines⁵⁰. The same study also used the AGREE II instrument to compare the popularity of guidelines with their assessed quality⁵⁰. The ASCO guidelines were found to receive the highest score for both rigour and popularity. Interestingly, the NCCN and St. Gallen guidelines were very popular with the surveyed oncologists, but achieved overall AGREE II domain scores below the high-quality threshold⁵⁰. Although the survey study was small, it demonstrated that high-quality scores did not directly correspond with increased use of a guideline. That observation might reflect barriers to uptake and adherence that were not addressed in the CPGs^{4,7,53,54}.

Factors that were thought to increase guideline uptake included prominence of the guideline panel members as opinion leaders in the field and successful dissemination techniques, particularly with respect to electronic or Internet tools⁵¹.

Successful uptake of guidelines requires effective implementation strategies²¹ that could include pilot-testing guidelines to identify facilitators and barriers to implementation, particularly factors influencing feasibility in local jurisdictions. Feasibility of guideline implementation depends on factors such as capacity, resource availability, and cultural and societal norms and practice⁴⁹. Additional tools such as summary documents or links to algorithms or checklists could also be helpful^{9,21,55,56}. Kastner *et al.*¹⁸ found that guideline implementability is influenced by two major factors: creation of the guideline content, and effective communication of the guideline content. Specific guideline characteristics shown to be associated with poor uptake include length and format of the guideline, lack of clarity, and applicability of recommendations²¹. However, oversimplification could lead to misinterpretation of the evidence, and thus a balance between simplicity and full clarity of guideline recommendations must be found. Some researchers suggest incorporating literature from the fields of cognitive research, behavioural science, and marketing to improve implementation strategies¹⁸.

Uptake of guideline recommendations can be influenced by resource implications and cost-effectiveness. Guidelines that place excess demands or require additional resources, or that necessitate acquisition of new skills or knowledge are often difficult to implement²¹. Unfortunately, those aspects of implementability were not considered in any of the guidelines assessed for our review. The NCCN is attempting to address the issue with its new “evidence block,” which is a separate guideline that incorporates affordability and the costs of therapies into its guidelines⁵⁷.

The abundance of BCA CPGs is not necessarily problematic. Although duplication of effort might be significant, attempts are increasingly being made to combine resources, as is evident in several joint collaborations by CCO’s PEBC and ASCO^{58,59}. The challenge lies in contextual issues of local resources and making CPGs more patient-focused. Moreover, CPGs might also have culture-building capabilities both at the local level and more broadly within the oncology community. Efforts to pool resources and subsequently adapt guidelines for local practice might be appropriate and might also increase CPG applicability and use.

Guidelines also face challenges of staying up to date in the face of emerging data⁶⁰. The maintenance of methodologic rigour can conflict with the need to remain relevant and current^{61,62}. One solution that organizations such as ASCO and the European Society of Medical Oncology have recommended is to conduct focused updates or electronic updates for smaller topics. The NCCN conducts an annual review of its guidelines, which could be a factor in their reported high rates of uptake²⁹.

An assessment of the quality of guideline recommendation content is important for further understanding the issues related to guideline implementation and applicability. It is important to recognize that high methodologic quality does not necessarily equate to high content quality.

The lack of quality assessments of guideline content is a recognized deficiency. The AGREE-REX project is currently developing a resource to complement the AGREE II instrument by evaluating the clinical credibility and implementability of CPGs¹³. Future research in this area will be important to improve guideline implementation.

In addition to informing clinicians about current practices, guidelines can highlight areas of insufficient evidence. When evidence is lacking, expert opinion and consensus recommendations can take on increased prominence, as was evident in the NCCN and St. Gallen recommendations. The lack of evidence can potentially result in increased bias². Transparency is necessary to counter that bias and is achieved by identifying a well-defined search strategy, justifications for including or excluding studies, voting results, and commercial and intellectual conflicts of interest. Reliance on expert consensus was evident in the clinical scenario involving SLNB after NAC for LABC. Data to guide decision-making in this context are limited, raising concerns about potential adverse patient outcomes. On reviewing the guidelines, it is evident that the medical literature contains gaps and that further research in this area is warranted.

In interpreting and using CPGs, clinicians must be vigilant in understanding the development and methodologic rigour involved. Attention should be given to the selection of studies for the guidelines and the interpretation of results. Guidelines should be transparent and up to date, and should reflect the limitations of the literature. Finally, context-specific applicability will determine which guideline truly makes sense for the practicing clinician to use in providing the best possible care for patients.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SDT's institution receives funding from Novartis for a trial in which she is a co-investigator.

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