

# Critical Evaluation of the Scientific Content in Clinical Practice Guidelines

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**BACKGROUND:** Increasing pressures to provide high-quality evidence-based cancer care have driven the rapid proliferation of clinical practice guidelines (CPGs). The quality and validity of CPGs have been questioned, and adherence to guidelines is relatively low. The purpose of this study was to critically evaluate the development process and scientific content of CPGs. **METHODS:** CPGs addressing management of rectal cancer were evaluated. We quantitatively assessed guideline quality with the validated Appraisal of Guidelines Research & Evaluation (AGREE II) instrument. We identified 21 independent processes of care using the nominal group technique. We then compared the evidence base and scientific agreement for the management recommendations for these processes of care. **RESULTS:** The quality and content of rectal cancer CPGs varied widely. Mean overall AGREE II scores ranged from 27% to 90%. Across the 5 CPGs, average scores were highest for the clarity of presentation domain (85%; range, 58% to 99%) and lowest for the applicability domain (21%; range, 8% to 56%). Randomized controlled trials represented a small proportion of citations (median, 18%; range, 13%-35%), 78% of the recommendations were based on low- or moderate-quality evidence, and the CPGs only had 11 references in common with the highest-rated CPG. There were conflicting recommendations for 13 of the 21 care processes assessed (62%). **CONCLUSIONS:** There is significant variation in CPG development processes and scientific content. With conflicting recommendations between CPGs, there is no reliable resource to guide high-quality evidence-based cancer care. The quality and consistency of CPGs are in need of improvement. *Cancer* 2015;121:783-9. © 2014 American Cancer Society.

**KEYWORDS:** evidence-based medicine, practice guidelines, rectal neoplasms, organizations, health services.

## INTRODUCTION

There are increasing pressures to provide evidence-based cancer care and to document concordance with quality standards. Recognizing these needs, there has been rapid proliferation of clinical practice guideline (CPG) recommendations over the last decade.<sup>1</sup> These CPGs aim to consolidate findings from increasingly expansive clinical research literature and to develop standardized approaches to high-quality care. However, concordance with guideline recommendations remains inadequate.<sup>2-4</sup>

Many have posited that clinicians' lack of adherence to guidelines may be a result of distrust in how CPGs are developed and in the recommendations that are put forth.<sup>5</sup> Developers of CPGs often fail to adhere to widely endorsed standards for the development of high-quality guidelines.<sup>6-9</sup> These standards aim to improve the quality of CPGs, ensure freedom from bias, and increase the likelihood of broad endorsement. Further, little attention has been given to disagreement between CPGs in scientific content. Conflicting recommendations may result from either differences in the evidence base used to synthesize recommendations or differences in interpretation of the same evidence. It is not known whether adherence to standards for high-quality CPG development might be associated with the use of higher-quality evidence.

In this context, we sought to critically evaluate CPGs on the basis of their overall development quality, the evidence base used to synthesize recommendations, and the scientific agreement between CPGs on key processes of care. An understanding of this relationship will help cancer care providers determine the reliability of CPG recommendations and better inform their clinical decision making.

## MATERIALS AND METHODS

In this study, we focused on recommendations for the management of rectal cancer. Rectal cancer requires well-coordinated, multidisciplinary care and, given highly variable patient outcomes, is a disease site in need of more

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standardized care and promulgation of best practices. Further, the evidence base for rectal cancer care is large and diverse, ranging from expert opinion to results from randomized controlled trials. This focus on 1 disease site allows for in-depth evaluation of the quality and content of specific care recommendations within the guidelines.

Five specialty societies or government-funded organizations producing rectal cancer CPGs listed in the National Guideline Clearinghouse and the Standards and Guidelines Evidence databases were selected from 17 societies and organizations via author consensus prior to data collection. Only authoring organizations that published on the multidisciplinary management of rectal cancer were included. The selected organizations and societies represent the key authorities on rectal cancer care in North America and Europe and were believed to have credibility with large constituencies; they are the, American Society of Colon and Rectal Surgeons (ASCRS),<sup>10</sup> Cancer Care Ontario (CCO),<sup>11-14</sup> European Society of Medical Oncology (ESMO),<sup>15</sup> National Comprehensive Cancer Network (NCCN),<sup>16</sup> and the National Institute for Health and Care Excellence (NICE).<sup>17</sup> The most up-to-date versions of the CPG documents and the authoring organizations were obtained from their respective websites. Only documents published between 2008 and 2014 were included in the analysis to ensure a contemporary comparison between CPGs with access to a similar evidence base.

The process of development and quality of reporting for each CPG was assessed using the Appraisal of Guidelines for Research & Evaluation (AGREE II) instrument.<sup>18</sup> The AGREE II is widely accepted as the international gold standard for the appraisal of guidelines,<sup>19</sup> developed by organizations in various settings. The instrument is composed of 23 items within 6 quality domains: 1) scope and purpose, 2) stakeholder involvement, 3) rigor of development, 4) clarity of presentation, 5) applicability, and 6) editorial independence. Each item is rated on a 7-point Likert scale. The AGREE II instrument allows for up to 4 appraisers to independently rate CPGs. Raters were blinded to each other's ratings, and achieved high interrater reliability, as evident by weighted kappa scores of 0.7-0.9. The Likert ratings from all 4 raters were used to compute a standardized score from 0% to 100% for each domain per AGREE standards. For CPGs with multiple documents that address different aspects of care (ie, CCO), the raters considered the documents collectively as one.

The CPG with the highest AGREE II 6-domain average was then used as the benchmark for comparing process-of-care recommendations across CPGs. Using the

nominal group technique,<sup>20-22</sup> we identified recommended processes relevant to the care of rectal cancer, across 5 clinical categories: 1) diagnosis and staging, 2) preoperative therapy, 3) operative management, 4) postoperative therapy, and 5) surveillance. The authors discussed each of the identified processes in a round-robin feedback session, and were given the opportunity to clarify their opinions regarding the relative importance of each care process, including the option of adding processes that were not initially identified. The authors then separately prioritized the identified processes. Overlapping processes of care were consolidated and ranked consecutively, and those with broad consensus were included. A final list of 21 distinct processes of care was developed. This list was redistributed to each panel member for approval. We evaluated the evidence used to inform recommendations for each of the 21 processes of care and compared the citations, level of evidence (high- vs low- or moderate-quality evidence), and the strength of the recommendations as reported by the CPG authors to the highest-rated CPG.

The complete reference list for each CPG was manually reviewed. Each citation was cross-checked with the reference list of the highest-rated CPG to identify shared references.

All statistical analyses were conducted using STATA special edition (version 13; StataCorp, College Station, TX).

## RESULTS

### ***Guideline Development: Organizational and CPG Characteristics***

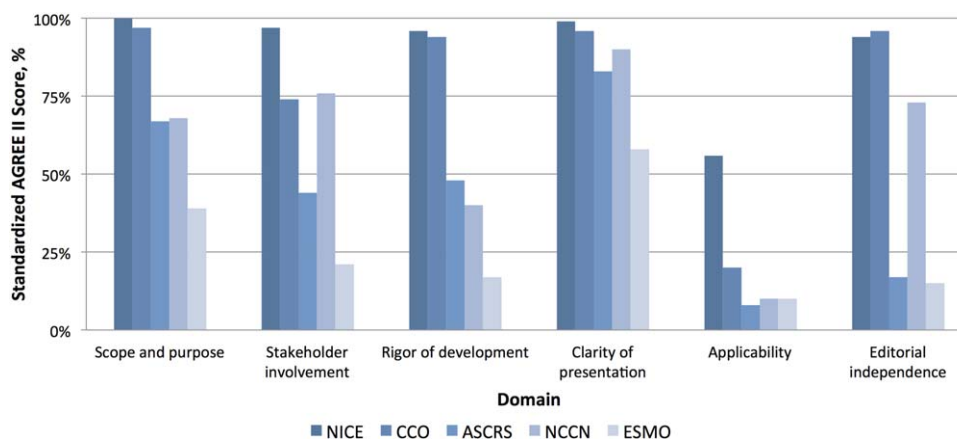
The characteristics of the CPG authoring organization are summarized in Table 1. Three are professional specialty societies or consortiums (ASCRS, ESMO, and NCCN), and 2 are government-associated multidisciplinary agencies (NICE and CCO). In all authoring organizations, a panel of individuals with clinical expertise was convened for the synthesis of CPG recommendations. The CPG panel comprised a multidisciplinary membership in all but 1 organization because ASCRS included only colon and rectal surgeons on its panel. Patient advocates were included on the CCO, NCCN, and NICE panels, but not on the ASCRS and ESMO panels. Financial support for the guideline developmental process originated from either the budget of professional organizations/societies (ASCRS, ESMO, and NCCN) or grants issued by the government or government-affiliated agencies (NICE and CCO).

Although the guidelines were developed over similar periods, the evidence used to develop and justify treatment recommendations differed. For example, the

**TABLE 1.** Organizational and Document Characteristics for Rectal Cancer Clinical Practice Guidelines (CPGs)

Characteristics	Clinical Practice Guidelines Authoring Organization				
	NICE	CCO	ASCRS	NCCN	ESMO
Body responsible	Guideline Development Group	Program in Evidence-Based Care	Standards Practice Task Force	Rectal Cancer Panel	Guideline Working Group
Multidisciplinary	Yes	Yes	No	Yes	Yes
Patient advocate	Yes	Yes	No	Yes	No
Funding source	Government	Government	Specialty society	Specialty society	Specialty society
Year published	2011	2008-2012	2013	2014	2013
Time frame for literature review	1806-2011	1999-2011	Through 2/2012	N/A	N/A
Rectal cancer CPGs distinct from colon cancer	No	No	Yes	Yes	Yes
Document length, pages	186	211	16	110	8
Number of references	245	206	154	486	40
Number of references shared with NICE	[ref]	10	11	10	6
Percent of references from RCTs	21%	14%	18%	13%	35%
Disclosure statement	Yes	Yes	No	Yes	Yes
Updating strategy	Yes	Yes	No	Yes	No
Dissemination	Online	Journal and online	Journal and online	Journal, online, and mobile app	Journal and online

Abbreviations: ASCRS, American Society of Colon and Rectal Surgeons; CCO, Cancer Care Ontario; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; RCTs, randomized controlled trials.



**Figure 1.** Comparison of the quality of the clinical practice guidelines using the AGREE II instrument. (ASCRS, American Society of Colon and Rectal Surgeons; CCO, Cancer Care Ontario; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence).

number of references ranged from 40 to 384 citations per CPG. The methods for developing the CPGs specifically included systematic reviews in the ASCRS, CCO, and NICE guidelines, but ESMO and NCCN did not report using systematic literature reviews as a part of their process.

#### Guideline Development: AGREE II Scores

The AGREE II scores for each CPG in all 6 domains are shown in Figure 1. Overall, rectal cancer CPGs from

NICE had the highest mean AGREE II score, 90% (range by CPG, 27%-90%). In the scope and purpose domain, only CCO and NICE clearly defined their scope, global objectives, and target populations. For the stakeholder involvement domain, only NICE and NCCN included patients, their representatives, and other stakeholders in the development of CPGs. The biggest differences were seen in the rigor of the development domain, with the NICE CPG scoring a 96% compared with 17% for the ESMO guideline. Scores for the

**TABLE 2.** Scientific Content Comparison Between Clinical Practice Guidelines

Recommendations	NICE	CCO	ASCRS	NCCN	ESMO
<b>Diagnosis and staging</b>					
Thorough history and physical exam, rigid proctoscopy, CEA	•	•	•	•	•
Complete preoperative colonoscopy with biopsy	•	•	•	•	•
CT colonography as an alternative to colonoscopy	•		•		•
Staging CT of chest, abdomen and pelvis, no additional staging imaging			•	•	
Pelvic MRI for all patients	•	•			•
Recommend against routine PET imaging	•		•	•	
Preoperative enterostomal therapist consult	•		•	•	
<b>Preoperative management</b>					
Discuss RC patients in a multidisciplinary tumor board	•	•	•	•	•
Do not offer neoadjuvant therapy for low-risk resectable RC	•	•	•	•	•
Consider SCRT with immediate surgery for moderate-risk RC	•				•
Consider LCCRT with interval surgery for borderline moderate-high risk	•	•	•	•	•
Offer LCCRT with interval surgery for high risk-operable cancer	•	•	•	•	•
<b>Operative management</b>					
Offer local excision when feasible for low-risk T1 tumors with further therapy if high-risk features or compromised margins	•	•	•	•	
Recommend laparoscopic surgery as an alternative to open surgery for patients suitable for both, and surgeons are appropriately trained	•		•		
<b>Adjuvant therapy</b>					
Assess pathologic staging after surgery before deciding whether to offer adjuvant therapy	•				
Offer adjuvant chemotherapy to patients who had surgery alone or had SCRT without chemotherapy	•	•	•	•	•
Offer adjuvant chemotherapy in all patients who received neoadjuvant chemotherapy or LCCRT		•	•	•	•
<b>Surveillance</b>					
Start surveillance 4-6 weeks after potentially curative intervention	•	•		•	
Minimum 2 CT scans of the chest, abdomen and pelvis in the first 3 years and CEA every 6 months for the first 3 years	•	•		•	•
Offer surveillance colonoscopy at 1 year; if normal repeat in 5 years	•			•	
Stop surveillance when patient and physician agree that the benefit no longer outweighs risk of tests, or patient cannot tolerate further therapy	•				

•Agreement in scientific content with the stated recommendation; a blank means that the guideline objectively disagrees or fails to mention the given recommendation. Note ASCRS does not have surveillance recommendations published after 2008.

Abbreviations: ASCRS: American Society of Colon and Rectal Surgeons; CEA, carcinoembryonic antigen; CCO, Cancer Care Ontario; ESMO, European Society of Medical Oncology; LCCRT, long-course chemoradiation therapy; NCCN: National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; SCRT, short-course radiation therapy.

clarity of presentation domain were generally high in all CPGs. In general, there was little information regarding potential organizational barriers, cost implications, and tools for application across all CPGs making the scores for the applicability domain the lowest across all guidelines. Last, only CCO and NICE CPGs included clear information about the potential conflicts of interest of guideline institutions or members as presented in the editorial independence domain scores.

**Guideline Content: Scientific Agreement**

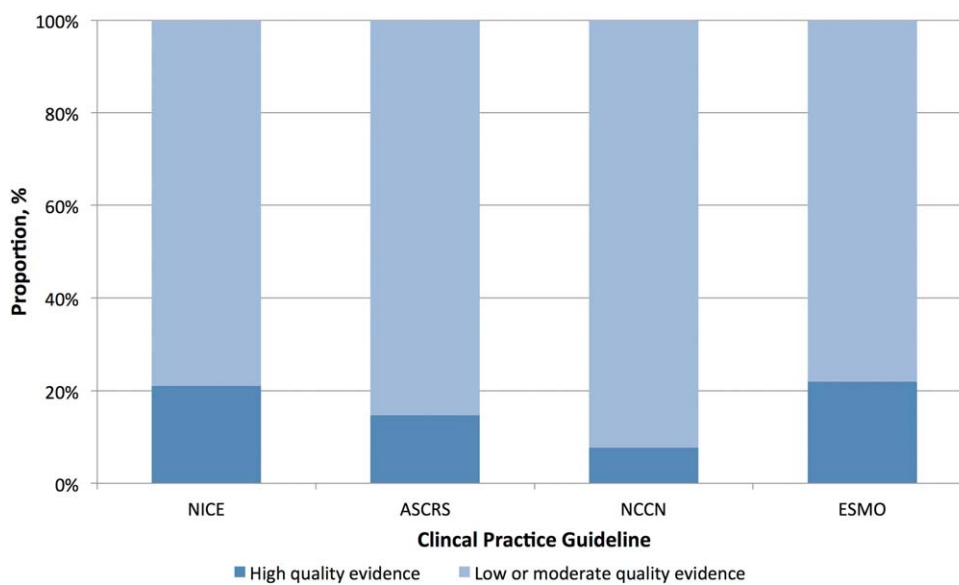
The 21 processes of care are compared in Table 2. Overall, the 5 CPGs had uniform agreement on their recommendations in only 8 of the 21 processes of care (32%), as described below. Of the 13 processes with disagreement, 6 recommendations were in direct conflict, and 7 were actually nonrecommendations, reflecting a lack of direct recommendations on a given issue.

**Diagnosis and staging**

Whereas all other CPGs defines rectal cancer as a tumor located up to 15 cm from the anal verge on rigid proctoscopy, thereby dividing the rectum into thirds, NCCN differs in its definition by limiting it to tumors 12 cm from the anal verge. Although all CPGs recommend a complete preoperative colonoscopic evaluation, only ASCRS, ESMO, and NICE mention the role of CT colonography as an alternative. ASCRS, NCCN and NICE CPGs recommend a CT scan of the chest, abdomen, and pelvis for staging, but CCO and ESMO recommend an initial chest x-ray, and ESMO recommends an abdominal ultrasound or MRI to assess for liver metastases.

**Preoperative therapy**

All CPGs acknowledge the need for a multidisciplinary tumor board for the management of rectal cancer patients and that preoperative chemotherapy and/or radiation



**Figure 2.** Distribution of the quality of evidence cited within each clinical practice guideline. Note: Cancer Care Ontario (CCO) does not separately grade the evidence, and is therefore not included (ASCRS, American Society of Colon and Rectal Surgeons; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence).

therapy are not indicated in low-risk or stage I resectable rectal cancer patients. The comparison highlights the differences in practice between North America and Europe in the use of short-course radiation therapy for moderate-risk rectal cancer patients. However, all CPGs recommend preoperative long-course chemoradiation therapy for high-risk or advanced-stage patients.

### Operative management

All CPGs advise the use of local excision techniques for low-risk/stage I rectal cancer and recommend further treatment if high-risk features are present on histopathology. Only ASCRS and NICE recommend laparoscopic rectal surgery as an alternative to the open approach. The NCCN discusses the role of laparoscopic surgery but recommends its use only in the context of a clinical trial, and CCO and ESMO do not specifically discuss the role of laparoscopic surgery.

### Adjuvant therapy

All other CPGs disagree with the NICE statement that postoperative pathological staging is more important than preoperative clinical staging in deciding whether to administer postoperative chemotherapy. All CPGs agree that patients with locally advanced or node-positive rectal cancers who did not receive preoperative chemotherapy should receive postoperative chemotherapy. However, the CPGs differ in their interpretation of evidence regarding

indications for postoperative chemotherapy among patients who received preoperative chemoradiation. Although all CPGs reference the same publication by Bossett and colleagues,<sup>23</sup> NICE does not make a recommendation because of insufficient evidence; CCO and NCCN acknowledge the lack of evidence but recommend adjuvant therapy based on expert consensus; ASCRS strongly recommends adjuvant therapy and grades the evidence as level 1A, and ESMO recommends adjuvant therapy and grades the evidence as level 2B. Of note, ASCRS also cites an additional subgroup analysis on this topic<sup>24</sup>; however, a subgroup analysis does not meet criteria for level 1A evidence, and the authors of that study appropriately caution that their analysis is exploratory in nature.<sup>25</sup>

### Surveillance

Only the NICE CPG clearly defines when surveillance begins and ends. Although NICE, CCO, and NCCN recommend routine interval CT scans and CEA measurements, ESMO reserves radiological and laboratory tests for symptomatic patients only. ASCRS did not include surveillance in this CPG version.

### Quality of evidence

In all CPGs, the majority of evidence used to synthesize the recommendations was of low-moderate quality (Fig. 2). High-quality evidence (as graded by the authoring organizations) only comprised 22% of citations.

The guidelines appear to use a varied evidence base despite a similar time frame for searching the evidence base. Using the citations in the NICE CPG (which includes 245 references) as the benchmark, the other documents only had 6 to 11 references in common with NICE.

## DISCUSSION

This study sought to evaluate the quality and scientific content of CPGs and compare the scientific basis for guidelines issued by various organizations. Using a validated guideline appraisal instrument, we identified wide differences in the quality of guideline development and reporting for CPGs, with overall scores ranging from 26% to 90%. The majority of the evidence that makes up the CPGs was of low to moderate quality, and there were substantial differences in interpretation of data. There were conflicting recommendations in 13 of the 21 specific processes of care for rectal cancer that we examined.

We previously reported that oncology CPGs failed to meet the Institute of Medicine's standards for guideline development.<sup>6</sup> The present study demonstrates that these inadequacies in development herald important differences in the scientific content and the synthesized recommendations contained within CPGs. Although it is well known that there is a relative paucity of high-quality evidence and randomized controlled trials in cancer care, an end user might expect that CPGs would examine the best available evidence and draw similar conclusions. We found, however, that despite "systematic reviews" of the literature in 3 widely used CPGs, there were only 6-11 reference citations shared with the highest rated CPG. Furthermore, even when using the same studies, CPGs interpreted their conclusions differently, assigned them differing levels of evidence quality, and formulated conflicting recommendations. It is important that CPGs be transparent in their methodology, clearly outlining areas in which evidence is insufficient and in which expert opinion has been used. For example, NICE and CCO are exemplars in this regard, as their CPGs identify gaps in evidence and explicitly state when a recommendation is based on expert opinion. Consensus statements may be appropriate when evidence is lacking; however, some recommendations within different CPGs are written with a degree of certainty that may be unwarranted given the lack of strong evidence, leaving clinicians without reliable guidance.

There are differences in how organizations develop guidelines. For example, the 2 highest-scoring CPGs were authored by government-related organizations in countries with nationally funded health systems. This is not surprising as broad-reaching policy decisions about resource allo-

cations for treatment warrant higher-quality guidelines. Furthermore, the composition of the CPG development groups varied considerably. Some included experts in a single specialty, whereas others encompassed multiple specialties; some panels included patient advocates. This may certainly influence what is included in the CPG documents based on stakeholders' perspectives. Even in panels with a multidisciplinary structure, access to the necessary methodological skills may have been limited. This highlights the possible lack of adoption of a standardized CPG development process and raises the question of whether greater oversight is needed in this regard.

Generally speaking, CPGs with high scores on the quality appraisal instrument performed consistently well in most other domains, except for the applicability domain, where most CPGs fell short. Lack of applicability could mean that despite the vast resources that are invested into developing CPGs, little consideration is given to how recommendations will be translated into practice. More efforts may be needed to focus on understanding barriers to the implementation of guidelines and how to better use evidence to inform decision making and treatment planning.

Because of increasing pressures to practice evidence-based medicine and adhere to standards of care, CPGs have become an increasingly important resource for clinicians. However, the quality of the development process of the guidelines is highly variable. More important, the content of the resultant recommendations themselves is variable, and it is possible that clinicians' modest uptake of guideline recommendations is directly related to perceptions that CPGs are not of sufficient quality. The downstream implications for measurement and possible enforcement of concordance with guideline recommendations, as well as continued variation in patient outcomes, are important to consider in this context.

Although the present study did not specifically address the effect of the conflicting CPGs on practice patterns, there is growing evidence that differences in practice are present even when CPGs are in full agreement on a specific recommendation. For example, Monson and colleagues<sup>26</sup> recently investigated variation in preoperative therapy for stage II/III rectal cancer patients and found suboptimal adherence to this recommendation, with significant differences based on hospital volume and geographic regions. The present study highlights some potential additional reasons for lack of adherence to guidelines including the lack of a unified CPG development process, conflicting recommendations, and poor applicability of the produced CPGs.

This study has several limitations. By intent, the analysis presented here does not address rectal cancer guidelines by all societies or organizations. CPGs that were not

included may perform better or worse on the quality appraisal instrument, but the comparison was limited to those that are the most frequently used in clinical care, and our findings are actually more likely to be generalizable because of that. We did not examine guidelines for a wide range of disease sites because of our focus on exact recommendations for specific processes of care, and rectal cancer is an ideal example of the complex interplay between multiple disciplines. Even though the study is limited in this regard, it is probable that oncology CPGs for different disease sites face similar challenges in their development and have similar deficiencies in evidence interpretation and scientific content. Furthermore, we relied on materials reported in the published versions of the CPGs, and our findings could be affected not only by the quality of the guidelines themselves, but also by the quality of the reporting process. Nonetheless, this also potentially puts the quality of the reporting process under scrutiny.

In conclusion, there is significant variation in CPG development processes, with associated differences in scientific content and interpretation of evidence, resulting in conflicting recommendations. These differences mean that there may be no comprehensive resource available to guide health care providers, which may limit the delivery of high-quality evidence-based cancer care. Clinicians are advised to be aware of potential gaps in evidence and conflicting recommendations when using CPGs. If CPGs are to be confidently used as standards of care going forward, guideline developers bear the burden of evaluating both their processes and resultant end product, based on endorsed standards for the development of high-quality guidelines.

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## CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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