Analytical Frameworks in Colorectal Cancer Guidelines: Development of Methods for Systematic Reviews and their Application

Analytical Frameworks in Colorectal Cancer Guidelines: Development of Methods for Systematic Reviews and their Application

By Samer Karam, MD

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AUTHOR: Samer Karam, MD

SUPERVISOR: Holger J. Schünemann

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Abstract

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Master of Health Research Methodology, 2021, Samer Karam, Department of Health Research Methodology, Evidence and Impact, McMaster University

Background: Analytical frameworks (AF) are graphical representation of the key questions answered by a systematic review and can support the development of guideline recommendations. Our objectives are to a) conduct a systematic review to identify, describe and compare all AFs published as part of a systematic and guideline development process related to colorectal cancer (CRC); and b) to use this case study to develop guidance on how to conduct systematic reviews of AFs. **Methods:** We conducted a systematic review and searched Medline and Embase from 1996 until December 2020. We also manually searched guideline databases and websites. We identified all guidelines in CRC that utilized an AFs and all systematic reviews in primary prevention, screening, and diagnosis of CRC that used AFs. We assessed quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation II tool. The systematic review was registered in PROSPERO, registration CRD42020172117. **Results:** We screened 34,505 records and identified 1166 guidelines on CRC and 3127 systematic reviews, of which 5 met our inclusion criteria identifying a total of 4 AFs in colorectal cancer. We describe our search strategy and methods for conducting systematic reviews for AFs. **Conclusion:** Few guidelines and systematic reviews are utilizing AFs in the development of recommendations. We developed methods for conducting a systematic review on AF

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To my parents and siblings, thank you for supporting me every step of the way and encouraging me to do my best.

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List of Abbreviations:

CPG: Clinical Practice Guideline

CRC: Colorectal Cancer

AF: Analytical framework

IOM: Institute of Medicine

WHO: World Health Organisation

GIN: Guideline International Network

USPSTF: U.S. Preventive Services Task Force

CTFPHC: Canadian Task Force on Preventive Health Care

JRC: Joint Research Centre

ECICC: European Commission Initiative on Colorectal Cancer

NICE: National Institute for Health and Care Excellence

CCA: Cancer Council Australia

ESGE: European Society of Gastrointestinal Endoscopy

AGA: American Gastroenterological association

ACG: American College of Gastroenterology

ACS: American Cancer Society

ACPGBI: Association of Coloproctology of Great Britain & Ireland

ACMG: American College of Medical Genetics and Genomics

ESMO: European Society for Medical Oncology

JSCCR: Japanese Society for Cancer of the Colon and Rectum

CCO: Cancer Care Ontario

PEBC: The Program in Evidence-based Care

WSES: World Society of Emergency Surgery

ACP: American College of Physicians

JSMO: Japanese Society of Medical Oncology

ASCO: American Society of Clinical Oncology

EGOSLIM: Expert Group on OncoSurgery management of Liver Metastases

ASCRS: American Society of Colon and Rectal Surgeons

ECCO: European Crohn's and Colitis Organisation

ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition

JSGE: Japan Gastroenterological Endoscopy Society

EAES: European Association for Endoscopic Surgery

CAG: Canadian Association of Gastroenterology

NCCN: National Comprehensive Cancer Network

SEOM: Spanish Society of Medical Oncology

GGPO: German Guideline Program in Oncology

BMJ: British Medical Journal

BSG: British Society of Gastroenterology

KSGE: Korean Society of Gastrointestinal Endoscopy

EHTG: European Hereditary Tumour Group

ASGE: American Society for Gastrointestinal Endoscopy

ACR: American College of Radiology

Declaration of Academic Achievement

The following is a declaration that Samer Karam, Holger J. Schünemann, Jan Brozek, and Thomas Piggott contributed to the study protocol, as well as reviewing, editing and writing the document. Siw Waffenschmidt created the systematic review search strategy. Dr. Samer Karam coordinated the systematic review, gathered reviewers, screened, collected, and analyzed data. Systematic reviewers included Andrea J. Darzi, Antonio Bognanni, Rami Z. Morsi**,** Elie E. Tannous, Rana Charide, Se-In Choe, Rosa Stalteri, Yung Lee, Thomas Piggott, Laura Jewell, Finn Schünemann, Miranda Langendam, Elena Parmelli, Zuleika Saz-Parkinson, Annett Roi, Nadia Vilahur, Yasman Vali.

Chapter 1. Background

Colorectal cancer (CRC) is currently the third most common cancer in men and second most in women according to the World Health Organization (WHO) (1, 2). Recently, there has been a surge in guideline development using scientific evidence compiled into systematic reviews to answer health related questions and inform recommendations(3, 4). Indeed, for CRC there are many systematic reviews, recommendations, and clinical practice guidelines that address the topic; however, the scope varies from screening and preventative services to oncological treatments both surgical and medical.

The U.S. Preventive Services Task Force (USPSTF) introduced diagrams called "analytical frameworks"(3-5), these analytical frameworks (AF) show the complex relationships between multiple interventions, intermediate outcomes, and final health outcomes graphically; outlining the systematic review questions tackled by the reviewers. With recent drive by journals and the scientific community to adopt visual aids to enhance and facilitate reader understanding(6), an AF would naturally be the ideal model to present systematic review questions graphically.

The European Commission's Joint Research Centre (JRC), in the context of the European Commission Initiative on Colorectal Cancer (ECICC), has a mandate to develop guidelines and a quality assurance scheme for Colorectal cancer (CRC). The project will begin with mapping all possible questions that may be relevant in choosing topics best suited for the ECICC. Part of this mapping process was to identify all AF developed in CRC systematic reviews or in the process of CRC guideline development. To do this we performed a systematic review of AF in CRC, and in doing so we developed techniques to conduct a systematic review of AF. To the best of our knowledge this is the first systematic review of AFs in any topic. With an increasing number of systematic reviews that utilize AFs, a systematic review of AF could help guideline developers to incorporate the work already done by others into an overarching AF.

Chapter 2. Analytical Frameworks in Colorectal Cancer Guidelines

2.1. Introduction

Health guidelines have been developed since the early 20th century; historically by an expert panel (7, 8). Systematic methods were brought to guideline development with the first Institute of Medicine (IOM) report on guidelines in the early 1990's, critically reviewed for World Health Organisation (WHO) and professional societies in the first decade of this millennial and in the context of the creation of the guideline international network (GIN) (9, 10). In 2011 the IOM outlined the core components for trustworthy guidelines (7, 11) that they:

1. Be based on a systematic review of the existing evidence;
2. Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
3. Consider important patient subgroups and patient preferences as appropriate;
4. Be based on an explicit and transparent process that minimises distortions, biases, and conflicts of interest;
5. Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations; and
6. Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

Finally, in 2012, the GIN-McMaster checklist laid out the tools and practical considerations for trustworthy guideline development followed by reporting standards (RIGHT) for guidelines (12).

To achieve this, guideline development using an evidence-based approach is usually centred on scientific evidence compiled to answer different key clinical questions of a health condition (3, 4). After guideline groups select a topic for guideline development and decide on the scope of the topic in question, they are required to review the evidence to inform recommendations (3, 4). At this stage of the development process guideline developers should outline the key questions, specifying

the interventions, relevant population, outcomes of interest, and clinical setting that will be addressed in the subsequent systematic review (3, 4, 8, 13). The U.S. Preventative Services Task Force (USPSTF) introduced diagrams, originally called "causal pathways" later changed to "analytical frameworks"(3-5). They developed this diagrammatic approach by expanding on previous models such as causal pathways (14), causal models (15), influence diagrams (16), and evidence models (17). The AF incorporates complex models that portray the relationship between multiple interventions, intermediate outcomes, and final health outcomes. Figure 2 presents a recent example of an AF that was developed by the USPSTF in consideration of its guideline for colorectal cancer screening (13).

An AF is a graphical diagram that clearly presents the specific questions that need to be answered by systematic reviews of existing evidence, with linkages that serve to relate interventions and outcomes. These linkages help in identifying questions to guide the systematic review, and provides an evidence map that identifies gaps in the evidence after based on the findings of the review process (18, 19). The AF is a key component of the guideline development process, using a diagrammatic format to specify a chain of reasoning to answer key clinical questions to produce a recommendation.

Although intuitively useful, few guideline groups begin their work of question formulation with developing an AF. To develop an AF the guideline group needs to define the: key questions, type of evidence and its relevance to the questions, criteria for evaluating the evidence (4, 7), and the chain of reasoning needed to produce a recommendation to a particular question. When considering all possible outcomes for each question it is essential to account for any complex interrelationships between the different outcomes of interest (e.g. benefits and harms) (4). Developing a graphical model, or a visual AF, is a good way to visualize the relationships between the outcomes and the key questions. A well-developed AF not only helps track the progress of the guideline development process, but also aids in transmitting often complex outcome relations (assessing benefits, harms, costs, or other) clearly to the reader. In addition, it helps others judge whether appropriate outcomes

were considered (intermediate, surrogate, or other) or if important outcomes were overlooked. Also, AFs allow others to assess the appropriateness of the questions asked from the outset of the guideline process (4).

2.1.1. Context

The European Commission's Joint Research Centre (JRC), in the context of the European Commission Initiative on Colorectal Cancer (ECICC), has a mandate to develop guidelines and a quality assurance scheme for Colorectal cancer (CRC). The project will begin with mapping all possible questions that may be relevant in this context and choosing the topics that are best suited for the ECICC. CRC is currently the third most common cancer in men and second most in women according to the World Health Organization (1, 2), making it a major worldwide health problem. Given the background above, we aimed to identify all possible AFs and search for relevant guidelines using a systematic approach, to map existing questions and recommendations in a recommendation mapping process (addressed separately).

Our preliminary searches for AFs revealed an AF used in guidelines regarding CRC screening developed by the USPSTF (13), however we noted that the use of AFs in the development of the guideline process is not consistent between different guideline groups.

2.1.2. Goals

The specific goals of this study include:

1. Identifying and describing existing analytical frameworks developed for colorectal cancer guidelines and recommendations.
2. Comparing the identified analytical frameworks.
3. Developing methods for conducting systematic reviews of analytical frameworks.

2.2. Methods

2.2.1. Study design

We used the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines for this study (20). We conducted a systematic review using Cochrane methodology of

existing guidelines, recommendations, and systematic reviews regarding CRC to identify studies that reported AF (21). We developed a protocol for this review that we registered in Prospero: [CRD42020172117]

2.2.2. Study selection

Five teams of two reviewers conducted title and abstract screening independently and in duplicate after completing a training and calibration exercise. We retrieved full texts of all citations that were deemed eligible by at least one reviewer for full text review. The reviewers then assessed the full texts for inclusion also independently and in duplicate. A third reviewer resolved disagreements when necessary for final inclusion. Reviewers used standardized screening forms for title abstract and full text screening. Systematic reviews were deemed eligible for inclusion if they were relevant to primary prevention, screening, and diagnosis in CRC and utilized an AF that informed an included Clinical Practice Guideline (CPG). Systematic reviews on treatment were excluded as treatment was not prioritized by the ECIC, however we did not exclude CRC treatment guidelines in our search. We followed the Population & Clinical Areas, Interventions, Comparators, Attributes of CPGs, and Recommendation (PICAR) framework (Table 1) to guide inclusion and exclusion of CPGs in our study.

Table 1. PICAR

PICAR item	***Eligibility criteria***
Population, clinical indication(s), and condition(s)	We included all CPGs/ recommendations that reported on CRC patients regardless of age, gender, or risk group of the target population. We excluded all records not on CRC.
Interventions	We included CPGs/ recommendations with any intervention whose scope was focused on primary prevention, screening, diagnosis, staging and prognosis, genetic and molecular

	testing, quality improvement, and referral of CRC.
Comparator(s), Comparison(s), and (key) Content	We included CPGs/ recommendations with any comparator or comparison whose scope was focused on primary prevention, screening, diagnosis, staging and prognosis, genetic and molecular testing, quality improvement, and referral of CRC
Attributes of eligible CPGs	We included records that report on recommendations or are CPGs regarding CRC that utilized an AF in the development process of the guideline. We had no language restriction, and we included all CPGs on CRC from 1996 onwards. We included national and international guidelines on CRC and had no AGREE II assessment cut-off for inclusion. We excluded older iterations of CPGs from same guideline groups only including the most recent CPG or update.
Recommendation characteristics and "other" considerations	We included all AFs on CRC. We included all recommendations on CRC developed using an AF.

	We included all key questions identified from the AFs.

2.2.3. Data sources and searches

We searched Medline and EMBASE from inception to September 2019 with the assistance of an information scientist (Table A 1), and also performed an update of the search from September 2019 through December 2020. The search combined free text words and medical subject headings (Mesh) indexed terms when applicable, such as "colorectal cancer", "guideline", "recommendation", "analytical framework" and "systematic review". We added a timeline filter starting in 1996, based on the date the USPSTF published the methods paper on AFs (22). Also, we manually searched CMA Infobase, NHS Evidence Search, TRIP database and the GIN library from 2014 till December 2020. We used no language restrictions.

2.2.4. Data extraction

We conducted a calibration exercise to pilot the data extraction form before commencing with the extraction process. Using a standardized form, a team of two reviewers extracted the data independently and in duplicate from the eligible studies and compared all results. A third reviewer checked the validity of the extracted studies.

For all the identified records with an AF, the reviewers extracted data on the following characteristics:

- General characteristics pertaining to the study (e.g., Author, year, country, language)
- Population (e.g., Target age, phase of disease state)
- Interventions (e.g., Screening type, treatment options)
- Outcomes (e.g., Key questions, final recommendations of the guideline)
- Analytical framework with all the linkages

2.2.5. Quality assessment

We assessed the quality and reporting of the CPGs using the Appraisal of Guidelines for Research and Evaluation version 2 (AGREE II) instrument (23). Two reviewers completed the assessment independently and in duplicate. We then calculated the domain scores as per the AGREE II user manual.

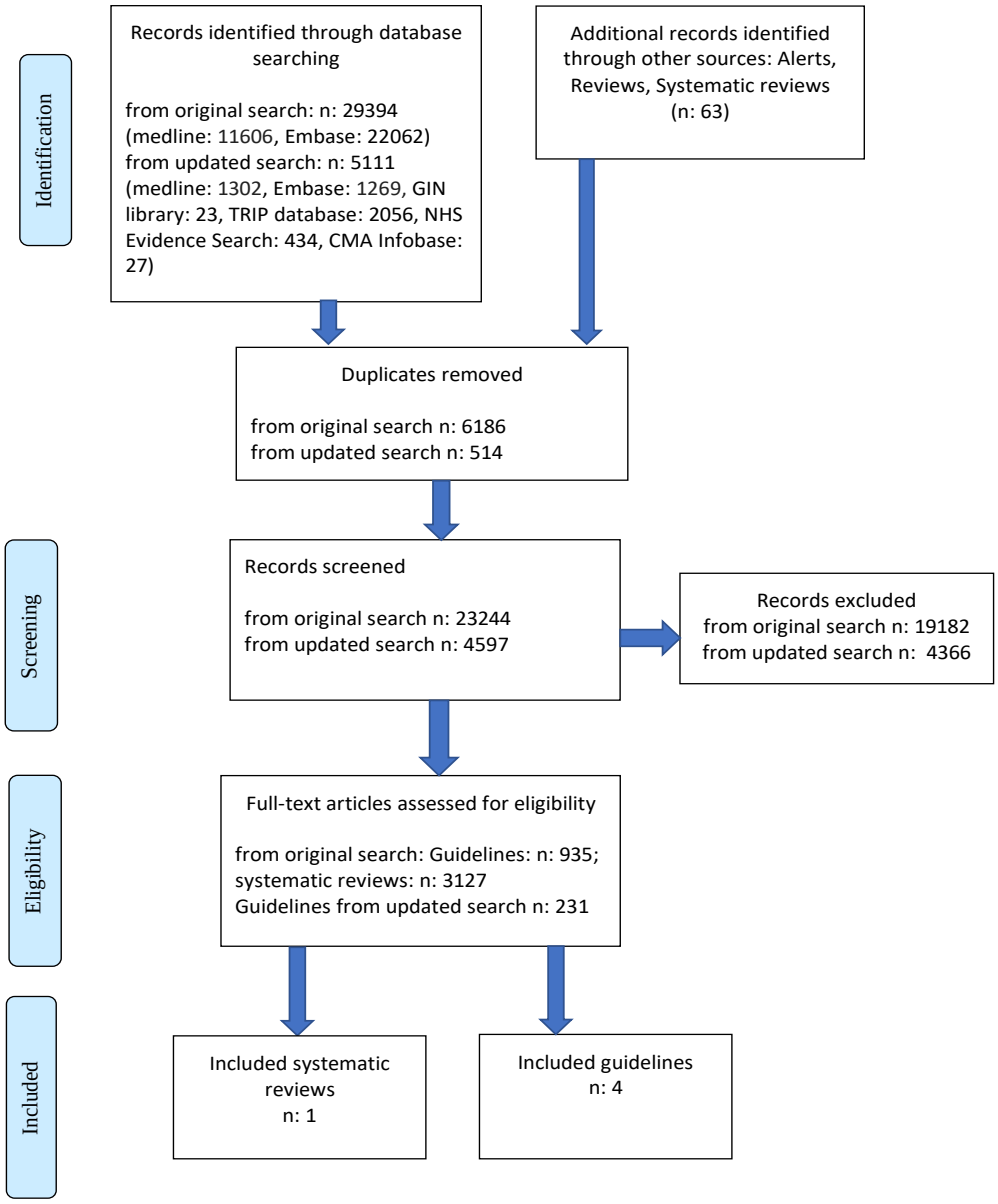
2.2.6. Data synthesis

We present the characteristics of the identified CPGs in a tabular format and used a narrative synthesis of included CPGs to summarize our findings. We present the key questions in the AFs with the final developed recommendations and the contextual questions used by the guideline groups.

2.3. Results

Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Our original search identified 29,394 citations of which we included 935 guidelines and 3,127 systematic reviews for full text assessment. After our screening process, we identified four CPGs with one associated systematic review that used an AF in the methods for developing recommendations (13, 24-27). We also identified one systematic review that contained an AF developed to inform an older version of the USPSTF CRC screening recommendations which we then excluded (28). When we conducted an update of our search in December 2020 and completed the manual search of the databases, we identified an additional 5,111 citations of which we assessed 231 guidelines for full text screening, none of which fulfilled our inclusion criteria. One of our included guideline is currently in the process of being updated (24), and the USPSTF recently published an update to the 2016 CRC screening guideline with an updated AF(29).

Figure 1: PRISMA flow chart



2.3.1. Description of the included clinical practice guidelines and systematic reviews

We identified four AFs from four CPGs and one associated systematic review on CRC (24-27). All four CPGs were national guidelines regarding CRC focusing on recommendations for a population of average risk to develop CRC (24-27). Three AFs with associated key questions were focused on CRC screening, and one AF was on CRC primary prevention using aspirin.

The first AF identified was in the USPSTF screening for CRC updated evidence report and systematic review (30), that was used for the development in the included USPSTF screening guideline (24). We originally identified this paper prior to conducting the systematic review during the protocol development and also found it in our search. The Canadian Task Force on Preventive Health Care (CTFPHC) described using an AF in the methods section to develop the recommendations on screening for CRC in primary care (25). We conducted a manual search for the online appendix to extract the AF. The Korean Guideline for Colorectal Cancer Screening used an AF for the development of their recommendations, and the AF was provided clearly in the guideline document (26). The USPSTF aspirin use for primary prevention of cardiovascular disease and CRC used an AF in the development of the recommendations; however, we had to conduct a targeted search of the USPSTF website to identify it as there was no mention of an AF in the recommendation statement (27, 31). Table A 2 and Table A 3 describe the final recommendations developed in the different CPGs with the associated grading of the evidence. Table 2 presents the characteristics of the included guidelines and Table 3 shows the characteristics of the included systematic reviews.

Table 2. Clinical practice guideline characteristics

Author, Year	Title	Country	Organization	Type of guideline	Methods used to grade the evidence	Perspective of guideline	Guideline priority topic
Bacchus, 2016(25)	Recommendations on screening for colorectal cancer in primary care	Canada	CTFPHC	National Guideline	GRADE	Health care setting	Screening
Bibbins-Domingo, 2016(24)	Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement	USA	USPSTF	National Guideline	USPSTF Grading and certainty of evidence	Health care setting	Screening
Sohn, 2015 (26)	The Korean guideline for colorectal cancer screening	Korea	Colon cancer screening revision committee	National Guideline	GRADE	Health care system	Screening

Bibbins-Domingo, 2016(27)	Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement	USA	USPSTF	National Guideline	USPSTF Grading and certainty of evidence	Population	Primary prevention

Table 3. Systematic review characteristics

First Author, Year	**Study Title**	**Data bases searched and time frame**	**Language restrictions**	Systematic review Priority/Topic	Studies identified: Type and Number	Analysis	Population	**Systematic review question**
Lin, 2016(13)	Screening for Colorectal Cancer Updated Evidence Report and Systematic	Searches of MEDLINE, PubMed,	English-language studies	Screening	For KQ1 randomized clinical trials (RCTs) or	Random-effects meta-analyses	asymptomatic screening population	1) What is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests

	Review for the US Preventive Services Task Force	and the Cochrane. Central Register of Controlled Trials for relevant studies published from January 1, 2008, through December 31, 2014, with surveillance through February 23, 2016.			otherwise con- trolled trials, for tests without trial-level evidence, well-conducted prospective cohort or population-based nested case-control studies were examined. For KQ2 diagnostic accuracy studies and for KQ3 all trials and	and narrative synthesis	s of individuals who were 40 years or older, either at average risk for CRC or not selected for inclusion based on CRC risk factors.	(alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, stool-based DNA or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? 2) What are the test performance characteristics (e.g., sensitivity and specificity) of the following screening tests (alone or in combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible

					observational studies that reported adverse events			sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, stool-based DNA or multitarget stool DNA tests, blood screening test, methylated SEPT9 DNA? 3) a. What are the adverse effects (i.e., serious harms) of the different screening tests (either as single application or in a screening program)? b. Do adverse effects vary by important subpopulations (e.g., age)?

2.3.2. Quality assessment

The AGREE II assessment showed an overall satisfactory quality over most domains as seen in Table 4. The CTFPHC screening guideline had the best overall quality of reporting.

Table 4. Quality assessment AGREE II

Author, Year	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigour of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence
Bacchus, 2016(25)	94.4%	72.2%	70.8%	97.22%	66.7%	100%
Bibbins-Domingo, 2016 prevention (25)	100%	41.7%	62.5%	97.2%	89.6%	91.7%
Bibbins-Domingo, 2016 screening(24)	72.2%	55.6%	61.4%	97.2%	66.7%	95.8%
Sohn, 2015(26)	77.8%	58.3%	66.7%	91.7%	66.7%	37.5%

2.3.3. Comparison of the analytical frameworks

For each AF identified we noted the key questions (Table 5 and 6) used to develop recommendations. Refer to Figure 2, 3, 4, and 5 for the diagrammatic AFs. We also presented the contextual questions identified by the guideline developing team, these questions are not systematically searched or presented in the AF and can be found in tables 6 and 7.

Table 5. Colorectal cancer screening key questions

	Bibbins-Domingo, 2016(24)	**Bacchus, 2016(25)**	**Sohn, 2015(26)**
Key questions	1) What is the effectiveness (or comparative effectiveness) of screening programs based on any of the following screening tests (alone or in combination) in reducing (a) incidence of and (b) mortality from colorectal cancer: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, guaiac fecal occult blood, fecal immunochemical, stool-based DNA or multitarget stool DNA tests, blood screening test, methylated *SEPT9* DNA? 2) What are the test performance characteristics (e.g., sensitivity and specificity) of the following screening tests (alone or in	1) What is the effectiveness of each CRC screening test to reduce CRC-specific mortality, all-cause mortality, or incidence of late-stage CRC in asymptomatic adults who are not at high risk for CRC[2]? a) What is the optimal age to start and stop screening and the optimal screening interval of asymptomatic adults not at high risk for CRC? b) What is the evidence that the clinical benefits of screening differ for the various	1) Is there enough evidence of screening benefit? 2) What is the optimal screening interval? 3) What is the optimal age to start and stop screening? 4) What is the incidence of

	combination) for detecting (a) colorectal cancer, (b) advanced adenomas, and (c) adenomatous polyps based on size: colonoscopy, flexible sigmoidoscopy, computed tomographic colonography, stool screening tests, high-sensitivity guaiac fecal occult blood, fecal immunochemical, stool-based DNA or multitarget stool DNA tests, blood screening test, methylated *SEPT9* DNA? 3) a. What are the adverse effects (i.e., serious harms) of the different screening tests (either as single application or in a screening program)? b. Do adverse effects vary by important subpopulations (e.g., age)?	screening tests, or by subgroups that may influence the underlying risk of CRC? 2) What is the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the CRC screening tests to detect CRC? 3) What is the incidence of harms of screening for CRC in adults not at high risk for CRC? What is the evidence that the harms of screening differ for the various screening tests or by subgroups that may influence the underlying risk of CRC?	harms of screening?

Table 6. Colorectal cancer primary prevention key questions and contextual questions

	Key questions	**Contextual questions**

USPSTF, 2016(27)	1. Does regular aspirin use reduce total cancer mortality or all-cause mortality in adults who take (or are eligible for taking) aspirin for the primary prevention of cancer? a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk†, or comorbid conditions? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 2. Does regular aspirin use reduce the incidence of cancer in adults who take (or are eligible for taking) aspirin for the primary prevention of cancer? a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk†, or comorbid conditions? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 3. Does regular aspirin use reduce colorectal cancer mortality in adults without a history of colorectal cancer, familial adenomatous polyposis (FAP), or Lynch syndrome? a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk†, or comorbid conditions? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 4. Does regular aspirin use reduce the incidence of colorectal cancer in adults without a history of colorectal cancer, FAP, or Lynch syndrome?	1. What are the relative and absolute contraindications for regular aspirin use? 2. What valid risk prediction tools to determine bleeding risk (e.g., gastrointestinal bleeding, hemorrhagic stroke, other major bleeding) are available for persons who are not contraindicated for regular aspirin use for the primary prevention of colorectal cancer, cardiovascular disease, or cancer in general? 3. What is the persistence of continued regular use in persons who initiate aspirin use for the prevention of colorectal cancer, cardiovascular disease, or cancer in general?

	a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk, or comorbid conditions? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 5. Does regular aspirin use reduce the incidence of colorectal adenoma in adults without a history of colorectal cancer, FAP, or Lynch syndrome? a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk†, or comorbid conditions? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 6. What are the serious harms of regular aspirin use for the primary prevention of cancer (at the dosage and duration required to achieve a preventive health effect) in adults who are appropriate for aspirin chemoprevention? a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk, comorbid conditions, or concomitant medication use? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)? 7. What are the serious harms of regular aspirin use for the prevention of colorectal cancer (at the dosage and duration required to achieve a preventive health effect) in adults without a history of colorectal cancer, FAP, or Lynch syndrome?	

	a. Does the effect of aspirin vary by a priori subgroups, such as age, sex, race/ethnicity, baseline cancer risk, comorbid conditions, or concomitant medication use? b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, recency of use)?	

Table 7. Colorectal cancer screening contextual questions

	Bibbins-Domingo, 2016(24)	Bacchus, 2016(32)	Sohn, 2015(26)
Contextual questions	1. What are the current rates of overall screening for colorectal cancer and screening with specific tests in the United States? 2. What is the adherence to testing for each of the currently available screening tests? What is the adherence to follow-up diagnostic colonoscopy for abnormal screening test results (i.e., fecal testing, flexible sigmoidoscopy, CT colonography)? 3. Do rates of screening or adherence to screening tests vary by important subpopulations (i.e., by age, sex, race/ethnicity)?	1. What are the patient preferences and values for screening for CRC? 2. What is the evidence for a higher burden of disease, a differential treatment response, differential performance, or barriers to implementation of CRC screening in the Aboriginal population, other ethnic populations, rural or remote populations, women, or the elderly? 3. What risk assessment tools are identified in the literature to assess the risk of CRC?	5) Is there enough evidence of screening benefit? 6) What is the optimal screening interval? 7) What is the optimal age to start and stop screening? 8) What is the incidence of harms of screening?

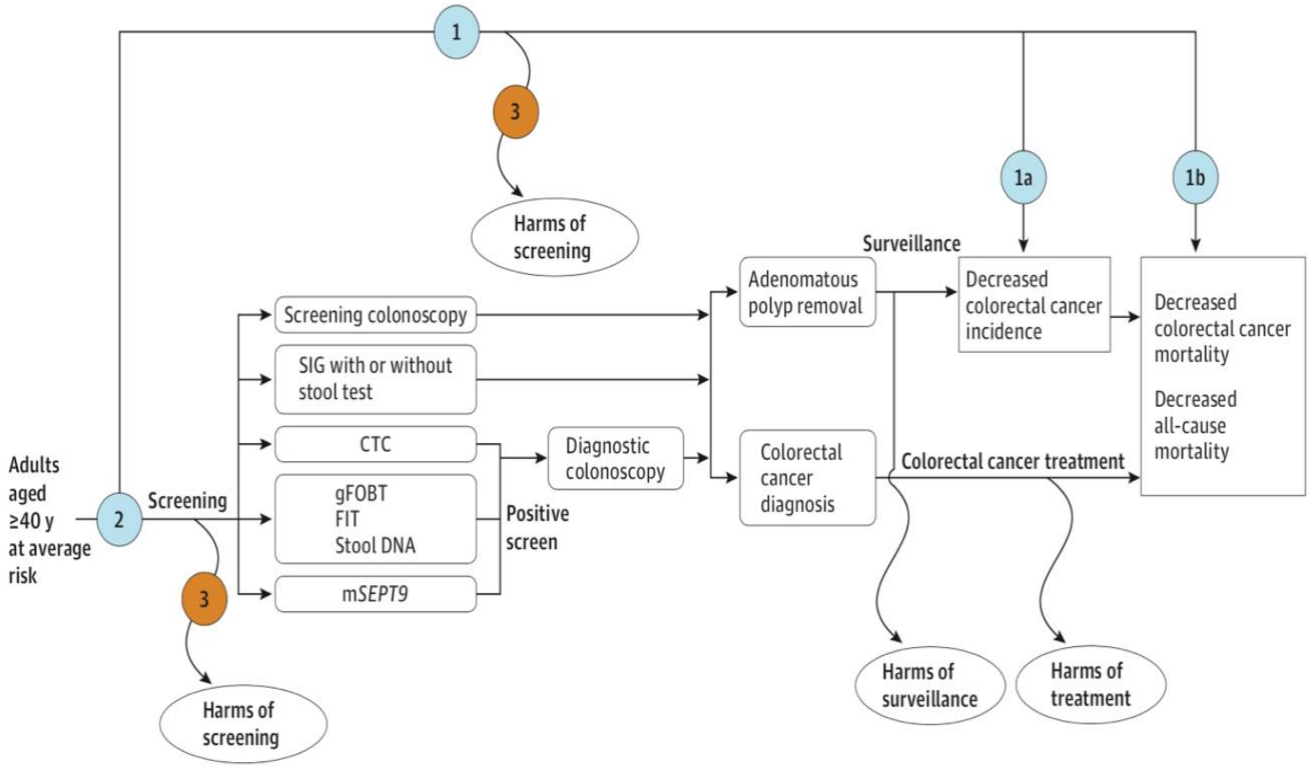
	4. What is the likelihood of progression or regression of small adenomas (i.e., measuring 6 to 9 mm) to colorectal cancer? 5. Does the natural history (progression or regression) of adenomas vary by race/ethnicity? 6. What is the distribution of colorectal lesions (colorectal cancer, advanced adenomas, small adenomatous polyps) by location in the colon (e.g., proximal versus distal colon)? 7. Does the distribution of lesions in the colon vary by important subpopulations (i.e., by age, sex, race/ethnicity)? 8. Are there differences in adenoma (and advanced adenoma) prevalence or count by race/ethnicity?	4. What are the cost-effectiveness and resource implications of screening for CRC?	

The USPSTF and CTFPHC screening CPGs both have three very similar key questions (24, 25), with the first key question looking at effectiveness of screening tests to reduce incidence and mortality of CRC. The second key question looked at the different screening tests performance characteristics (e.g. sensitivity and specificity), while the third key question looked at adverse effects of the different screening tests. While the key questions are similar, the AF produced by the USPSTF (Figure 2) was more detailed showing clear linkages between the screening tests, diagnostic tests, and the intermediate and final outcomes (24). The key questions and sub-questions were also clearly indicated along the pathways helping to form a complete picture of the reasoning behind the key questions and the scope of the guideline. The AF (Figure 3) by the CTFPHC was simpler and lacked the interventions along the pathway not presently answered by the guideline focusing on the key questions along the path (25).

The identified Korean screening CPG has four key questions (26). The first question looked at the screening benefit which corresponds to the first questions of both the USPSTF and CTFPHC CPGs who looked at the effectiveness (24, 25). Another key question looked at the incidence of harms of screening which corresponds to the third key question in the USPSTF and CTFPHC CPGs. The developed AF (Figure 4) showed more detail than the AF developed by the CTFPHC, but it also lacked the intermediate outcomes.

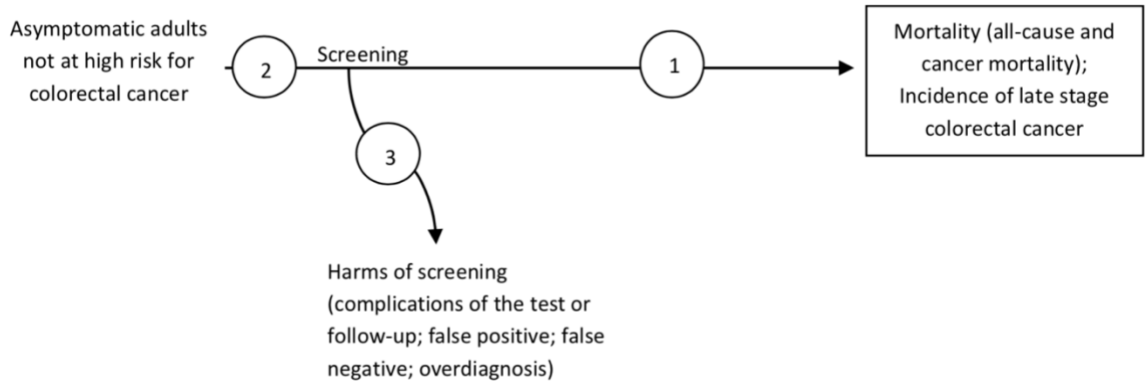
The USPSTF analytic framework (Figure 5) for aspirin use to prevent cardiovascular disease and CRC contained seven key questions to develop the recommendations (27). The AF had all key questions clearly positioned in the linkages, and it considered multiple intermediate and final outcomes.

Figure 2: Analytic framework for USPSTF Screening for Colorectal Cancer



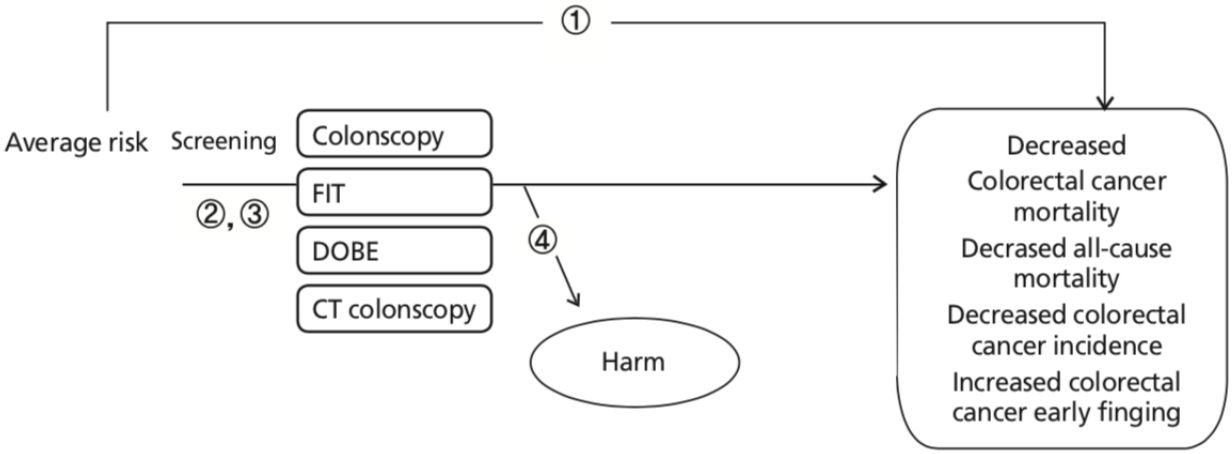
Reproduced with permission from *JAMA. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. 2016. Jama 315, no. 23: 2576-2594.* Copyright© (2016) American Medical Association. All rights reserved.

Figure 3: Analytic framework for the CTFPC:



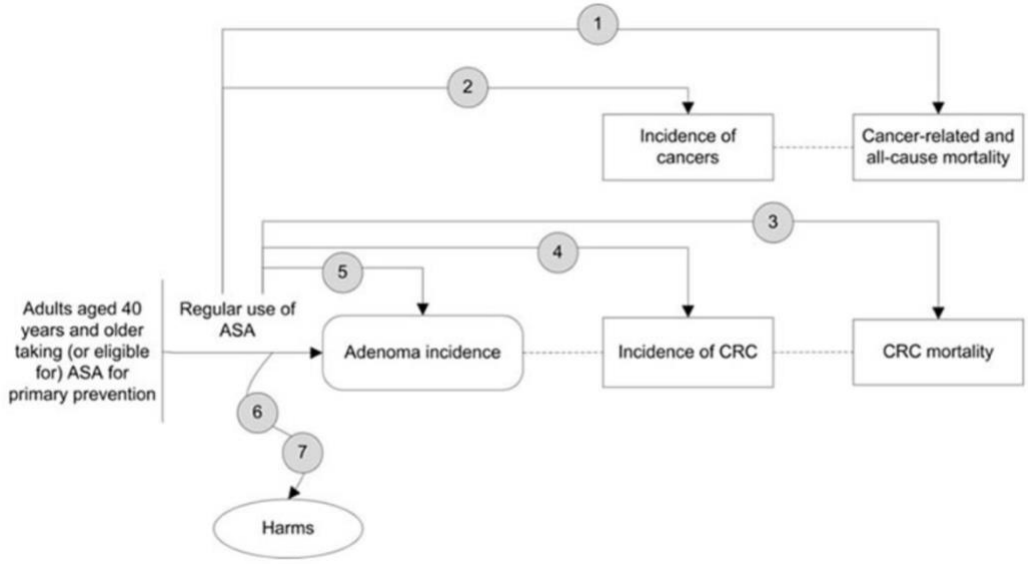
Reproduced with permission from Public Health Agency of Canada. *Appendix to: Canadian Task Force on Preventive Health Care. Recommendations on screening for colorectal cancer in primary care. CMAJ 2016. DOI:10.1503/cmaj.151125.* Copyright ©{2016}, Public Health Agency of Canada.

Figure 4: Analytic framework of the Korean CRC Guideline:



Sohn, D. K., Kim, M. J., Park, Y., Suh, M., Shin, A., Lee, H. Y., ... & Kim, Y. (2015). The Korean guideline for colorectal cancer screening. Journal of the Korean Medical Association, 58(5), 420-432.

Figure 5: Analytic framework for Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer USPSTF



Abbreviations: ASA = aspirin; CRC=colorectal cancer.

From *Annals of Internal Medicine, Chubak J, Kamineni A, Buist DSM, et al.: Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet], Evidence Syntheses, No. 133*.Copyright © [2015] American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

2.3.4. Proposed methodology to conduct a systematic review of analytical frameworks

To develop an approach to systematically review AFs (Table 8), we consulted with an information scientist to identify potential Mesh terms with the goal to maximize the sensitivity of our search. We included various terms in our search that authors could potentially use to indicate an AF such as "causal pathway", "analytical diagram", and "evidence framework". We included both systematic reviews and guidelines. In the original search we identified 935 CPGs and 3127 systematic review to screen full text, among them only two systematic reviews and three CPGs included AFs (13, 24-26, 28). One of the AFs in a systematic review was excluded as it was informing an outdated CPG (28). Only the Korean CRC screening guideline had the graphical AF in the published guideline statement (26), while CTFPHC only mentioned that an AF was established in the methods section

of the published guideline and it is available in the online appendix (25). The published USPSTF CRC screening guideline statement had no mention of an AF and had no methods section (24), but we already identified the corresponding AF used in the systematic review (13).

We then manually searched for the organizational procedural manuals, and we revisited the methods section in the CPGs and assessed how key questions and recommendations were developed if it was not described in the manuals. In this way we identified the USPSTF and the CTFPHC procedural manual that describes the use of an AF for the development of the recommendations (19, 32). Utilizing this method, we identified the AF of the primary prevention CPG by the USPSTF that was not initially included by our reviewers (27). No other major guideline group mentions the use of AFs in the development process. Table A 4 in the supplement shows the major guideline groups identified and the methods used to develop key questions and recommendations. When we performed an update of our search, we only included CPGs for full text review, as we only identified one systematic review with an AF in the original search that would have already been identified by looking at the CPGs.

Table 8: Proposed method for systematic review of analytical frameworks

1. Conduct a sensitive search with a suggested time limit of 1996
2. During full text screening search the methods section and online resources in all relevant guidelines
3. Search for the procedural manuals of the guideline organizations for utilization of analytical frameworks

2.4. Discussion

2.4.1. Summary of findings

We conducted a systematic review to identify the utilizations of AFs in the development of key questions for CRC systematic reviews. We identified four AFs used in CRC guideline development

process (24-27). We also developed an approach to perform systematic reviews for AFs efficiently without losing rigour.

2.4.2. Limitations

Despite our systematic approach, AFs were often not readily identifiable without a careful search of the methods section and online resources. Thus, we may have potentially missed some guidelines that used an AF. To overcome this challenge, we also searched procedural manuals of major guideline organizations, but that will increase the workload of those conducting systematic reviews of existing AFs. We potentially missed AFs developed by organizations for internal use that were not published. Another limitation is we excluded systematic reviews on treatment of CRC as it was beyond the scope of our work with ECICC.

2.4.3. Strengths

To the best of our knowledge this is the first systematic review of AFs. We explored different techniques to increase the efficiency of conducting a systematic review on AFs without compromising the rigour in the methods, such as focusing the search on CPGs, with a meticulous review of the guideline methods, appendices, and supplementary material. We also searched guideline groups procedural manuals to identify organizations who use AFs regularly in the development process. We had no language restrictions and identified three English and one Korean CPGs with AFs. We provide the literature search approach in the appendices.

2.4.4. Implications for practice

As the purpose of an AF is to identify systematic review questions in a structured manner and to ultimately serve as an evidence map (22), various guideline developers can incorporate the contextual information and review questions in their own systematic reviews. Guideline developers can systematically search and identify AFs in a given topic and incorporate the work already done to construct a more comprehensive or overarching AF. This bottom-up approach will have gaps in the linkages and traditional methods will need to be implemented to develop an overarching AF

(see Figure 6). An overarching AF can help guideline developers engage with guideline panels to identify key questions and recommendations that they may want to prioritize, having a better overview of the complexity and multidimensionality of healthcare topics such as cancer prevention and care.

Figure 6: Overarching analytical framework

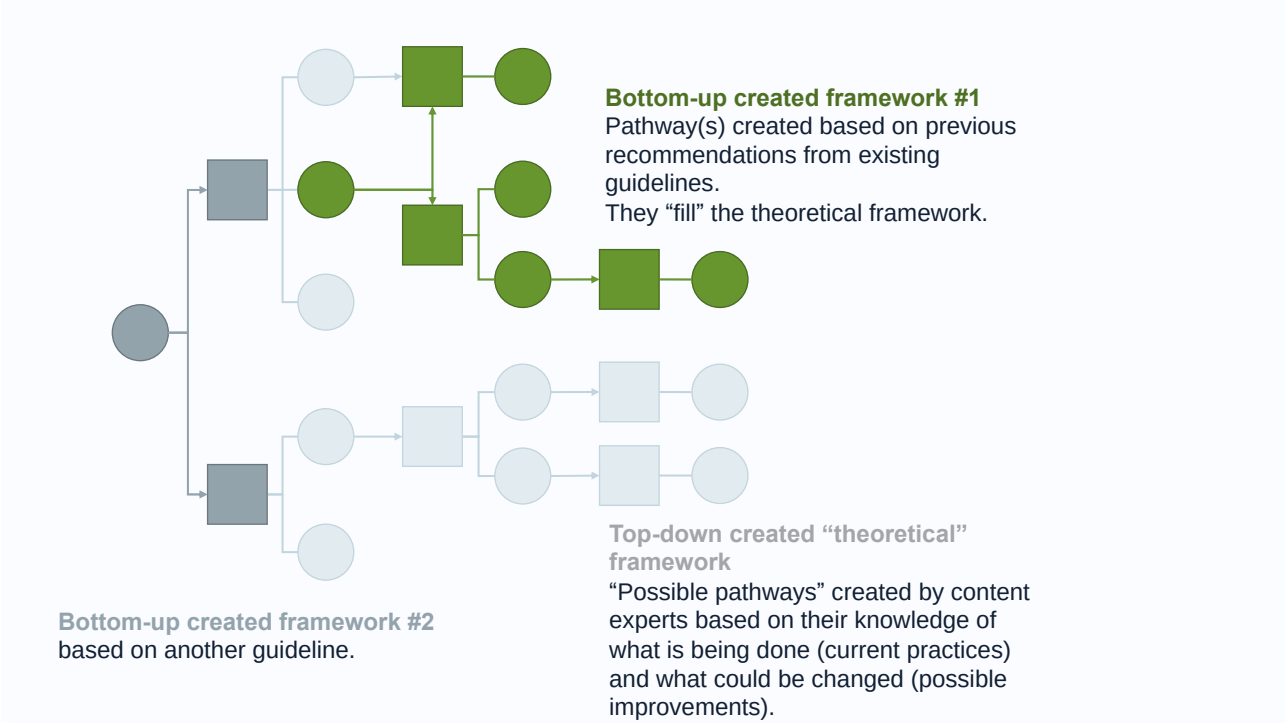


Figure. 3 shows a hypothetical overarching analytical framework. and figure. Framework #1 and #2 (grey and green) show hypothetical analytical frameworks identified using a systematic search developed using a top-down approach. Incorporating the previously developed analytical frameworks can contribute to the overarching analytical framework using a bottom-up approach. This approach identifies overlap in analytical frameworks by various guideline groups, and by using a traditional top-down approach gaps can be identified completing an overarching analytical framework.

For conducting a systematic review on AF, we propose a systematic search of all CPGs that meet the scope of the review that should include a meticulous review of the methods section, appendixes, and all supplementary material because the AF is often produced by the methods team and not always clearly presented in the recommendations document. A review of the procedural manuals of

key organizations that currently use AFs should also be conducted. At this time, most systematic review authors do not use AFs in the development of key questions, and when done it often is in relation to a CPG to inform recommendations. Thus, at this time there is little added benefit of including systematic reviews in the search since CPGs sufficiently capture the AFs. In topics with more widespread adoption of AFs the inclusion of systematic reviews in the search must be performed. A time limit of the search starting from 1996 should be done as this corresponds to the inception of AFs.

2.4.5. Implications for research

We found very few systematic reviews that used AFs in CRC, and when utilized by a guideline group the AFs were often hard to find. As more emphasis on visual aids have been required by publishing journals and the scientific community(6), AFs could be an ideal model to present systematic review questions graphically in a diagrammatic format. Adoption of AFs by various groups would increase guideline development transparency and help identify gaps in literature. We compared the average quality of the guidelines with AF to guidelines that did not use an AF that were identified for the ECICC overview of guidelines. Guidelines with AF in CRC had a better overall AGREE score of 76% compared to 59% when an AF is not utilized (Table A 5, Table A 6). While this is not a representative sample as we compared four guidelines with an AF vs 115 guidelines without an AF, it is suggestive of improved reporting in guidelines that utilized a diagrammatic AF in the development process.

2.5. Conclusion

We identified four CRC guidelines that utilized a diagrammatic AF in their development process (24-27). Only the Korean CRC screening guideline presented the AF in the guideline recommendation statement (26). We identified two guideline groups that currently utilize AFs in the guideline development process, the USPSTF and the CTFPHC, and both used a top down

approach of developing an AF (19, 32). When conducting a systematic review of AFs, a meticulous search through the CPG documents and the online resources must be completed.

2.6. Contributors

SK, HJS, JB, DO and TP designed the study protocol. SK coordinated the study. SW created the search strategy. SK, AD, RM, ET, AB, TP, RS, RC, LJ and FS assessed eligibility of records at title and abstract. SK, and AD searched for guidelines manually. SK, AD, RM, ET, AB, RC, SC, ML, LP, EP, ZSP, NV, YV, YL and FS assessed eligibility of full text articles. SK, RM, RC, SC, YL extracted data and performed quality assessment using the AGREE II tool. SK settled disputes. SK analyzed and interpreted the data with HJS, and JB. SK and HJS drafted the manuscript, with writing contributions from JB. All authors interpreted and made edits to the manuscript.

Chapter 3. Conclusions

3.1. Main conclusions

We identified four AFs in our systematic review, all the AFs were developed in the context of a CRC guideline development process. In the context of CRC guidelines, the AFs were developed in the context of primary prevention and screening. We also identified two guideline groups that always utilize analytical frameworks in the guidelines they develop according to the procedural manuals, the USPSTF and the CTFPHC(19, 32). No other major guideline group that develops CRC guidelines use AF as part of the guideline development process. From the identified AFs, only the Korean CRC screening guideline presented the AF in the guideline recommendation statement (26). The CTFPHC mentions an AF in the methods section in the guideline statement and the AF is found in the online appendix. The USPSTF guideline statements have no mention of an AF but the systematic reviews with the AF could be found as part of the online material and the systematic reviews are usually independently published(13).

3.2. Systematic review of analytical framework methods

To conduct a systematic review of AF, the search should be inclusive to include all systematic reviews and CPGs in the topic of interest. In our systematic review we did not identify any AF outside of a guideline development process, this may not be the case in topics other than CRC. From the identified guidelines only the Korean CRC screening guideline presented the AF in the guideline recommendation statement (26), which necessitates the careful review of the methods section, appendixes, and the supplementary material. From the identified guidelines, a review of the organizations procedural manual should be conducted as not to miss any AF. Also, a sensible time limit of the search starting from 1996 should suffice as it was when the USPSTF first described AFs.

3.3 Systematic review outcome

The resulting systematic review of AF would result in a compilation of all AF in a given topic, presented graphically with all systematic review key questions. With these systematic reviews, various guideline developers can incorporate the review questions identified in their own systematic reviews. By incorporating the work already done to develop various AFs in a given topic, the resulting evidence map can help build a more comprehensive or overarching AF.

Appendices:

Table A 1. Search

Database: Embase <1974 to 2020 December 22>

Search Strategy:

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1 colon cancer.mp. or exp colon cancer/ (296745)

2 rectal cancer.mp. or exp rectum cancer/ (235306)

3 exp colon tumor/ (333118)

4 exp rectum tumor/ (265919)

5 1 or 2 or 3 or 4 (389663)

6 exp practice guideline/ (575708)

7 Systematic review.mp. or exp "systematic review"/ (350427)

8 health technology assessment.mp. or exp biomedical technology assessment/ (18906)

9 recommendation*.mp. (379722)

10 6 or 7 or 8 or 9 (1203699)

11 analytic* framework*.mp. (3086)

12 analytic* pathway*.mp. (46)

13 analytic* algorithm*.mp. (760)

14 evidence* framework*.mp. (139)

15 causal* algorithm*.mp. (57)

16 causal* diagram*.mp. (201)

17 analytic* diagram*.mp. (5)

18 causal* pathway*.mp. (2813)

19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (7093)

20 limit 19 to yr="1996 -Current" (6820)

21 10 or 20 (1209814)

22 5 and 21 (22062)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid

MEDLINE(R) 1946 to Present

Search Strategy:

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1 exp Rectal Neoplasms/ or exp Colonic Neoplasms/ or exp Colorectal Neoplasms/ or colorectal cancer*.mp. (236123)

2 exp Practice Guideline/ or exp Guideline/ or guideline*.mp. (491424)

3 Systematic review.mp. or exp "Systematic Review"/ (199342)

4 Health technology assessment.mp. or exp Technology Assessment, Biomedical/ (14399)

5 recommendation*.mp. (272692)

6 2 or 3 or 4 or 5 (862413)

7 analytic* framework*.mp. (2772)

8 analytic* pathway*.mp. (41)

9 analytic* algorithm*.mp. (449)

10 evidence* framework*.mp. (107)

11 causal* algorithm*.mp. (43)

12 causal* diagram*.mp. (179)

13 analytic* diagram*.mp. (4)

14 causal* pathway*.mp. (2161)

15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (5743)

16 limit 15 to yr="1996 -Current" (5527)

17 6 or 16 (867331)

18 1 and 17 (11606)

Table A 2. CRC Screening Recommendations

Guideline, Year	**Recommendations**	**Strength of recommendation**
USPSTF, 2016 (24)	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years	A recommendation
	The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking	C recommendation

	into account the patient's overall health and prior screening history	
CTFPHC, 2016(25)	We recommend screening adults aged 60 to 74 years for colorectal cancer with FOBT (gFOBT or FIT) every two years or flexible sigmoidoscopy every 10 years. We recommend screening adults aged 50 to 59 years for colorectal cancer with FOBT (gFOBT or FIT) every two years or flexible sigmoidoscopy every 10 years. We recommend not screening adults aged 75 years and older for colorectal cancer. We recommend not using colonoscopy as a screening test for colorectal cancer.	Strong recommendation; moderate-quality evidence Weak recommendation; moderate-quality evidence Weak recommendation; low-quality evidence Weak recommendation; low-quality evidence
Korean guideline, 2015(26)	We recommend annual or biennial FIT for screening for colorectal cancer in asymptomatic adults, beginning at 45 years of age and continuing until 80 years There is no evidence for the risks or benefits of FIT in adults older than 80 years Selective use of colonoscopy for colorectal cancer screening is recommended, taking into consideration individual preference and the risk of colorectal cancer	Recommendation B Recommendation I Recommendation C

	There is no evidence for the risks or benefits of double-contrast barium enema for colorectal cancer screening in asymptomatic adults There is no evidence for the risks or benefits of computed tomographic colonography for colorectal cancer screening in asymptomatic adults	Recommendation I Recommendation I

Table A 3. CRC Primary prevention guidelines

Guideline, Year	**Recommendations**	**Strength of recommendation**
USPSTF, 2016(27)	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	Recommendation B Recommendation C

	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	Recommendation I
	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	Recommendation I

Table A 4. Guideline Group Methods

Group	**Method**
USPSTF(19)	Analytical Framework during the development phase
CTFPHC (32)	Analytical Framework during the development phase
NICE(33)	No analytical framework used; structured review questions agreed on in the development phase
CCA(34)	No analytical framework, shortlisting and voting process of key questions formatted in a PICO framework
ESGE(35)	No analytical framework, working group develop key questions following a PICO format
AGA(36)	No analytical framework, development of guideline questions using GRADE framework
ACG(37, 38)	No analytical framework, methods not clearly defined

ACS(39)	No analytical framework, systematic reviews will be commissioned, and the scope will be made defined by the development group from the outset.
ACPGBI(40)	No analytical framework, develop questions in a PICO format
ACMG(41)	No analytical framework, developed by adaptation of recommendations
ESMO(42, 43)	No analytical framework, author responsibility in conceptualizing and literature search
US Multi-Society Task Force(44, 45)	No analytical framework, utilization of a systematic review to develop a consensus guideline
JSCCR(46)	No analytical framework, clinical questions are raised with added recommendations with each update
CCO/PEBC(47)	No analytical framework, members of guideline development group will set the topic, purpose and scope of the project and PEBC will complete the review
WSES (48)	No analytical framework, the Scientific Secretariat agreed on six key questions to develop the guidelines
ACP (49)	No analytical framework, guidelines committee draft key questions in PICO format
JSMO(50)	No analytical framework, no methods cited
ASCO(51)	No analytical framework, multidisciplinary expert panel develop protocol with key questions
EGOSLIM(52)	No analytical framework, a modified Delphi method used to achieve consensus

Canadian Gastrointestinal Cancer Consensus Conference 2016(53)	No analytical framework, recommendations developed by consensus opinions of health care professionals involved
ASCRS(54)	No analytical framework, systematic search done, and recommendations initially prepared by subcommittee
ECCO (55)	No analytical framework, the working groups drafted relevant questions on topics
ESPGHAN(56)	No analytical framework, Key questions identified by the core team
European Code against Cancer (57)	No analytical framework, the working group define clinical questions according to the PICO format
JSGE(58)	No analytical framework, followed the MINDS framework to evaluate clinical questions
The Asia Pacific Working Group (59)	No analytical framework, the steering committee drafted a list of statements
EAES(60)	No analytical framework, a group of experts formulated a list of key questions
CAG(61)	No analytical framework, key clinical questions identified, and GRADE approach utilized
NCCN(62)	No analytical framework, clinical questions are identified during the annual Institutional Review process
SEOM (63, 64)	No analytical framework, methods for question prioritization are unclear
GGPO(65)	No analytical framework, based on systematic reviews on key questions
BMJ Rapid Recommendations(66)	No analytical framework, the panel developed key questions to inform the recommendations

BSG(67)	No analytical framework, the guideline group will develop a list of key questions to address in compliance with the NICE process
KSGE (68)	No analytical framework, the subcommittee selected key questions
EHTG (69)	No analytical framework, a PICO model was used for selected key questions
ASGE(70)	No analytical framework, clinical questions were prioritized by a consensus process grading topics by patient important outcomes
ACR(71)	No analytical framework, panel selects and prioritizes clinical conditions.

Table A 5: Analytical frameworks quality assessment AGREE II total score

Author, Year	**Domain 1: Scope and Purpose**	**Domain 2: Stakeholder Involvement**	**Domain 3: Rigour of Development**	**Domain 4: Clarity of Presentation**	**Domain 5: Applicability**	**Domain 6: Editorial Independence**	**Total % score**
Canadian Task Force, 2016 **(25)** Bacchus, 2016	94.4%	72.2%	70.8%	97.2%	66.7%	100.0%	**84%**
Bibbins-Domingo, 2016 (**24)**	72.2%	55.6%	61.5%	97.2%	66.7%	95.8%	**75%**
Sohn, 2015**(26)**	77.8%	58.3%	66.7%	91.7%	66.7%	37.5%	**66%**
Bibbins-Domingo, 2016**(25)**	100.0%	41.8%	62.5%	97.2%	89.6%	91.7%	**80%**
Average score	**86.1%**	**57.0%**	**65.4%**	**95.8%**	**72.4%**	**81.2%**	**76%**

Table A 6: Colorectal cancer guidelines quality assessment AGREE II total score

Author, Year	**Domain 1: Scope and Purpose**	**Domain 2: Stakeholder Involvement**	**Domain 3: Rigour of Development**	**Domain 4: Clarity of Presentation**	**Domain 5: Applicability**	**Domain 6: Editorial Independence**	**Total % score**

Wolf, 2018(72)	80.6%	88.9%	69.8%	94.4%	87.5%	100.0%	**87%**
Cunningham, 2017(73)	38.9%	33.3%	9.4%	77.8%	20.8%	58.3%	**40%**
Gollins, 2017(74)	38.9%	33.3%	9.4%	77.8%	20.8%	58.3%	**40%**
Leong, 2017(75)	38.9%	33.3%	9.4%	77.8%	20.8%	58.3%	**40%**
Moran, 2017(40)	27.8%	11.1%	17.7%	72.2%	2.1%	45.8%	**29%**
Hampel, 2015(41)	52.8%	33.3%	22.9%	66.7%	31.3%	83.3%	**48%**
Hegde, 2014(76)	58.3%	22.2%	15.6%	61.1%	29.2%	58.3%	**41%**
Robertson, 2017(77)	66.7%	41.7%	50.0%	77.8%	29.2%	50.0%	**53%**
Giardiello, 2014(44)	36.1%	44.4%	47.9%	83.3%	43.8%	50.0%	**51%**
Glynne-Jones, 2017(78)	16.7%	27.8%	33.3%	77.8%	29.2%	62.5%	**41%**
Johnson, 2014(79)	58.3%	41.7%	51.0%	86.1%	33.3%	50.0%	**53%**
Rubenstein, 2015(80)	83.3%	72.2%	75.0%	86.1%	54.2%	58.3%	**72%**
Van Cutsem, 2016(81)	44.4%	30.6%	33.3%	66.7%	22.9%	83.3%	**47%**
Yoshino, 2018(82)	41.7%	58.3%	41.7%	69.4%	29.2%	87.5%	**55%**
Stjepanovic , 2019 (83)	66.7%	41.7%	32.3%	80.6%	27.1%	75.0%	**54%**
Del Giudice, 2014(84)	77.8%	63.9%	53.1%	58.3%	35.4%	70.8%	**60%**
Pisano, 2018(48)	55.6%	50.0%	63.5%	72.2%	6.3%	87.5%	**56%**
Wilt, 2015(85)	61.1%	63.9%	30.2%	88.9%	83.3%	70.8%	**66%**

Yamazaki, 2018(50)	52.8%	19.4%	19.8%	58.3%	14.6%	58.3%	**37%**
Hashiguchi, 2019(46)	100.0%	72.2%	52.1%	88.9%	35.4%	62.5%	**69%**
van Leerdam, 2019 (86)	100.0%	75.0%	53.1%	77.8%	4.2%	54.2%	**61%**
Hassan, 2019(87)	88.9%	25.0%	47.9%	58.3%	16.7%	58.3%	**49%**
Dumonceau, 2017(88)	50.0%	47.2%	49.0%	55.6%	27.1%	58.3%	**48%**
Cubiella, 2018(89)	94.4%	30.6%	34.4%	94.4%	56.3%	91.7%	**67%**
Syngal, 2015(90)	58.3%	36.1%	42.7%	63.9%	47.9%	66.7%	**53%**
Adam, 2015(52)	77.8%	30.6%	38.5%	83.3%	31.3%	70.8%	**55%**
Bossé, 2016 (53)	77.8%	41.7%	21.9%	52.8%	29.2%	75.0%	**50%**
Costas-Chavarri, 2019(91)	100.0%	100.0%	85.4%	100.0%	66.7%	75.0%	**88%**
Vogel, 2017(92)	55.6%	27.8%	77.1%	86.1%	35.4%	20.8%	**50%**
El-Shami, 2015(93)	77.8%	52.8%	76.0%	80.6%	52.1%	100.0%	**73%**
Sepulveda, 2017(94)	97.2%	61.1%	82.3%	100.0%	72.9%	75.0%	**81%**
Lopes, 2019 (95)	88.9%	100.0%	72.9%	86.1%	50.0%	70.8%	**78%**
Steele, 2015 (96)	58.3%	30.6%	61.5%	86.1%	35.4%	0.0%	**45%**
Durno, 2017(45)	61.1%	36.1%	49.0%	77.8%	41.7%	66.7%	**55%**
Annese, 2015(55)	27.8%	47.2%	55.2%	61.1%	25.0%	50.0%	**44%**
Hyer, 2019(97)	94.4%	55.6%	75.0%	97.2%	47.9%	54.2%	**71%**
Armaroli, 2015(98)	66.7%	47.2%	71.9%	72.2%	35.4%	91.7%	**64%**
Cohen, 2019(99)	80.6%	33.3%	62.5%	86.1%	35.4%	54.2%	**59%**

Herzig, 2017(100)	61.1%	25.0%	60.4%	88.9%	35.4%	0.0%	**45%**
Rex, 2017 (101)	80.6%	22.2%	61.5%	91.7%	37.5%	50.0%	**57%**
Tanaka, 2015(102)	80.6%	52.8%	62.5%	80.6%	37.5%	62.5%	**63%**
Baraniskin, 2017(103)	36.1%	16.7%	11.5%	27.8%	22.9%	50.0%	**27%**
Vera, 2019(104)	55.6%	0.0%	16.7%	52.8%	37.5%	66.7%	**38%**
Vasen, 2014(105)	50.0%	19.4%	18.8%	50.0%	12.5%	54.2%	**34%**
Sollano, 2017(106)	66.7%	50.0%	60.4%	69.4%	39.6%	8.3%	**49%**
Lee 2015 (107)	61.1%	66.7%	37.5%	86.1%	33.3%	25.0%	**52%**
Sung, 2014(59)	80.6%	63.9%	71.9%	83.3%	41.7%	100.0%	**74%**
Yuan, 2019 (108)	47.2%	25.0%	19.8%	80.6%	20.8%	12.5%	**34%**
Morino 2015(60)	41.7%	41.7%	37.5%	55.6%	0.0%	20.8%	**33%**
Committee on Practice Bulletins—Gynecology and the Society of Gynecologic Oncology 2014(109)	41.7%	16.7%	20.8%	52.8%	2.1%	0.0%	**22%**
Marzo-Castillejo 2014(110)	69.4%	13.9%	21.9%	75.0%	8.3%	20.8%	**35%**
Ahmed, 2015(111)	97.2%	72.2%	36.5%	77.8%	41.7%	58.3%	**64%**
Leddin, 2018(61)	100.0%	97.2%	83.3%	100.0%	79.2%	100.0%	**93%**
Benson, 2017(112)	41.7%	69.4%	37.5%	55.6%	37.5%	58.3%	**50%**

Tinmouth, 2016(113)	91.7%	63.9%	80.2%	88.9%	52.1%	62.5%	**73%**
Gomez-Espana, 2019(64)	61.1%	50.0%	36.5%	72.2%	18.8%	58.3%	**49%**
Gonzalez-Flores, 2016(114)	66.7%	44.4%	45.8%	83.3%	27.1%	58.3%	**54%**
Segura, 2014(63)	50.0%	8.3%	31.3%	86.1%	10.4%	54.2%	**40%**
Taniguchi, 2015(115)	33.3%	16.7%	10.4%	50.0%	10.4%	66.7%	**31%**
Jenkins, 2018(116)	80.6%	27.8%	52.1%	88.9%	35.4%	58.3%	**57%**
Kahi, 2016 (37)	80.6%	47.2%	62.5%	88.9%	33.3%	54.2%	**61%**
Vogl, 2019(117)	66.7%	47.3%	50.0%	88.9%	43.8%	54.2%	**58%**
Zeimet, 2017(118)	69.4%	19.4%	16.7%	69.4%	8.3%	75.0%	**43%**
Prof. Dr. Wolff Schmiegel, PD Dr. Christian P. Pox; updated 2019(119)	66.7%	61.1%	69.8%	72.2%	50.0%	58.3%	**63%**
Heresbach 2016(120)	80.6%	25.0%	17.7%	55.6%	10.4%	20.8%	**35%**
Boardman, 2020(121)	80.6%	72.2%	58.3%	88.9%	50.0%	50.0%	**67%**
Bisschops, 2019(122)	75.0%	66.7%	75.0%	91.7%	63.5%	83.3%	**76%**
Argiles, 2020(123)	69.4%	63.9%	86.5%	88.9%	45.8%	54.2%	**68%**
Chiorean, 2020(124)	100.0%	91.7%	84.4%	86.1%	60.4%	66.7%	**82%**
Colas, 2020(125)	72.2%	72.2%	53.1%	58.3%	41.7%	29.2%	**54%**

Gracia-Alfonso, 2020 (126)	66.7%	61.1%	37.5%	63.9%	39.6%	70.8%	**57%**
Guillén-Ponce, 2020 (127)	75.0%	47.2%	61.5%	66.7%	43.8%	41.7%	**56%**
Gupta, 2020(128)	97.2%	86.1%	78.1%	80.6%	45.8%	45.8%	**72%**
Gupta, 2019(129)	75.0%	61.1%	56.3%	50.0%	37.5%	33.3%	**52%**
Hashiguchi, 2019(46)	100.0%	97.2%	70.8%	86.1%	50.0%	66.7%	**78%**
Heald, 2020(130)	83.3%	72.2%	57.3%	61.1%	39.6%	75.0%	**65%**
Helsingen, 2019(66)	100.0%	100.0%	94.8%	94.4%	58.3%	91.7%	**90%**
Ishida, 2018(131)	86.1%	80.6%	66.7%	77.8%	47.9%	62.5%	**70%**
National Heatlh, 2020(132)	61.1%	58.3%	30.2%	44.4%	29.2%	25.0%	**41%**
Monahan, 2020(133)	94.4%	86.1%	81.1%	72.2%	56.3%	58.3%	**75%**
NICE, 2020174)	88.9%	66.7%	55.2%	75.0%	56.3%	70.8%	**69%**
O'Leary, 2020(134)	88.9%	83.3%	64.6%	83.3%	50.0%	58.3%	**71%**
Park,2020(68)	97.2%	83.3%	87.5%	94.4%	47.9%	83.3%	**82%**
Provenzale, 2020(135)	83.3%	80.6%	74.0%	72.2%	50.0%	58.3%	**70%**
Qaseem, 2019(136)	94.4%	88.9%	88.5%	94.4%	70.8%	58.3%	**83%**
Ren, 2020(137)	77.8%	50.0%	39.6%	38.9%	45.8%	37.5%	**48%**
Rutter, 2020(138)	94.4%	94.4%	86.5%	94.4%	87.5%	91.7%	**91%**
Salvatore, 2020(139)	83.7%	69.4%	76.0%	88.9%	60.4%	87.5%	**78%**
Seppala,2020(69)	100.0%	88.9%	86.5%	83.3%	79.2%	91.7%	**88%**

Shaukat, 2020(140)	97.2%	88.9%	79.2%	88.9%	58.3%	41.7%	**76%**
Spada, 2020 (141)	91.7%	72.2%	92.7%	94.4%	75.0%	79.2%	**84%**
Tanaka, 2020(142)	80.6%	55.6%	76.0%	80.6%	54.2%	62.5%	**68%**
Tischkowitz, 2020(143)	75.0%	77.8%	79.2%	83.3%	58.3%	62.5%	**73%**
van Leerdam, 2019(144)	97.2%	86.1%	90.6%	94.4%	70.8%	75.0%	**86%**
Yang, 2020(70)	97.2%	77.8%	81.3%	94.4%	58.3%	41.7%	**75%**
You, 2020(145)	83.3%	77.8%	77.1%	88.9%	70.8%	79.2%	**80%**
Vecchione, 2020(146)	50.0%	55.6%	62.5%	66.7%	33.3%	83.3%	**59%**
Moreno, 2018(147)	66.7%	30.6%	22.0%	75.0%	16.7%	58.3%	**45%**
Dubé 2019(148)	100.0%	75.0%	55.2%	83.3%	35.4%	50.0%	**66%**
Alberta Helath services 2017(149)	100.0%	61.1%	38.5%	86.1%	27.1%	45.8%	**60%**
BC Guidelines, 2016 (150)	61.1%	61.1%	28.1%	58.3%	27.1%	41.7%	**46%**
Del Giudice 2017(151)	100.0%	75.0%	54.2%	75.0%	27.1%	66.7%	**66%**
Alberta Helath services 2019(152)	100.0%	61.1%	38.5%	86.1%	27.1%	45.8%	**60%**
Dunn 2020 (153)	75.0%	55.6%	38.5%	55.6%	31.3%	45.8%	**50%**
Fowler 2016(154)	66.7%	38.9%	27.1%	72.2%	16.7%	33.3%	**42%**

Hadjiliadis 2018(155)	63.9%	91.7%	65.6%	77.8%	29.2%	70.8%	**66%**
Hassan 2020(156)	86.1%	63.9%	73.9%	86.1%	41.7%	83.3%	**72%**
Cancer Council Australia 2017(157)	97.2%	97.2%	78.1%	86.1%	41.7%	70.8%	**79%**
Cancer Council Australia 2019(158)	97.2%	97.2%	78.1%	86.1%	41.7%	70.8%	**79%**
Stoffel 2014(159)	69.4%	52.8%	45.8%	88.9%	29.2%	62.5%	**58%**
Benson, 2018(160)	44.4%	66.7%	41.7%	61.1%	39.6%	75.0%	**55%**
NICE 2017(161)	88.9%	69.4%	56.3%	77.8%	56.3%	70.8%	**70%**
NICE 2017(162)	63.9%	66.7%	54.2%	77.8%	56.3%	66.7%	**64%**
Beets-Tan, 2018(163)	63.9%	41.7%	55.2%	83.3%	31.3%	70.8%	**58%**
Hüneburg, 2019(164)	44.4%	36.1%	28.1%	77.8%	54.2%	62.5%	**51%**
Average score	**72.3%**	**55.5%**	**53.0%**	**76.8%**	**39.3%**	**59.8%**	**59%**

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