Gastroenterology 2018;155:909–925

CONSENSUS STATEMENT

World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer

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BACKGROUND & AIMS: Colonoscopy examination does not always detect colorectal cancer (CRC)— some patients develop CRC after negative findings from an examination. When this occurs before the next recommended examination, it is called interval cancer. From a colonoscopy quality assurance perspective, that term is too restrictive, so the term *post-colonoscopy colorectal cancer* (PCCRC) was created in 2010. However, PCCRC definitions and methods for calculating rates vary among studies, making it impossible to compare results. We aimed to standardize the terminology, identification, analysis, and reporting of PCCRCs and CRCs detected after other whole-colon imaging evaluations (post-imaging colorectal cancers [PICRCs]). **METHODS:** A 20-member international team of gastroenterologists, pathologists, and epidemiologists; a radiologist; and a non-medical professional met to formulate a series of recommendations, standardize definitions and categories (to align with interval cancer terminology), develop an algorithm to determine most-plausible etiologies, and develop standardized methodology to calculate rates of PCCRC and PICRC. The team followed the Appraisal of Guidelines for Research and Evaluation II tool. A literature review provided 401 articles to support proposed statements; evidence was rated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. The statements were voted on anonymously by team members, using a modified Delphi approach. **RESULTS:** The team produced 21 statements that provide comprehensive guidance on PCCRCs and PICRCs. The statements present standardized definitions and terms, as well as methods for qualitative review, determination of etiology, calculation of PCCRC rates, and non-colonoscopic imaging of the colon. **CONCLUSIONS:** A 20-member international team has provided standardized methods for analysis of etiologies of PCCRCs and PICRCs and defines its use as a quality indicator. The team provides recommendations for clinicians, organizations, researchers, policy makers, and patients.

Keywords: Quality Measures; AGREE II; Colonoscopy; CT Colonography.

Although colonoscopy is pivotal for the diagnosis and prevention of colorectal cancer (CRC), cancers can be diagnosed months or years after a colonoscopy that is negative for CRC or CRC precursor lesions.

To prevent CRC, a colonoscopist must both detect the premalignant polyps and resect them completely.[1,2] Post-colonoscopy CRCs (PCCRCs), that is, cancers diagnosed after a colonoscopy in which no cancer was found, can arise from missed cancers, and missed or incompletely resected benign lesions.[3–11] The proportion of PCCRCs detected shortly after the exam that arise from rapidly progressing

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Abbreviations used in this paper: **AA, advanced adenoma; CRC, colorectal cancer; CTC, computed tomographic colonography; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MSI, microsatellite instability; PCCRC, post-colonoscopy colorectal cancer; PICRC, post-imaging colorectal cancer.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.05.038

AGA SECTION

precancerous polyps (new cancer or accelerated biology-related cancer), remains to be determined, but is certainly low.[12] Reasons for missed lesions include inadequate bowel preparation and colonoscopist-dependent factors, such as incomplete colonoscopy, short cecal withdrawal time, and suboptimal inspection technique.[6,13,14] Adenoma miss rates and incomplete polypectomy rates vary between colonoscopists,[15–17] and patients of colonoscopists with low adenoma detection rates have higher interval cancer rates.[14,18]

These findings indicate opportunities for improved colonoscopy performance, for using cancer appearing after a negative colonoscopy as an important benchmark for quality, and for standardizing methodologies to allow more direct comparisons between services.[19]

Aim

The literature on PCCRC diagnosed after a colonoscopy in which no cancer was found lacks agreement on terminology, methodology, or analysis of causation. We recently published guidance on the screening term *interval cancer*[7] (which may or may not relate to colonoscopy); however, these 2 terms are not synonymous, as described later, and no standardized performance measure guidelines exist. To address these concerns, the World Endoscopy Organization convened a working group to use an evidence-based consensus process to make recommendations for future investigators, policy makers, clinical services, and patients.

The aims of the PCCRC project were:

1. To standardize terminology and definitions relating to PCCRC
2. To describe the relationship between PCCRC terminology and interval cancer terminology
3. To standardize the categorization of the potential explanations for PCCRC occurrence
4. To create colonoscopy, histology, and radiology minimum data sets to facilitate PCCRC analysis
5. To develop a standardized definition for a PCCRC rate performance measure and a standardized methodology for its calculation, thus allowing benchmarking and comparison between services
6. To recommend appropriate action for services in the monitoring and review of PCCRC cases and PCCRC rates
7. To consider whether the PCCRC concept can be extended to radiological colorectal imaging; and
8. To provide a research manuscript checklist for authors and peer reviewers of PCCRC papers.

Methodology

Our methodology was based on AGREE II (Appraisal of Guidelines for Research and Evaluation) tool.[20] A multidisciplinary team of international experts was selected, including gastroenterologists, pathologists, epidemiologists, a radiologist and a patient representative, to ensure wide range of expertise and broad representation to cover all aspects of our topic.

The approach taken was to:

1. Determine the purpose of having a performance measure of PCCRC to align recommendations with purpose and the rationale for such
2. Develop a series of key questions relating to PCCRC
3. Conduct a systematic literature search of these questions; and
4. Formulate a set of recommendations using a modified Delphi consensus approach.

The Core (initial) group consisted of 14 members (13 voting and 1 non-voting). Members were then allocated to 2 working groups on the etiology of PCCRCs and performance of PCCRC rates in colonoscopy and radiology practice. Key questions were compiled by the project writing group.

Each working group addressed the following key questions:

1. Etiology working group (7 members, 1 of whom participated in both groups):
   a. Which terminology should be used to describe etiology categories?
   b. What are the risk factors and possible explanations of PCCRC?
   c. How should we ascribe possible explanations?
   d. What should be the minimum colonoscopy, histology, and radiology data set to examine PCCRC?
   e. What molecular tests should be performed to examine PCCRC?
   f. How to prevent PCCRC in high-risk groups?
2. Performance working group (8 members, one of whom participated in both groups):
   a. How should PCCRCs be calculated and reported?
   b. How should PCCRC rates be monitored?
   c. How should PCCRC papers be peer-reviewed?
   d. Radiology—Can we, and how do we extend the methodology to post-imaging CRC?

A comprehensive literature search was performed in PubMed and Cochrane databases, for articles published in English language from 2006 until present (see Supplementary Material for details), which ultimately yielded 402 articles providing background and supporting the statements. We limited our search to articles from 2006 and later, aiming for our database to reflect current practice. All members were asked to and added other key references during the consensus process.

Each working group provided initial draft statements, along with supporting text and suggested references, related to their respective sub-topic; each member voted anonymously, via electronic correspondence, on the resulting 33 statements,

using an agreement scale of 1 (strongly agree) to 5 (strongly disagree). A modified Delphi process was followed, with consensus requiring at least 80% agreement. In areas of continuing disagreement, a recommendation for or against a particular statement (compared with a specific alternative) required both >50% of participants in favor and <20% preferring the comparator. Failure to meet this criterion resulted in no recommendation.

Following votes and comments, statements were iteratively added, and others reduced or merged. Before the second voting round, the group added 7 additional international experts for a total of 20 voting members plus a non-voting patient representative who provided input during the rest of the consensus process. Ultimately, statements achieved consensus after a fourth, final voting round (Figure 1).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating quality of evidence and strength of recommendations was utilized during statement development (Table 1). The GRADE tool separates the strength of evidence from the strength of recommendation.[21]

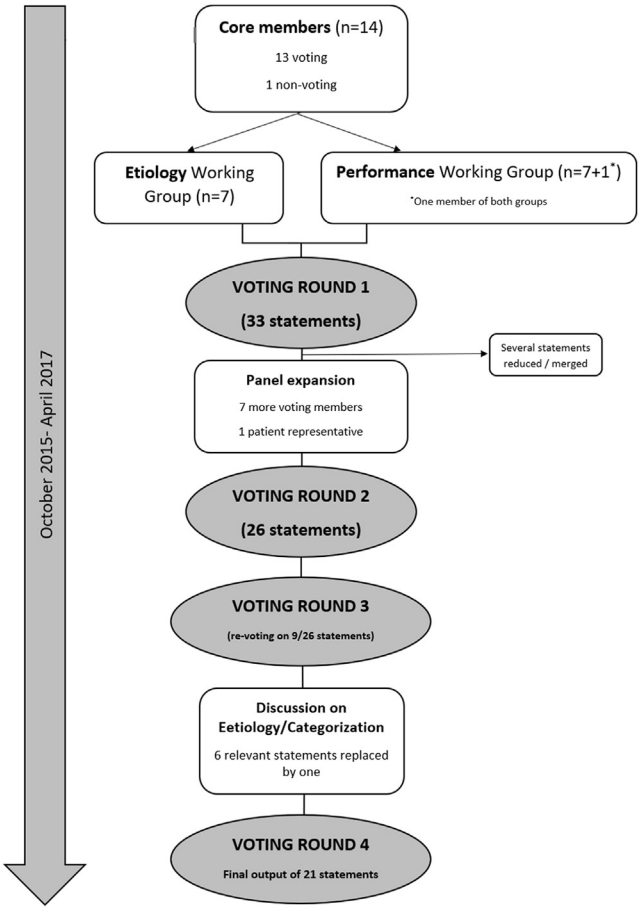

Figure 1. Consensus voting flowchart.

Statements and Evidence

Terminology and Definitions

Statement 1. We recommend that *post-colonoscopy colorectal cancer* (PCCRC) be the preferred term for cancers appearing after a colonoscopy in which no cancer is diagnosed. *GRADE of evidence: very low; strength of recommendation: strong.*

Statement 2. PCCRCs can be sub-categorized into:

- **Interval cancers (where the cancer is identified before the next recommended screening or surveillance examination)**
- **Non-interval cancers (where the cancer is identified at [type A] or after [type B] a recommended screening or surveillance interval, or where no subsequent screening or surveillance interval for repeat examination was recommended [type C], up to 10 years after the colonoscopy)**

GRADE of evidence: very low; strength of recommendation: strong.

The term *interval cancer* is primarily a screening and surveillance term; its precise definition is a CRC diagnosed after a colorectal screening examination or test in which no cancer is detected, and before the date of the next recommended exam.[7] Although this is an important definition for screening and surveillance programs, this terminology does not fit precisely with all that is required for colonoscopy quality assurance purposes. Many colonoscopy procedures, particularly diagnostic procedures, do not result in a recommendation for a further colonoscopy and, therefore, there is no "interval." While from a screening program perspective, a cancer found at a subsequent screening colonoscopy is a screening "success" and not an interval cancer by definition,[7] from a colonoscopy quality point of view, study of these procedures is worthwhile, as there might have been a missed opportunity to identify a cancer or identify/fully resect a precancerous lesion at the prior exam. Furthermore, interval cancers may arise from non-colonoscopic aspects of a screening program (eg, after a negative fecal occult blood test). For these reasons, the term *post-colonoscopy colorectal cancer*, first coined in 2010, is recommended as an all-encompassing, overarching term (Table 2).[9]

PCCRCs can be subcategorized into true interval cancers, that is, those identified before the next recommended screening or surveillance examination, and non-interval cancers. Non-interval cancers may be further subcategorized into those that occur at or after a recommended screening or surveillance interval, and those where no subsequent screening or surveillance procedure was recommended. The interval cancer subcategory will usually be a measure of quality of the colonoscopy, as it presumes that the recommended surveillance interval will pre-empt the occurrence of CRC before the next planned procedure. The non-interval cancer subcategory may similarly be a measure of quality of the colonoscopy but may also reflect the "correctness" or appropriateness of the current screening or surveillance interval recommendations (for cancers occurring at or after the recommended surveillance interval) or the wisdom of a "once-only" screening colonoscopy recommendation itself (for cancers occurring without any repeat exam having been planned).

Examples of PCCRCs subcategories are provided in Table 2. This categorization may aid discussions about

Table 1. Overview of the GRADE Tool

Quality of evidence	Strength of recommendation
High: further research is very unlikely to change our confidence in the estimate of effect	Strong: when the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not
Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	Weak: when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced
Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	
Very low: any estimate of effect is very uncertain	

potential quality implications and learning points from a case; for example, a non-interval PCCRC type B could be because of poor adherence to surveillance intervals, or due to an incomplete surveillance colonoscopy due to suboptimal preparation or an incomplete exam, leading to delays in cancer diagnosis.

We should also stress that cancers for which colonoscopy is not considered "gold standard" for their diagnosis (eg, neuroendocrine tumors, or squamous cell carcinomas of the anorectum) are not included in the PCCRC nomenclature.

Qualitative Review of Post-Colonoscopy Colorectal Cancer Cases

This section outlines the recommended methodology for assessing an individual PCCRC case.

Statement 3. We recommend that services implement a formal process to identify and register PCCRC cases, so they can be reviewed for potential causative factors. Ideally, this should be on a prospective basis, by reviewing whether each newly diagnosed CRC may be a PCCRC. If such methodology is not feasible, then the service should perform an annual retrospective review of all CRC cases diagnosed in the last year. ***GRADE of evidence: very low; strength of recommendation: strong.***

Statement 4. We recommend that services perform a root cause analysis (see Table 3) of every PCCRC case identified to determine the most plausible explanation for the PCCRC, and where appropriate to identify and implement changes in practice to improve performance, monitoring them for effectiveness. ***GRADE of evidence: very low; strength of recommendation: strong.***

Table 2. Post-Colonoscopy Colorectal Cancer Subcategories

	PCCRC subcategories			
		Non-interval type		
	Interval type	Type A	Type B	Type C
	Detected before recommended screening/surveillance interval	Detected at recommended screening/surveillance interval	Detected after recommended screening/surveillance interval	Where no screening/surveillance interval had been recommended
Case examples (see Supplementary Material for further examples)	Patient with 2 small adenomas is advised to return for surveillance in 5 y; 4 y later anemia develops; colonoscopy reveals CRC	Patient with a 15-mm adenoma is advised to return for surveillance in 3 y. On surveillance at 3 y CRC is found	Patient with 3 small adenomas is advised to return for surveillance in 3 y. Patient misses this, returns 4 y later with CRC.	Patient investigated for history of change in bowel habit—colonoscopy normal. No further investigation recommended. Five years later patient develops symptoms and a colonoscopy reveals CRC.
Possible implication other than colonoscopy quality (note all may relate to poor-quality index colonoscopy)	The recommended screening/surveillance interval may be too long	The recommended screening/surveillance interval may be too long	Reinforces importance of adherence to recommended screening/surveillance intervals	Review whether subsequent screening/surveillance may have been appropriate

Table 3. Root Cause Analysis checklist for PCCRC/PICRCs

Patient demographics
Age, *y*
Sex, *male/female*
High-risk cohort? (inflammatory bowel disease, hereditary forms of CRC), *yes/no*
Details of procedure that led to cancer diagnosis
Procedure date
Procedure type
Procedure indication (screening/site-check/surveillance/symptom-driven [state symptom]/therapeutic/other abnormal investigation/other/unknown)
Cancer details
Location
Macroscopic appearance (eg, pedunculated, exophytic, ulcerated, or diffusely infiltrating)
Tumor size (horizontal or width), *mm*
Histologic type
Tumor grade, *low/high*
Microscopic tumor extension (pT)
Number of regional lymph nodes evaluated/number of positive lymph nodes (pN)
Vascular lymphatic invasion
Perineural invasion
Tumor budding (if available)
Extranodal tumor deposits
Resection margins
Treatment planned
Treatment intent (curative/palliative/unknown)
TNM stage
Dukes stage
Details of preceding procedure
Procedure date
Procedure type
Procedure indication (screening/site-check/surveillance/symptom-driven [state symptom]/therapeutic/other abnormal investigation/other/unknown)
Unit ID/name/location
Endoscopist ID
Endoscopist mean withdrawal time for year of procedure, *min*
Endoscopist adenoma detection rate for preceding year, %
Make/type of endoscope
Quality of bowel preparation (use validated scale where possible; or good/adequate/inadequate/not recorded)
Extent of procedure
If incomplete, what was the reason (eg, looping, luminal stricture)
Photo of cecum if reached
Retroflexion performed
Withdrawal time
Colonoscopy result (cancer/polyps/other abnormality/normal/unknown)
If polyp(s) found:
Number of polyps identified
List the following for each polyp (continue over if required): 1. Size of polyp (s) (mm) 2. Site of polyp (s) 3. Polyp morphology (Paris) 4. Histologic type of polyp (adenoma, serrated) 5. Dysplasia grade (high, low, none) 6. Method of polyp removal (cold snare, cold biopsy, hot biopsy, hot snare, piecemeal endoscopic mucosal resection (EMR), en-bloc EMR, endoscopic submucosal dissection, not removed) 7. Completeness of lesion excision (not assessed, incompletely resected, completely resected, not removed)
Polyp 1
Polyp 2
Polyp 3
Polyp 4
Polyp 5
Follow-up plan from preceding procedure
Follow-up plan (screening/surveillance/site-check endoscopy/refer for therapy/conservative/no recommendation given/unknown)
What follow-up interval was recommended?
Was the follow-up plan (if applicable) adhered to?
If not, provide reason for deviation:
For computed tomography colonography, fill in relevant sections above and also record:
Fecal tagging
Intravenous contrast
Final PCCRC categorization (refer to World Endoscopy Organization PCCRC categorization)
What is the most plausible PCCRC etiology? (see etiology algorithm)
Any deviation from planned management pathway?
What is the PCCRC subtype? (refer to PCCRC subcategories table)

Root cause analysis of PCCRC cases helps to identify shortcomings in quality that might be correctable, for potential performance management (Table 3).[6,7]

To achieve this, robust methods to capture and analyze PCCRC cases should be established. Ideally, this should be performed prospectively (ie, by reviewing each CRC case as it is diagnosed). Where this is not possible, regular audits of all new CRC cases should be performed; we suggest this occur at least annually and includes colonoscopy history for every new CRC case.

Because PCCRCs are relatively infrequent, it is important that the learning from root cause analysis, and potential changes in practice, be shared not only with the relevant endoscopist, but with all colonoscopists in the service. A proposed root cause analysis checklist is illustrated in Table 3. As seen in the checklist, we recommend that individual cases are assessed as being screen-related or not.

Statement 5. We suggest the use of the term *most plausible explanation* when describing the etiology of PCCRC cases, given the inherent uncertainties in this process. Determining the precise etiology of a PCCRC is challenging, given current uncertainties about cancer biology (eg, the mean sojourn time from polyp to cancer due to multiple pathways to cancer initiation and progression). Potential factors for PCCRCs include whether the precursor lesion was "undetected" or "detected but not resected" and whether an a priori visualized lesion was completely resected.[22–26] Given these uncertainties, we suggest the use of the term *most plausible explanation* when describing the etiology of PCCRC cases.

GRADE of evidence: very low; strength of recommendation: weak

Statement 6. To facilitate the use of a common language when categorizing PCCRCs according to their most plausible explanations, we suggest that the following categories be used:

- **Possible missed lesion, prior examination adequate**
- **Possible missed lesion, prior examination negative but inadequate**
- **Detected lesion, not resected**
- **Likely incomplete resection of previously identified lesion**
- **Likely new CRC**

Disclaimer: Categorization of PCCRCs according to their most plausible explanations should be used to facilitate quality assurance work or research. This categorization should not be used to define accountability at individual level or as a measure to define or support medico-legal decision making.

We suggest that the following descriptors be used when the following parameters are met (see Figure 2):

1. **Most plausible explanations "Possible missed lesion, prior examination adequate"**
   - **Colonoscopy within the last 4 years that did not detect cancer, where:**
     - **no advanced adenoma (AA, ie, ≥1 cm in size and/or villous and/or containing high-grade dysplasia) was identified in the same bowel segment; and**
     - **there is evidence of cecal intubation; and**
     - **adequate bowel prep was documented**
2. **Most plausible explanation "Possible missed lesion, prior examination negative but inadequate"**
   - **Colonoscopy within the last 4 years that did not detect cancer, where:**
     - **no AA was identified in the same bowel segment**
     - **but where either:**
       - **cecal intubation was not achieved/documented; or**
       - **bowel prep was inadequate**
3. **Most plausible explanation "Detected lesion, not resected"**
   - **Colonoscopy within the last 4 years that did not detect cancer, where:**
     - **AA was identified in the same bowel segment and**
     - **The lesion was not resected**
4. **Most plausible explanation "Likely incomplete resection of previously identified lesion"**
   - **Colonoscopy within the last 4 years that did not detect cancer, where:**
     - **AA was resected from the same bowel segment and**
     - **there was no endoscopic/histologic confirmation of complete resection**
5. **Most plausible explanation "Likely new cancer"**
   - **Last colonoscopy >4 years before CRC detection**

In addition to these 5 categories, we suggest adding the modifying statement "deviation from the planned management pathway" when there is clear evidence of deviation from the planned management pathway. For example, where a polyp was identified at colonoscopy, with a plan to remove at a later date, which never happened.

GRADE of evidence: low; strength of recommendation: weak.

Definitions of these scenarios vary in the literature (see Table 4), highlighting a need for uniform terminology.[22–24,26] Here, we provide our consensus-based categorization construct.

We recognize this construct has not been validated, is influenced by the time of observation (eg, with longer follow-up, a higher percentage of PCCRCs will be designated as new cancers), that certain cases might not fit neatly into 1 of the 5 categories, and the potential for misclassification. For example, a PCCRC after a colonoscopy 5 years ago that resected an AA would be assigned to "likely new cancer," however, a plausible alternative is that this PCCRC arose from incomplete resection of the adenoma. Alternatively, a PCCRC attributed to incomplete resection could also result from a different missed synchronous lesion located in the same segment.

Other algorithms that have adjudicated "missed" cancers have used 30 months and 36 months as a cutoff,[27] although natural history studies of the polyp-to-cancer sequence generally support longer time frames. For example, microsimulation modeling estimated that the mean dwell time (from normal mucosa to cancer) ranges from 10.6 to 25.8

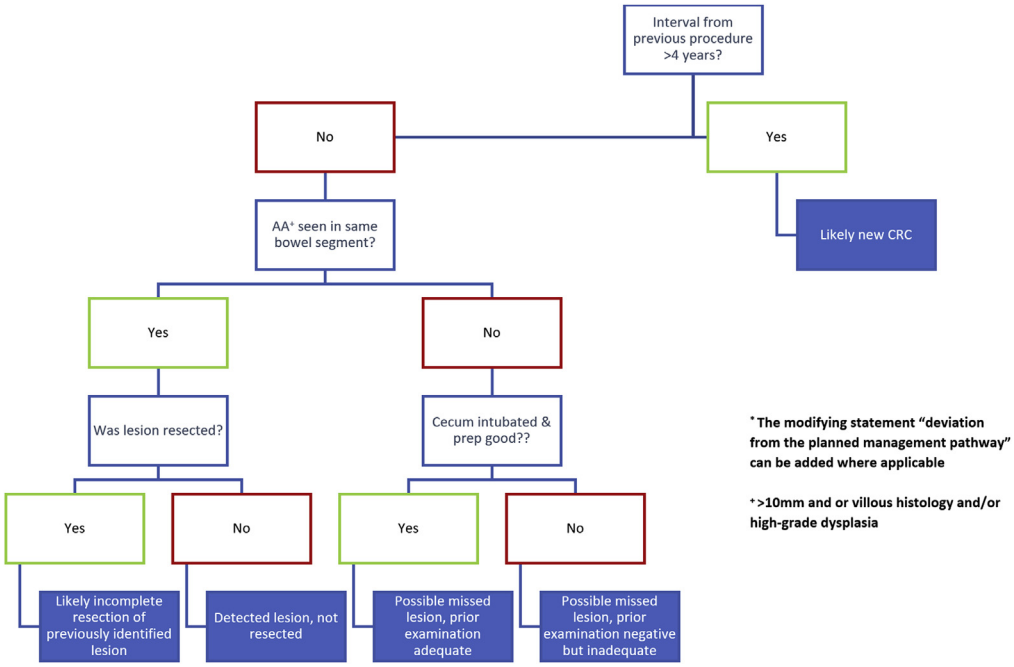

Figure 2. Most plausible PCCRC explanation.

Table 4. Potential Explanations of PCCRC from Different Studies

First author, year, country (study type)	Incomplete resection	Missed cancer/lesion	New cancer
Pabby, 2005,[22] USA (RCT)	"…occurred at the site of a previous adenoma and… absence of a suspicion at endoscopy for residual neoplasia"	1. Different from the site of a previous adenoma 2. Within 30 mo or fewer (regardless of size or stage) 3. More than 30 mo and had all features of an advanced cancer	1. Different from the site of a previous adenoma 2. More than 30 mo 3. No or only 1 feature of advanced cancer
Huang, 2012,[23] China (hospital-based)	"occurred at the site of 'resected tumors' (ie, adenoma or early cancer)"	1. Different from the site of a previous adenoma 2. Within 30 mo or fewer (regardless of size or stage) 3. More than 30 mo and had all features of an advanced cancer	1. Different from the site of a previous adenoma 2. More than 30 mo 3. No or only 1 feature of advanced cancer
Robertson, 2014,[24] USA (RCT)	"…had to be a significant adenoma in the same segment. If three or more years had passed, then and adenoma ≥5 mm in size or with villous histology or with high-grade dysplasia was considered significant. If fewer than 3 years had passed, then an adenoma ≥1 cm in size, or with villous histology or with high-grade dysplasia was considered significant."	1. No significant adenoma in same segment on last exam 2. Within 36 mo or fewer (regardless of size or stage)	1. No significant adenoma in same segment on last exam 2. More than 36 months (regardless of size or stage)
Le Clercq, 2014,[25] The Netherlands (population-based)	"…cancer diagnosed in the same anatomical segment as a previously resected advanced adenoma"	1. Different from the site of a previous advanced adenoma 2. Within 36 mo or fewer (regardless of size or stage) 3. More than 36 mo and had all features of an advanced cancer	1. Different from the site of a previous advanced adenoma 2. More than 36 mo 3. No or only 1 feature of advanced cancer

years.[28] Even more relevant, one estimate of the mean sojourn time of preclinical cancer progressing to a detected cancer ranged from 4.5 to 5.8 years.[29]

PCCRCs may differ from detected CRCs, including having shorter dwell times; this is possibly why we see an excess of rapidly growing right-sided lesions in PCCRCs. Much published data are for left-sided series (ie, flexible sigmoidoscopy data). There was much discussion within the group on this issue and it was concluded that using a period of 48 months is a reasonable assumption, while being cognizant of the uncertainties of the natural history of the disease.

Although arbitrary and undoubtedly imperfect, this definition provides both objectivity and standardization to categorization, aiding quality assurance and comparisons between series.

This 4-year cutoff is used to assign the most plausible etiology. In statement 16, a 3-year cutoff is used to calculate the PCCRC rate—the reasons for this difference are described in that section.

Examples of this categorization are provided in the relevant Supplementary Material.

Statement 7. To facilitate attribution of PCCRC etiology, we recommend that endoscopy/pathology services should collect the following minimum data set for each procedure:

- **Date of colonoscopy**
- **Patient age**
- **Patient sex**
- **Procedure indication (screening, surveillance, symptomatic)**
- **Predisposing risk factors for CRC (eg, high-risk cohort such as ulcerative or Crohn's colitis or hereditary forms of CRC, such as Lynch syndrome and familial adenomatous polyposis)**
- **Quality of bowel preparation (using a validated score)**
- **Extent of exam (including photodocumentation of 2 of 3 cecal hallmarks: appendiceal orifice, ileocecal valve, terminal ileum)**
- **Location of all visualized polyps**
- **Estimated size of all visualized polyps**
- **Paris classification of all visualized polyps by segment of colon**
- **Type of endoscopic resection (cold snare, cold biopsy, hot biopsy, hot snare, endoscopic mucosal resection or endoscopic submucosal dissection)**
- **Completeness of polyp resection, as judged by the endoscopist (not resected, incompletely resected, completely resected). State if the lesion is excised en bloc or in a piecemeal fashion.**
- **Completeness of polyp resection, as judged by the histopathologist (not assessed/not assessable, incompletely resected, completely resected) and supported by photo-documentation. State if the lesion is received fragmented or en-bloc**
- **Other colonic pathology (such as diverticulosis or inflammatory bowel disease)**
- **Post-procedure management plan**

GRADE of evidence: low; strength of recommendation: strong.

Statement 8. We recommend that other endoscopist-related performance measures, such as cecal intubation rates, adenoma detection rates, and cecal withdrawal times, are routinely collected by the endoscopy service and are used to assist in the review of PCCRC cases. ***GRADE of evidence: low; strength of recommendation: strong.***

To facilitate attribution of PCCRC etiology and associated performance measure metrics,[30] the routine capture of a minimum data set is required. Most of these items should be incorporated into routine procedural documentation, through an electronic endoscopy reporting system.

- Modality of endoscopic resection (cold snare, cold biopsy, hot biopsy, hot snare, endoscopic mucosal resection, or endoscopic submucosal dissection)
- Cecal intubation (including photo-documentation, eg, at least 2 quality images to document 2 of the 3 landmarks: ileocecal valve, appendiceal orifice, and terminal ileum)
- Quality of bowel preparation (using a validated score) that assesses prep quality after all efforts to clean the colon wall
- Polyp sizes, measured against the known diameter of biopsy forceps or a snare to minimize inter-observer variation
- Although imperfect, the Paris polyp classification[22] is the most standardized morphology categorization available and endoscopists should be encouraged to use it, either in descriptive terms (eg, flat lesion with depressed component) or in Paris "shorthand" (eg, Paris 0–IIa/c). As a "next best option," in cases where endoscopists are not entirely comfortable with the full Paris classification, the morphology of each polyp should be characterized as sessile, pedunculated, or flat
- Polyp location using the 9 cardinal colon segments (ie, cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid colon, and rectum)
- Polypectomy details including:
  - Polypectomy instrument (eg, snare, biopsy forceps)
  - Use of electrocautery (yes/no; electrocautery machine; settings)
  - Special technique (eg, endoscopic mucosal resection or endoscopic submucosal dissection)

- Piecemeal or en-bloc excision
- Completeness of resection (endoscopically and histologically)

To ensure complete polypectomy, clear demarcation of the lesion (use digital chromoendoscopy if needed) should be achieved before resection ideally in a single-piece fashion, and close inspection should be performed after resection.

We suggest monitoring both endoscopist factors (ie, cecal intubation rates,[10] adenoma detection rate or polyp detection rate,[14,18,31,32] withdrawal time[33] and associated patient factors, ie, patient age, significant comorbidities, diverticular disease).[34]

Statement 9. To facilitate detailed descriptions of PCCRC, we recommend that clinical and pathology services should collect the following minimum data set for each CRC:

- **Was the CRC detected in the context of screening, surveillance, or a symptom-driven procedure?**
- **Date and type of previous colorectal imaging before the episode of care in which CRC was detected**
- **Tumor location**
- **Macroscopic appearance (eg, pedunculated, exophytic, ulcerated, or diffusely infiltrating)**
- **Tumor size (horizontal or width in mm)**
- **Histologic type**
- **Tumor grade (low/high)**
- **Microscopic tumor extension (pT)**
- **Number of regional lymph nodes evaluated/number of positive lymph nodes (pN)**
- **Vascular lymphatic invasion**
- **Perineural invasion**
- **Tumor budding (where recommended, see below)**
- **Tumor deposits**
- **Resection margins**

GRADE of evidence: low; strength of recommendation: strong.

Screening programs and studies on PCCRC should include the standard parameters that are recommended in consensus documents, such as the Royal College of Pathologists, the Nationwide Network and Registry of Histology and Cytopathology in the Netherlands (PALGA), the National Health Service Bowel Cancer Screening Program in the United Kingdom or the American College of Pathologists.[35–37]

The minimum data set or core data items for CRC histopathology report are: type of excision, location, tumor size, histologic tumor type, histologic differentiation, local invasion (pT), tumor budding, lymph node status (pN), stage, vascular invasion, resection margins, tumor deposits, other abnormalities or lesions, and presence/absence of metastases (pM) when biopsy material from a metastatic lesion is available.[38]

Additional data items, considered by some authors as non-core are: nature of invasive margin (expansive, infiltrating or both), specimen length, macroscopic intactness of mesorectum, intra- and peritumoral lymphocytic response.[25,35,37,39–43]

Tumor budding is defined as a single tumor cell or a cell cluster consisting of 4 or fewer tumor cells. Tumor budding is counted on H&E. The hot spot method (in a field measuring 0.785 mm^2 at the invasive front) is recommended.[44] A 3-tier system should be used along with the budding count in order to facilitate risk stratification in CRC. Tumor budding is an independent predictor of lymph node metastasis in pT1 CRC, and is an independent predictor of survival in stage II CRC44. Tumor budding should be taken into account along with other clinicopathologic features in a multidisciplinary setting. Tumor budding and tumor grade are not the same.[45]

Photodocumentation of the surgical resection specimens is recommended. The macroscopic appearance of the tumor in the surgical specimen can provide complementary information that may, together with microscopic appearance and other factors, help to correctly classify the tumor.

Statement 10. We recommend that microsatellite stability/microsatellite instability (MSI) status be assessed on all PCCRC cases either by immunohistochemistry or polymerase chain reaction. RAS mutations, BRAF mutations, or other targetable molecular alterations should be determined when indicated. *GRADE of evidence: low; strength of recommendation: strong.*

Given PCCRCs are not always due to procedural factors, all services should consider examining molecular features associated with a more rapid progression to cancer.

Mismatch repair proteins or MSI status should be performed on all CRCs or at minimum all CRCs diagnosed at age younger than 70 years. Detection of defective mismatch repair in CRCs can be used to cost effectively screen CRC patients for possible Lynch syndrome, which accounts for approximately 2%–3% of all CRCs. Lynch syndrome diagnosis has prognostic and therapeutic implications, which include genetic family assessment and counseling.[46]

An MSI-high phenotype indicates that mismatch repair deficiency in the cancer may be sporadic or have a germline mutation in one of several DNA mismatch repair genes (eg, MLH1, MSH2, MSH6, or PMS2) or an altered EPCAM (TACSTD1) gene. For tumors with immunohistochemical loss of expression for MLH1, testing for BRAF gene mutation (V600E) or MLH1 methylation analysis is indicated.[47] Approximately 15% of sporadic CRC are MSI. BRAF gene V600E mutation is not present in hereditary cancers, and loss of MLH1 is mostly due to a germline mutation and genetic testing should be performed. Loss of MSH2 or MSH6 expression strongly suggests Lynch syndrome. PMS2 loss is often associated with loss of MLH1 and is only independently meaningful if MLH1 is intact.

K-N-RAS and BRAF mutations, or other targetable molecular alterations should be determined when appropriate.

Current recommendations from the American Gastroenterology Association and the National Comprehensive Cancer Network recommend patients with stage IV CRC who are candidates for anti-EGFR antibody therapy should have their tumor tested for K-N-RAS and BRAF mutations.[43]

Quantitative Assessment: Post-Colonoscopy Colorectal Cancer Rate

This section outlines the recommended methodology for assessing PCCRC rates across services.

Statement 11. The PCCRC rate is an important performance measure of the ability of colonoscopy to detect and prevent CRC. We recommend that it should be used to monitor the quality of a colonoscopy service. ***GRADE of evidence: very low; strength of recommendation: strong.***

The PCCRC rate of a colonoscopy service determines its efficacy in detecting and preventing cancer and should, therefore, be the principal measure of quality in colonoscopy, driving performance improvement within the service. Monitoring PCCRC rates facilitates benchmarking and comparison between endoscopy services. A powerful method for quality improvement is to have a minimum performance standard and as performance improves, to raise the bar periodically. Where there is no well-defined minimum standard, funnel plots can be used to identify outliers, as described in the following.

Patients and payers of health care increasingly want to know how they might improve outcomes and achieve best value for money.[9] The PCCRC rate can provide a benchmark measure to compare performance to facilitate payer and patient choice, as well as to inform decisions for system-wide quality improvement interventions. In an ideal system, a low PCCRC rate would be incentivized. The PCCRC rate may also be used to support decisions for system-wide quality improvement interventions, for example, if an intervention were known to reduce PCCRC rate, it would be possible to predict a cost of reducing 1 PCCRC using that intervention.

Surrogate measures of colonoscopy quality, such as cecal intubation rate, adenoma detection rate, and withdrawal time are easier to capture than PCCRC rate[48–51]; however, they are only surrogates of the true outcome that matters most to patients, that is, a post-colonoscopy cancer.[52]

Statement 12. We recommend that the PCCRC rate should only be used to benchmark services if the required data quality and the necessary databases linkages are available. ***GRADE of evidence: low; strength of recommendation: strong.***

Statement 13. We recommend that PCCRC rates should be externally reported at a service level, rather than for individual endoscopists. We recommend that PCCRC rates should be displayed with 95% confidence intervals and, where appropriate, plotted on a funnel plot to identify outliers more readily. ***GRADE of evidence: low; strength of recommendation: strong.***

The calculation of PCCRC rates is complex—calculation cannot simply rely on the colonoscopy service, but rather requires a collaborative approach within a multidisciplinary health care system, including epidemiologists and cancer registries, with agreed data collection, adherence to confidentiality requirements and oversight by experts. Clinical services should be cautious about publishing their PCCRC rate unless they are confident about the quality and completeness of the data. For example, patients might move from their catchment area, precluding capture of subsequent cancer, leading to a false reassurance of a low rate. Only linkage of population-based databases can provide accurate rates for comparison between services. If comprehensive and accurate colonoscopy and cancer databases are not in place, then it is impossible to calculate an accurate rate.[53]

Large sample sizes of cancer are required to provide estimates of PCCRC rate with sufficient precision: rates will not be interpretable for small samples.[19]

From this example (Table 5), assuming a 3% CRC yield at colonoscopy and a mean PCCRC of 8.6%, 9,967 colonoscopies would be required to have 80% power to detect poor performance (based on unacceptable PCCRC rate of 12.9%, ie, 50% more than the mean); or 2,767 colonoscopies if based on unacceptable figure of 17.2% (100% more than mean). Thus, although calculating individual PCCRC rates is inaccurate due to imprecision, a root cause analysis should be performed routinely on every PCCRC case and discussed with the colonoscopist who performed the original colonoscopy.

Funnel plots of estimates provide a visual method of determining whether there is sufficient sample size to rely on the estimate of PCCRC rate calculated from the sample and to use confidence intervals to estimate uncertainty.

Statement 14. While for epidemiologic and research purposes, there remains a benefit in

Table 5. An Illustration of Sample Sizes Required for PCCRC Rate Calculation

Current PCCRC rate, %	Example of unacceptably high PCCRC rate, %	No. of procedures where cancer found necessary to detect poor performance (α, 5% 1-sided)		
		60% Power	70% Power	80% Power
8.60[19]	17.20	42	59	83
8.60	12.90	162	220	299

performing various analyses of PCCRC-related data, we suggest that for quality assurance purposes, a standardized method to calculate an unadjusted PCCRC rate be used to permit the benchmarking of services. We recommend that this "unadjusted PCCRC rate" be calculated as the number of PCCRCs divided by the total of the number of PCCRCs plus the number of detected cancers, expressed as a percentage. ***GRADE of evidence: very low; strength of recommendation: strong.***

To date, no 2 published studies have used the same methodology for calculating PCCRC rate. Morris et al[19] demonstrated that PCCRC rates, using the same data, vary from 2.5% to 7.7%, depending on the methodology used. Having a single method to calculate rates will enable more reliable comparisons of rates between studies and jurisdictions.

A CRC may be both a detected cancer (if it was diagnosed by colonoscopy within 6 months) and a PCCRC (if there was also a prior colonoscopy between 6 and 36 months earlier)—in which case the 1 cancer will contribute to both categories—excluding such cases from the PCCRC count, as some previous studies have done, will markedly decrease the PCCRC rate.

The unadjusted PCCRC rate described has the advantage of being clinically relevant, simpler to calculate and, at least from a methodological perspective (1-sensitivity), is unaffected by the prevalence of CRC in the population undergoing colonoscopy. Practices with highly atypical patient populations (eg, solely colitis surveillance patients) might not be suitable for benchmarking PCCRC rates. Modest data exist for using a PCCRC rate as a performance measure. Therefore, additional research exploring different methodologies and their correlations with other performance measures is needed. Examples of other calculations include PCCRCs per 100,000 person-years' follow-up, and PCCRCs per 1000 persons diagnosed within a defined time period since the last negative colonoscopy. This method has the advantage that it reflects persons-time at risk and accounts for loss to follow-up,[54] and is in line with the method proposed within the Europe Against Cancer Programme,[55] a standard methodology for describing interval cancers in other screening programs. This method would typically require linking a defined cohort of subjects with a negative colonoscopy to a comprehensive population-based cancer registry.

When comparing PCCRC rates, age standardization, adjustment for time period of measurement and stratification by sex may be considered given the potential variation in these cancer risk factors between cohorts.

The proportionate interval cancer incidence (also called the proportional incidence method) aims to overcome the challenge of variation in risk factors between cohorts by evaluating interval cancer incidence against the background incidence. This is calculated by dividing the observed number of interval cancers during a given period by the (estimated) cancer incidence expected in the absence of screening during that period. In other screening programs, the proportionate interval cancer incidence has been used to compare sensitivity between different settings,[56] for example, breast cancer screening and fecal occult blood testing. However, its applicability to PCCRCs is not known and further methodological research is required (see Supplementary Material).

Statement 15. We recommend that the unadjusted PCCRC rate is calculated based on the date the person had the colonoscopy, with the term *detected cancer* being used to describe cancers diagnosed by the colonoscopy or within 6 months of the date of the colonoscopy, and the term *post-colonoscopy colorectal cancer* used to describe cancers identified beyond 6 months of the date of the colonoscopy. ***GRADE of evidence: very low; strength of recommendation: strong.***

If a colonoscopy is of inadequate quality to exclude cancer or a polyp because of poor colon cleansing or inability to inspect the entire colon, a repeat procedure or other investigation is usually scheduled. In other situations, biopsies may not detect a cancer suspected at the time of colonoscopy, but a cancer is confirmed at subsequent surgery. To avoid inappropriately assigning such delays to the colonoscopy, and to allow time for linkages of regional databases, a 6-month grace period is considered a pragmatic solution to permit complex cases to be diagnosed.[19,34]

Although this may misclassify a small number of cancers actually missed on an initial complete colonoscopy, and subsequently spotted in a colonoscopy performed within 6 months due to, for example, ongoing symptoms, we expect these cases to be exceptions rather than the rule.

Further qualitative research is required before a different interval can be proposed.

Statement 16. We suggest that when the unadjusted PCCRC rate is calculated, the follow-up period since the last colonoscopy is denoted with a suffix—Ny where N refers to the number of years' follow-up after the last colonoscopy. For consistency and to permit benchmarking, we recommend that as a minimum, all services should report the PCCRC rate for an interval of 3 years (PCCRC-3y). ***GRADE of evidence: low; strength of recommendation: weak.***

Regardless of the quality of colonoscopy, the number of PCCRCs detected will increase over time—rates for a 3-year period will differ from a 10-year period. Given our current paucity of knowledge, there is value in reporting rates after different follow-up periods; however, when PCCRC is used as a benchmark to compare services the rate needs to be defined for a set follow-up period.

Our panel's consensus was that this should be set at 3 years—this decision takes into account various factors, including:

- an adequate sample size for statistical purposes
- the need to reflect contemporaneous (rather than historical) practice as much as possible
- cancer biology and sojourn times

It is important to understand that this 3-year cutoff relates to the calculation of PCCRC rate and has been recommended for the reasons stated above. It is distinct from the

use of a 4-year cutoff when reviewing a PCCRC to determine the most plausible etiology, which relates more to a lesion's biology, as described in Statement 6. Ideally, the PCCRC-1y, PCCRC-5y, and PCCRC-10y rates should be also calculated, to develop an evidence-base for various time cutoffs.

Precise methodology for PCCRC-3y rate calculation is given below:

Identify all people undergoing a colonoscopy in a certain year

- Each colonoscopy is labeled according to the outcome of the test:
  - True-positive colonoscopy (where a CRC was detected at that procedure, or within 6 months—a "detected CRC")
  - False-negative colonoscopy (where a CRC was detected between 6 and 36 months of the procedure—a "PCCRC")
  - True-negative colonoscopy (no CRC detected within 36 months of the procedure)

Note:

- A person may have had several tests within each time period. However, only 1 true-positive and 1 false-negative test should be included for each CRC:
  - Only the closest true-positive test to the CRC diagnosis should be included
  - Only the closest false-negative test should be included; any further false-negative tests should be re-classified as true-negative tests
- A person may also have been diagnosed with more than 1 CRC. Each colonoscopy should only be included once and should relate to the closest subsequent CRC
- The PCCRC-3y rate is then calculated as: false negatives / (true positives + false negatives) %

It should be noted that PCCRC nomenclature is designed for colorectal adenocarcinoma; cancers for which colonoscopy is not considered "gold standard" for their diagnosis (eg, neuroendocrine tumors or squamous cell carcinomas of the anorectum) should not be included. Likewise, given that adenocarcinoma of the appendix may not be apparent endoscopically, we recommend that these are not included.

Statement 17. Where exclusions in the population on which PCCRC is calculated are felt to be necessary, these should be stated explicitly in the methodology. However, we recommend that a PCCRC rate involving the entire cohort of adult patients, without exclusions, is also provided. ***GRADE of evidence: very low; strength of recommendation: strong.***

When large-scale populations are studied, it is unlikely that small cohorts of high-risk patients will significantly affect PCCRC rates significantly; thus, inclusion of all CRC patients is encouraged. It is recognized, however, that various services may opt to exclude such cohorts to their PCCRC calculation.

High-risk CRC cohorts, for whom more frequent surveillance is recommended[57–59] include patients with previous CRC or advanced/multiple colonic polyps,[57,58,60–63] Lynch syndrome,[57] and longstanding extensive colitis,[59] where there is possibly a different dysplasia–carcinoma pathway or an accelerated adenoma–carcinoma pathway that might influence the appearance of premalignant lesions and the speed of development into cancer.[64,65]

Non-Colonoscopic Imaging of the Colon

Statement 18. We recommend that in the wider context of all colorectal imaging investigations, ***post-imaging colorectal cancer*** **(PICRC) is the preferred term for cancers appearing after a colorectal imaging investigation that is negative for CRC. Similar to PCCRC, PICRC should be used to describe cancers identified beyond 6 months of the date of the imaging procedure.** ***GRADE of evidence: very low; strength of recommendation: strong.***

Although colonoscopy is currently the most frequent method for investigating the colon, it is not the only colonic investigation. Currently, computed tomographic colonography (CTC) is the only widely available alternative to colonoscopy, but other technologies, such as capsule endoscopy, are emerging. Therefore, to future proof the terminology, it is proposed that the term post-imaging colorectal cancer can be used to extend the applicability of the term beyond colonoscopy to all colonic imaging techniques.

We believe radiology would benefit greatly from such a framework, and it makes sense for the definitions, time frame, caseload requirements, sample size, and methodology to be aligned as far as possible with colonoscopy. The current focus should be CTC because barium enema is essentially an historical examination.[66]

Statement 19. While it may be possible to calculate PICRC rates across different services using a particular colonic imaging technique, such as CTC, we suggest that it is potentially misleading to use PICRC rate to compare between different colonic imaging technique, for example, to compare CTC and colonoscopy, unless the populations being investigated are well-matched or randomized. If this is impossible, comprehensive adjustment for all known covariate factors associated with PICRC should be undertaken. The same methodological and sample size considerations described for colonoscopy should also be applied for radiologic imaging. ***GRADE of evidence: low; strength of recommendation: weak.***

There are relatively few studies reporting long-term PICRC rates for CTC.[66–71] A recent systematic review found only 12 studies regarding this topic, reporting on just under 20,000 patients, with a pooled PICRC rate of 4.4% at average follow-up of 3 years.[72] Although this rate is comparable to that reported for colonoscopy, these data were mostly derived from either research trials or single-center audits, with no large-scale series encompassing the routine clinical practice of an entire health care system.

Because CTC and colonoscopy are often applied in differing clinical scenarios, with CTC commonly being reserved for patients who are either deemed unsuitable for colonoscopy or in whom it has failed, there are likely to be substantial differences between the populations undergoing each examination. This is likely to translate to different PICRC rates irrespective of the diagnostic accuracy of the 2 techniques. The same methodological and sample size considerations described for colonoscopy (above) should also be applied for CTC.

Statement 20. To facilitate adjudication of PICRC case etiology, we recommend that radiology services should collect the following minimum data set for all radiology procedures. Essential:

- **Date of procedure**
- **Type of procedure**
- **Imaging site name/code**
- **Indication for colonic examination**
- **Reason for use of radiologic examination rather than colonoscopy**
- **Bowel cleansing agent used, dose, and quality of cleansing**
- **Fecal tagging agent used, dose, and quality of tagging**
- **Gas used for and quality of colonic distension**
- **Patient positioning during image acquisition**
- **Findings in each colonic segment**
  - **Details of polyps/cancers found if applicable (number, size, morphology)**

Desirable:

- **Details on interpreter(s) of images (name, lifetime experience, number of cases interpreted in previous 24 months)**
- **CT image acquisition details (slice thickness/reconstruction interval/dose parameters)**
- **Use of intravenous contrast and antispasmodic**
- **Mode of interpretation and use of computer-assisted detection**
- **Subsequent management recommendations**
  - **Discharge/repeat examination/refer for endoscopy/surgery/other**
  - **If referral for endoscopy, relevant minimum dataset to be completed**
  - **If repeat radiology what was the recommended/actual interval**

GRADE of evidence: low; strength of recommendation: strong.

Statement 21: We recommend that if a PICRC is diagnosed, the following data should be sought retrospectively, including by review of CTC images. Essential

Findings in segment of colon where PICRC was subsequently found (number, size, morphology, and histology of polyps/cancers; presence/absence of diverticular disease; other colonic diagnoses).

- **Actual patient management, and any difference from that originally recommended at the time of CTC reporting.**
- **Impression of the likely nature of the missed lesion (technical error, perceptual/reader error, non-diagnosable/" invisible" lesion, unknown).**

Desirable

- **Findings in the remainder of the colon (ie, segments other than where the PICRC was diagnosed).**
- **Details on interpreter(s) of images (positive predictive value over last 24 months, polyp detection rate for proven adenomas 6 mm+ over last 24 months).**

GRADE of evidence: very low; strength of recommendation: strong.

Individuals undergoing radiologic examination are often selected for imaging on the basis of suitability or otherwise for colonoscopy. The factors that make colonoscopy difficult or impossible (eg, diverticular disease) may also increase the risk of PICRC. It is therefore important to record the spectrum of patients referred for imaging to permit meaningful interpretation of PICRC rates.[4,19,73,74]

There are no published data linking radiologist performance to PICRC rates. However, experience and case volume are associated with higher diagnostic sensitivity in some studies, and with higher detection rates in observational studies, meaning it is plausible that PICRC rate is operator-dependent.[75–77]

If PICRCs are detected, it is highly desirable to reexamine the entire imaging data set in an attempt to determine the underlying reasons for PICRC. We recognize that this may not be possible, for example, if CTC images have been deleted; nevertheless, such data should still be sought wherever practicable. Missed lesions at CTC (eg, during diagnostic test accuracy studies) are classified variably in the literature, but a common scheme is technical error (ie, part of the scanned volume cannot be adequately evaluated, eg, due to poor colonic distension, or retained untagged stool); perceptual or reader error (ie, in retrospect, an abnormality—a polyp or cancer—is visible on the CTC images, and was overlooked by the reader at the time of scan reporting); and truly non-diagnosable/"invisible" lesions (ie, CTC may be deemed normal, even in retrospect). In the context of PICRC, the final category will include some polyps that are non-detectable at CTC (eg, too small, or completely flat) and some new lesions (eg, CRC developing via a rapid carcinogenesis pathway).[78–81] Ideally, such

review should be performed by an experienced, independent CTC radiologist.

Research Priorities

A proposed checklist for peer review of future papers on the topic is available in the Supplementary Material.

We consider the following to be the key research questions:

- What is the natural history of adenomas and serrated lesions?
- How does natural history of adenomas and serrated lesions differ in the proximal/distal colon?
- What is the natural history of CRC, including the sojourn time of stages and of the preclinical phase?
- How does natural history of CRC differ in the proximal/distal colon?
- How can the above be used to refine etiology categorization?
- To what extent do different methodologies for the calculation of PCCRC rates correlate with, add to, or improve on the methodology in this manuscript?
- To what extent does PCCRC rate correlate with other colonoscopy performance measures?
- Can qualitative research of the pathways to the point of CRC diagnosis help refine the current 6-month cutoff between detected CRCs and PCCRCs?
- Validation of the recommended method of reporting a PCCRC rate
- To what extent is a PCCRC-1y rate predictive of a PCCRC-3y rate?
- What are the strengths and weaknesses of different methodologies (eg, number of PCCRCs expressed per 100,000 person-years' follow-up, number of PCCRCs diagnosed within a defined time period since the last negative colonoscopy per 1000 persons with a negative colonoscopy)? Can these be correlated with other performance measures?
- Would including large (10 mm+) polyps in the calculate of a missed lesion rate be advantageous?
- What information from the pathology report is useful to identify a high-risk patient?
- To what extent can PCCRC rate calculation be automated?
- Can electronic endoscopy reporting systems be modified to capture key data?
- What are the PCCRC rates in special groups such as those with inflammatory bowel disease or hereditary CRC syndrome?
- What are the most effective interventions to reduce unwarranted variation in PCCRC rates?
- Which screening modalities are most effective at minimizing PCCRC, in particular in relation to the serrated pathway?

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.05.038.

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Received November 27, 2017. Accepted May 15, 2018.

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Acknowledgments
Author contributions: Matthew D Rutter, Silvia Sanduleanu, and Iosif Beintaris conceived and designed the project, supervised the consensus process, drafted the manuscript, performed critical revisions, and finalized the manuscript. Roland Valori, Han Mo Chiu, Douglas A. Corley, Miriam Cuatrecasas, Evelien Dekker, Anna Forsberg, Ulrike Haug, Michal F. Kaminski, Takahisa Matsuda, Gerrit A. Meijer, Eva Morris, Andrew A. Plumb, Linda Rabeneck, Douglas Robertson, Robert E. Schoen, Harminder Singh, Jill Tinmouth, and Graeme P. Young were voting members during the consensus process and performed critical revisions of the manuscript. Jola Gore-Booth provided input during the consensus process.

Conflicts of interest
These authors disclose the following: Roland Valori is joint director of a small Limited Liability Partnership called Quality Solutions for Healthcare that provides advice and support for quality improvement and quality assurance within and outside of endoscopy, mostly in the United Kingdom and Ireland. It also delivers colonoscopy training internationally, some of which is reimbursed and some of which is not. Evelien Dekker has received a research grant from Olympus and endoscopic equipment on loan from Olympus and Fujifilm. Andrew A. Plumb has received payment for educational lectures organized by Warner Chilcott, a pharmaceutical company, and the medical device company Acelity. Silvia Sanduleanu has received a research grant from Olympus, as well as speaker fees/travel reimbursement from Falk and AbbVie. Harminder Singh is a member of the Advisory Board for Pendopharm and has received research funding from Merck Canada. Jill Tinmouth is a paid Lead Scientist for the ColonCancerCheck program, the CRC screening program in Ontario. The remaining author disclose no conflicts.

Examples of Post-Colonoscopy Colorectal Cancer Categorization

Case 1: Patient with normal colonoscopy (to terminal ileum, good prep) to investigate iron deficiency anaemia. No surveillance recommended. Returns a year later with persistent anaemia, has repeat colonoscopy; ascending colon CRC found. *PCCRC–non-interval type C;* **possible missed lesion, prior examination adequate**

Case 2: Patient with colonoscopy 2 years ago for rectal blood loss, reported as negative (adequate prep) but cecal pole not reached due to looping. Ten-year screening colonoscopy recommended. Returns 9 months later with liver metastases; repeat colonoscopy reveals cecal cancer. *PCCRC-interval type;* **possible missed lesion, prior examination negative but inadequate**

Case 3: Patient has en bloc endoscopic mucosal resection of 20-mm lateral spreading tumor–granular type in the transverse colon polyp. Histology states tubulovillous adenoma with low-grade dysplasia, "completeness of excision cannot be confirmed." Patient returns in 3 years for surveillance, distal transverse colon cancer is found. *PCCRC–non-interval type A;* **likely incomplete resection of previously identified lesion**

Case 4: Patient with normal colonoscopy (good prep, cecal photo taken) performed to investigate loose stool. No surveillance recommended. Returns after 54 months with anaemia, colonoscopy reveals sigmoid CRC. *PCCRC–non-interval type C;* **likely new CRC**

Case 5: Elderly inpatient has colonoscopy (good prep, terminal ileum photographed) for rectal bleeding; 3-cm lateral spreading tumor–granular type villous adenoma seen in rectum. Plan is made for outpatient colonoscopy within 4 weeks for polypectomy, but patient develops myocardial infarction needing intensive therapy unit; returns 8 months later with rectal cancer. *PCCRC–non-interval type B;* **detected lesion, not resected, deviation from the planned management pathway**

Case 6: Patient has screening colonoscopy; nothing abnormal seen to cecum but bowel prep inadequate, advised to return in 1 year. Sigmoid CRC is diagnosed at that time. *PCCRC–non-interval type A;* **possible missed lesion, prior examination negative but inadequate**

Case 7: A 53-year-old patient undergoes ileocolonoscopy to investigate diarrhea. Bowel prep good. Two 10-mm adenomas resected from sigmoid. Three-year surveillance recommended. Reattends in 3 years and is diagnosed with CRC in ascending colon. *PCCRC–non-interval type A;* **possible missed lesion, prior examination adequate**

Case 8: Patient undergoes screening CTC, prep is good, 15-mm sessile polyp is described in the descending colon. Colonoscopy recommended. Patient does not attend his colonoscopy appointment. Presents 2 years later with rectal bleeding—colonoscopy reveals descending colon CRC. *PICRC–non-interval type B;* **detected lesion, not resected, deviation from planned management pathway**

Case 9: Patient undergoes screening colonoscopy, which diagnoses a 35-mm lateral spreading tumor–non-granular type polyp in transverse colon. The endoscopist removes the lesion piecemeal and recommends follow-up at 3 months. Because of logistical issues (ie, long waiting list) the patient undergoes colonoscopy 10 months later, where cancer is found at the EMR site. *PCCRC–non-interval type B;* **likely incomplete resection of previously identified lesion, deviation from the planned management pathway**

Case 10: An 82-year-old with significant comorbidities undergoes colonoscopy (good prep) for iron deficiency anaemia. A 30-mm lateral spreading tumor–non-granular identified in cecum. Options discussed with patient, who chooses conservative management. Patient presents 3 years later with symptomatic cecal CRC. *PCCRC–non-interval type C;* **detected lesion, not resected**

Case 11: Patient participates in a colonoscopy screening program. Colonoscopy shows no abnormalities (complete but prep is inadequate). A 10-year follow-up advised. One year later patient presents with rectal blood loss. Colonoscopy shows an early depressed carcinoma in the rectosigmoid. *PCCRC-interval type;* **possible missed lesion, prior examination negative but inadequate**

Literature Review

We used the search terms *colorectal cancer AND interval cancer*, *healthcare quality assurance AND colorectal cancer* and *healthcare quality assurance AND colorectal cancer AND interval cancer*. This initial search returned 1030 articles. Abstracts were reviewed and articles that were considered irrelevant were excluded from the library. Several additional key papers that were considered key to the project were added by Working group members during the voting process. This led to a final pool of 401 articles providing background and supporting the statements.

Proposed Checklist for Peer Review of PCCRC/PICRC Papers

		Recommendation
Title and abstract	1	(a) The project's design is indicated with a commonly used term in the title or the abstract (eg, PCCRC, PICRC) (b) An informative and balanced summary of what was done and what was found is provided in the abstract.
Introduction		
Background/rationale	2	The scientific background and rationale for the project is explained.
Objectives	3	Specific objectives, including any prespecified hypotheses, are clearly stated.
Methods		
Study design	4	Key elements of project design (eg, observational study, systematic review) are presented early in the paper
Setting	5	The setting, locations, and relevant timeframes, including periods of recruitment/analysis, follow-up, and data collection are described. Analysis setting (eg, endoscopist or service/unit's level) is clearly defined.
Participants	6	Eligibility criteria and sources and methods of selection of participants are given. Methods of follow-up are described. The rationale for choice of cases and controls—if applicable—is stated. Selection/exclusion of particular patient cohorts (eg, patients with increased CRC risk due to genetic syndromes or inflammatory bowel disease) is described, if applicable.
Variables	7	PCCRC rate calculation method is explained, clearly describing the numerator and denominator used to produce rates. Diagnostic criteria (eg, colonoscopy, CT colonography) are stated.
Data sources/measurement	8	Sources of data (eg, endoscopy reports, screening databases) and details of methods of assessment (eg, unadjusted PCCRC rate, ie, number of PCCRCs divided by the total of the number of PCCRCs plus the number of detected cancers, expressed as a percentage) are given.
Bias	9	Any efforts to address potential sources of bias are described.
Study size	10	Study size and the rationale for it are discussed.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Statistical methods are described (b) Any methods used to examine subgroups and interactions are described (c) Explanation is given on how missing data were addressed (d) If applicable, explain how loss to follow-up and matching of cases and controls was addressed
Results		
Participants	13	(a) Numbers of PCCRC cases analyzed are reported (b) A flow diagram is used
Descriptive data	14	(a) Characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders are given (b) Number of participants with missing data for variable of interest is indicated. (c) If applicable, follow-up time (eg, average and total amount) is reported.
Outcome data	15	Numbers of outcome events (PCCRC/PICRC) over time are reported. The unadjusted PCCRC rate has been calculated based on the date the person had the colonoscopy, with the term *detected cancer* being used to describe cancers diagnosed by the colonoscopy or within 6 months of the date of the colonoscopy, and the term *post-colonoscopy colorectal cancer* used to describe cancers identified beyond 6 months of the date of the colonoscopy; the follow-up period since the last colonoscopy is denoted with a suffix –Ny where N refers to the number of years' follow-up after the last colonoscopy. Any exclusions in the population on which PCCRC is calculated are stated explicitly in the methodology
Main results	16	(a) Give unadjusted estimates and, if applicable, cohort-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which cohorts were adjusted for and why they were included
Other analyses	17	Other analyses done, for example, analyses of subgroups and interactions, and sensitivity analyses, are reported.
Discussion		
Key results	18	Key results with reference to project objectives are summarized.
Limitations	19	Limitations of the study, taking into account sources of potential bias or imprecision are discussed.
Interpretation	20	A cautious overall interpretation of results considering objectives, limitations, results from similar studies, and other relevant evidence is provided.
Generalizability	21	Generalizability (external validity) and value of the project results are discussed.
Other information		
Funding	22	Source of funding and the role of the funders for the present project are stated.

Post-Colonoscopy Colorectal Cancer Rate Calculation Methodological Research

Modest data exist for using a PCCRC rate as a performance measure. Therefore, additional research exploring different methodologies and their correlations with other performance measures is needed. Examples of other calculations include PCCRCs per 100,000 person-years' follow-up, and PCCRCs per 1000 persons diagnosed within a defined time period since the last negative colonoscopy. This method has the advantage that it reflects persons-time at risk, accounts for loss to follow-up, and is in line with the method proposed within the Europe Against Cancer Programme, a standard methodology for describing interval cancers in other screening programmes. This method would typically require linking a defined cohort of subjects with a negative colonoscopy to a comprehensive population-based cancer registry. The *proportionate interval cancer incidence* (also called the proportional incidence method) aims to overcome the challenge of variation in risk factors between cohorts by evaluating interval cancer incidence against the background incidence. This is calculated by dividing the observed number of interval cancers during a given period by the (estimated) cancer incidence expected in the absence of screening during that period. In other screening programs, the proportionate interval cancer incidence has been used to compare sensitivity between different settings, for example, breast cancer screening and fecal occult blood testing. However, its applicability to PCCRCs is not known and further methodological research is required. Ideally, this would be done in a cohort of persons with negative colonoscopy where it can be assumed that quality of colonoscopy was similar across the cohort, where adequate information on demographic, patient and lesion factors is available and that is large enough to be stratified into subgroups according to these factors. Based on such data, the various measures that describe the frequency of PCCRCs could be compared within and between subgroups. This would provide insights regarding their correlation and robustness and the relevance of taking adjustment factors into account when heterogeneous settings are compared.