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TITLE PAGE

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

Short Title:

The WEO Consensus on PCCRC/PICRC.

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Conflicts of Interest:

Roland Valori is joint director of a small Limited Liability Partnership called Quality Solutions for Healthcare which provides advice and support for quality improvement and quality assurance within and outside of endoscopy, mostly in the UK 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.

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Rest of the authors have no conflicts of interest to declare.

Author Contribution:

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.

1. INTRODUCTION

Although colonoscopy is pivotal for the diagnosis and prevention of colorectal cancer (CRC), cancers may 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), i.e. cancers diagnosed after a colonoscopy in which no cancer was found, may 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 pre-cancerous 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 ADRs 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].

2. 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 two terms are not synonymous, as shall be described later, and no standardized performance measure guidelines exist. To address these concerns, the World Endoscopy Organization (WEO) 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 datasets 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
8. To provide a research manuscript checklist for authors and peer-reviewers of PCCRC papers

3. METHODOLOGY

Our methodology was based on The Appraisal of Guidelines for Research and Evaluation (AGREE II) 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
4. Formulate a set of recommendations using a modified Delphi consensus approach

The Core (initial) group consisted of 14 members (13 voting and one non-voting). Members were then allocated to two 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, one 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 dataset 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 & 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 online supplementary material for details) which ultimately provided 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. Prior to 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 GRADE system for rating quality of evidence and strength of recommendations was utilised during statement development (Table 1). The GRADE tool separates the strength of evidence from the strength of recommendation[21].

4. STATEMENTS & EVIDENCE

TERMINOLOGY & DEFINITIONS

Statement 1. We recommend that Post-Colonoscopy Colorectal Cancer (PCCRC) is 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 following 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]. Whilst 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 (QA) 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 pre-cancerous lesion at the prior exam. Furthermore, interval cancers may arise from non-colonoscopic aspects of a screening program (for example after a negative fecal occult blood test). For these reasons, the term "Post-colonoscopy colorectal cancer" (PCCRC), first coined in 2010, is recommended as an all-encompassing, overarching term (see table 2)[9].

PCCRCs can be subcategorized into true interval cancers, i.e. those identified prior to 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 categorisation may aid discussions as to 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 (for example, neuroendocrine tumours, or squamous cell carcinomas of the anorectum) are not included in the PCCRC nomenclature.

QUALITATIVE REVIEW OF PCCRC 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.

Root Cause Analysis (RCA) 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 (i.e. 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 occurs at least annually and includes all prior colonoscopy history for every new CRC case.

Because PCCRCs are relatively infrequent, it is important that the learning from RCA, and potential changes in practice, be shared not only with the relevant endoscopist, but with all colonoscopists in the

service. A proposed RCA 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 (e.g. 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 categorising PCCRCs according to their most plausible explanations, we suggest that the following categories should 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 QA 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 should be used when the following parameters are met (see figure 2):

a. 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, i.e. ≥1cm 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**

b. 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**

c. 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**

d. 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/histological confirmation of complete resection**

e. Most plausible explanation "Likely new cancer"

- **Last colonoscopy > 4 years prior to CRC detection**

In addition to the above five 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 recognise this construct has not been validated, is influenced by the time of observation (e.g. with longer follow-up, a higher percentage of PCCRCs will be designated as new cancers), that certain cases might not fit neatly into one of the 4 categories, and the potential for misclassification. For example, a PCCRC after a colonoscopy 5 years ago that resected an advanced adenoma 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 cut-off[27], although natural history studies of the polyp-to-cancer sequence generally support longer time frames. For example, microsimulation modelling estimated that the mean dwell time (from normal mucosa to cancer) ranges from 10.6 to 25.8 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 is for left-sided series (i.e. 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, whilst being cognisant of the uncertainties of the natural history of the disease.

Whilst arbitrary and undoubtedly imperfect, this definition provides both objectivity and standardization to categorization, aiding QA and comparisons between series.

This 4-year cut-off is used to assign the most plausible etiology. In statement 16, below, a 3-year cut-off 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 online supplementary document.

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

- **Date of colonoscopy**
- **Patient age**
- **Patient sex**
- **Procedure indication (screening, surveillance, symptomatic)**
- **Predisposing risk factors for CRC (e.g. 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 photo-documentation 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, EMR, ESD)**
- **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 dataset 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, EMR, ESD)
- Cecal intubation (including photo-documentation, e.g. at least 2 quality images to document 2 of the 3 landmarks: ileocecal valve, appendiceal orifice, 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 minimise 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 (e.g. flat lesion with depressed component) or in Paris "shorthand" (e.g. 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 nine cardinal colon segments (i.e. cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid colon and rectum).
- Polypectomy details including
    - Polypectomy instrument (snare, biopsy forceps, etc)
    - Use of electrocautery (yes/no; electrocautery machine; settings)
    - Special technique (e.g. EMR, ESD)
    - 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 (i.e. cecal intubation rates[10], ADR or polyp detection rate [14, 18, 31, 32], withdrawal time[33] and associated patient factors (i.e. 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 dataset 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 prior to the episode of care in which CRC was detected**
- **Tumor location**
- **Macroscopic appearance (e.g. 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 NHS Bowel Cancer Screening Program in the UK or the American College of Pathologists[35-37].

The minimum dataset or core data items for colorectal cancer histopathology report are: type of excision, location, tumor size, histological tumor type, histological 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 tumor cells or less. Tumor budding is counted on Hematoxylin-Eosin. The hot spot method (in a field measuring 0.785mm^2 at the invasive front) is recommended[44]. A three-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 CRC[44]. Tumor budding should be taken into account along with other clinicopathological features in a multidisciplinary setting. Tumor budding and tumor grade are not the same[45].

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

Statement 10. We recommend that MSS/MSI status should be assessed on all PCCRC cases either by immunohistochemistry or PCR. 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.

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

Patients with a microsatellite instability-high (MSI-H) phenotype indicates that mismatch repair deficiency in their cancer may be sporadic or have a germline mutation in one of several DNA mismatch repair (*MMR*) 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 NCCN recommend patients with stage IV colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *K-N-RAS* and *BRAF* mutations[43].

QUANTITATIVE ASSESSMENT: PCCRC 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 below.

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 incentivised. 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 one 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, i.e. 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 healthcare 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 may 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%, i.e. 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 routinely be performed 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. Whilst for epidemiological and research purposes, there remains a benefit in performing various analyses of PCCRC-related data, we suggest that for quality assurance purposes, a standardized method to calculate an unadjusted PCCRC rate should be used to permit the benchmarking of services. We recommend that this "unadjusted PCCRC rate" is 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 two published studies have used the same methodology for calculating PCCRC rate. Morris et al 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[19].

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 ago) - in which case the one 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 (e.g. 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" Program" (EACP)[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 online 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" (PCCRC) 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 period of grace 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:

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

It is important to understand that this 3-year cut-off 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 cut-off 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-1 year, PCCRC-5 year and PCCRC-10 year rates should be also calculated, to develop an evidence-base for various time cut-offs.

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

- Identify all people undergoing a colonoscopy in a certain year
- Each **colonoscopy** is labelled 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 one true positive and one 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 one 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 (for example, neuroendocrine tumours, 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 recognised, 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 Computerised 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" (PICRC) 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, timeframe, caseload requirements, sample size, methodology etc. to be aligned as far as possible with colonoscopy. The current focus should be CTC since Barium Enema is essentially a historical examination[66].

Statement 19. Whilst 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 radiological 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-centre audits, with no large-scale series encompassing the routine clinical practice of an entire healthcare system.

Since 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 two 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 dataset for all radiology procedures.

ESSENTIAL:

- **Date of procedure**
- **Type of procedure**
- **Imaging site name / code**
- **Indication for colonic examination**
- **Reason for use of radiological 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 (CAD)**
- **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 (i.e. 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 6mm+ over last 24 months).**

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

Individuals undergoing radiological examination are often selected for imaging on the basis of suitability or otherwise for colonoscopy. The factors that make colonoscopy difficult or impossible (e.g. 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 re-examine the entire imaging dataset in an attempt to determine the underlying reasons for PICRC. We recognize that this may not be possible, e.g. if CTC images have been deleted; nevertheless, such data should still be sought wherever practicable. Missed lesions at CTC (e.g. during diagnostic test accuracy studies) are classified variably in the literature, but a common scheme is (a) technical error (i.e. part of the scanned volume cannot be adequately evaluated, for example due to poor colonic distension, or retained untagged stool); (b) perceptual or reader error (i.e. 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 (c) truly non-diagnosable / "invisible" lesions (i.e. 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 (e.g. too small, or completely flat) and some new lesions (e.g. CRC developing via a rapid carcinogenesis pathway)[78-81]. Ideally, such review should be performed by an experienced, independent CTC radiologist.

5. RESEARCH PRIORITIES

A proposed checklist for peer review of future papers on the topic is available as online supplementary material.

We consider the following list 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 cut-off 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 (e.g. 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 (10mm+) polyps in the calculate of a missed lesion rate be advantageous?
- What information from the pathology report is useful to identify a hig-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 IBD 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?

REFERENCES

1. **Rex DK**, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24-8.
2. **van Rijn JC**, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-50.
3. **Lakoff J**, Paszat LF, Saskin R, et al. Risk of developing proximal versus distal colorectal cancer after a negative colonoscopy: a population-based study. Clin Gastroenterol Hepatol 2008;6:1117-21; quiz 1064.
4. **Bressler B**, Paszat LF, Chen Z, et al. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. Gastroenterology 2007;132:96-102.
5. **Govindarajan A,** Rabeneck L, Yun L, et al. Population-based assessment of the outcomes in patients with postcolonoscopy colorectal cancers. Gut 2015.
6. **Rabeneck L**, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. Clin Gastroenterol.Hepatol. 2010;8:275-279.
7. **Sanduleanu S**, le Clercq CM, Dekker E, et al. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. Gut 2015;64:1257-67.
8. **Leddin D**, Enns R, Hilsden R, et al. Colorectal cancer surveillance after index colonoscopy: guidance from the Canadian Association of Gastroenterology. Can J Gastroenterol 2013;27:224-8.
9. **Rabeneck L**, Paszat LF. Circumstances in which colonoscopy misses cancer. Frontline Gastroenterol 2010;1:52-58.
10. **Baxter NN**, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
11. **Baxter NN**, Sutradhar R, Forbes SS, et al. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology 2011;140:65-72.
12. **Arain MA**, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol 2010;105:1189-95.
13. **Sanduleanu S**, Masclee AM, Meijer GA. Interval cancers after colonoscopy-insights and recommendations. Nat Rev Gastroenterol Hepatol 2012;9:550-4.
14. **Corley DA**, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298-306.
15. **Pohl H**, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144:74-80.e1.
16. **Lieberman DA**, Holub JL, Moravec MD, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. Jama 2008;300:1417-22.
17. **Soetikno RM**, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. Jama 2008;299:1027-35.
18. **Kaminski M**F, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795-803.
19. **Morris EJ,** Rutter MD, Finan PJ, et al. Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. Gut 2015;64:1248-56.
20. **Brouwers MC**, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Cmaj 2010;182:E839-42.

21. **Guyatt GH**, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
22. **Pabby A,** Schoen RE, Weissfeld JL, et al. Analysis of colorectal cancer occurrence during surveillance colonoscopy in the dietary Polyp Prevention Trial. Gastrointest Endosc 2005;61:385-91.
23. **Huang Y**, Gong W, Su B, et al. Risk and Cause of Interval Colorectal Cancer after Colonoscopic Polypectomy. Digestion 2012;86:148-154.
24. **Robertson DJ**, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut 2014;63:949-56.
25. **le Clercq CM**, Bouwens MW, Rondagh EJ, et al. Postcolonoscopy colorectal cancers are preventable: a population-based study. Gut 2014;63:957-63.
26. **le Clercq CM**, Sanduleanu S. Interval colorectal cancers: what and why. Curr Gastroenterol Rep 2014;16:375.
27. **Chen TH,** Yen MF, Lai MS, et al. Evaluation of a selective screening for colorectal carcinoma: the Taiwan Multicenter Cancer Screening (TAMCAS) project. Cancer 1999;86:1116-28.
28. **Kuntz KM,** Lansdorp-Vogelaar I, Rutter CM, et al. A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. Medical decision making : an international journal of the Society for Medical Decision Making 2011;31:530-9.
29. **Brenner H**, Altenhofen L, Katalinic A, et al. Sojourn time of preclinical colorectal cancer by sex and age: estimates from the German national screening colonoscopy database. Am J Epidemiol 2011;174:1140-6.
30. **Kaminski MF**, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. United European Gastroenterol J 2017;5:309-334.
31. **Chiu SY**, Chuang SL, Chen SL, et al. Faecal haemoglobin concentration influences risk prediction of interval cancers resulting from inadequate colonoscopy quality: analysis of the Taiwanese Nationwide Colorectal Cancer Screening Program. Gut 2015.
32. **Baxter NN**, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol 2012;30:2664-9.
33. **Shaukat A**, Rector TS, Church TR, et al. Longer Withdrawal Time Is Associated With a Reduced Incidence of Interval Cancer After Screening Colonoscopy. Gastroenterology 2015;149:952-7.
34. **Singh S**, Singh PP, Murad MH, et al. Prevalence, Risk Factors, and Outcomes of Interval Colorectal Cancers: A Systematic Review and Meta-Analysis. Am J Gastroenterol 2014.
35. Reporting Lesions in the NHS Bowel Cancer Screening Programme: the NHS BCSP Publication 1, 2007.
36. Pathologists RCo. Standards and Datasets for Reporting Cancers — Dataset for Colorectal Cancer Histopathology Reports. 3rd edition, 2014.
37. Pathologists CoA. College of American Pathologists. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum., 2013.
38. AJCC Cancer Staging Manual, Eighth Edition, 2016.
39. **Quirke P,** Risio M, Lambert R, et al. Quality assurance in pathology in colorectal cancer screening and diagnosis-European recommendations. Virchows Arch 2011;458:1-19.
40. **Vieth M**, Quirke P, Lambert R, et al. Annex to Quirke et al. Quality assurance in pathology in colorectal cancer screening and diagnosis: annotations of colorectal lesions. Virchows Arch 2011;458:21-30.

41. **Hamilton SR BF**, Boffetta P, Ilyas M, Morreau H, Nakamura, S-I QP, Riboli E, Sobin LH. Carcinoma of the colon and rectum. IN: Bosman FT, World Health Organization, International Agency for Research on Cancer. editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer, 2010, p134-46:
42. **Koelzer VH**, Zlobec I, Lugli A. Tumor budding in colorectal cancer--ready for diagnostic practice? Hum Pathol 2016;47:4-19.
43. **Benson AB**, 3rd, Venook AP, Cederquist L, et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:370-398.
44. **Koelzer VH**, Zlobec I, Berger MD, et al. Tumor budding in colorectal cancer revisited: results of a multicenter interobserver study. Virchows Arch 2015;466:485-93.
45. **Lugli** et al. Recommendations for reporting tumour budding in colorectal cancer based on the International Tumor Budding Consensus Conference. Virchows Archiv 2016;469-Suppl 1: S172. PS-16-116.
46. **Rubenstein JH**, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology 2015;149:777-82; quiz e16-7.
47. **Giardiello FM**, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: A consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointestinal Endoscopy;80:197-220.
48. **Jover R**, Zapater P, Bujanda L, et al. Endoscopist characteristics that influence the quality of colonoscopy. Endoscopy 2016;48:241-7.
49. **von Karsa L**, Patnick J, Segnan N, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 2013;45:51-9.
50. **Rex DK**, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Am J Gastroenterol 2015;110:72-90.
51. **Lee TJ,** Rutter MD, Blanks RG, et al. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012;61:1050-7.
52. **Kaminski MF**, Wieszczy P, Rupinski M, et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology 2017;153:98-105.
53. **Gotfried J,** Bernstein M, Ehrlich AC, et al. Administrative Database Research Overestimates the Rate of Interval Colon Cancer. J Clin Gastroenterol 2015;49:483-90.
54. **Moss S**, Ancelle-Park R, Brenner H, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Evaluation and interpretation of screening outcomes. Endoscopy 2012;44 Suppl 3:SE49-64.
55. **Sankila R**, et a. Evaluation and monitoring of screening programmes. Europe against cancer programme, 2001.
56. **Bulliard JL**, Sasieni P, Klabunde C, et al. Methodological issues in international comparison of interval breast cancers. Int J Cancer 2006;119:1158-63.
57. **Cairns SR,** Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-89.
58. **Lieberman DA,** Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57.
59. **Annese V**, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 2013;7:982-1018.

60. **Valentin F**, Guarinos C, Juarez M, et al. Endoscopic surveillance in patients with multiple (10-100) colorectal polyps. Endoscopy 2016;48:56-61.
61. **Jover R**, Bretthauer M, Dekker E, et al. Rationale and design of the European Polyp Surveillance (EPoS) trials. Endoscopy 2016.
62. **Castells A**, Andreu M, Binefa G, et al. Postpolypectomy surveillance in patients with adenomas and serrated lesions: a proposal for risk stratification in the context of organized colorectal cancer-screening programs. Endoscopy 2015;47:86-7.
63. **Hassan C**, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842-51.
64. **Sanduleanu S,** Rutter MD. Interval colorectal cancers in inflammatory bowel disease: the grim statistics and true stories. Gastrointest Endosc Clin N Am 2014;24:337-48.
65. **Laine L**, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015;148:639-651.e28.
66. **Halligan S**, Wooldrage K, Dadswell E, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1185-1193.
67. **Atkin W**, Dadswell E, Wooldrage K, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1194-1202.
68. **Badiani S,** Hernandez ST, Karandikar S, et al. CT Colonography to exclude colorectal cancer in symptomatic patients. Eur Radiol 2011;21:2029-38.
69. **Kim DH**, Pooler BD, Weiss JM, et al. Five year colorectal cancer outcomes in a large negative CT colonography screening cohort. Eur Radiol 2012;22:1488-94.
70. **Lung PF,** Burling D, Kallarackel L, et al. Implementation of a new CT colonography service: 5 year experience. Clin Radiol 2014;69:597-605.
71. **Thomas S,** Atchley J, Higginson A. Audit of the introduction of CT colonography for detection of colorectal carcinoma in a non-academic environment and its implications for the national bowel cancer screening programme. Clinical Radiology 2009;64:142-147.
72. **Obaro A PA**, Fanshawe TR, Torres US, Baldwin-Cleland R, Taylor SA, Halligan S, Burling D. Post-imaging colorectal cancer or interval cancer rates after computed tomographic colonography: A systematic review and meta-analysis. The Lancet Gastroenterology and Hepatology [in press] 2017.
73. **Cooper GS**, Xu F, Barnholtz Sloan JS, et al. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer 2012;118:3044-52.
74. **Singh H**, Nugent Z, Demers AA, et al. Rate and predictors of early/missed colorectal cancers after colonoscopy in manitoba: a population-based study. Am J Gastroenterol 2010;105:2588-96.
75. **Taylor SA**, Halligan S, Burling D, et al. CT colonography: effect of experience and training on reader performance. Eur Radiol 2004;14:1025-33.
76. ESGAR CT Colonography Study Group Investigators. Effect of Directed Training on Reader Performance for CT Colonography: Multicenter Study. Radiology 2007;242:152-161.
77. **Plumb AA**, Halligan S, Nickerson C, et al. Use of CT colonography in the English Bowel Cancer Screening Programme. Gut 2014;63:964-73.
78. **Park SH**, Ha HK, Kim MJ, et al. False-negative results at multi-detector row CT colonography: multivariate analysis of causes for missed lesions. Radiology 2005;235:495-502.
79. **Doshi T**, Rusinak D, Halvorsen RA, et al. CT colonography: false-negative interpretations. Radiology 2007;244:165-73.

80. **Slater A,** Taylor SA, Tam E, et al. Reader error during CT colonography: causes and implications for training. Eur Radiol 2006;16:2275-83.
81. **Plumb AA**, Fanshawe TR, Phillips P, et al. Small Polyps at Endoluminal CT Colonography Are Often Seen But Ignored by Radiologists. AJR Am J Roentgenol 2015;205:W424-31.

FIGURE LEGENDS

Figure 1. Consensus voting flowchart

Figure 2. Most plausible PCCRC explanation

TABLE LEGENDS

Table 1. Overview of the GRADE tool.

Table 2. PCCRC Subcategories

Table 3. Root Cause Analysis checklist for PCCRC/PICRCs

Table 4 - Potential Explanations of PCCRC from different studies

Table 5. An illustration of sample sizes required for PCCRC rate calculation