Decision Letter (JCQ-2026-0038)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0038

Body: 15-Nov-2026

Dear Dr Ishihara:

Manuscript ID JCQ-2026-0038 entitled "Optimal Surveillance Colonoscopy Intervals Following Adenoma Removal: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
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2. Click "Author" at the top left of the screen at "Home" page.
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5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

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Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
This is a generally well-written meta-analysis, employing sound methodology, including PRISMA guidelines and risk-of-bias (RoB) assessment. It is logical to expect that increased surveillance frequency would lead to a higher cumulative adenoma detection rate (ADR). However, whether this increase in ADR justifies more frequent surveillance remains debatable, particularly given the absence of a significant difference in the incidence of interval colorectal cancer (CRC), a finding that has been consistently reported in studies evaluating extended surveillance intervals.

The clinical question of whether more-intensive or less-intensive surveillance colonoscopy should be recommended is arguably incomplete without a clearly defined clinical objective. If the intention is simply to demonstrate that more frequent surveillance increases cumulative ADR, the findings of this meta-analysis adequately support that conclusion. However, a more fundamental question remains: what is the clinical value of achieving a higher cumulative ADR if this does not translate into a reduction in interval CRC?

An increase in ADR at the organisational level may lead to more frequent surveillance colonoscopy under current surveillance guidelines. However, in the absence of a demonstrable reduction in interval CRC, it is difficult to establish a logical basis for inferring a subsequent reduction in CRC-specific mortality.

If the clinical question is whether more-intensive or less-intensive surveillance colonoscopy should be recommended to:

Reduce the incidence of CRC; or
Improve overall CRC-related outcomes,

I remain unconvinced that this meta-analysis adequately addresses either question.

Overall, this is a well-written meta-analysis. My recommendation is to refine the clinical question, making its intended objective more specific, and to adjust the conclusions accordingly.

Colonoscopy capacity and resource constraints are also important considerations in any discussion of surveillance strategies. The broader and perhaps more fundamental question is how best to identify individuals who would benefit from colonoscopy to detect advanced adenomas and ultimately prevent CRC, taking into account both diagnostic and surveillance colonoscopy.

The incidence of CRC detected through diagnostic colonoscopy and the yield of surveillance colonoscopy are established, and the findings are relatively clear. Simply increasing surveillance frequency should not necessarily be the best answer. As the authors rightly acknowledge, personalised surveillance intervals may represent the future direction of practice. However, we are clearly not yet at a stage where this can be reliably implemented.

Reviewer: 2

Comments to the Author
This review addresses a relevant question. However, several issues limit the interpretation and clinical application of its findings.

1.Clinical interpretation. Greater cumulative detection of preneoplastic lesions does not establish a clinical benefit from more-intensive surveillance. Additional detection may contribute to cancer prevention, but may also cause overdiagnosis, unnecessary treatment and more-intensive subsequent surveillance. These potential consequences are not adequately evaluated. The recommendation to favour additional examinations is therefore not supported by lesion detection alone. Colorectal cancer incidence and mortality should guide the clinical interpretation, as recommended in the available practice guidelines and expert recommendations (Rutter, Gut 2020; Gupta, Gastroenterology 2020; Hassan, Endoscopy 2020; Rutter, Gastroenterology 2020).

2.Comparability of trials. The review combines studies conducted in substantially different eras of endoscopic technology and quality assurance. Additional examinations in older trials may partly compensate for lesions missed or incompletely removed at baseline. The authors should describe baseline colonoscopy quality, justify pooling and perform sensitivity analyses restricted to trials with quality standards relevant to current practice, where possible. An I^2 of zero does not establish clinical comparability. This issue should also inform the GRADE assessment of indirectness.

3,Consistency with registration. The accessible PROSPERO record lists colorectal cancer and advanced neoplasia as main outcomes, whereas the manuscript designates advanced neoplasia as the sole primary outcome. Several registered outcomes, including mortality, cancer stage and adherence, are not presented or individually accounted for. Differences in subgroup and sensitivity analyses also require explanation, with dates and reasons for amendments.

4.Extraction and synthesis. Replacing the weighted EPoS II estimates with crude event proportions requires justification and sensitivity analyses addressing missing outcome data. The analysis populations and denominators must also be traceable for every trial. For example, the National Polyp Study randomized 699 and 719 participants, whereas the plots use 338 and 428. The follow-up periods assigned to the Danish comparisons also require verification.

6.Figures and reporting. The direction-of-benefit labels in Figure 2 are reversed: a negative risk

difference, calculated as more-intensive minus less-intensive surveillance, favours more-intensive surveillance for colorectal cancer incidence. The supplementary search strategies, study flow, RoB 2 assessments and GRADE explanations were unavailable in the review materials. Finally, the PRISMA entries marking excluded studies and protocol amendments as “not applicable” require correction or clarification.

Date Sent: 15-Nov-2026

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Author's Response to Decision Letter for (JCQ-2026-0038)

Optimal Surveillance Colonoscopy Intervals Following Adenoma Removal: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Dear Editor and Reviewers,
Thank you for your careful evaluation of our manuscript and for your constructive comments. We have revised the manuscript to clarify the clinical interpretation, methodological limitations, and reporting of the review. Our point-by-point responses are provided below.

Reviewer 1
This is a generally well-written meta-analysis, employing sound methodology, including PRISMA guidelines and risk-of-bias (RoB) assessment. It is logical to expect that increased surveillance frequency would lead to a higher cumulative adenoma detection rate (ADR). However, whether this increase in ADR justifies more frequent surveillance remains debatable, particularly given the absence of a significant difference in the incidence of interval colorectal cancer (CRC), a finding that has been consistently reported in studies evaluating extended surveillance intervals.
The clinical question of whether more-intensive or less-intensive surveillance colonoscopy should be recommended is arguably incomplete without a clearly defined clinical objective. If the intention is simply to demonstrate that more frequent surveillance increases cumulative ADR, the findings of this meta-analysis adequately support that conclusion. However, a more fundamental question remains: what is the clinical value of achieving a higher cumulative ADR if this does not translate into a reduction in interval CRC?
An increase in ADR at the organisational level may lead to more frequent surveillance colonoscopy under current surveillance guidelines. However, in the absence of a demonstrable reduction in interval CRC, it is difficult to establish a logical basis for inferring a subsequent reduction in CRC-specific mortality.
If the clinical question is whether more-intensive or less-intensive surveillance colonoscopy should be recommended to:
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Overall, this is a well-written meta-analysis. My recommendation is to refine the clinical question, making its intended objective more specific, and to adjust the conclusions accordingly.
Colonoscopy capacity and resource constraints are also important considerations in any discussion of surveillance strategies. The broader and perhaps more fundamental question is how best to identify individuals who would benefit from colonoscopy to detect advanced adenomas and ultimately prevent CRC, taking into account both diagnostic and surveillance colonoscopy.
The incidence of CRC detected through diagnostic colonoscopy and the yield of surveillance colonoscopy are established, and the findings are relatively clear. Simply increasing surveillance frequency should not necessarily be the best answer. As the authors rightly acknowledge, personalised surveillance intervals may represent the future direction of practice. However, we are clearly not yet at a stage where this can be reliably implemented.
Response: Thank you for your thoughtful comments and for recognizing the methodological strengths of this meta-analysis. We agree that surveillance should ultimately prevent colorectal cancer (CRC) and improve patient outcomes, rather than simply increase lesion detection. We retained the original Clinical Question because it addresses the practical choice between surveillance strategies. CRC incidence and advanced colorectal neoplasia were evaluated as primary outcomes, with adenoma detection and serious adverse events as secondary outcomes. Restricting the question to CRC prevention alone would omit clinically relevant information about lesion detection and procedural safety.
Advanced colorectal neoplasia is a clinically relevant precursor-lesion outcome, although greater detection does not establish a preventive benefit. More-intensive surveillance increased cumulative detection, but the advanced-neoplasia finding was not robust to exclusion of EPoS II. The revised Discussion distinguishes cumulative detection from per-examination yield.
The pooled CRC incidence did not differ significantly between strategies (RD, −0.03 percentage points; 95% CI, −0.23 to 0.17). Neither equivalence nor a mortality benefit can be inferred. We revised the Clinical Question Box, Abstract, and Conclusions to explicitly acknowledge the absence of a demonstrated reduction in CRC incidence. We also expanded the Discussion to address procedural burden, potential overdiagnosis, unnecessary treatment, subsequent surveillance, and endoscopy capacity. The relative allocation of diagnostic and surveillance colonoscopy was beyond the scope of the review. We agree that a validated individualized surveillance algorithm remains unavailable. The revised Discussion qualifies the interpretation of specific schedules and emphasizes baseline neoplasia risk and colonoscopy quality, without advocating uniformly shorter intervals. (Page 3, Lines 26–33; Page 15, Lines 262–276).

Reviewer 2
This review addresses a relevant question. However, several issues limit the interpretation and clinical application of its findings.

Comment 1
Clinical interpretation. Greater cumulative detection of preneoplastic lesions does not establish a clinical benefit from more-intensive surveillance. Additional detection may contribute to cancer prevention, but may also cause overdiagnosis, unnecessary treatment and more-intensive subsequent surveillance. These potential consequences are not adequately evaluated. The recommendation to favour additional examinations is therefore not supported by lesion detection alone. Colorectal cancer incidence and mortality should guide the clinical interpretation, as recommended in the available practice guidelines and expert recommendations (Rutter, Gut 2020; Gupta, Gastroenterology 2020; Hassan, Endoscopy 2020; Rutter, Gastroenterology 2020).
Response: Thank you for this important comment. The revised Discussion distinguishes increased lesion detection from clinical benefit and addresses procedural burden, potential overdiagnosis, unnecessary treatment, and subsequent surveillance. Neither CRC prevention, a mortality benefit, nor equivalent procedural safety has been established.
The revised interpretation emphasizes baseline risk and colonoscopy quality, consistent with the guidelines cited in References 3, 6, and 7. The Conclusions explicitly acknowledge that reduced CRC incidence has not been demonstrated. (Page 15, Lines 269–276).

Comment 2
Comparability of trials. The review combines studies conducted in substantially different eras of endoscopic technology and quality assurance. Additional examinations in older trials may partly compensate for lesions missed or incompletely removed at baseline. The authors should describe baseline colonoscopy quality, justify pooling and perform sensitivity analyses restricted to trials with quality standards relevant to current practice, where possible. An I^2 of zero does not establish clinical comparability. This issue should also inform the GRADE assessment of indirectness.
Response: Thank you for highlighting this issue. Pooling was based on the common randomized comparison of surveillance intensity after adenoma removal. Differences in baseline clearance, examination quality, and surveillance schedules limit clinical comparability despite an I^2 of 0%. A sensitivity analysis restricted to contemporary colonoscopy quality standards was not feasible because comparable quality indicators were unavailable. EPoS II (Jover et al., N Engl J Med. 2026;395:1051–1061; Reference 11) required high-quality baseline colonoscopy and demonstrated noninferiority of 5-year versus 3-year initiation for CRC incidence at interim assessment, within the prespecified 0.7-percentage-point margin. Differences in lesion definitions and baseline colonoscopy quality informed the GRADE downgrade for indirectness for advanced colorectal neoplasia. (Page 13, Lines 223–227).

Comment 3
Consistency with registration. The accessible PROSPERO record lists colorectal cancer and advanced neoplasia as main outcomes, whereas the manuscript designates advanced neoplasia as the sole primary outcome. Several registered outcomes, including mortality, cancer stage and adherence, are not presented or individually accounted for. Differences in subgroup and sensitivity analyses also require explanation, with dates and reasons for amendments.
Response: Thank you for identifying this discrepancy. CRC incidence and advanced colorectal neoplasia are now designated as primary outcomes, consistent with PROSPERO (CRD420261530836). Advanced adenoma data are included in the advanced-neoplasia synthesis. Following a change in the systematic review personnel, analyses were adapted to data availability. Mortality was not pooled because comparable data were insufficient; cancer stage because events were sparse and reporting inconsistent; and adherence because definitions and schedules differed. The planned subgroup and sensitivity analyses were adapted to the available data, yielding follow-up-duration subgroups and a sensitivity analysis excluding EPoS II. Exact amendment dates could not be established from the available records. (Page 9, Lines 135–139).

Comment 4
Extraction and synthesis. Replacing the weighted EPoS II estimates with crude event proportions requires justification and sensitivity analyses addressing missing outcome data. The analysis populations and denominators must also be traceable for every trial. For example, the National Polyp Study randomized 699 and 719 participants, whereas the plots use 338 and 428. The follow-up periods assigned to the Danish comparisons also require verification.
Response: Thank you for this methodological comment. Observed event counts were used to derive comparable unadjusted effects across trials, because adjusted cumulative incidences were not consistently available. This approach does not correct for missing outcome data. In EPoS II, advanced adenoma cumulative incidences were 14.55% versus 11.07% with IPW and 10.82% versus 10.66% in the intention-to-treat analysis with censoring. Excluding EPoS II yielded an RR of 0.89 (95% CI, 0.62–1.28). This assesses trial influence, not missing-data bias; a harmonized missing-data analysis was not feasible with aggregate data. The outcome-specific denominators were 338/428 in the National Polyp Study (699/719 randomized; completed examinations, Table 6; CRC counts, Table 3), 701/763 in the Japan Polyp Study (1,087/1,079 randomized; per-protocol, Table 2), 164/172 in Lieberman et al. (300/294 randomized; protocol-adherent population), and 5,397/5,389 in EPoS II (5,401/5,398 randomized; 13 excluded for missing age, Table 2).
For Kronborg et al. (1983), the 4-year assessment was selected to harmonize follow-up horizons. For Kronborg et al. (2006), the A/B and E/F cohorts contributed 48-month data (Tables II and IV); Table 1 reports mean observation times of 8.8, 10.3, and 5.2 years, calculated from person-years. All three cohorts were combined for serious adverse events (7/475 versus 3/469; Table VII). Advanced adenomas and advanced neoplasia, and adenomas and broader neoplastic lesions, were pooled as clinically related outcomes using trial-specific definitions. The Discussion acknowledges definition differences and selection bias. (Page 10, Lines 156–160).

Comment 5
Figures and reporting. The direction-of-benefit labels in Figure 2 are reversed: a negative risk difference, calculated as more-intensive minus less-intensive surveillance, favours more-intensive surveillance for colorectal cancer incidence. The supplementary search strategies, study flow, RoB 2 assessments and GRADE explanations were unavailable in the review materials. Finally, the PRISMA entries marking excluded studies and protocol amendments as "not applicable" require correction or clarification.
Response: Thank you for identifying these issues. Figure 2 has been corrected so that negative risk differences favor more-intensive surveillance. Direction labels across Figures 1–4 are now consistent with their respective outcomes; effect estimates are unchanged. We apologize that the Supplement was unavailable during review. It includes search strategies (Table S1), subgroup and sensitivity analyses (Table S2; Figure S2), GRADE assessments (Table S3), study selection (Figure S1), and RoB 2 assessments (Figures S3–S6). The manuscript now specifies downgrading for indirectness (advanced neoplasia), imprecision (CRC), and inconsistency and imprecision (serious adverse events). Adenoma detection was not downgraded. For PRISMA Item 16b, Figure S1 reports reasons for all 83 full-text exclusions in aggregate, rather than individual citations. For Item 24c, the analytical deviations are explained in our response to Comment 3. (Figure 2, Page 24; Supplementary Appendix).

We sincerely thank both reviewers for their constructive comments, which have helped improve the clinical interpretation and transparency of our manuscript.

Sincerely,
Masashi Ishihara.

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