

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Interventions to improve early cancer diagnosis of symptomatic individuals: A scoping review
AUTHORS	Okoli, George; Lam, Otto; Reddy, Viraj; Copstein, Leslie; Askin, Nicole; Prashad, Anubha; Stiff, Jennifer; Khare, Satya Rashi; Leonard, Robyn; Zarin, Wasifa; Tricco, Andrea; Abou-Setta, Ahmed

VERSION 1 – REVIEW

REVIEWER	Jenniskens, Kevin Universitair Medisch Centrum Utrecht, Julius Center
REVIEW RETURNED	11-Aug-2021

GENERAL COMMENTS	<p>Comments for the authors</p> <p>With great interest I've read your manuscript on interventions for early diagnosis of cancer in symptomatic patients. I think in the time of Covid-19 related delays of standard care, identifying methods that aid in early detection of cancer is more important than ever. I would like to commend the authors with the tremendous amount of work they have done, and the extensive overview of a substantial number of papers (>100) on this subject. Although I've read your report with great interest, I think it could still benefit from some adjustments and additions. You can find my proposed comments in the sections below</p> <p>Major comments</p> <ul style="list-style-type: none">• My main concern for this paper is that you describe different interventions, and describe their results with regard to the effectiveness parameters the authors assessed. However, to ensure that effectiveness estimates are reliable, a proper risk of bias assessment and GRADE summarization of evidence is required to be able to draw conclusions with regard to this. Given that there are numerous included studies with study designs such as case control, and cross sectional, there may be a high risk of bias, preventing any reliable estimates on effectiveness of interventions to be made. You mention this yourselves in the last paragraph before the conclusions. Yet in the body of the text you suggest that we can distinguish those that are effective from those that aren't based on what the authors conclude (e.g. from the abstract: Common themes among the effective interventions were multidisciplinary collaboration and the use of a nurse navigator). Refrain from drawing conclusions on effectiveness, or frame it in
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	<p>such a way that you will consider effectiveness based solely on the author conclusions of the primary papers themselves.</p> <ul style="list-style-type: none"> • Title: I would state more clearly that you focus on providing an overview of interventions for early cancer diagnosis. Now it only becomes apparent from the abstract • I miss some sort of quality appraisal of the included studies. I reckon that a QUADAS or Cochrane ROB assessment is too much, but perhaps you can consider alternatives? We have recently published a paper in which we use a 'light' version based on the known risk of bias tools (Jenniskens, 2021, Effectiveness of contact tracing apps for SARS-CoV-2, Supplementary file 2). Perhaps you could consider this for your paper as well. • What are the settings you focus on? Are they limited to the GP, or does this also include interventions at secondary and/or tertiary care settings? • Introduction: What I miss a bit is the urgency of this scoping review. You provide a list of options in for early cancer diagnosis, then why do this review at all? You are not providing an assessment and meta-analysis of their effectiveness. <p>Minor comments</p> <ul style="list-style-type: none"> • Abstract: please provide some information on in-exclusion criteria of the types of studies you are including (experimental observational prospective case control etc) • Introduction: see if you can incorporate a concrete research question that you try to address in this review. There are bits and pieces in the last section, but one clear sentence can really help the reader narrow down what your focus area is. • Introduction: please provide references for Interventions such as centralized or coordinated diagnostic services, multidisciplinary team development and support, patient navigational strategies and referral pathways, service targets or benchmarks for wait times, and technology to support diagnosis have been implemented with varying levels of success.” • Methods: the four goals described in the methods section seem very specific and related to the project that this paper was a product of. They seem to come out of nowhere and are very specific (within Canada and abroad). Try making these more concise and don't refer to these as the review questions, but rather the elements that you planned to extract data on. • Flowchart: split up the 104 included studies in published and grey literature, so that the numbers correspond with the numbers in the text • Appendix 1: You mention the use of an appropriate risk of bias tool according to the papers that you find, but you did not use such a tool in this paper
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REVIEWER	Kuodi, Paul Lira University, Department of Public Health, Faculty of Health Sciences
REVIEW RETURNED	21-Aug-2021

GENERAL COMMENTS	I commend the reviewers for undertaking the important task of synthesizing data on initiatives to improve early cancer diagnosis. The generated information has potential to provide user-friendly
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	<p>evidence summary for health policy-makers, cancer program managers, oncologists, cancer program implementers among other stakeholders, and for informing further efforts aimed at improving timely cancer diagnosis as well as identifying gaps for future research.</p> <p>The methodology for the research is well documented and follows standard guidelines for the conduct of a scoping review. The procedures were carried out in accordance with a priori review plan that is replicable. The reporting also follows recommended documentation format.</p> <p>However, a few issues have been identified which have important repercussions on the results and usability of the scoping review findings. The last three review questions need streamlining to avoid inclusion of studies that do not address the main objective of the review. Many studies that do not necessarily report initiatives for timely cancer diagnosis were included in the review because they reported results that were useful in answering review question 2, 3 and 4. The inclusion of irrelevant studies in the synthesis of data has made making meaningful conclusions from the review difficult.</p> <p>The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. My main concern for this paper is that you describe different interventions, and describe their results with regard to the effectiveness parameters the authors assessed. However, to ensure that effectiveness estimates are reliable, a proper risk of bias assessment and GRADE summarization of evidence is required to be able to draw conclusions with regard to this. Given that there are numerous included studies with study designs such as case control, and cross sectional, there may be a high risk of bias, preventing any reliable estimates on effectiveness of interventions to be made. You mention this yourselves in the last paragraph before the conclusions. Yet in the body of the text you suggest that we can distinguish those that are effective from those that aren't based on what the authors conclude (e.g. from the abstract: Common themes among the effective interventions were multidisciplinary collaboration and the use of a nurse navigator). Refrain from drawing conclusions on effectiveness, or frame it in such a way that you will consider effectiveness based solely on the author conclusions of the primary papers themselves.

Our response: Thank you for your observation and suggestions. We agree that systematic reviews of efficacy/ effectiveness should properly conduct risk of bias assessment and GRADE the quality of the evidence prior to making conclusions. Having said that, as our intent was to conduct a scoping, rather than systematic, review we do not believe these assessments are possible within this study design. We summarized the author-defined effectiveness of interventions, and organized interventions with similar themes across the effective and ineffective studies. To clarify this in the manuscript, we have revised the abstract (line 103, methods (line 308) and conclusions (line 671).

2. Title: I would state more clearly that you focus on providing an overview of interventions for early cancer diagnosis. Now it only becomes apparent from the abstract

Our response: Thank you for the suggestion. We have revised accordingly.

3. I miss some sort of quality appraisal of the included studies. I reckon that a QUADAS or Cochrane ROB assessment is too much, but perhaps you can consider alternatives? We have recently published a paper in which we use a 'light' version based on the known risk of bias tools (Jenniskens, 2021, Effectiveness of contact tracing apps for SARS-CoV-2, Supplementary file 2). Perhaps you could consider this for your paper as well.

Our response: Thank you for the suggestion. Your paper was an interesting read and a good reference for use in some of our upcoming rapid evidence syntheses. In line with the JBI's guidance for the conduct of scoping reviews, study quality or the risk of bias assessments was not undertaken. Having said that, we do agree that any full systematic review of the effectiveness of interventions should conduct risk of bias assessments.

4. What are the settings you focus on? Are they limited to the GP, or does this also include interventions at secondary and/or tertiary care settings?

Our response: Thank you for pointing this out. We have added a statement to clarify that this review focused on interventions in any clinical setting – "Study participants were individuals of any age presenting in any clinical settings with symptoms" (line 227).

5. Introduction: What I miss a bit is the urgency of this scoping review. You provide a list of options in for early cancer diagnosis, then why do this review at all? You are not providing an assessment and meta-analysis of their effectiveness.

Our response: While we agree in the benefit of conducting meta-analyses of interventions in a systematic review, the scoping review methodology does not lend itself to quantitative pooling of study results. Instead, we summarized the literature to determine the extent and characteristics of the available interventions and how their implementation and how successful the interventions might have been, as per recognized standards to conducting scoping reviews. That said, we agree with making this point clearer and have revised the introduction to address the concern raised (lines 167 to 171).

6. Abstract: please provide some information on in-exclusion criteria of the types of studies you are including (experimental observational prospective case control etc)

Our response: We have added this information – "Published and unpublished literature (grey literature) of any study type in the English language were searched for from January 2017 to January 2021" (lines 81 to 83).

7. Introduction: see if you can incorporate a concrete research question that you try to address in this review. There are bits and pieces in the last section, but one clear sentence can really help the reader narrow down what your focus area is.

Our response: Thank you for this suggestion. We have revised the introduction to reflect this suggestion (lines 169 to 171).

8. Introduction: please provide references for Interventions such as centralized or coordinated diagnostic services, multidisciplinary team development and support, patient navigational strategies and referral

pathways, service targets or benchmarks for wait times, and technology to support diagnosis have been implemented with varying levels of success.”

Our response: We have deleted this list as it a classification that will later be introduced in the results section.

9. Methods: the four goals described in the methods section seem very specific and related to the project that this paper was a product of. They seem to come out of nowhere and are very specific (within Canada and abroad). Try making these more concise and don't refer to these as the review questions, but rather the elements that you planned to extract data on.

Our response: We have revised the methods to reflect the suggestions (lines 216 to 223).

10. Flowchart: split up the 104 included studies in published and grey literature, so that the numbers correspond with the numbers in the text

Our response: We have done as suggested. Thank you!

11. Appendix 1: You mention the use of an appropriate risk of bias tool according to the papers that you find, but you did not use such a tool in this paper

Our response: Thank you for highlighting this oversight. We have deleted this statement from appendix 1.

Reviewer 2

1. Title: See comment on the annotated draft

Our response: Thank you for the suggested title. We have revised the title according.

2. Pg. 10 (line 192-201): This seems to be the main review question for this study. These questions (2, 3 4) are broad and do not appear to be subset questions of the main review question and should be focussed accordingly in line with the main question. (Included studies considered under these questions should first meet the condition for the main review question, - i.e., they should report initiatives/care pathways, or interventions aimed at improving timely cancer diagnosis). As is currently reported by the reviewers, these questions appear to be stand alone review questions. Attempting to answer several review questions in a single study is a feat that is likely to end in futility rendering the resulting synthesised information not usable.

Our response: Thank you for the comments. We did not specify primary or secondary questions for the review. We would like to clarify that the entire questions were the focus of our review and, as such, any published or unpublished articles reporting data on any of the questions were included. We have however revised the statements and we hope this provides the clarity needed (lines 216 to 223).

3. Pg. 14- 16 – Initiatives to enhance accurate and timely cancer diagnosis: The reviewers have described very interesting initiatives to improve timely cancer diagnosis. I draw the attention of the reviewers, to the 2017 World Health Organisation “GUIDE TO CANCER EARLY DIAGNOSIS”. Accordingly, potential interventions to strengthen early cancer diagnosis falls in 3 broad categories; 1. Interventions to raise awareness and accessing cancer care; 2. Interventions to strengthen clinical evaluation, diagnosis and staging of cancer; 3. Interventions to strengthen access to cancer treatment;

Using the WHO guideline, the reviewers can make the scoping review data better by categorising the reported interventions by included studies into the three categories.

Our response: Thank you for the suggested categorization, which is one of a few available categorizations on the topic. This categorization has elements that are out of scope of this review. For example, interventions to raise awareness are part of the patient interval (prior to presentation) which was not a focus of our review. For consistency with previous work, we utilized the categorization that was used for the previous report by the Partnership (reference 9).

4. After categorising initiatives to improve timely cancer diagnosis, the reviewers should single out from among the described interventions those interventions they deem as innovative stating reasons for classifying these innovations as innovative. Reviewers should identify the performance metric to measure improvements only from among the studies describing initiatives to enhance accurate and timely cancer diagnosis above. Reviewers should identify the specific considerations for underserved populations only from among the studies describing initiatives to enhance accurate and timely cancer diagnosis above.

Our response: This review did not seek to specify innovative interventions; rather, it sought to provide an overview on the available interventions. As such, we would like to refrain from singling out from among the described interventions, those interventions that we may deem as innovative. Secondly, we would like to clarify that we identified the performance metrics to measure improvements, and we identified the specific considerations for underserved populations from among the included studies. For studies to be included in this review, they must have reported on an initiative to enhance accurate and timely cancer diagnosis as established in our methods.

5. Pg. 39-48; Pg. 67-70 – Effective interventions & Ineffective interventions: The two tables of results reporting effective and ineffective interventions are equally important, therefore they should all be reported on the body of the article. Accordingly, table of ineffective interventions should not be placed as an appendix. On concerns on the length of the 2 tables; Included studies should only be studies reporting initiatives to improve timely diagnosis of cancer. This approach will significantly cut down on the number of studies meeting the review's inclusion criteria. In addition, the approach will improve the precision and usefulness of the scoping review results.

Our response: Thank you for this observation and the suggestions. We agree that the two tables of results reporting effective and ineffective interventions are equally important; therefore, should be reported in the body of the article. However, due to the limit on the number of tables/figures, we made the difficult choice to move the smaller table (for ineffective interventions) to the appendices, which are still easily accessible to the reader. We believe that limiting studies included in the tables to only certain studies may introduce a form of reporting bias.

6. Pg. 25-28 – Discussion, limitations, conclusions: The discussion should be focussed on the review question and its sub set questions. The discussion should be streamlined in accordance with the proposed revisions and recommendations.

Our response: We agree with this comment and believe our discussion section is aligned with our review questions. That said, we welcome any specific suggestions with regards to improving the quality and readability of the discussion, limitations and conclusions sections.

VERSION 2 – REVIEW

REVIEWER	Jenniskens, Kevin Universitair Medisch Centrum Utrecht, Julius Center
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	<p>I would like to thank that authors and complement them with the nice revisions to their manuscript. Most of the points I made have been addressed very good, and I am happy with teh changes they made.</p> <p>Although I am mostly in accordance with the changes they have provided to the manuscript, I would like to make a final suggestion. My main point of commentary was with regard to conclusions on effectiveness of these interventions identified in the scoping review. Although the authors have included a short phrase in the methods section on this ("Effectiveness of an intervention was author-defined.") and state the conclusion was slightly changed, I still feel it is not properly addressed in the rest of the paper. I would recommend expanding a bit on this sentence in the methods section, and assessing it as a limitation in the discussion section.</p> <p>Some motivation on why I keep hammering on this: My main 'fear' would be that readers look at your paper and conclude that certain measures work better than others, which you can't conclude from a scoping review without providing proper RoB assessment or even GRADE. It is an excellent starting point, which is why I think the paper is an important piece of evidence that is worth publishing, but I would like to nuance any statements made on the effectiveness of any intervention a bit more.</p>
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REVIEWER	Kuodi, Paul Lira University, Department of Public Health, Faculty of Health Sciences
REVIEW RETURNED	14-Oct-2021

GENERAL COMMENTS	<p>The authors have satisfactorily addressed the comments raised on the manuscript.</p> <p>One last concern that needs to be addressed.</p> <p>The scoping review was conducted at the height of COVID-19 pandemic. The impact of COVID-19 on timely diagnosis of symptomatic cancer is not discussed in the manuscript. It is important to add this element to the discussion section considering studies published within the review period have been affected by the pandemic. Furthermore, the review findings are a continue of work from a past published review therefore the need to show how the pandemic has impacted the current results compared to past published findings.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1

1. "I would like to thank that authors and complement them with the nice revisions to their manuscript. Most of the points I made have been addressed very good, and I am happy with the changes they made. Although I am mostly in accordance with the changes they have provided to the manuscript, I would like to make a final suggestion. My main point of commentary was with regard to conclusions on effectiveness of these interventions identified in the scoping review. Although the authors have included a short phrase in the methods section on this ("Effectiveness of an intervention was author-defined.") and state the conclusion was slightly changed, I still feel it is not properly addressed in the rest of the paper. I would recommend expanding a bit on this sentence in the methods section, and assessing it as a limitation in the discussion section. Some motivation on why I keep hammering on this: My main 'fear' would be that readers look at your paper and conclude that certain measures work better than others, which you can't conclude from a scoping review without providing proper RoB assessment or even GRADE. It is an excellent starting point, which is why I think the paper is an important piece of evidence that is worth publishing, but I would like to nuance any statements made on the effectiveness of any intervention a bit more."

Our response: Thank you so much for the feedback. We completely agree with you and have addressed the concern raised regarding our summary on effectiveness of interventions. In the methods section, we provided more clarity on how effectiveness was determined (lines 225 to 231) and discussed associated limitations in the discussion (lines 585 to 598).

Reviewer 2

1. The authors have satisfactorily addressed the comments raised on the manuscript. One last concern that needs to be addressed. The scoping review was conducted at the height of COVID-19 pandemic. The impact of COVID-19 on timely diagnosis of symptomatic cancer is not discussed in the manuscript. It is important to add this element to the discussion section considering studies published within the review period have been affected by the pandemic. Furthermore, the review findings are a continue of work from a past published review therefore the need to show how the pandemic has impacted the current results compared to past published findings.

Our response: Thank you very much for the feedback. We totally agree with the suggestion to compare our findings with the findings from the previous review on the same topic and we have now done so (lines 543 to 551). We have also added a bit on the impact of COVID-19 on timely diagnosis of symptomatic cancer in the discussion (lines 551 to 560).