

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)	Risk factors for emergency presentation with lung and colorectal cancers: a systematic review.
AUTHORS	Mitchell, Elizabeth; Pickwell-Smith, Benjamin; Macleod, Una

VERSION 1 - REVIEW

REVIEWER	Hubbard, Richard University of Nottingham – UK I carry out research into the patient pathway for people with Lung Cancer
REVIEW RETURNED	04-Dec-2014

GENERAL COMMENTS	<p>Actually i enjoyed this paper - and whilst the findings are not unexpected (as the authors themselves confirm) for me this is a solid and useful addition to the Evidence base.</p> <p>I have no issues with the methodology and it does not surprise me that there was so much heterogeneity - perhaps it would be worth subgrouping the studies a bit according to methodology and/or perhaps country</p> <p>The search terms are the in the appendix - and i suspect this reflects the complexity - it would be nice of some more details of these were in the methods</p> <p>Finally i would perhaps emphasise that although earlier diagnosis may not ultimately improve survival it is transformative to the patient experience - particularly in lung cancer where the prognosis is so awful</p>
-------------------------	--

REVIEWER	Alan Askari St. Mark's Hospital, Imperial College London, United Kingdom
REVIEW RETURNED	05-Dec-2014

GENERAL COMMENTS	<p>Thank you for the opportunity to review this paper. I congratulate the authors on a well written manuscript.</p> <p>This study is a systematic review investigating causal or contributing factors of emergency presentation in Colorectal and Lung cancer. The authors have defined emergency presentation clearly and have clear outcomes.</p> <p>The methodology is sound, with a clear search strategy. Appropriate</p>
-------------------------	--

	<p>checklists have been used to ascertain study quality (such as the Newcastle-Ottawa scale) and PRISMA guidelines have been followed.</p> <p>The discussion is well balanced and a reasoned explanation is given for the findings of the studies.</p> <p>I have the following comments:</p> <ul style="list-style-type: none"> - Search limited to 1996-2014: is there a reason for this? If so, it should be reported. - Have the authors considered ethnicity as a contributing factor? There is evidence in the literature to suggest that certain ethnic groups are at higher risk of being diagnosed during an emergency presentation. In Colorectal Cancer, certain ethnicities engage less with screening services as well as further investigations (flexible sigmoidoscopy and colonoscopy) as such invasive investigation are culturally less acceptable. - Article summary: The authors state: 'This review has for the first time synthesised available evidence'. This is inaccurate, technically, data synthesis has not taken place, data synthesis is essentially a Meta Analysis. In this study, the OR has been reported but there has not been any synthesis of new data from the published studies. This term should be removed as it may mislead the reader. - Strengths & Limitations Page 12 Line 21: The authors state that 'No randomised controlled trials were identified'. Whilst this is a fair statement to make when carrying out reviews, in the context of emergency presentation, it is unsurprising and essentially impossible to do. Also, there is once again reference to 'synthesis' of data ('definitive synthesis'). A definitive synthesis would be a Meta Analysis and Meta Regression of appropriate variables to control all confounders that may contribute to emergency presentation. By the authors own admission, this has been impossible to do. <p>Overall, the manuscript requires minor changes before suitability for publication.</p>
--	---

REVIEWER	Ryan Courtney University of New South Wales, National Drug and Alcohol Research Centre, Australia
REVIEW RETURNED	09-Dec-2014

GENERAL COMMENTS	<p>This manuscript has potential but the "quality" grading system is questionable, and at least, requires a lot more explanation and justification in the method section.</p> <p>There are a number of quality grading tools available but little to no justification is given on why the unnamed tool used in references 8 and 9 was selected. The grading system is very limited in the methodological properties that it does assess. It needs justification, and if used its limitations and strengths compared to other existing tools should be critiqued in the method or discussions section.</p> <p>Further, the grading of evidence by methodological quality is not articulated in the abstract and should also be included in the</p>
-------------------------	---

	<p>introduction to guide the reader. I see no real benefit of including studies in the systematic review that demonstrated “low” strength of evidence and they should be excluded from further review, once graded.</p> <p>Abstract – Insert “To” before “identify”</p> <p>Why was the time period 1996-2004 (18 year period) chosen? Justification needed.</p> <p>Introduction – While the relationship between presentation route and survival is discussed there is no mention of the relationship between staging of disease and presentation route. This should be articulated in this section.</p> <p>Detail on the grading of evidence and measurement tool used should be included in the introduction. It would be of benefit to the reader if the existing literature was critiqued, in relation to previous attempts to grade evidence related to delay in diagnosis or treatment (irrespective of route of clinical presentation).</p> <p>Conclusions – first sentence after “there” needs to be deleted from text.</p> <p>For the most part, this manuscript is important and does provide further evidence on emergency presentation for colorectal cancer and lung cancer. The grading of evidence section however requires substantial improvements and further justification.</p>
--	--

REVIEWER	Lindsay Forbes King's College London, UK
REVIEW RETURNED	10-Dec-2014

GENERAL COMMENTS	<p>Thank you for asking me to review this important and interesting systematic review. I have no concerns about the robustness of the methods, although I have several comments about the reporting that I hope may contribute to improving it. When ticking the boxes above I felt that answering ‘no’ where I have done so was a little over-harsh, because this is a robust review - but this does highlight the areas that I think could be improved.</p> <p>Reporting of methods and results</p> <p>In the methods, both in the abstract and the main text, it would be helpful to set out the research questions more clearly and all elements of the PICOS/PECOS.</p> <p>The ‘Population’ was not clearly described in the abstract – ‘individuals or groups of patients or primary care practitioners’ – I didn’t understand that at all – all patients? At first reading I thought the authors were examining risk factors for emergency presentation among primary care practitioners.</p> <p>The authors said they included studies of any design, however, it is not clear whether they included, for example, qualitative studies or single case reports. The results suggest not but this is not explicit. There are two different questions being posed by the review, the first being, I think, what is the effectiveness of interventions to reduce emergency presentations of cancer? and the second, I think, what are the risk factors for being diagnosed with cancer via emergency presentation versus being diagnosed with cancer after being referred through outpatients?</p> <p>For the first question, the PICOS needs to describe the type of intervention of interest, the comparator(s) and the outcomes - I assume the outcome in this context would be emergency presentation compared with presentation through outpatients, but this was not made explicit.</p> <p>For the second question, the PECOS (population exposure</p>
-------------------------	--

	<p>comparator outcome study design) needs to describe the exposures of interest (e.g. age, sex, SEP, not having a GP, ethnic group, marital status practice list size etc etc), the outcome of interest (emergency presentation of cancer) and the comparator (having cancer diagnosed via a different route). Also, clearly RCTs or other interventional studies are not appropriate for this type of research question.</p> <p>In the results, it was not clear how many studies of the different designs asking the two types of question were found. Even after reading the table, I remained a bit unsure – ‘observational’ describes a group of study designs, including case reports, cohort studies, case series and case-control studies, and using that word alone to describe a study design is insufficient. I think the studies described as observational were actually case-series, although I have not read all of them. It would be helpful if the early part of the results set out a description of how many studies attempted to answer each of the research questions and how many of each study design.</p> <p>In the section on patient-related risk factors for emergency presentation, I found it difficult to work out how many studies had actually examined each risk factor – it would be helpful if the authors, before giving each element of the synthesis, stated how many studies had actually examined each of these. There is a key difference between ‘evidence of no effect’ and ‘no evidence of effect’.</p> <p>In the discussion, the first paragraph, despite being labelled ‘principal findings’, does not provide many key findings answering the research questions – these appear in the second paragraph.</p> <p>Overall presentation</p> <p>I felt that throughout the article, the language was imprecise, a little over-wordy and in some places unscientific. Key – but not the only - examples are:</p> <p>Conclusion of abstract</p> <ul style="list-style-type: none"> - ‘patient-related factors’ - I struggle to think of a risk factor for emergency presentation that is not in some way patient-related, so the sentence comes across as somewhat stating the obvious. ‘have an influence on diagnosis of cancer during an emergency presentation’ – I think you mean ‘increase the risk of being diagnosed with cancer after emergency presentation rather than after referral to outpatients’ <p>Introduction</p> <ul style="list-style-type: none"> - ‘Despite the undoubted benefits of improving the diagnostic pathway for these patients’ – I am not sure that the science yet tells us that this is the case. It is probably true, but by no means do we know that this is even possible. - ‘dearth of evidence relating the factors that influence the presentation itself’. Do you mean a dearth of evidence setting out the risk factors for being diagnosed with cancer after emergency presentation rather than via referral through outpatients? <p>Methods – assessment of evidence</p> <ul style="list-style-type: none"> - ‘population relates to the method of determining required levels of participation’. I am not very clear what this means <p>Results</p> <ul style="list-style-type: none"> - 1st para – ‘the majority dealt with factors relevant to patients’ – what factors are not relevant to patients? (similar issue at the end of para 3 of the results) - In the results, ORs are interpreted as risks. It would, for example, be more accurate to say at the end of para 2 of page, 9 ‘in addition, one study found that the odds of emergency presentation was increase in those with no children’ - History section ‘had an effect on presenting behaviour’ - I was
--	--

	<p>puzzled by this because being diagnosed after emergency presentation or not is not entirely down to patient behaviour.</p> <p>Discussion</p> <ul style="list-style-type: none"> - Final sentence of para 1 – very imprecise. I am not sure what the authors mean by ‘interactions’ and, isn’t the problem that there is limited research evaluating’ interventions rather than ‘identifying’ them? - Strengths and limitations: ‘only five studies were rated as insufficient’ – of insufficient quality? If they were insufficient, why were they included? <p>Some other specific points</p> <ul style="list-style-type: none"> - The authors report ranges of ORs in the abstract: I don’t think this is particularly helpful, especially without confidence intervals. - Article summary – does not give any findings.
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer Name: Hubbard

1. I have no issues with the methodology and it does not surprise me that there was so much heterogeneity – perhaps it would be worth subgrouping the studies a bit according to methodology and/or perhaps country.

- Given the relatively small number of studies included in the review, and the fact that most were simply retrospective analyses of data from patient records, we are not sure that subgrouping studies as suggested would provide any additional information to the reader. However, if the editorial team think that this would provide added value to the paper we will be happy to try to group studies in some way.

2. The search terms are the in the appendix – and I suspect this reflects the complexity – it would be nice of some more details of these were in the methods.

- We have inserted some details on the terms used in the Methods section as suggested (Page 5).

3. Finally I would perhaps emphasise that although earlier diagnosis may not ultimately improve survival it is transformative to the patient experience – particularly in lung cancer where the prognosis is so awful.

- We have added a sentence to the Discussion to make the suggested point (Page13).

Reviewer Name: Alan Askari

4. Search limited to 1996-2014: is there a reason for this? If so, it should be reported.

- This time limit was selected as it covers the period following the introduction of the Calman-Hine report (1995), which transformed cancer services in England and Wales. We have added a sentence clarifying this (Page 5).

5. Have the authors considered ethnicity as a contributing factor? There is evidence in the literature to suggest that certain ethnic groups are at higher risk of being diagnosed during an emergency presentation. In Colorectal Cancer, certain ethnicities engage less with screening services as well as further investigations (flexible sigmoidoscopy and colonoscopy) as such invasive investigation are culturally less acceptable.

- We considered any factor relevant to emergency presentation that was identified by the literature. Ethnicity was considered in some identified studies, and where this was the case it has been reported in Tables 1-4 and in the text (Page 9, end of paragraph 1).

6. Article summary: The authors state: 'This review has for the first time synthesised available evidence'. This is inaccurate, technically, data synthesis has not taken place, data synthesis is essentially a Meta-Analysis. In this study, the OR has been reported but there has not been any synthesis of new data from the published studies. This term should be removed as it may mislead the reader.

- We disagree with the reviewer that data synthesis involves meta-analysis. Meta-analysis is a quantitative synthesis of evidence, while we have carried out a narrative synthesis of evidence. This is standard in reviews where heterogeneity precludes quantitative synthesis. As such, we would prefer to leave our original sentence as it stands.

7. Strengths & Limitations Page 12 Line 21: The authors state that 'No randomised controlled trials were identified'. Whilst this is a fair statement to make when carrying out reviews, in the context of emergency presentation, it is unsurprising and essentially impossible to do. Also, there is once again reference to 'synthesis' of data ('definitive synthesis'). A definitive synthesis would be a Meta-Analysis and Meta Regression of appropriate variables to control all confounders that may contribute to emergency presentation. By the authors own admission, this has been impossible to do.

- Please see response to Item 6 above. In the Strengths and limitations section, we have clarified that RCTs in this area would be unlikely (Page 12).

Reviewer Name: Ryan Courtney

8. There are a number of quality grading tools available but little to no justification is given on why the unnamed tool used in references 8 and 9 was selected. The grading system is very limited in the methodological properties that it does assess. It needs justification, and if used its limitations and strengths compared to other existing tools should be critiqued in the method or discussions section.

- As reported in the Assessment of evidence section (Page 6), we used available quality assessment tools where study design allowed. However, the majority of studies included in the review involved either secondary analysis of routine data, medical records review or questionnaire administration. As such, there was no validated tool available to assess these descriptive studies. Instead, we used a tool that we developed in previous reviews for such studies and that has been written up and accepted in earlier peer-reviewed publications in the British Journal of Cancer. As this method was also found to be acceptable to the other three reviewers, we have not provided additional justification of it or critiqued it against other recognised tools which have been designed to assess different types of studies to these.

9. Further, the grading of evidence by methodological quality is not articulated in the abstract and should also be included in the introduction to guide the reader.

- Since grading evidence by methodological quality is part of the methods of a systematic review, we have included it in the Methods section rather than in the Introduction. We believe that including this in the rationale for undertaking the study would be more confusing for the reader.

10. I see no real benefit of including studies in the systematic review that demonstrated “low” strength of evidence and they should be excluded from further review, once graded.

- It is standard practice in reviews (including in Cochrane reviews) to include all identified and relevant studies regardless of their methodological quality. This helps to provide a complete overview of the evidence base in an area, and ensures that the review is not biased in its reporting of particular findings (e.g. if all of the low quality studies relating to a specific variable were excluded this might give an inflated assessment of the overall impact of that variable). Instead, low quality studies should be included, and the evidence interpreted accordingly.

11. Abstract – Insert “To” before “identify”

- The additional word has been inserted as suggested (Page 2).

12. Why was the time period 1996-2014 (18 year period) chosen? Justification needed.

- Please see response to Item 4 above.

13. Introduction – While the relationship between presentation route and survival is discussed there is no mention of the relationship between staging of disease and presentation route. This should be articulated in this section.

- While we agree with the reviewer that staging of disease is important, we have not studied that in this review. It is likely that the relationship between staging and presentation route is complex, and for clarity and simplicity, we would prefer to maintain the focus of this review on patient and practitioner factors associated with presentation.

14. Detail on the grading of evidence and measurement tool used should be included in the introduction. It would be of benefit to the reader if the existing literature was critiqued, in relation to previous attempts to grade evidence related to delay in diagnosis or treatment (irrespective of route of clinical presentation).

- Please see response to Item 9 above.

15. Conclusions – first sentence “there” needs to be deleted from text.

- The additional word has been deleted as suggested (Page 13).

Reviewer Name: Lindsay Forbes

16. In the methods, both in the abstract and the main text, it would be helpful to set out the research questions more clearly and all elements of the PICOS/PECOS.

- Rather than try to outline this in the text, we have included this information in Appendix 2.

17. The ‘Population’ was not clearly described in the abstract – ‘individuals or groups of patients or primary care practitioners’ – I didn’t understand that at all – all patients? At first reading I thought the

authors were examining risk factors for emergency presentation among primary care practitioners.

- Please see response to Item 16 above.

18. The authors said they included studies of any design, however, it is not clear whether they included, for example, qualitative studies or single case reports. The results suggest not but this is not explicit.

- We considered any study of emergency presentation regardless of study design; the designs of studies that were included have been reported in Tables 1-3. We have added some text to the Criteria for inclusion section to clarify this (Page 5). We did not identify any relevant qualitative studies and have added this to the Search results section (Page 7).

19. There are two different questions being posed by the review, the first being, what is the effectiveness of interventions to reduce emergency presentations of cancer? and the second, what are the risk factors for being diagnosed with cancer via emergency presentation versus being diagnosed with cancer after being referred through outpatients?

For the first question, the PICOS needs to describe the type of intervention of interest, the comparator(s) and the outcomes – I assume the outcome in this context would be emergency presentation compared with presentation through outpatients, but this was not made explicit.

- We have included relevant information in Appendix 2.

For the second question, the PECOS (population exposure comparator outcome study design) needs to describe the exposures of interest (e.g. age, sex, SEP, not having a GP, ethnic group, marital status practice list size etc etc), the outcome of interest (emergency presentation of cancer) and the comparator (having cancer diagnosed via a different route). Also, clearly RCTs or other interventional studies are not appropriate for this type of research question.

- Please see response to Item 7. We have included relevant information in Appendix 2.

20. In the results, it was not clear how many studies of the different designs asking the two types of question were found. Even after reading the table, I remained a bit unsure – ‘observational’ describes a group of study designs, including case reports, cohort studies, case series and case-control studies, and using that word alone to describe a study design is insufficient. I think the studies described as observational were actually case-series, although I have not read all of them. It would be helpful if the early part of the results set out a description of how many studies attempted to answer each of the research questions and how many of each study design.

- We have labelled many of the studies as ‘observational’ as most involved retrospective analysis of routinely collected data. As such, they were not true ‘case-series’ and so we have not labelled them as such. Cohort, case-control and cross-sectional studies have been labelled accordingly in Tables 1-3. If the editorial team think that it would be helpful, we could add the data collection methods used by studies to the tables. Only one study evaluated an intervention and we have added a sentence reporting this in the Search results section (Page 7).

21. In the section on patient-related risk factors for emergency presentation, I found it difficult to work out how many studies had actually examined each risk factor – it would be helpful if the authors, before giving each element of the synthesis, stated how many studies had actually examined each of these. There is a key difference between ‘evidence of no effect’ and ‘no evidence of effect’.

- The number of studies looking at each of the risk factors is covered by Table 4. We have added some additional text to the title of the table to clarify this.

22. In the discussion, the first paragraph, despite being labelled 'principal findings', does not provide many key findings answering the research questions – these appear in the second paragraph.

- The heading 'Principal findings' relates to the first section of the Discussion rather than to the first paragraph, and as such findings are also reported in paragraphs 2-4. The first paragraph outlines general findings from the review, namely that there is a paucity of evidence in this area as a whole and in relation to specific factors.

Conclusion of abstract

23. 'Patient-related factors' - I struggle to think of a risk factor for emergency presentation that is not in some way patient-related, so the sentence comes across as somewhat stating the obvious.

- We consider patient-related factors to be those that relate to patients prior to diagnosis of cancer i.e. socio-demographic characteristics (such as age, sex, ethnicity, deprivation), history (such as use of health care services, lifestyle factors, help seeking), and cancer symptoms. We do not believe that this is stating the obvious, as we have also considered practitioner factors in our review, and have used this term to distinguish between the two.

24. 'Have an influence on diagnosis of cancer during an emergency presentation' – I think you mean 'increase the risk of being diagnosed with cancer after emergency presentation rather than after referral to outpatients'.

- We have altered the sentence to clarify as suggested (Page 2).

Introduction

25. 'Despite the undoubted benefits of improving the diagnostic pathway for these patients' – I am not sure that the science yet tells us that this is the case. It is probably true, but by no means do we know that this is even possible.

- We would argue that our original statement is correct as there is no doubt that there is benefit in terms of patient experience (as pointed out in Item 3 above). In addition, if we could identify those factors that are associated with EP and then were able to intervene to 'change' these factors so that patients had outcomes equal to those of 2WW presenters, then there would be undoubted survival benefit. We do agree that it is still unclear whether delay influences outcomes. Mitchell and Macleod are co-authors on a systematic review currently in press in the British Journal of Cancer that will summarise the evidence to date regarding the association between time to diagnosis and outcomes in cancer. It will report that for colorectal cancer, whilst many studies reported no associations, more reported a positive than a negative association. The lung studies have mixed findings. For this paper, we would prefer to leave our original statement as it is.

26. 'Dearth of evidence relating the factors that influence the presentation itself'. Do you mean a dearth of evidence setting out the risk factors for being diagnosed with cancer after emergency presentation rather than via referral through outpatients?

- We had accidentally omitted the word 'to' from our original submission, thereby altering the meaning of the sentence. We have altered it accordingly (Page 4).

Methods – assessment of evidence

27. 'Population relates to the method of determining required levels of participation'. I am not very

clear what this means.

- We have reworded the sentence to clarify as suggested (Page 6).

Results

28. 1st para – ‘the majority dealt with factors relevant to patients’ – what factors are not relevant to patients? (similar issue at the end of para 3 of the results).

- Please see response to Item 23 above.

29. In the results, ORs are interpreted as risks. It would, for example, be more accurate to say at the end of para 2 of page, 9 ‘in addition, one study found that the odds of emergency presentation was increase in those with no children’.

- While we agree with the reviewer that technically these relate to the odds of an event happening, we have used the term ‘risk’ throughout the paper for consistency, as not all of the studies reported ORs. In addition, since the purpose of the review was to identify factors that increased the likelihood of someone being diagnosed as the result of an emergency presentation, we believe that describing identified factors as risks is appropriate in that context,

30. History section ‘had an effect on presenting behaviour’ – I was puzzled by this because being diagnosed after emergency presentation or not is not entirely down to patient behaviour.

- This section relates to the symptoms experienced by patients, their previous use of health services and screening, and other factors that may influence whether or not they present with potential cancer symptoms, such as co-existing disease. We believe that it is appropriate to consider that these aspects of a patient’s history influence presenting behaviour, which in turn influences time to presentation, and consequently may influence whether the pathway to diagnosis is via referral or emergency presentation.

Discussion

31. Final sentence of para 1 – very imprecise. I am not sure what the authors mean by ‘interactions’ and, isn’t the problem that there is limited research evaluating’ interventions rather than ‘identifying’ them?

- We have reworded the sentence to clarify as suggested (Page 11).

32. Strengths and limitations: ‘only five studies were rated as insufficient’ – of insufficient quality? If they were insufficient, why were they included?

- Please see response to Item 10 above.

33. The authors report ranges of ORs in the abstract: I don’t think this is particularly helpful, especially without confidence intervals.

- The odds ratios reported in the abstract present the range of ORs relevant to patient age across studies, and as such it was not possible to include confidence intervals. However, we believe that this provides a good indication of the impact of age and as such would prefer to include them.

34. Article summary does not give any findings.

- We have included a section on findings as suggested (Page 3).

VERSION 2 – REVIEW

REVIEWER	Lindsay Forbes Kings College London UK
REVIEW RETURNED	11-Feb-2015

GENERAL COMMENTS	<p>Thanks for asking me to review this paper again. It is improved. I have some minor comments:</p> <ol style="list-style-type: none"> 1. I think the abstract should mention the quality of the studies found 2. I still think that the tables should describe the design of the studies called 'observational' because the case-control studies etc are also observational. 3. bottom of page 8 - what do the authors mean by 'deprivation'? 4. middle of page 9 - one study found that the risk of EP was increased in those with no children but then gives a OR with a CI widely straddling 1. 5. I still think that the first para of the discussion should identify the key messages <p>I hope this helps, it is a useful addition to our knowledge of this area.</p>
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Lindsay Forbes

1. I think the abstract should mention the quality of the studies found.

- We have revised the abstract to include this.

2. I still think that the tables should describe the design of the studies called observational.....

- Most of the included studies involved retrospective analysis of routinely collected data and were labelled as 'observational' as they do not readily fit with a specific study design. That being the case, and in order to try to deal with the reviewer's suggestion, we have included details of the data collection methods for the relevant table entries.

3. Bottom of page 8: what do the authors mean by 'deprivation'?

- The term deprivation is used throughout the paper to mean socio-economic deprivation. We have clarified this on page 8, and in the Article Summary and Conclusion.

4. Middle of page 9: one study found that the risk of EP was increased in those with no children but then gives an OR with a CI widely straddling 1.

- We have rechecked the citation and reported the OR and CIs as presented in the original paper. Childlessness was significant in univariate but not multivariate analysis; we have revised the relevant sentence to clarify this.

5. I still think that the first para of the discussion should identify the key messages.

- We have moved the second half of the first paragraph to the 'Implications for clinicians, policy, and research' section of the Discussion, and have slightly reworded the remainder of the first paragraph and incorporated the second to include more of the results.