Dear editors,

Thank you for the opportunity to revise and resubmit our manuscript. We would like to express our gratitude to the editors and reviewers for their constructive comments and we believe that the changes have strengthened our paper.
Our responses are provided after each comment and we have also tracked the changes in the manuscript.

On behalf of all the authors,

Sincerely,
Cristiano Rampinelli, MD

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistician), John Fletcher, Rubin, Tiago Villanueva. Written comments from José Merino and Georg Roggla.

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers, including the patient reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

1. This study does not involve any complex statistical modelling, rather it calculates individual cumulative radiation exposure for a cohort of patients, using data from a lung cancer screening program and then uses data from tables published by the National Research Council to derive life attributable risk estimates by age, sex and organ. The limitations of these published tables are mentioned in the Discussion ie. that the estimates are, "…..a consensus opinion of a committee and the inferred risk at lower doses probably overestimates the risk of cancer induction" (Page 12.) It is appropriate to highlight the relatively imprecise nature of the estimates in the Results section as well.
As discussed, the main source of imprecision relies on the use of attributable cancer risk estimates from the BEIR VII report. Such imprecision cannot be quantified numerically but, as suggested by the committee, we now highlighted the imprecise nature of the estimates in the Results section. We also added information about the range of the cumulative radiation doses received by participants to the COSMOS study. This is not a measure of imprecision, but is it reflects effective exposure variation across the study participants. This information was previously presented only as supplementary material.

2. Changing the LARs reported in Table 3 to rates (eg. x per 10,000) would make it easier to compare between age and sex cohorts.
As suggested, the LARs in Table 3 have been reported x 10.000 persons.

3. Modelling is one way to approach this issue but it is also possible to undertake an observational study (see Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute

myocardial infarction. CMAJ March 8, 2011 vol. 183 no. 4 First published February 7, 2011, doi: 10.1503/cmaj.100463. This study showed increasing cancer incidence with increased exposure to cardiac imaging in a study of 80,000 patients with a heart attack.) Please comment on choice of study design.
Our study is built on a lung cancer screening trial conducted in heavy smokers. First, we have complete and accurate information about lung cancer incidence, but we do not obtained confirmation about the diagnosis of other forms of cancer. Second, since our screening protocol included 3 or 6-month recall LD-CT and PET in the presence of suspect nodules, by design, lung cancer patients in our study received higher levels of radiation than those without lung cancer. Third, even if information about other forms of cancer would have been available, the size of our cohort (5203 participants) would have been too small to perform an observational study such as the one by Eisenberg et al. For these reason, we performed a "modelling" study, based however on real exposure data. We believe this is not relevant to our study and should not be discussed in the manuscript.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
In making a decision about acceptance, there are two large issues:

- Does this pass the "so what?" test – i.e. if the methods are solid is there enough interest for BMJ readership about the potential risk-benefit of radiation to justify publication? The medical community seems to have a bit of a "split personality" approach to this. On the one hand, if we believe in ALARA (as low as reasonably achievable), then we have to believe that there is some risk, even from the low radiation resulting from CT exams (at least on a population basis). If this is the case then there is utility to modeling it. On the other hand, there is legitimate concern that overblown public perception of risk may lead to avoidance of imaging that has benefit. The Hendee article does the best job of speaking about this from the perspective of not doing risk estimates (the pendulum swinging back). What is really interesting about this article is that it provides some evidence (given that it may be highly speculative) that the risk of not getting screened outweighs any radiation risk of getting screened. One of the major arguments of Hendee is that population based risk may be overblown by the media and extrapolated by individual patients. This article may have the opposite effect – providing clinicians who want to do LDCT lung cancer screening with a publication that can alleviate fears that people may have about radiation when deciding to engage in CT lung screening. From this perspective it may actually serve a public health mission to publish this data assuming the methods are as solid as can be expected. The other side of this, however, is that if we are willing to publish population based data on radiation risk we should be willing to accept it in other analyses.

- Are the methods solid. The major issue here is that the authors are presenting this data as prospective data and emphasizing this methodology in their manuscript. While this data is used, the real methodology is actually the estimation of risk benefit using BIER VII data and estimates of LAR from cancer etc. While the methodology should cite the prospective data, it should focus much more explicitly on the modeling methodology. This requires a major revision. The "intervention" is not the prospective enrollment, it is the analysis, and the paper should be very explicit about this.

- **In response to the first issue highlighted, we agree with your point of view on the 'personal' approach of the medical community to the low-dose radiation problem.**
We are aware of the intrinsic limits of the model adopted, nevertheless we believe that is important to provide a quantitative risk (even if potentially speculative) based on real exposure data. This may help clinicians and patients taking the decision whether get screened or not.

- **With regard to the second point raised, we agree that the presentation of the Material and Methods could be misleading. Therefore, we moved the 'Population and study design', 'Low-dose CT protocols' and 'PET-CT scan' paragraphs in the appendix, focusing on the retrospective methods used to estimate radiation exposure and induced cancer risk: we think this makes the paper more explicit on the methodology used.**

Materials and methods

This should begin with the modeling as a separate distinct section. The "model assumptions from prospective data" should be its own section.
Please, see comment above. After a brief introduction the Materials and Methods section now begin with 'Radiation exposure from CT screening' followed by 'Cancer risk estimation'.

The detail about scanner protocols can be much abbreviated or even left out and referred to in the citations.
As suggested, we moved the paragraph in question to the appendix.

Overall, the manuscript would benefit form close reading by a native English speaker.

Specific comments:

Page 4
- Line 34-36: Says that the "increased risk of ca related to LD radiation doses [repetitive], and its magnitude is still controversial"—it's not just that risk of radiation from LD CT is controversial, the risk of radiation induced malignancy for all CT <50mSv (which is basically ALL CT – including standard doses) is still controversial
In order to be more understandable, the sentence has been rephrased.

- Line 49: "95% credibility interval" I think they meant confidence interval
This has been corrected.

Page 5
- Line 6-9: I take issue with the notion that you can't estimate what will happen to "real cohorts of smokers" with models given all the data we have on the history and progression of lung cancer in smokers combined with screening guidelines
This sentence was misleading, therefore has been omitted from the text.

Page 6
- Line 27-57:did they strictly stick to the protocols – if yes, how they evaluated this, if no then what were the variations in dose?

Yes, the protocol was fixed and strictly applied to all the screened subjects. Each CT scan (acquisition parameters and dose calculation) was checked with Radimetrics software to assess the compliance to CT protocols.

Page 8

- Results about “average effective dose” need greater clarification. Was this normally distributed? If so how was this determined? What is standard deviation? Would it be reasonable to also put the range(s) as well as median and IQRs?
  - Same goes for cumulative effective doses (Line 37)

The effective radiation dose received by the participants at baseline screening round and the effective cumulative radiation doses received at the 3rd, 5th or 10th screening round were NOT normally distributed. This is mostly due to the few participants who underwent recall CT(s) and PET and were exposed to more exams. We corrected the whole manuscript, presenting median doses instead of the mean. We also provided information on the minimum and maximum values in the results section (This information was previously presented only in the supplementary tables).

- In eTable 1 and 2 what does +/- standard deviation mean? Is that one standard deviation? 1.96 SD? Is that a 95% CI? Here we are seeing some differences… can they comment on why if it was a standard protocol the organ doses are so varied?

It was one standard deviation. We used a standard protocol but the cumulative dose varied depending first on the number of exams received (in case of suspect nodules, some participants had recall LD-CT and eventually PET). Second, the organ doses vary because the software used for the dose calculation 11 different phantoms, 6 for women and 5 for men. This allows an optimal evaluation of exposure according to sex and body habitus. Thus, even with the same protocol, the dose calculation may provide different results for a single LD-CT exam.

- Is it b/c of shielding due to different body habitus while using SAME protocol? Is it b/c there was variation in the protocol?

Different factors may account for organ dose variation: a) the phantoms used for organ dose calculation (see comment above), b) the number of the LDCTs received by each subject, c) slight dose differences among the scanners used.
We added a sentence in the text to clarify this point.

Is it b/c some people only got one scan but others got multiple a year (this still wouldn't account for the variation in baseline imaging though)

As described above, the number of scans per year is a source of variation.
The baseline is also subjected to variation due to recall scans. In the paper we referred ‘baseline’ to the whole year (baseline scan + recalls) and not to baseline scan only. In Materials and Methods section we changed “baseline scan+ screening rounds performed + recalls” into “screening rounds performed + recalls” (please see comment in the annotated version of the manuscript).

Page 9

- Line 14: Table 3—It is difficult to look at/make comparisons, please standardize the denominator and report per 1,000 persons (or something)

In order to allow easier comparisons, we reported the LAR for 10,000 persons.

- Line 16: here is something that is a problem and you want to really state clearly—this is a study that was forward looking and reports number of cancers caught in their screening test, but this study didn’t have a control arm and there is no direct comparison being made between subjects scanned over 10 years and people who were not. Rather they are estimating CT induced cancers from a calculation. Someone reading this quickly could think that they OBSERVED 2.8 additional cancers based off how this is reported as 2.8/5203.

We emphasized that the number of cancers is estimate and not observed.

- Line 30-42: this is a confusing paragraph—how did they calculate this, where is my table? Also aren’t you just reporting what BEIR VII Table 12D-1 tells you when you draw differences btwn genders?

The LARs are presented according to the results reported in Table 3. As you stated, these results reflect the differences between genders reported in the BEIR VII tables. We've now specified that at page 9 line 32-33.

o In figure 1 please label it better w/ something to the effect of Lung Cancers estimated to be attributable to CT radiation per 1000 people screened

We've labeled the Figure 1 according to your comment.

Page 10

- Re: BMI/body habitus—please explain why this is relevant and talk about this more in the methods section

Usually, coefficients for organ doses and effective doses estimation are calculated on the "standard" patients, without taking into account body habitus. Such a calculation, performed with a fixed protocol, would led to the same radiation dose estimate for all the patients. We emphasized the strength of the size-specific calculation in the Methods section and we also addressed that in the Discussion.

- Line 45: "This highlights how the esteem[?] of organ and effective doses" do you mean estimate?

Yes, this has been corrected.

- Line 54: What do you mean dose for 6 and 5 groups of patients? Isn't this something that should be in methods?

Yes, in the methods we've now explained better how the software works in matching patients to phantoms.

Page 11

- Line 43: If the radiation is trivial given the early cancers we are catching why would we consider a higher age for women?

We agree that this sentence was misleading, therefore has been omitted from the text as also suggested by the other reviewers.

Page 12

- Line 10-17: Glosses over the controversy of the LNT model. doesn't discuss that the BEIR VII report itself states that w/ doses <100mSv "statistical limitations make it difficult to evaluate cancer risk" or that in the Health Physics Society statement doses <50mSv are considered to small to observe health risks

We highlighted the position of the Health Physics Society ("warns against quantitative estimation of health risks that might be too small to be observed or nonexistent below 50-100 mSv").

Additional Questions:
Please enter your name: Chris Moore

Job Title: Associate Professor

Institution: Yale University School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: Currently funded by AHRQ 5R18HS023778-02 as PI for "MINIMIZING UNNECESSARY IRRADIATION FROM RENAL COLIC CT SCANS IN THE UNITED STATES"

Reviewer: 2

THIS IS A PATIENT REVIEW

Comments:
1. Are the study's aims and the issue and questions that the paper addresses relevant and important to you as a patient? Do you think it would be relevant to other patients like you? What about carers?

Addressing patient concerns about the risks of additional radiation exposure due to lung cancer screening is essential to make screening more attractive to those at high risk for developing lung cancer. I've heard patients express concern about this increased risk; I can't say I've heard a lot of carers express this concern, but then carers rarely go to support forums before a patient has been diagnosed with cancer.
Thank you for your point of view on this topic.

2. Are there any areas that you find relevant as a patient or carer that are missing or should be highlighted?

Some parts of the paper were difficult for me to understand due to choice of wording and use of several different ways of expressing risk (e.g., both ratios and percentages).

The paper did a good job of achieving its first objective of assessing cumulative radiation exposure. Whether it assessed lifetime attributable risk of cancer incidence is less clear. I need a clearer statement of how baseline risk for cancer incidence is determine for people who have NOT had lung cancer screening--does it take into consideration body types, age, sex, past exposures, lifestyles? Is there some widely-accepted calculation of cancer incidence for patients with a 20-pack-year history of smoking? Without understanding the baseline, I can't see how the estimated radiation exposure from LDCT and PET-CT scans increases the risk of future cancers. This study would have the most impact for me if I get a clearly understood statement of (1) my risk for future cancers WITHOUT screening, AND (2) my risk for future cancers WITH screening.
There is overwhelming evidence that tobacco smoking causes lung cancer and several tools (prediction models) exists to quantify an individual risk of developing (or dying from) lung cancer, based mainly on his age, smoking history and past-exposure to asbestos. (see Maisonneuve P, Bagnardi V, Bellomi M, et al. Lung cancer risk prediction to select smokers for screening CT--a model based on the Italian COSMOS trial. Cancer Prev Res (Phila). 2011;4:1778-89. Tammemagi MC, Lam S. Screening for lung cancer using low dose computed tomography. BMJ. 2014;27;348:g2253).
We added information about these instruments in the revised manuscript.

Found myself wondering how much radiation exposure could be contributed by the radioactive glucose tracer (FDG) used with PET scans. Its contribution to overall radiation exposure should be calculated before it is dismissed as insignificant.
The exposure from a single PET/CT examination has been calculated and its contribution (as reported in the Discussion) was found to be 4mSv.

3. From your perspective as a patient, would the treatment, intervention studied, or guidance given actually work in practice? Is it feasible? What challenges might patients face that should be considered?

The conclusions of this study could be used during shared decision making as patient and provider discuss whether lung cancer screening is appropriate. However, the conclusions would have to be presented in a form more understandable to patients.

I am concerned that the paper states (p. 11) "…further studies may consider a higher starting age for screening in high-risk women." This seems to ignore the fact that lung cancer incidence over the past two decades have been INCREASING in women, especially in younger women.
We agree that this sentence was misleading, therefore has been omitted from the text as also suggested by other reviewers.

4. Are the outcomes that are being measured in the study or described in the paper the same as the outcomes that are important to you as a patient? Are there others that should have been considered?

Yes, the outcome (whether radiation from lung cancer screening increases my lifetime risk of developing cancer) is important to me as a lung cancer patient/advocate.

5. Do you have any suggestions that might help the author(s) strengthen their paper to make it more useful for doctors to share and discuss with patients?

Need a bit more background in the abstract about how radiation exposure puts patients at increased risk of future cancers.

Find a more concrete way to express how much radiation exposure from low-dose lung cancer screening increases my risk of developing future cancers. Example:
Without lung cancer screening, a 50-year-old woman has an AA% chance of developing cancer in the next 20 years. If that 50-year-old woman undergoes lung cancer screening for 10 years, her risk of developing a new cancer increases to BB%.

At several points in the paper, statements are made as apparent fact without providing the reasoning. Example (from page 12): "…BEIR VII Report is the correct way to proceed to perform risk estimates for the individuals [31] …." This statement does cite a paper that addresses the topic, but does not explain what conclusion in that paper causes the authors to believe this statement to be true. Rather than just using an endnote citation, please state the authors and their conclusions that support the statement in the text--those of us not intimately familiar with the topic need more background to help us understand why this statement is true.
We appreciate your comment and we understand that this topic is controversial and challenging. However, in our opinion this statement does not need any further elucidation, because based on scientific studies reported by the International Commission of Radioprotection.

6. The level of patient involvement in the research described, and if and how it could have been improved. Authors are now required to state if and how they involved patients in setting the research agenda and the design and implementation of the study and include this information in a box within the manuscript. If there was no patient involvement we would welcome your ideas on how this could have been done. We

hope this will help authors think of the best ways to include patients in their future research and further progressive patient involvement in the research enterprise.

Patients were not involved in this study. If the researchers had involved patients prior to writing this paper, they might have gained a better concept of specific patient concerns about increased cancer risk due to lung cancer screening radiation exposure, as well as language that could effectively communicate the increased risk to patients.
Thank you for your pertinent comment on this topic. We agree with you and we'll consider your suggestion for our future studies.

Additional Questions:
Please enter your name: Janet Freeman-Daily

Job Title: lung cancer patient/activist

Institution: GrayConnections.net

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I have advocated for and/or written articles (without compensation) in support of Centers for Medicare and Medicaid coverage of low dose CT lung cancer screening.

The following have provided or will provide me with stipends and/or travel expenses for speaking at their conference or event:
- Center for Information and Study on Clinical Research Participation (CISCRP)
- Global Resources for Advancing Cancer Education (GRACE)
- International Association for the Study of Lung Cancer (IASLC)
- LUNGevity Foundation
- Partners Healthcare
- Patient Power
- PeerView Press (for Continuing Medical Education event)
- PersonalGenomes.org
- Smart Patients
- Stanford Medicine X (ePatient Scholar Program)

- University of California at San Diego
- University of Colorado

• The following have reimbursed or will reimburse me for travel expenses related to attending a conference or event:

- American Association for Cancer Research (Scientist-Survivor Program)
- American Lung Association
- American Medical Association
- International Association for the Study of Lung Cancer
- LUNGevity Foundation
- NOVA Research Company and National Institutes of Health
- Perry Communications Group, Inc.
- University of Colorado

The following organizations have paid me fees or provided in-kind compensation for consulting with pharmaceutical companies:

- AstraZeneca
- Chandler Chico
- Ignyta
- Oncogenex
- Oncothyreon Inc

I serve or have served on unpaid advisory boards for:

- American Lung Association
- Bonnie J. Addario Lung Cancer Foundation
- FasterCures
- Lung Cancer Foundation of America
- Virginia Mason Medical Center

Reviewer: 3

THIS IS A PATIENT REVIEW

Comments:
As a 58 year old female patient who has undergone regular lung CT scans and CT/PET scans over the past 12 years, due to pulmonary neuroendocrine tumours, I am very interested in the findings of this study. In particular, in reducing the amount of radiation whilst maintaining an effective dose for screening/diagnostic purposes, is one which all clinicians should consider for, and with their patients. This would be relevant to other patients like myself and those caring for patients who need to understand the risks of lung CT screening.

• I am a little surprised to see such young asymptomatic women enrolled in the original 10 year screening study. Although clearly this paper does not deal with the protocol or ethics of the original study, I find it difficult to imagine that there was not already evidence of younger women being at higher risk of developing radiation cancers from high dose or repeated CT screening.

Young women were enrolled in the COSMOS study because of their heavy-smokers status (high-risk subjects). As you supposed, it is well known that the risk of radiation-induced cancer increases when the exposure age decreases: what is original in this study is the quantification of risk among healthy, high-risk subjects enrolled in a lung cancer screening program.

• The information in this paper is extremely technical but the discussion does offer a recommendation to not screen younger asymptomatic women and also concludes that more studies are required to determine optimal doses based on models that take into account an individual patient's gender/weight/body type. In the UK I am not certain if lung CT screening programmes have the support of the NHS or clinicians and in

any case, for me, I would have not met the criteria as I was neither a smoker in the high risk category or old enough to be enrolled. My first solid tumour would not have been found from such screening.
• The outcomes that are being measured in the study are important to me as a patient because I need to be informed of the risk to me of developing radiation induced lung and other major cancers. To date this has not happened but the assumption has always been that my clinicians had tools and data to guide them in reducing this risk as much as possible.
• As mentioned earlier I think the recommendation is particularly relevant for younger women and despite it's technical language I do think this paper could be introduced to stimulate discussion between patients and clinicians as it does provide some useful ways of describing and comparing risk.
Thank you for the above appreciated comments.

• There was no patient involvement in this study which is understandable as the study aim was to use 10 years of data to evaluate radiation exposure and estimation of LAR of cancer. The overall discussion however, may have benefited from patient's views and input because the information it provides is increasingly important for informed consent.
We agree and we will consider your suggestions for future studies.

Additional Questions:
Please enter your name: Anna Allford

Job Title: Patient reviewer

Institution: Patient reviewer

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Reviewer: 4

Comments:
In this study the lifetime attributable risk for cancer induction is described for a lung cancer screening population over 10 years. Based on data for the COSMOS study, the authors approximate based on BEIR VII

data that radiation may theoretically induce 3 cancers in their population of 5203 and can be compared to the 259 lung cancers diagnosed over that time.

The strength lies in the real world population and the clear writing. It provides a reference point for discussing the risks and benefits of screening.

It should be noted (and addressed in the discussion) that they did not assess the benefit of the detection of other important findings and that they did not consider the additional risks that may occur due to CT studies of the neck or abdomen to follow up incidental findings that occurred in those regions.
This comment is pertinent. In fact, we did not consider the benefit and the additional radiation exposure due to incidental findings: we have now mentioned this topic in the discussion.

The authors provide the ratio of 3 induced cancers to 259 detected lung cancers for the entire population or 92.5 lung cancers detected for every theoretical cancer induced. I would suggest that the authors provide this ratio as a separate column in table 3 for each age/gender group.
We modified the table as suggested.

The authors discuss both the NLST and screening in the US as approved by CMS. To the extent possible the authors should draw some distinctions between their population and the US based statistics.

-The COSMOS population is both younger and has a lower smoking amount for study entry

-For lung cancer screening in the US, CMS recommends a CTDIvol of <3 mGy which is higher than the radiation reported in this study.

-The current US screening nodule management paradigm in the American College of Radiology Lung-Rads guideline, which is somewhat more conservative with follow up than what was done during COSMOS

The above concepts can be collated into a recommendation that screening programs evaluate and identify their practice based risk/benefit ratio for screening
According to your comments, we added a paragraph in Discussion where the points above have been addressed.
As they highlight new technologies that may allow for lower CT doses, they should not forget the fact that limiting follow ups between screening exams through more conservative nodule follow up and more judicious use of PET/CT than initially prescribed by COSMOS will also lower population doses
We have incorporated the response to this comment in the previous one.

I do not believe the last line of the conclusion is necessarily supported by the evidence in this manuscript as written. I think it is important to consider that the risk benefit profile differs by age and may inform individual assessment, but I do not believe that blanket enrollment criteria can be similarly adopted from this data. The last sentence could be either omitted or rephrased
As suggested by you and the other reviewers, the last sentence has been omitted.

Minor comments:

p. 10 ln45 change “esteem” to “estimate”
Changed.

p.12 ln25-31 is a bit confusing as written. Stating in two sentences may better delineate the appropriate risk estimate procedure (BEIR VII age and gender) from effective dose which is not a risk estimate and a measure better suited for comparisons when discussing radiation protection/reduction
According to your suggestion, we rephrased the sentence to make it more understandable.

Additional Questions:
Please enter your name: James Ravenel, MD

Job Title: Professor of Radiology; Chief of Thoracic Imaging

Institution: Medical University of South Carolina

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: Yes

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: As I perform lung cancer screening in my institution, the results could conceivably influence that program

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supplemental file with file designation 'Revised Manuscript Marked copy'. Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision. Please include these items in the revised manuscript to comply with BMJ style (see: http://www.bmj.com/about-bmj/resources-authors/article-submission/article-requirements and http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists).

Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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3. Patient confidentiality forms when appropriate (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality).

4. Competing interests statement (see http://resources.bmj.com/bmj/authors/editorial-policies/competing-interests)

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10. Patient involvement statement (see http://www.bmj.com/about-bmj/resources-authors/article-types/research).

11. Please ensure the paper complies with The BMJ's style, as detailed below:

a. Title: this should include the study design eg "systematic review and meta-analysis."

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other registered study- the last line of the abstract must list the study registration number and the name of the register.

c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

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iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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g. Footnotes and statements

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