

## Peer Review File

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### Response to Reviewer Comments

<p><b>Reviewer A</b>          The overall topic of screening and early detection in the Middle East and Africa is important and little is written on it. However, I have major concerns regarding whether this manuscript is responsive to its mission</p>		
Reviewer A comments	Response	Change(s) made in the manuscript
<p>Methods: Who are the experts and how are they chosen? Were they only oncologists? How is this a consensus document, what is the process for consensus? How were questions chosen? How did they decide what information to use to formulate their opinions?</p>	<p>Thank you for the comment.          Details of experts and the consensus process have been included in the Supplementary information.</p>	<p>Supplementary Table 1          (Table numbers in the supplementary file have been revised)</p>
<p>I can't tell if this relates only to screening or is it a separate document for early detection as well in the non-screening setting?</p>	<p>Thank you for your question.          The experts discussed both screening and early detection during the advisory board meeting (ABM) so we have included information on both.</p>	-
<p>Countries are listed in Table 1, but this is not discussed. Consistent information about all of the topics such as extent of smoking are not included for each country. For each topic there should be consistent</p>	<p>Thank you for the comment.          While we have included the Globocan data for all countries in MEA, we have focussed primarily on the countries represented by experts attending the ABM. We have added a sentence regarding the same in the Methods section.</p>	<p>Page 6 Lines 108 to 111</p>

presentation about the information and when unavailable should say it is unavailable.		
All the discussion about mutations is far too much for this manuscript and much of it should be deleted.	The section regarding genetic mutations involved in lung cancer has been edited as recommended.	Pages 10, 11, and 12 Lines 259 to 302
Screening criteria for lung cancer: This seems to be a relatively superficial review of overall literature rather than a discussion about how things are chosen for this current population  Guidelines for early detection of lung cancer: Again a superficial literature review, but nothing related to a consensus discussion.  Lung cancer risk prediction models: superficial review of the topic and confuses overall risk and nodule risk predictors. They are separate topics.	The section, "Screening criteria for lung cancer", has been revised based on the inputs of other reviewers also.  The section "Guidelines for early detection of lung cancer" describes about the existing guidelines for early detection of lung cancer. So, no change has been made in this section.  The section, "Lung cancer risk prediction models", has also been revised based on the provided inputs.	Page 12 Lines 320 to 328  Page 13 Line 329 to Page 14 Line 363  Page 14 Lines 377 to 381
Screening guidelines for pulmonary nodules management in lung cancer patients: This title is incorrect, as this section describes workup for indeterminate nodules, not nodules in cancer patients. Also, it seems to be a review of other protocols and I don't see how this represents a consensus of what might be something recommended for the population being addressed in this manuscript.	The information regarding intermediate nodules has been deleted and a concluding section has been added in the end of the paragraph. Currently, the paragraph describes the methods recommended by various guidelines for the screening of pulmonary nodules.	Page 15 Lines 416-419
Screening practice for lung cancer across MEA: This section needs to be greatly expanded. What is actually going on in each country. Are they screening, do they have enough scanners, are they using CXR, many countries have TB clinics and use that as an entry point. Dramatic differences in wealth of many of these	The content in this section has been incorporated following deliberations during the ABM among the key experts from MEA region. Considering the provided inputs provided by the esteemed reviewer, the section "Screening practice for lung cancer in MEA" has been updated.	Page 16 Lines 433 to 435; Page 16 Line 443 to 447

countries, and this needs to be discussed. Problems in one country totally different than other countries.

Topics that need to be included relate to what is currently going on in each country, how might screening be implemented in different countries, surely you would not be able to workup every 6 mm nodule in places that hardly have CT scanners. How would you choose risk populations in different countries, are you looking for identical risk factors in each country? So much variability in terms of resources, some countries don't have enough CT scans, some don't have PET scans or the ability to do biopsies. Need to think about different protocols.

There needs to be far more thorough description of current status, what the specific questions the experts think need to be answered, how it would be different in different countries. As point of departure, even in the US where there are adequate numbers of scanners, and screening is paid for by insurance, still, only 5% of eligible are being screened. The problems would be far greater in MEA. I think a set of questions that considers what might be best to maximize opportunity in MEA needs to be considered.

AI has the potential to be an equalizer, and similarly, and perhaps even more important than the AI is a system for management of the screening population. How do you track participants and call them back for follow up etc.

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Where did Figure 2 come from? Was this part of the consensus? not discussed in the manuscript.	Figure 2 is the part of section 8.1 “Recommended referral programs for improving early lung cancer detection”. It was mentioned in the manuscript (Page number 14; line no.453). A brief description of Figure 2 has been added now for better clarity.	Page 19, Lines 535 to 543
<p><b>Reviewer B</b> Your paper is well written and the methodology is well exposed. I have some comments:</p>		
<b>Reviewer B comments</b>	<b>Response</b>	<b>Change(s) made in the manuscript</b>
Page 2, key recommendations: why hepatocellular carcinoma?	We thank you for noticing this error. We have revised it.	Page 3; Key recommendations
MEA: it should be spelled out	Thank you for the comment. We have spelled out MEA at first mention in the abstract and text.	Page 4 Line 39 Page 5 Line 80
section 8.1: chest X ray is not effective as screening tool for lung cancer	We thank the reviewer for highlighting this important point. We have removed the mentioning of chest x-ray as a screening tool for lung cancer.	Page 19 Line 545 Page 19 Line 547
line 460: please add radiologists, pathologists and oncologists	Thank you for the comment. We have added the information	Page 19 Line 551
<p><b>Reviewer C</b> As I understand it the goal of this initiative is to improve the outcomes for patients with lung cancer in the region, with the intent is to have an impact in overall healthcare in countries in the region. I will start by outlining my mindset which may not fit with that of the authors. To have an impact, I think you need a document that is informative, considers all relevant aspects and is sufficiently grounded on insight and expertise to be helpful. I think the first step his to clearly articulate what the questions are that will to be addressed. This is not easy but is a crucial first step. When writing research grants it sometimes takes a few months to clearly articulate the objectives in an actionable manner. It is also important to have a clear vision of what the final product will entail. This includes who the audience is and what one expects the subsequent actions to be. Next would be to carefully organize the process. The people involved need to have expertise and represent all relevant viewpoints and have no conflicts of interest. I would think that help from external advisors who have experience in addressing the issues would also be useful. There would need to be a thoughtful outline of what information is needed in order to make the best possible decisions. Finding this information, especially in a region that has countries with tremendously disparate resources, is difficult. Defining what is missing and finding either surrogates or developing a plan to acquire the missing information would be part of the project. Regarding the information needed</p>		

I would think that a crucial aspect would be the ability to benchmark this against other aspects of healthcare in the region and against other parts of the world in which similar interventions have been undertaken. Specifically, what is the proportion of lung cancer deaths relative to other cancer deaths or deaths in general, what is likely to happen in the foreseeable 10 years? If this establishes that lung cancer deaths are sufficiently important to warrant redirecting resources in this direction then a clear understanding of what is causing the high death rate is needed. Understanding the barriers and the particular challenges of the regional settings is crucial to developing a plan to address them. For example, it is easy to say that people should not smoke but achieving this especially among populations with low income is challenging and there are regional customs that will not be overturned by a simple statement. If the major problem is that people with lung cancer are not receiving effective care it is important to understand whether the problem is the availability of effective treatment, access to effective treatment, cultural and societal aspects that impact patients' willingness to be treated, etc. Screening is a completely different issue. Decisions regarding patients with lung cancer involves a limited number of patients, and specifics regarding their motivation for treatment and facilities needed. Screening involves a large healthy population whose motivation is entirely different and the resources and facilities needed are different. Implementation of screening has proven difficult even in well-resourced healthcare systems with particular challenges being willingness of those at risk to be screened, compliance with annual screening and the work involved with management of incidental findings. Whether the issues are prevention, management of those with lung cancer, or screening a healthy at-risk population, the barriers and the ability to address them is markedly different depending on local aspects.

<b>Reviewer C comments</b>	<b>Response</b>	<b>Change(s) made in the manuscript</b>
<p>Assessment of the manuscript on screening for lung cancer in MEA</p> <p>The goal of this project is very unclear. It seems to intermingle screening of a healthy population with management of patients diagnosed with lung cancer often even in the same paragraph. The organization of the project appears to be rather loose or perhaps it is simply not well explained. There is talk about a steering committee and an external panel which would seem to imply that there is a primary workforce that is different from both of those. However, it is unclear whether there actually are different entities, who is in these entities, how they were chosen, and how they represent the relevant stakeholders. There does not appear to be any management of conflicts of interest.</p>	<p>Currently, there is a lack of well-established screening and referral guideline in majority of the MEA countries despite the escalating prevalence of lung cancer in MEA region. This consensus was developed based on the opinions and suggestions of 10 oncology experts from MEA with evidence-based recommendations about lung cancer screening and early detection. With its potential to influence public health policies in the MEA region, this paper provides practical and well-founded contributions to lung cancer screening strategies.</p> <p>Further, the manuscript transparently discloses industry funding, demonstrating a commitment to openness and acknowledging potential conflicts of interest. Regarding the scientific writer's role, an explanation of the scientific writer's involvement in the process has been clearly mentioned in the</p>	<p>-</p>

<p>There was industry funding for the project and there does not appear to be any management of conflict of interest of the panel. The relationship of the funder to the process or outcomes is unclear. I do not mean to imply that there is anything nefarious, but these are very concrete things that suggest this was a poorly organized project. There appears to have been a scientific writer involved although what their role in the process was also not explained.</p> <p>The information assembled in this project is rather spotty. There are bits of information relative to particular aspects in particular countries, but these are not assembled into a cohesive picture. There is reference to several sources of information such as Globocan or IARC that are a great resource for benchmarking and an overall picture, but this benchmarking against other healthcare issues or other countries is really not developed in a way that facilitates decision-making. For example, when the ASIR and the ASMR from Globocan is brought up (a great resource for comparisons) the only benchmarking that is done is to say that the problem in the MEA region is less than in the rest of the world. A statement is made about cost effectiveness based on expert opinion which cites an advocacy group, while ignoring many publications that have actually defined the cost effectiveness. Most importantly how cost-effectiveness elsewhere relates to the MEA region is not addressed. I don't see that the information that is assembled in this manuscript is organized in a way that defines the issues and provides a foundation for assessment of resource allocation.</p>	<p>acknowledgment section, elucidating their contributions without ambiguity.</p> <p>Regarding cost-effectiveness, the comparison between lung cancer screening and screening of other cancers has been cited in the current manuscript, while the majority of the existing publications predominantly concentrate on cost variations within lung cancer screening methods or disparities across different countries. The purpose of citing the cost-effectiveness of lung cancer screening in conjunction with other cancer screening methods is to highlight the economic considerations associated with diverse cancer screening initiatives.</p>	
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The conclusions strike me as being naive and not founded on any evidence presented. It is stated that a screening and referral guideline (again mixing the issues of screening a healthy population and treating those with disease) will improve outcomes. But nothing in the manuscript explains how. If resources are not available, if access or cultural barriers exist, then a written guideline will certainly have no effect. The mere existence of a written guideline, even in well-resourced areas, has generally had very little impact - so to assert that this will improve patient outcomes is naive. Next, it is asserted that research may prove cost effective but there was nothing in the manuscript that outlined further research and what the impact would be. The statement appears to be rather wishful, hoping that a statement alone will reallocate funding. Finally, there is the statement that local governments need to be convinced to initiate large scale programs, but there is nothing in this manuscript that substantiates the feasibility of screening throughout the countries in the region or provides a basis for rational decision-making about allocation of available funds.

I am certainly not biased against screening, guidelines for management of patients with lung cancer, research on lung cancer or prevention - in fact my career has been based on all of these. However, statements based on beliefs or desires don't seem to move things forward as much as solid evidence and thoughtful, balanced arguments. Sometimes it can be useful to outline an unmet need to raise awareness. Perhaps that is the purpose of this project. However, I have trouble seeing

The conclusion has been revised based on the given inputs.

Page 21 Lines 590 to 594

<p>how this manuscript will have any impact in convincing local governments as is stated as the unmet need. And if the purpose is simply to raise awareness, I don't see how there is sufficient benchmarking to define the issue that people need to be more aware of.</p>		
<p><b>Reviewer D</b>  This is a nicely written and thoroughly researched review of the evidence in lung cancer screening adapted to the MENA population. Here are some issues that require the authors attention</p>		
<b>Reviewer D comments</b>	<b>Response</b>	<b>Change(s) made in the manuscript</b>
<p>In the key recommendations:  replace "Well-established screening and referral guidelines for hepatocellular carcinoma" with "Well-established screening and referral guidelines for lung cancer"</p>	<p>We thank you for identifying this error. We have revised it.</p>	<p>Key recommendations.  Page 3</p>
<p>Page 10 Line 308: Note that a recent update in recommendations eliminated the concept of "years since quitting" from the definition of eligible population. (<a href="https://doi.org/10.3322/caac.21811">https://doi.org/10.3322/caac.21811</a>)</p>	<p>Thank you for the comment. We have revised the criteria per the recent guidelines.</p>	<p>Page 12 Lines 323 to 325</p>
<p>Supplementary table I:  EGFR, ALK, ROS1... mutations are not only found in adenocarcinoma. The column histology seems too be misleading.</p>	<p>Thank you. We have removed the histology column.</p>	<p>Supplementary table 1</p>
<p>Supplementary table II:  In the Nelson trial: the criterion of size (&gt; 500 mm<sup>3</sup>) is defined a positive screening. Also, progression defined as doubling time of &lt; 400 days for indeterminate nodules is considered positive.</p>	<p>Thank you for the comment. We have revised the criteria.</p>	<p>Supplementary table 2</p>
<p>Major:</p>	<p>A clarification regarding Figure 2 has been added in the text, as suggested.</p>	<p>Page 19 Lines 542 to 543</p>



<p>The algorithm seems to be based on chest X ray although the authors themselves admit that chest x-ray is not a good lung cancer screening tool.</p> <p>It is noteworthy that although NLST compared Chest CT to X ray, Nelson trial did not, since the superiority of chest CT had been largely demonstrated by then. If the authors mean that in MENA countries where finances or logistics render low-dose CT screening are impossible to deliver, CXRs on an annual basis should be considered, this should be more clearly stated. But starting the referral pathway by a chest radiography does not seem to be an appropriate strategy in 2023.</p>		
<p><b>Reviewer E</b></p> <p>In this review manuscript, Allehebe et al. review and make their recommendation on lung cancer screening and nodule management. This is a very comprehensive review on the basic numbers/information pertinent to the specific population in this area of the world. I commend the authors for their work. I have the below comments:</p>		
<p><b>Reviewer E comments</b></p>	<p><b>Response</b></p>	<p><b>Change(s) made in the manuscript</b></p>
<p>1) The main question involves around the actual recommendation for lung cancer screening, which is the crux of the review.</p> <p>a. Are the authors recommending a country-specific recommendation? Could they not come to a consensus as an MEA region?</p> <p>b. In the US, the criteria for lung cancer screening have been revised to age <math>\geq 50</math> and pack-year <math>\geq 20</math>. Section 4.2 seem to indicate high lung cancer prevalence in similar age groups in the MAE population, yet the age recommendation is 55. The rationale for this was not clearly stated in the manuscript.</p>	<p>Thank you for your insightful comments. Please consider the following responses</p> <p>a. The authors emphasize the critical need for the development and implementation of guidelines for lung cancer screening in the all the MEA countries, taken into account the unique healthcare landscapes, socio-economic factors, and prevalence of risk factors within individual countries. This has been mentioned in the conclusion section of the manuscript.</p> <p>b. The screening criteria has been revised (age <math>\geq 50</math> and pack-year <math>\geq 20</math>).</p>	<p>Page 12 Lines 323 to 325</p>

<p>c. As a physician practicing in the US, I am very intrigued by the non-cigarette form of tobacco that is prevalent in the MAE region (one shisha is equivalent to 100 cigarettes). As such, did you consider including this as a part of the pack-year requirement?</p> <p>d. The UAE recommendation for LDCT is unclear. Does one need to meet all 4 criteria to be eligible? PLCOm2012 model includes age and smoking, and I believe this model was meant to replace the age and pack-year based criteria, so it is odd to have the age and pack-year criteria AND the PLCOm2012 model.</p>	<p>c. Currently, non-cigarette tobacco products have not been considered in the pack-year requirement.</p> <p>d. The guidelines in South Africa and the Gulf regions stipulate that high-risk individuals must fulfill all four criteria to qualify for annual screening for lung cancer, (Ref 60 and 61). The sentence in the manuscript has also been revised for better clarity.</p>	<p>Page 12 Lines 320-321</p>
<p>2) Because this is such a thorough review, it is almost too lengthy. One could consider focusing just on lung cancer screening eligibility and separate out the parts about nodule management (sections 5.2-3) and program building (sections 6-8).</p>	<p>The section regarding the management of indeterminate nodules has been removed from the text and a concluding section has been added at the end of the paragraph for better clarity.</p> <p>The section recommended referral program has also been revised based on the inputs of other reviewers.</p>	<p>Page 15 Lines 416 to 419</p>
<p>3) Minor points:</p> <p>a. First line under Key recommendations on page 2 states hepatocellular carcinoma.</p> <p>b. In section 5.2, authors state risk prediction models are used to “select high-risk individuals for LDCT scans” (Lines 315-316). I believe these models are used to stratify risk of malignancy in nodules detected on CT, not to stratify risk of lung cancer to recommend LDCT as the authors state.</p> <p>c. Table 2 can be better aligned such that similar topics can be in the same column (Indication for LDCT for UAE is in the 3rd column while it is the first column under Saudi Arabia)</p>	<p>a) We thank you for highlighting this error. We have revised it.</p> <p>b) We have revised the statement</p> <p>c) Since the individual country guidelines are formatted differently, we were unable to align the columns in Table 2 without affecting the content.</p>	<p>Key recommendations. Page 3 Page 14 Lines 377 to 381</p>
<p><b>Reviewer F</b></p>		

<p>This is great that lung cancer screening (LCS) is getting some traction and attention in this area of the world. It is rare that I hear much coming from this region. There should be no geographical borders to the early detection and cure for this pervasive international killer.</p>		
<b>Reviewer F comments</b>	<b>Response</b>	<b>Change(s) made in the manuscript</b>
<p>Under Key Recommendations, 34, referral guidelines for hepatocellular carcinoma ...is this an error?</p>	<p>We thank you for noticing this error. We have revised it.</p>	<p>Page 3, Key recommendations</p>
<p>62 – 65, And many others, it is recommended to use destigmatizing ‘person-first language’, individuals that smoke, persons that previously smoked, individuals without a smoking history.</p>	<p>We have revised the terminology.</p>	<p>Revised at every instant</p>
<p>72, Surprised how low the 5-year survival rate is. 89, Glad to see AI was considered. 142, Shocking that tobacco use is anticipated to grow to &gt;62% adults by 2025! 187 on, Many other risk factors mor endemic to this area. I have not heard incense often addressed. 229, The EGFR and targetable mutation distributions are fascinating, illustrating the need for personalized risk assessment and management. 267, Imperative that risk modeling evolves and is implemented.</p>	<p>Thank you for your review comments.</p>	<p>-</p>
<p>276, I would advocate 50 – 80 years. 55 – 74 years is generally considered to be archaic by nearly all models presently sourced. Same, 20 Pack-years. Family history is so important and PLCom2012 takes this into account.</p>	<p>We have revised the age criteria per the recent guidelines</p>	<p>Page 12 Lines 323 to 325</p>
<p>331, Risk cut-off of 1.5%, 6 year risk of developing lung cancer, is the eligibility....</p>	<p>We have revised the sentence as per the suggestion</p>	<p>Page 14 Line 392</p>
<p>355, It is unclear if chest radiography refers to chest x-ray or CT here, though CT is most certainly the implication.</p>	<p>We have removed this section based on the inputs of other reviewers</p>	<p>Page 15 and 16 Lines 419 to 434</p>

<p>367 – 370 and beyond, It is interesting and hopeful to see the potential level of consensus and collaboration developing in the MEA. It would be ideal to coalesce the different perspectives and approaches and streamline the implementation of LCS. The differences are too small to preclude a regional effort to promote LCS.</p> <p>376, 25% of LC being found in the early stages is just dismal.</p>	<p>Thank you for the review.</p>	<p>-</p>
<p>380, While the barriers presented are well documented historically, the mounting evidence and experience has formidably debunked these considerations. Programmatic and system-level review and management of discovered LCS and IPNs considerably lessens the potential harm and should be advocated. I would like to know if considerations are given to regional identification, review, tracking, and management; it would go a long way to fostering regional uptake.</p>	<p>Thank you for your comment. We have highlighted the need for a considerate and adaptable approach tailored to each nation's unique characteristics in section 6 “Screening practice for lung cancer across MEA region”.</p>	<p>Page 16 Lines 446 to 450</p>
<p>384, While education continues to present a barrier, this should be easily attainable with a coordinated and multidisciplinary effort.</p>	<p>Thank you for your comment. We have highlighted the benefits of a multidisciplinary approach later in the draft.</p>	<p>Page 19 Lines 528, 552, and 555</p>
<p>389 and beyond, agreeably lack of access and ability to follow-up are realistic barriers and need to be addressed. Sometimes, the necessity demonstrated by a large scale screening program is required to catalyze the build out of supporting networks and capacity.</p>	<p>Thank you for your comment. We have included a sentence on the effect of large-scale screening networks.</p>	<p>Page 17 Lines 476 to 477</p>
<p>425, All good ideas and worthy of consideration and implementation.</p>	<p>Thank you very much for your comments.</p>	<p>-</p>

444, Good, and 'home grown', data is invaluable in moving the dial and garnering provider and administrative buy-in.		
456, Would caution wording here. LDCT LCS is not for patients with overt s and syx of LC, hemoptysis, or unexplained wt loss of 15 lbs in a year.	Thank you for pointing this out. We have removed the mention of LDCT in this context.	Page 19 Line 551
494, Are there efforts to collaborate across MEA borders, or was this meant to be merely a regional assessment of individual nations?	The steering committee meeting was held to discuss the different screening and referral criteria in the individual countries across the MEA region with the aim of collaborating and applying practices across borders.	-
Thank you; I found the article to be intriguing, and somewhat hopeful. With minor modifications, I would most definitely advocate for publication.	Thank you very much for your review.	-