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)	Comparing the diagnostic accuracy of five common tumor biomarkers and CA19-9 for pancreatic cancer: a protocol for a network meta-analysis of diagnostic test accuracy
AUTHORS	Ge, Long; Pan, Bei; Song, Fujian; Ma, Jichun; Zeraatkar, Dena; Zhou, Jianguo; Tian, Jinhui

VERSION 1 – REVIEW

REVIEWER	Ayumu Taguchi Ayumu Taguchi, MD, PhD Assistant Professor The University of Texas MD Anderson Cancer Center USA
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	The protocol is well described. According to the low incidence of pancreatic cancer, in order to actually translate pancreatic cancer biomarkers to the clinic, it is critical to identify pancreatic cancer patients among high risk population. Therefore my suggestion is that it would be useful, if possible, to assess potential of biomarkers in differentiating pancreatic cancer patients from subjects with higher risks of pancreatic cancer, such as benign pancreatic disease (chronic pancreatitis and pancreatic cysts), family history, type 2 diabetes, as well as from healthy controls.

REVIEWER	Ionut Negoi Carol Davila University of Medicine and Pharmacy Bucharest, Emergency Hospital of Bucharest, Romania
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	Thank you for the opportunity to review the interesting manuscript entitled ‘Common tumor biomarkers based-on CA19-9 in the diagnosis of pancreatic cancer: protocol of a network meta-analysis of diagnostic test accuracy’. The authors present an interesting protocol for a diagnostic network meta-analysis. The article has merits to be accepted, after major revision. Major concerns: The title is unclear for me. ‘…based-on CA 19-9…’ Do you mean different combinations of screening strategies, all of them including CA 19.9? In Abstract the authors state the aim “ of CA19-9, CA242, CEA,

	CA125, microRNAs, and K-ras". Will they investigate only CA19.9 biomarker, CA19.9+imagistics, or all of the above? Please clarify! Strengths and limitations: Will the authors discuss the screening or early diagnosis in subgroups of patients (unspecific symptoms, high risk, etc.)? In Introduction: Please specify the highest PPV, NPV, and AUC for different screening tests presented in the literature. In Methods: Please specify the main comparisons which will be included in the network meta-analysis (CA 19.9 vs echography vs. CA 19.9+echo vs. EUS vs EUS vs CA 19.9 vs. microRNA 21, etc..). Minor concerns: Please review the English language of the manuscript. In Methods, you affirm that you will register in PROSPERO database, But at the beginning, you mentioned the registration number from PROSPERO. Please, correct! In Abstract you stated that you would use STATA and R. In Methods you did not specify where you will use R.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Ayumu Taguchi
Institution and Country: Ayumu Taguchi, MD, PhD, Assistant Professor, The University of Texas MD Anderson Cancer Center, USA Competing Interests: None declared

Comment: The protocol is well described. According to the low incidence of pancreatic cancer, in order to actually translate pancreatic cancer biomarkers to the clinic, it is critical to identify pancreatic cancer patients among high risk population. Therefore my suggestion is that it would be useful, if possible, to assess potential of biomarkers in differentiating pancreatic cancer patients from subjects with higher risks of pancreatic cancer, such as benign pancreatic disease (chronic pancreatitis and pancreatic cysts), family history, type 2 diabetes, as well as from healthy controls.

Answer: Thank you very much for your interest to our study. We agree you that it's critical to identify pancreatic cancer among high risk populations. Because present study is based on published diagnostic trials, we have added subgroup analyses based on baseline characteristics of included patients to explore the diagnostic value of biomarkers for different high risk populations (Page 7-8).

Reviewer: 2
Reviewer Name: Ionut Negoi
Institution and Country: Carol Davila University of Medicine and Pharmacy Bucharest, Emergency Hospital of Bucharest, Romania Competing Interests: None declared

Comment: Thank you for the opportunity to review the interesting manuscript entitled 'Common tumor biomarkers based-on CA19-9 in the diagnosis of pancreatic cancer: protocol of a network meta-analysis of diagnostic test accuracy'.
The authors present an interesting protocol for a diagnostic network meta-analysis.
The article has merits to be accepted, after major revision.

Answer: Thank you very much for your interest to our study.

Major concerns:
The title is unclear for me. '…based-on CA 19-9…' Do you mean different combinations of screening strategies, all of them including CA 19.9?

Answer: We are very sorry. We have revised the title and believe it's clearer. Revised title is "Comparing the diagnostic accuracy of single or combination between five common tumor biomarkers and CA19-9 for pancreatic cancer: a protocol for a network meta-analysis of diagnostic test accuracy".

Comment: In Abstract the authors state the aim " of CA19-9, CA242, CEA, CA125, microRNAs, and K-ras". Will they investigate only CA19.9 biomarker, CA19.9+imagistics, or all of the above? Please clarify!

Answer: our objective is to evaluate and compare the accuracy of single and combination tests of CA19-9, CA242, CEA, CA125, microRNAs, and K-ras gene mutation for diagnosing pancreatic cancer. We believe it's clearer now after removing the misleading sentence: "A combination detection between tumor markers, imaging approaches, or tumor markers and imaging approaches might be the future of pancreatic screening."

Strengths and limitations: Will the authors discuss the screening or early diagnosis in subgroups of patients (unspecific symptoms, high risk, etc.)?

Answer: Based on the reporting of original studies, we have added more subgroup analyses including cut-off level and risk factors of patients (such as family history, diabetes). In addition, we add "present meta-analysis will be based on the reporting of included original studies, some expected baseline characteristics of patients may be not reported for subgroup analyses." as our limitation.

In Introduction: Please specify the highest PPV, NPV, and AUC for different screening tests presented in the literature.

Answer: Because of the differences of different studies, and the quality of different studies is not clear, we don't agree to add the highest PPV, NPV, and AUC for different screening tests before systematically assessing these tests. That will mislead the readers. For example, Ma et al.'s study resulted that the PPVs of CA19-9, CEA, CA19-9+CEA were 95.39, 93.33, and 91.14, respectively. That should be high PPV. (Ma Z, Ma Q, Wang Z. An evaluation of the diagnostic value of CA19-9 and CEA levels in patients with pancreatic cancer. Journal of Nanjing Medical University. 2009 May 1;23(3):199-202.) However, most of clinical practice guidelines state CA19-9 with a low PPV. (Takaori K, Bassi C, Biankin A, et al. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. Pancreatology 2016;16(1):14-27.) So in Introduction section, we have revised our description to more clearly explain this problem.

In Methods: Please specify the main comparisons which will be included in the network meta-analysis (CA 19.9 vs echography vs. CA 19.9+echo vs. EUS vs EUS vs CA 19.9 vs. microRNA 21, etc..).

Answer: In eligible criteria section, we have stated that we will compare single and combination tests of CA19-9, CA242, CEA, CA125, microRNAs, and K-ras gene mutation, and each eligible study should assess at least two of these tests, one of them is CA19-9. So the combinations between tests of interest are unpredictable. This is a protocol, we will include all comparison groups involving above tests of interest. However, this is also a meta-analysis, we will base on included studies, and compare all single and combination tests mentioned above. We have stated more clearly in Eligible criteria and Geometry of the network sections.

Minor concerns:
Please review the English language of the manuscript.

Answer: We have checked and revised typographical/ grammatical errors throughout the manuscript

Comment: In Methods, you affirm that you will register in PROSPERO database, But at the beginning, you mentioned the registration number from PROSPERO. Please, correct!

Answer: We are very sorry. We have corrected as “We have registered the protocol on the international prospective register of systematic review (PROSPERO)”.

Comment: In Abstract you stated that you would use STATA and R. In Methods you did not specify where you will use R.

Answer: We are very sorry. We have specified R 3.4.1 will be used to draw network plot (Geometry of the network section) and calculate indirect comparisons.

VERSION 2 – REVIEW

REVIEWER	Ayumu Taguchi The University of Texas MD Anderson Cancer Center
REVIEW RETURNED	18-Oct-2017

GENERAL COMMENTS	I feel that this manuscript is now acceptable for publication.

REVIEWER	Ionut Negoi Carol Davila University of Medicine and Pharmacy Bucharest, Emergency Hospital of Bucharest, Romania
REVIEW RETURNED	20-Oct-2017

GENERAL COMMENTS	The authors made all the suggested recommendations. I think that the manuscript can be accepted in the current form.