Reviewer's report

Title: Does Risk for Ovarian Malignancy Algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: a meta-analysis

Version: 1 Date: 11 March 2012

Reviewer: Toon Van Gorp

Reviewer's report:

The authors perform a meta-analysis on the performance of CA125, HE4 and ROMA as tumor markers for the detection of ovarian cancer or epithelial ovarian cancer. This is interesting because several authors have published conflicting results.

To my opinion the manuscript is not yet ready for publication. The description of the methods and results lack transparency and the whole manuscript is very confusing.

• Major Compulsory Revisions

1) The authors should divide the manuscript into 2 major parts:
   a. Performance of CA125/HE4/ROMA in Ovarian Cancer (OC)
   b. Performance of CA125/HE4/ROMA in Epithelial Ovarian Cancer (EOC)

   The performance of CA125/HE4/ROMA in subsets of patients should be left out of the manuscript since this is not a relevant question. In fact, at the moment the manuscript is confusing and the methods and results section lack transparency. When reading the manuscript it is never clear what kind of analysis is performed. All figures and tables should also be divided in 2 parts or, even better, use different tables for the different outcomes and split all tables/figures.

2) Table 1 only includes 5 studies. It is not clear to me why the other 6 studies are not mentioned. Please also put the studies in alphabetical or chronological order.

3) It is not clear to me how the authors handle different cut-off values when they compare sensitivity and specificity between the different studies. E.g. for HE4 different cut-offs of 70 pM, 72 pM, 74.2 pM, etc. are used. The different cut-offs will influence the sensitivity and specificity to the extent that they are not comparable, and yet, the authors compare the different studies. The same can be said about ROMA (premenopausal 13.1 – 12.5 and postmenopausal 14.4 - 27.7). I have severe statistical concerns about this. To my opinion, only AUC’s can be compared because they do not depend on the different cut-offs.

4) Table 2: it is not clear to me why in most of the studies only one of the index tests is regarded as low concern for applicability and the others high concern for applicability, even when all tests are performed according to standard operating
procedures. ROMA is actually being sold as a combination of 2 EIA’s!! Please look at: http://www.he4test.com/row/professionals/inserts.html So why is the CA125 EIA high concern and the HE4 EIA not?? EIAs are general practice. So the following question: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Should be answered with low.

5) Results section: 2nd paragraph: only reference 15, 17, 18, 20, 22, 23 are mentioned. Why are references 16, 19 and 21 not mentioned? Did they not contribute to the 2879 patients? Again, it is not clear whether you are discussing only EOC or also OC. Please clarify.

6) Please always clarify in the results section which of the studies are being mentioned. For example: “Within 9 of 11 studies, the results interpretation of index tests and reference standard tests were blind with each other.” Which studies?? Another example: “When evaluating patients selection with QUADAS-2, 4 of the total 11 studies with consecutive enrollment were considered as low risk of bias, 2 studies with non-consecutive enrolling were regarded as high risk of bias and 5 studies was unclear.” Which studies?? This should be corrected in the whole manuscript.

7) Figure 3: please provide the reader also with summary forest plots, not only the forest plots of the individual studies

8) Figure 4: please provide information on the studies depicted in this summary ROC graph + provide whether OEC or OC was the outcome

9) Figure 5: again: outcome EOC or OC??

10) The authors fail to mention a comparison between the summary AUC of CA125, HE4 and ROMA with corresponding 95%CI and whether the differences are statically different. The authors refer to Table 3, but this table is very confusing and they do not provide p-values or differences in AUc with the corresponding 95%CI. This information is crucial for the discussion and conclusion whether the use of ROMA will increase the diagnostic accuracy

11) Methods section: LMP tumors and borderline tumors are the same. LMP tumors should not be considered as early stage ovarian cancer. LMP tumours can present as advanced stage as well.

• Minor Essential Revisions

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1) Background: please clearly mention that CA125 is FDA approved, not for the diagnosis of ovarian cancer, but for monitoring disease reponse.

2) Background: CA125 is also less expressed in mucinous tumours. Please correct the third sentence of the second paragraph.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.