

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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obgyn@greenjournal.org.

Date: Mar 07, 2022
To: "Richard George Moore" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-145

RE: Manuscript Number ONG-22-145

The MAGIC Algorithm for the prediction of malignancy in women with a pelvic mass

Dear Dr. Moore:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 28, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The study is of interest to gynecologists who care for women with pelvic masses and rely on serum biomarkers. The manuscript is difficult to follow especially in reference to the goals of the paper, but also to changing terminology throughout the paper.

Objective of study: Initially in the methods this is described as a pilot study to develop algorithms to estimate the risk of malignancy, with as few as 50 women needed. In the abstract though, it appears it was to evaluate if the rare cell gene expression could be detected. The latter seems more of a pilot with the former goal likely requiring a larger population to account for the multiple comparisons. It may be much clearer if the authors start with first describing whether the circulating tumor cells and rare circulating cells were detected and in which of the 62 cancers that were found (20 of which are not GYN origin and 14 of which were uterine). Were there certain gene transcripts from Table 1 that were more closely related to certain cancers? how can these data be used in future for the other cancers?

Results: The broad patient base may not be of benefit in looking at these algorithms as a uterine mass is treated very differently than an ovarian cyst so the serum biomarkers alone would not be the distinctive factor. The authors did differentiate the ovarian cancer in Table 4, which is helpful. In table 4, there are several serum biomarkers tested that are currently used in evaluation -for these comparisons which seem outside the pilot, it would be nice to see a sample size and a discussion of what correction would be used for multiple comparisons. What p-value is relevant with so many comparisons? it is not clear why this evaluation of the serum biomarkers is needed if this is already available in the literature. The focus of the pilot study seems to be the CTC and RCCs and I'd prefer table 4 to show some of the single gene and combined gene expression with serum biomarkers data rather than serum biomarkers alone.

Figure 1 is not needed as the same data are available in Figure 2.

In lines 168-172, it explains what the final gene expressions are in the model- i'd like to know their relevance to the different tumor types.

table 5 - this seems to be the first place that the gene signature is introduced and I'm not sure how those genes were picked over the MAGIC ones?

table 6 - another variable is introduced here which is not well explained. The predictive probability thresholds need to be described in the methods as to how they were set. And it seems that important results are in the figure legend that are not elsewhere in the results regarding AUC for different stages of EOC.

Discussion:

The entire first page of discussion focuses only on the current known biomarkers without mention of CTC, RCCs. Lead with the current results on how the gene expression has enhanced the detection. In lines 241-246 is another iteration of the objective of the study which slightly differs from prior ones. It also explains why the serum biomarkers were checked which

again does not seem important to the current study. I would drop the testing of the other biomarkers that have been well established in the literature and focus a lot more on gene expression from the various tumor types available in this study. lines 251-254 explain why some of the individual gene markers did well but then those are not including in the final algorithm - it would be really helpful to understand the 8 genes included in MAGIC. Overall I think the topic is interesting and there is a lot of potential for the current data to enhance pelvic mass evaluation. The focus of the paper should really be on the gene expression data and the different cancers in the database and how they perform for different situations.

Reviewer #2:

This prospective clinical trial evaluated a liquid biopsy assay combining biomarkers and rare cell gene expression analyses for the detection of malignancy in women with a pelvic mass.

I- INTRODUCTION:

-needs to be expanded to support the rationale for the study.

The MAGIC algorithm is compared to the ROMA and OVA1 which as stated has been approved by the FDA and incorporated in the ACOG guideline. My understanding is that the ROMA is not intended as a screening or stand alone diagnostic assay but must be interpreted with clinical judgement and radiological assessment. In addition the RMI score or IOTA is more widely used (in Canada). Please justify the comparison of the MAGIC to the ROMA algorithm. Has the ROMA or OVA1 algorithms shown to have made a clinical difference in referral and or survival. Please include justification for the need to add gene expression analysis.

II- METHODS: The age range is wide which represents patients with different types of ovarian cancer. Please explain your rationale for the inclusion of the specific biomarkers listed in line 105-107. Why are other biomarkers such as BHCG, Ca 19-9 not included.

III- RESULTS: I found the results reporting very clear and easily comprehensible. The tables and figures were effective. For the menopausal status why do you include the FSH level when menopausal status is a clinical diagnosis with an accepted definition of no menses for one year.

IV- DISCUSSION: The authors report a statistical significant difference between the ROMA biomarkers with AUC =88.9% currently approved and in use vs. AUC=95.1% with the multivariate model combining the expression level of 8 genes and 4 serum biomarkers.

1- Does this statistical significance translate into a clinical difference?

2- Have you considered a cost analysis to ensure the cost effectiveness of using the MAGIC model.

4- How feasible is rare cell gene expression analyses. Is this a technique that is difficult to do? Would the adoption of this MAGIC model be done in only a few specialized centres? It would be important to comment on this in the context of external validity.

Reviewer #3:

Comments to the author:

The authors present a prospective pilot trial looking at predictive models for malignant pelvic masses using rare gene cell expression combined with serum biomarkers. Using univariate and multivariate logistic regression and ROC-AUC they were able to compare different combinations of biomarkers and rare gene cell expression. The results suggest the combination of gene expression and biomarkers (MAGIC algorithm) was superior to any combination or individual screen alone. Other clinically relevant findings were a relatively high sensitivity and specificity for early stage ovarian cancer.

Abstract:

Line 8 Define liquid biopsy. It is not clear from the abstract if this is serum only and or test performed on pathologic tissue.

Introduction:

Line 42 I could not find the algorithm or ACOG endorsement in reference 10. Was this the correct reference for this

statement?

Line 44-47 Expand on other examples like colorectal cancer and gene detection as a screening tool.

Materials and methods:

Line 68-71 Be more specific about pelvic mass. Does this also include clearly seen fibroids? Did all referrals have concerning imaging? Did they also have serum markers drawn? It appears all surgical evaluation was done with gyn/onc so this may bias the sensitivity/specificity of the test. What was the referral process and general practice in the community? Did all patients have an ACOG algorithm marking them as high risk? If so, which one was used?

Line 78 What types of masses had image guided biopsy? Tissue confirmation vs entire specimen will vary by histology. ie it may take multiple fields to get 10 atypical cells HPF for sarcoma vs ascites yield from ovarian cancer.

Results:

Table 1 Explain the purpose of housekeeping genes. The average reader may not be familiar with them. From what I could find "They gain scientific value in two ways. On the one hand they represent the minimal set of genes required to sustain life. On the otherhand Housekeeping genes are widely used as internal controls for experimental studies¹. The reliability of any relative RT-PCR experiment can be improved by including an invariant endogenous control (reference gene) in the assay to correct for sample to sample variations in RT-PCR efficiency and errors in sample quantification. A biologically meaningful reporting of target mRNA copy numbers requires accurate and relevant normalization to some standard and is strongly recommended in quantitative RT-PCR. " <https://www.genomics-online.com/resources/16/5049>

Table 2

Is there more information on other risk factors like parity, family history, BRCA carrier and type of imaging?

Discussion:

Line 212-216 There should also be some discussion of risk stratification using ultrasound scoring indices as well. This can also be used along with biomarkers to improve sen/spec and PPV. *Ultrasound ObstetGynecol*2021 Sep 17. doi: 10.1002/uog.24777. Online ahead of print.

STATISTICS EDITOR COMMENTS:

Table 1: There were 72 variables in this list, minus 13 housekeeping, leaving n = 59 candidate variables. Eight were included within the final model. Given that the number of CA cases = 62, this seems to be an overfitted model. It is likely from inclusion of so many candidates, that some of the inputs may be spuriously associated. In order to support this model, it needs to be applied to a different population of women with benign vs CA.

Table 2: Need units for age. The proportion of cancers (34%) is much higher prevalence than a representative sample of women undergoing procedures for possible CA. That does not influence the metrics of sensitivity, specificity or AUC, but it skews the PPV and NPV values. Should instead cite the LR(+) and LR(-).

Table 4: All AUCs should include CI, and then the p-values are redundant and should be omitted.

Table 5, lines 150-154: Need to show the performance parameters when all serum biomarkers were included in the model, so as to compare with the MAGIC algorithm, which was comprised of 13 variables. All other comparisons in this Table were combinations of fewer than 13 variables.

Table 6: Need to include CIs for all estimates and omit the PPV and NPV. The subsets (premenopausal and postmenopausal) have smaller samples, thus wider CIs and should probably be in supplemental material.

Fig 1: Need to include CIs for the AUC.

Fig 2: Need to include CIs for all AUCs.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
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2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

- * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
- * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."
*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

6. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic

accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

7. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

8. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
- * If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or *précis*. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

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If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 28, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Deputy Editor, Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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REVIEWER COMMENTS:

Obstetrics & Gynecology Manuscript Number ONG-22-145

The MAGIC Algorithm for the prediction of malignancy in women with a pelvic mass.

Cover Letter for Revised Manuscript: ONG-22-145

April 10, 2022

Dear Editorial Staff,

Please find below responses to the reviewers' questions and comments. We have placed the authors responses in "Blue font" for clarity. In each of the responses we have indicated the changes that have been made to the manuscript.

The authors believe this is a much-improved manuscript through the guidance and comments of the reviewers. We feel this is an important trial with findings significant to the practice of gynecology and to the journal Obstetrics and Gynecology.

Transparency declaration statement from the manuscript's lead author Richard G. Moore, MD

The lead author Richard G. Moore, MD affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Thank you for your consideration. We look forward to hearing from you.

Sincerely,

Richard Moore, M.D.

Richard G. Moore, MD, FACS, FACOG

Professor

Chief: Division of Gynecologic Oncology

Director: Targeted Therapeutics Laboratory WCI

Chair: Gynecology Service Line WCI

Wilmot Cancer Institute

Department of Obstetrics and Gynecology

University of Rochester Medical Center

University of Rochester



REVIEWER COMMENTS:

Obstetrics & Gynecology Manuscript Number ONG-22-145

The MAGIC Algorithm for the prediction of malignancy in women with a pelvic mass.

Reviewer #1 Comments:

The study is of interest to gynecologists who care for women with pelvic masses and rely on serum biomarkers. The manuscript is difficult to follow especially in reference to the goals of the paper, but also to changing terminology throughout the paper.

Response to Reviewer 1:

We have made clarifications to the goals of the study and have addressed the issue by changing terminology throughout the manuscript. For instance, Rare Circulating Cells (RCCs) and Circulating Tumor Cells (CTCs) are now referred to together as “captured circulating cells” or “circulating cells captured from blood” throughout the text.

Objective of study:

- *Initially in the methods this is described as a pilot study to develop algorithms to estimate the risk of malignancy, with as few as 50 women needed. In the abstract though, it appears it was to evaluate if the rare cell gene expression could be detected. The latter seems more of a pilot with the former goal likely requiring a larger population to account for the multiple comparisons. It may be much clearer if the authors start with first describing whether the circulating tumor cells and rare circulating cells were detected and in which of the 62 cancers that were found (20 of which are not GYN origin and 14 of which were uterine).*

Response to Reviewer 1:

This was indeed a pilot study to evaluate the detection of malignancy in women with a pelvic mass using multiplexed gene expression analysis of cells captured from peripheral blood samples (Rare Circulating Cells and Circulating Tumor Cells) based on their size and deformability by a liquid biopsy system. We did not specifically identify or quantify Rare Circulating Cells (RCCs) and/or Circulating Tumor Cells (CTCs) in the cells that were captured from the blood samples, but instead isolated mRNA from the captured cells to evaluate the expression of multiple cancer-related genes and housekeeping genes to develop algorithms for the detection of malignancy.

We acknowledge in the revised manuscript that the MAGIC algorithm will need to be tested in a much larger validation study comprised of a cohort of the general population. We have modified the objective statements in the revised manuscript to reflect this.

In response to the reviewer’s comment “62 cancers that were found (20 of which are not GYN origin and 14 of which were uterine)” we note in the revised manuscript that all patient presented with a pelvic mass as the diagnosis. Patients with a previous diagnosis over the past 5 years of a cancer were not eligible for inclusion to the study. Therefore, patients with a known endometrial cancer were not included. Some patients had metastatic cancers to the ovary and endometrial cancer patients presented with pelvic masses prior to their diagnosis of endometrial cancer. It is important to include these patients as they are part of a cohort of women that will present with a pelvic mass. It is also important to assess these patients for a malignancy prior to surgery.

REVIEWER COMMENTS:

Obstetrics & Gynecology Manuscript Number ONG-22-145

The MAGIC Algorithm for the prediction of malignancy in women with a pelvic mass.

- *Were there certain gene transcripts from **Table 1** that were more closely related to certain cancers?*

Response to Reviewer 1:

The majority of the genes we explored were identified through a literature search as being either related to ovarian cancer or to cancer in general. We also included some housekeeping genes to help gauge the quality and quantity of RNA and background cells present in the samples.

We have added in a description of the genes that were included in the final algorithm and their relevance to gynecological cancers.

- *How can these data be used in future for the other cancers?*

Response to Reviewer 1:

In the Discussion section we have added the following comments: “The liquid-biopsy and multiplex gene expression technologies are being investigated for detection of multiple cancer types, including ovarian, endometrial, breast, prostate and lung cancer. The liquid biopsy device (the Parsortix® system) is currently under FDA review for De Novo clearance as a device for the capture and harvest CTCs from the peripheral blood of women with metastatic breast cancer for use in subsequent downstream evaluations”.

Results:

- *The broad patient base may not be of benefit in looking at these algorithms as a uterine mass is treated very differently than an ovarian cyst so the serum biomarkers alone would not be the distinctive factor. The authors did differentiate the ovarian cancers in **Table 4**, which is helpful.*

Response to Reviewer 1:

The patient population included in this study were women diagnosed with a pelvic mass using imaging and who were scheduled for surgery either due to symptoms or to rule out a malignancy. The pathologic diagnosis of the pelvic mass (benign or malignant) was unknown at the time of the enrollment into the study and blood collection. Also, any patients with a diagnosis of cancer concurrently or within the past 5 years were excluded from the trial. Patients with a uterine mass with the diagnosis of an endometrial cancer did not meet enrollment criteria. The women diagnosed with an endometrial cancer in this trial presented with a pelvic mass. This is not uncommon, particularly in patients with uterine papillary serous carcinomas and carcinosarcomas.

The inclusion of all women presenting with a pelvic mass is important, as it represents the general population of women that will be referred to gynecologists and gynecologic oncologist. The inclusion and exclusion criteria have been clarified in the Methods section.

REVIEWER COMMENTS:

Obstetrics & Gynecology Manuscript Number ONG-22-145

The MAGIC Algorithm for the prediction of malignancy in women with a pelvic mass.

*In **Table 4**, there are several serum biomarkers tested that are currently used in evaluation. For these comparisons, which seem outside the pilot, it would be nice to see a sample size and a discussion of what correction would be used for multiple comparisons. What p-value is relevant with so many comparisons?*

Response to Reviewer 1:

As this was a pilot study, no statistically justified sample size was determined, and no corrections were made for multiple comparisons. We were simply trying to determine a combination of biomarkers and genes that were multivariately capable of predicting the presence of malignancy so that the resulting algorithm could be applied prospectively to a larger independent test set. We have added a statement to the discussion of the necessity for a validation trial for the MAGIC algorithm in the general population.

- *It is not clear why this evaluation of the serum biomarkers is needed if this is already available in the literature. The focus of the pilot study seems to be the CTC and RCCs and I'd prefer **Table 4** to show some of the single gene and combined gene expression with serum biomarkers data rather than serum biomarkers alone.*

Response to Reviewer 1:

We agree with the reviewers' comments. Our initial thought was to show how these known biomarkers and biomarker combinations performed in the group of patients enrolled into the study for the detection of malignancy and compare their performance to the genes alone and in combination. We can now see that the presentation of specific biomarker combinations relating to the ROMA, OVA1 and OVERA assays detracted from the primary purpose of the study and have therefore focused on the evaluation of the individual genes, gene combinations and gene/biomarker combinations in the revised manuscript.

- ***Figure 1** is not needed as the same data are available in **Figure 2**.*

Response to Reviewer 1:

We agree with the reviewers' comment. The redundant Figure 1 has been removed from the revised manuscript.

- *In lines 168-172, it explains what the final gene expressions are in the model - i'd like to know their relevance to the different tumor types.*

Response to Reviewer 1:

In this pilot study we were focused on the detection and identification of malignancy alone. We did not perform a sub-analysis of histologic subtypes as there are not enough of any one histologic tumor type within the malignancy group. It did not make sense to break it down by histological subtype.

We have added in a description of the genes that were included in the final algorithm and their relevance to gynecological cancers.

REVIEWER COMMENTS:

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- **Table 5** - *this seems to be the first place that the gene signature is introduced and I'm not sure how those genes were picked over the MAGIC ones?*

Response to Reviewer 1:

We have included additional detail in the data analysis section on how the data was evaluated and the algorithms were developed.

- **Table 6** - *another variable is introduced here which is not well explained. The predictive probability thresholds need to be described in the methods as to how they were set. And it seems that important results are in the figure legend that are not elsewhere in the results regarding AUC for different stages of EOC.*

Response to Reviewer 1:

We have removed the comparison between pre- and post-menopausal women as this is a small sample set and this comparison is not relevant to the objectives of the pilot study. Also, the expression of mRNA in the captured rare cells and CTCs should not vary with menopausal status.

We instead have added in a comparison of the performance for three different multivariate algorithms (the MAGIC algorithm, a gene only algorithm, and a serum biomarker only algorithm) to differentiate between benign (excluding LMP) vs. all cancers.

Discussion:

- *The entire first page of discussion focuses only on the current known biomarkers without mention of CTC, RCCs. Lead with the current results on how the gene expression has enhanced the detection.*

Response to Reviewer 1:

The Discussion portion of the manuscript has been re-written to focus on the CTC technology and the use of CTC gene expression for detection of malignancies. We have only briefly touched on the use of serum biomarkers to provide a background.

- *In lines 241-246 is another iteration of the objective of the study which slightly differs from prior ones. It also explains why the serum biomarkers were checked which again does not seem important to the current study. I would drop the testing of the other biomarkers that have been well established in the literature and focus a lot more on gene expression from the various tumor types available in this study.*

Response to Reviewer 1:

We agree with the reviewer's assessment and as such have focused the revised manuscript on evaluation of the gene expression results and the gene expression results combined with the serum biomarkers to improve prediction.

REVIEWER COMMENTS:

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- *Lines 251-254 explain why some of the individual gene markers did well but then those are not including in the final algorithm - it would be really helpful to understand the 8 genes included in MAGIC.*

Response to Reviewer 1:

We have added detailed descriptions of the genes that were included in MAGIC algorithm.

Overall, I think the topic is interesting and there is a lot of potential for the current data to enhance pelvic mass evaluation. The focus of the paper should really be on the gene expression data and the different cancers in the database and how they perform for different situations.

Response to Reviewer 1:

We agree with the reviewer's assessment and have tried to focus the revised manuscript on the gene expression data.

REVIEWER COMMENTS:

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Reviewer #2 Comments:

This prospective clinical trial evaluated a liquid biopsy assay combining biomarkers and rare cell gene expression analyses for the detection of malignancy in women with a pelvic mass.

INTRODUCTION:

- *Needs to be expanded to support the rationale of the study. The MAGIC algorithm is compared to ROMA and OVA1, which as stated has been approved by the FDA and incorporated in the ACOG guideline. My understanding is that ROMA is not intended as a screening or stand-alone diagnostic assay but must be interpreted with clinical judgement and radiological assessment. In addition, the RMI score or IOTA is more widely used (in Canada). Please justify the comparison of the MAGIC to the ROMA algorithm.*

Response to Reviewer 2:

We agree with the Reviewer that comparison of the MAGIC algorithm to ROMA and other serum-based algorithms is outside of the scope of this manuscript. In the revised manuscript, we have tried to make the objective of this pilot study clearer. As a result, we have focused on the evaluation of the genes, alone and in combination with the serum biomarkers. We have also removed any comparison to ROMA and other serum-based algorithms.

- *Have the ROMA or OVA1 algorithms been shown to have made a clinical difference in referral and or survival?*

Response to Reviewer 2:

Our initial thought was to show how these known biomarkers and biomarker combinations performed in the group of patients enrolled into the study for the detection of malignancy and compare their performance to the genes alone and in combination. We can now see that the presentation of specific biomarker combinations relating to the ROMA, OVA1 and OVERA assays detracted from the primary purpose of the study and have therefore focused on the evaluation of the individual genes, gene combinations and gene/biomarker combinations in the revised manuscript.

- *Please include justification for the need to add gene expression analysis.*

Response to Reviewer 2:

ROMA, OVA1 and IOTA are imperfect and cannot 100% predict the presence of malignancy prior to surgery. The purpose of this pilot study was to evaluate the ability of genes to predict malignancy, with the hope that this would add to the predictive capability of the serum biomarkers. The other benefit of gene expression analysis, including CTC evaluation, is that this would enable the potential for pre-biopsy diagnosis and characterization of the tumor, which you cannot get from serum biomarker and/or imaging evaluations.

REVIEWER COMMENTS:

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METHODS:

- *The age range is wide, which represents patients with different types of ovarian cancer.*

Response to Reviewer 2:

This was an all-inclusive study of any woman with a pelvic mass who was scheduled for surgical evaluation at a single gynecological facility. The primary objective of this pilot study was to show the feasibility of evaluating cancer-related gene expression in cells captured using a liquid biopsy system for detection of malignancy in women with a pelvic mass, not to differentiate between different types of cancer.

- *Please explain your rationale for the inclusion of the specific biomarkers listed in line 105-107.*

Response to Reviewer 2:

ROMA, OVA1, Overa are the approved biomarker algorithms currently in use, and the biomarkers measured in this study are the ones included in one or more of those biomarker algorithms.

- *Why are other biomarkers, such as BHCG and Ca 19-9, not included?*

Response to Reviewer 2:

These biomarkers are not specifically related to ovarian cancer, nor are they included in any currently used multi-biomarker algorithms for pelvic mass differentiation. There are also numerous publications that have evaluated BHCG and CA19-9 in pelvic mass risk assessment and these two biomarkers do not compliment the biomarkers chosen in this study.

RESULTS: I found the results reporting very clear and easily comprehensible. The tables and figures were effective.

- *For the menopausal status, why do you include the FSH level when menopausal status is a clinical diagnosis with an accepted definition of no menses for one year?*

Response to Reviewer 2:

Only reason FSH was included is because it is a biomarker that is included in the OVA1 (Overa) biomarker algorithm. In the original version of the manuscript, we correlated the expression of FSH with menopausal status due to the subjectivity of the menopausal status declaration by the subjects just to show that most of the clinical determinations agreed with the biomarker accepted as being one of menopausal status. However, because this is entirely irrelevant to this manuscript, this correlation has been removed from the first paragraph of the Results.

REVIEWER COMMENTS:

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DISCUSSION: The authors report a statistical significant difference between the currently approved and in use ROMA biomarkers with an AUC = 88.9% vs. an AUC = 95.1% with the multivariate model combining the expression level of 8 genes and 4 serum biomarkers.

- Does this statistical significance translate into a clinical difference?*

Response to Reviewer 2:

We are planning on applying this algorithm to an independent prospective cohort to determine utility. In a pilot study such as this, one cannot assess clinical significance using the same population of patients that were used to generate your predictive algorithms. However, if the results hold up in an independent testing cohort, even an increase of a few percentage points in the identification of malignancy would be expected to have a clinical impact.

- Have you considered a cost analysis to ensure the cost effectiveness of using the MAGIC model.*

Response to Reviewer 2:

This is a pilot study, so not at this point.

- How feasible is rare cell gene expression analyses. Is this a technique that is difficult to do? Would the adoption of this MAGIC model be done in only a few specialized centres? It would be important to comment on this in the context of external validity.*

Response to Reviewer 2:

The capture of CTCs and RCCs is an automated process using the Parsortix system. The isolation of mRNA is a basic laboratory procedure. The analysis of the mRNA will be performed on a multiplexed gene expression chip that will also be automated. Initially, these systems will be made available to isolated CLIA certified labs, but they will eventually be made available to all CLIA certified labs.

REVIEWER COMMENTS:

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Reviewer #3 Comments:

The authors present a prospective pilot trial looking at predictive models for malignant pelvic masses using rare gene cell expression combined with serum biomarkers. Using univariant and multivariant logistic regression and ROC-AUC they were able to compare different combinations of biomarkers and rare gene cell expression. The results suggest the combination of gene expression and biomarkers (MAGIC algorithm) was superior to any combination or individual screen alone. Other clinically relevant findings were a relatively high sensitivity and specificity for early-stage ovarian cancer.

Abstract:

- *Line 8 – Define liquid biopsy. It is not clear from the abstract if this is serum only and or test preformed on pathologic tissue.*

Response to Reviewer 3:

We have revised the objective statement in the abstract to make this clearer. The objective is now stated as follows: “This pilot study was designed to evaluate the detection of malignancy in women with a pelvic mass using multiplexed gene expression analysis of cells captured from peripheral blood based on their size and deformability by a liquid biopsy system.”

Introduction:

- *Line 42 – I could not find the algorithm or ACOG endorsement in reference 10. Was this the correct reference for this statement?*

Response to Reviewer 3:

Thank you for pointing out this erroneous reference. We have corrected the reference to point to ACOG guidelines.

- *Line 44-47 – Expand on other examples like colorectal cancer and gene detection as a screening tool.*

Response to Reviewer 3:

Unfortunately, the limitations on the number of words which may be used in the introduction (250 words) restricts what we are able to say, so we have included only pelvic mass related information.

REVIEWER COMMENTS:

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Materials and methods:

- *Line 68-71 – Be more specific about pelvic mass. Does this also include clearly seen fibroids? Did all referrals have concerning imaging? Did they also have serum markers drawn?*

Response to Reviewer 3:

The patient population included in this study were women diagnosed with a pelvic mass using imaging and who were scheduled for surgery either due to symptoms or to rule out a malignancy. The pathologic diagnosis of the pelvic mass (benign or malignant) was unknown at the time of the enrollment into the study and blood collection. Also, any patients with a diagnosis of cancer concurrently or within the past 5 years were excluded from the trial. Patients with a uterine mass with the diagnosis of an endometrial cancer did not meet enrollment criteria. The women diagnosed with an endometrial cancer in this trial presented with a pelvic mass. This is not uncommon, particularly in patients with uterine papillary serous carcinomas and carcinosarcomas.

The inclusion of all women presenting with a pelvic mass is important, as it represents the general population of women that will be referred to gynecologists and gynecologic oncologist. The inclusion and exclusion criteria have been clarified in the Methods section.

Yes, all women had serum drawn for biomarker testing.

- *It appears all surgical evaluation was done with gyn/onc so this may bias the sensitivity/specificity of the test. What was the referral process and general practice in the community? Did all patients have an ACOG algorithm marking them as high risk? If so, which one was used?*

Response to Reviewer 3:

As this was a pilot study, it was conducted in the GYN/ONC setting to ensure that we had a sufficient number of malignancies to develop our predictive algorithms. If this would have been conducted in a general practice setting, we would have needed a much larger number of patients to obtain a sufficient number of malignancies for evaluation. This trial was designed in a similar manner to the pilot trial for ROMA with a planned validation trial in the general population similar to the FDA recommended study design for ROMA. A validation trial would require approximately 500 patients to achieve the enrollment of 50 patients with cancer. Validation study(ies) will be done in the generalist setting so that we will be able to more appropriately evaluate the algorithm in a population with an incidence of malignancy that more closely represents the general population. Both the ROMA and OVA1 algorithms were developed in a similar manner (i.e. using a high risk population for early development and a more general population for testing/validation).

REVIEWER COMMENTS:

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- *Line 78 – What types of masses had image guided biopsy? Tissue confirmation vs entire specimen will vary by histology. ie it may take multiple fields to get 10 atypical cells HPF for sarcoma vs ascites yield from ovarian cancer.*

Response to Reviewer 3:

The patients who underwent image guided biopsy had imaging findings that were highly suspicious for malignancy. The biopsies had a final pathology with a histologic diagnosis reviewed by a gynecologic pathologist for verification of the malignancy.

Results:

- **Table 1** – Explain the purpose of housekeeping genes. The average reader may not be familiar with them.

From what I could find, they gain scientific value in two ways: A) On the one hand, they represent the minimal set of genes required to sustain life. B) On the other hand, housekeeping genes are widely used as internal controls for experimental studies (https://url.emailprotection.link/?bpoL6cDwtAHwkhMDDNovSTN3_C-uZ8qooG7biTZlifHqjl3BOWIMdosl9hWLu7pTqZtnfl8D_oVYE5tnP0NkGxi0P3upeSKUdd37r2eXaPH1B6NVBqqvUIEO_yjZeKrXUqQd5KMnWl8HaRGUBkOqiXP1S203uvxV1ODcmyzHwvGRnZ_FwuM6SkOy9CObjzGwmC03tOFjWAb9CjG91DY2IUvfogkL9rOKB4ndJOc38BoV_Kp6EpS55FW_e0AR9U08LdUMdYTjeYpeLeGuh_IzlwfSHUhpUAYVzqJlclBjmNxxctqkSRuH5npg-9jDNG2cf33QMi0QPuidnGi3Px2UQ3eXkrEWPZe1SLb6C7zuM3CLPEIFwR2yEur3bqn17nY3j).

The reliability of any relative RT-PCR experiment can be improved by including an invariant endogenous control (reference gene) in the assay to correct for sample-to-sample variations in RT-PCR efficiency and errors in sample quantification. A biologically meaningful reporting of target mRNA copy numbers requires accurate and relevant normalization to some standard and is strongly recommended in quantitative RT-PCR.

Response to Reviewer 3:

The genes we explored were identified through literature as being primarily related to ovarian cancer and/or cancer in general. The housekeeping genes were included to help gauge the quality of the RNA and the relative levels of background cells (primarily white blood cells) present in the lysates. We have added this description into the Materials and Methods section of the revised manuscript.

- **Table 2** – Is there more information on other risk factors like parity, family history, BRCA carrier and type of imaging?

Response to Reviewer 3:

While this type of information could all be used in an algorithm, they were not included because we only wanted to develop an assay that was based on assay results obtained from blood samples and not rely on other subjective information that may or may not be consistently available for all patients.

REVIEWER COMMENTS:

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Discussion:

- *Line 212-216 – There should also be some discussion of risk stratification using ultrasound scoring indices as well. This can also be used along with biomarkers to improve sen/spec and PPV. Ultrasound Obstet Gynecol 2021 Sep 17. doi: 10.1002/uog.24777. Online ahead of print.*

Response to Reviewer 3:

In this pilot study, we are trying to develop a laboratory-based assay. The imaging was only used to verify the presence of a pelvic mass in the patient population.

REVIEWER COMMENTS:

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STATISTICS EDITOR COMMENTS:

Table 1: *There were 72 variables in this list, minus 13 housekeeping, leaving $n = 59$ candidate variables. Eight were included within the final model. Given that the number of CA cases = 62, this seems to be an overfitted model. It is likely from inclusion of so many candidates, that some of the inputs may be spuriously associated. In order to support this model, it needs to be applied to a different population of women with benign vs CA.*

Response to Statistics Editor:

We agree with the Statistics Editors comment: The plan is to develop a predictive algorithm using this population and apply the resulting algorithm to an independent sample set for verification of its performance.

Table 2: *Need units for age. The proportion of cancers (34%) is much higher prevalence than a representative sample of women undergoing procedures for possible CA. That does not influence the metrics of sensitivity, specificity or AUC, but it skews the PPV and NPV values. Should instead cite the LR(+) and LR(-).*

Response to Statistics Editor:

Age values are in years. We have included LR(+) and LR(-) in our evaluations.

Table 4: *All AUCs should include CI, and then the p-values are redundant and should be omitted.*

Response to Statistics Editor:

95% CI's have been included for all ROC-AUC values and p-values for each individual logistic regression model have been removed in the revised manuscript.

Table 5, lines 150-154: *Need to show the performance parameters when all serum biomarkers were included in the model, so as to compare with the MAGIC algorithm, which was comprised of 13 variables. All other comparisons in this Table were combinations of fewer than 13 variables.*

Response to Statistics Editor:

This table has been modified based on the new results presentation plan to focus on the genes and genes + biomarkers. However, for each of the multivariate logistic regression models, we let the software chose the variables by using backwards stepwise logistic regression. This has been added to the data analysis description in the Methods section.

Table 6: *Need to include CIs for all estimates and omit the PPV and NPV. The subsets (premenopausal and postmenopausal) have smaller samples, thus wider CIs and should probably be in supplemental material.*

Response to Statistics Editor:

Evaluation of results by menopausal status have been removed.

REVIEWER COMMENTS:

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Fig 1: *Need to include CIs for the AUC.*

Response to Statistics Editor:

95% CI's have been included for all ROC-AUC values and p-values have been removed in the revised manuscript.

Fig 2: *Need to include CIs for all AUCs.*

Response to Statistics Editor:

95% CI's have been included for all ROC-AUC values and p-values have been removed in the revised manuscript.

REVIEWER COMMENTS:

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EDITORIAL OFFICE COMMENTS:

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2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

- Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-bylines authors).
- Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- Name the IRB or Ethics Committee institution in the Methods section (if applicable).
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4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: *"The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been*

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explained." *The manuscript's guarantor. If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

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- For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). **Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted.** Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race. Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

Not Applicable

- Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://url.emailprotection.link/?bsoawhyrjZqpxgliP2mCKGuToLQ0Q2QsWHZc2aA9mUe0t5rQ8zhVctPOypYlbErdM9ziRbHdRUMhd0aw97hULQDsJB917tyS61ltGCbidUJkQoonucGgotvvTO3DRPUvLX5HoKBVpqV2GS6qsyvnayeMs4bykbrHBt6MYC4Ewe8qq5CVIDssop Rt4ONNip-3OdIWtWoYZuBuli0WHjAof2Dx7R09uLFwRiDCI6EXk5wyv9TxJ3x5Ub_WPwN2T-ntQ50Xs7OSbyi39rnAE9T1KhTSosVZVXAfy2zsxsC6Av0B0qjwGWw-

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[yld_v8vl7cECazYL1_e3cnM1b_fKNu0qos6Eyo5x_2i2Ant0YjcVdemPkODqivBFk_y52kjZoG](#). In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

7. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://url.emailprotection.link/?bv1aaXG3ECb9dgKAKb_zXWavC5gimp2II9lee_6lf_LhYTSHDSNQ-987akMnaHnpnabME71mM7EWb4GqI5bnmWFWT4BRGaRU7kLNRt-evuo2Hukd2aITelxfCufgraGO-VxD6clheVAi_zD8_4jigxXX97P7aoayif2OdubNkIXfyRynow5nnu3EeH5nSXNk5RIRH-k0Am75wZ1Y9oroZMGgQheGzIz8DpwY8mDSU-A_1qgzXi9_FF3r3mx3fH6663RlyN-r-rNyM1NbX3LAdT0uk-484mKII-68WetI7ECiftkoUrp63QHbSQ0ExxfXjC-LidWnHx_wyJ2C1eEKvUt-NJNtJAn4igEQubcfZ26nOjCQYFTu9JQ8Nj2BU8uONO3zxM4ACmVKhCRaXglVYPnXMoOYozjd4YnPV3TSCGJWcEs4tvzn_FvmdHDNK8GnVVHmWvh481C1Z607SaobE6A~~ and the gynecology data definitions at https://url.emailprotection.link/?bEJOUT7Qkiai3H0bhqUTT0YftZGmhuRF7iu7S1kp4CrO0DgTGFrNNDxleZGw-npg-yg6xFtfb8M8vA7xhlmjgsirt4i7_V9Pjq3uyebZdT5zA7WtyT8hTXgxic9BulnSMsuBtfa6oaSpMqlfW3hwC33L3bgMSsaHVJrJ2_tBAWh9Q2o4q0L5o0E8Mr80oSHLGamE-KC5n000hTt-l-a67nQHQ_O68Bp6bWASh00Euv_FgMBD54HpxgSEUyr-oCtP-8vA-aMi1LpndMjsGjb_N5Z8FzJFYjQXvNbR96fHmLGL--5KMFPqoT_OwgXySdDH4ig_IE1e0Hfg8FMFnYiuF4wbwJoc0hcHf-Zp2E_5rJigwEMlghQYrgpUiOe1-zYtCOL357IWY4a8IARj8s_osPuXxQ-txeiE8vFRISHVGfQ71WV7aX6gHrQHtSkIGEUPlWlw0f0r1CkgbHQgIKw~~. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
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