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)*
- Email correspondence between the editorial office and the authors*

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

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Jul 20, 2018

To: "Elizabeth Suh-Burgmann"

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-18-1193

RE: Manuscript Number ONG-18-1193

Prospective validation of ultrasound-based ovarian cancer risk assessment in a large community-based population

Dear Dr. Suh-Burgmann:

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).

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 Aug 10, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This manuscript describes the performance of a quantitative system assigned to ultrasound-based characteristics of adnexal masses in the prediction of ovarian cancer.

It is a large population based cohort that prospectively follows these patients to the appropriate outcomes of either histologic results at surgery or minimum one-year clinical follow-up.

Overall, the manuscript is well written and easy to read.

1. The categories 0, 1, 2, 3 and X were predictive of outcomes, but this correlation has been well established in many other papers on this topic, some of which you mentioned (IOTA) and others that you did not (Univ of Kentucky morphology index, web-based OTI as described by Twickler et al, just to name a couple). Notably, your category scale closely mirrored the descriptive categories described in the 2010 "Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement", another paper that I do not believe was cited. Although it was reassuring to see the ultrasound-based criteria perform well in prediction of malignancy in your large community-based population, I do not know that this study provides enough new information on the subject to warrant publication in this journal.

Reviewer #2: Suh-Burgmann and colleagues examined performance of a system the standardized ultrasound reporting for ovarian cancer risk assessment. Comments for the authors:

Abstract

1. Recognizing that space is limited, some indication of what the various categories of findings are would be helpful.

2. "Correlated" should be replaced with associated or other similar terminology.

3. The risk of cancer for a category 1 ultrasound was 0.2% vs. 0.1% for normal/benign findings. It seems that this category would be of little clinical utility.

Introduction

4. Introduction is well written.

5. Line 79-80 are difficult to follow and should be reworded.

Methods

6. Clarify whether this was a prospective cohort study or a retrospective review of patients during a 1 year period. Would seem to be the later if patients were not consented and followed in some way prospectively.

7. If a patient with a mass/cyst did not undergo surgical evaluation were they assumed to have benign findings? If so could this bias the results?

8. If a patient underwent surgical evaluation at another institution was this captured?

9. Some description of the training and characteristics of the ultrasound providers need to be included. Given the somewhat subjective nature of some of the criteria this could have an important influence on diagnostic accuracy.

Results

10. Correlation should be removed. This is the association between two continuous variables.

11. How are age-standardized risks for ovarian cancer determined in this context (lines 194-196)?

12. It would be very useful to report results stratified by age.

13. Should consider including performance characteristics (sensitivity, specificity) for each category of tracing.

Discussion

14. There needs to be a description of how this specific grading system has previously performed in other populations.

Reviewer #3: I applaud this study. I think it is so important that we devise a system for ovarian cancer risk assessment by ultrasound in a community based setting.

I feel the revision of Category 0 from 2016 to 2017 (lines 241-246) was appropriate. Although stated in line 243 that this complicated" interpretation of outcomes" which I am not clear on exactly what this means, I think the initial Category 0 was to broad for the community based radiologist.

I also think another limitation, which the authors acknowledge, is lack of expert review (lines 274-277). I think if expert review correlated with the community based U/S findings it would further validate the findings.

STATISTICAL EDITOR'S COMMENTS:

1. lines 49-50: Although it is cited in Results, it would be worthwhile to cite the counts among the 36,768 with ovarian cancer (n = 38).

2. lines 205: The study design allows for associations, not prediction or causation.

3. Table 3: Should cite the meaning of the estimates (adjusted odds ratios). The odds are a useful metric, but ovarian cancer is relatively rare, so a "number needed to examine" to identify a case of ovarian CA would be useful information, but Categories 2, 3 and X are referenced to Category 1.

5, Suppl table 2: The top row of this deserves citation in the main text. However, the format, rather than citing small percentages, should be in terms of reciprocals, including CIs and contrasting the rates of ovarian CA with the Normal/0 group. For example, for the normal U/S group the rate was 1:968, with CI: 1:1367-1:708. Should also cite whether the rates of the normal/0 group were statistically different from the Category 1 rate. I do not see the actual counts in the text, but using the rates and CIs of Suppl Table 2, I presume the counts of ovarian cancer for categories 1, 2, 3 and X were 8, 18, 15 and 48, for a sum of 89. If the counts are correct, then the rate for category 0 is statistically indistinguishable from Category 1 and those categories comprise the majority of the patients. It is only for Categories 2, 3 and X that the rates are significantly higher than for the other groups, ranging from 1:8 to 1:78 examinations. Unfortunately, Categories 0 and 1 comprised 95% of the exams, while including 46 of 127 cases of ovarian CA. So, the U/S system does satisfactorily stratify risk, it is far from perfect and unfortunately > 1/3 of ovarian CA cases had low risk U/S.

6. Also, the CIs for the rates in Suppl Table 2 appear to be calculated based on assumption of normality. The counts and percentages are relatively low and the CIs should be based on a binomial or Poisson model, not normality.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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, as well as subsequent author queries. 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:
    1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
    2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Based on the forms that have been submitted the following people have not met the criteria for authorship. Elizabeth Suh-Burgman, Tracy Flanagan, Todd Osinski, Mubarika Alavi. On the third page of the agreement form, under the section labeled "Authorship," items #2-4, in addition to either 1a or 1b, MUST be checked off in order to qualify for authorship. These contributors should be moved to the acknowledgments, or they could resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

3. 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.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

6. 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 22 typed, double-spaced pages (5,500 words. Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of…" or "Comprehensive investigations into…" or "A discussion of…" should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 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. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

15. 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.

16. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 2: Please upload a high res version of this figure (tiff, eps, jpeg)."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

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.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

* * *

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Aug 10, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

If you would like your personal information to be removed from the database, please contact the publication office.

August 5, 2018,

RE: Manuscript Number ONG-18-1193

Dear Editorial Board,
Thank you for your careful review of our manuscript "Prospective validation of ultrasound-based ovarian cancer risk assessment in a large community-based population," and for the opportunity to respond to your comments, and the comments of the reviewers.

Please find our point by point responses to reviewer comments below. We have submitted a revised manuscript using the "track changes" function, reflecting the revisions made, as well as a clean copy.

 REVIEWER COMMENTS:

Reviewer #1: This manuscript describes the performance of a quantitative system assigned to ultrasound-based characteristics of adnexal masses in the prediction of ovarian cancer.

It is a large population based cohort that prospectively follows these patients to the appropriate outcomes of either histologic results at surgery or minimum one-year clinical follow-up.

Overall, the manuscript is well written and easy to read.

1. The categories 0, 1, 2, 3 and X were predictive of outcomes, but this correlation has been well established in many other papers on this topic, some of which you mentioned (IOTA) and others that you did not (Univ of Kentucky morphology index, web-based OTI as described by Twickler et al, just to name a couple). Notably, your category scale closely mirrored the descriptive categories described in the 2010 "Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement", another paper that I do not believe was cited. Although it was reassuring to see the ultrasound-based criteria perform well in prediction of malignancy in your large community-based population, I do not know that this study provides enough new information on the subject to warrant publication in this journal.

We appreciate that there have been several previous algorithms in addition to those described by the IOTA group but in the interest of space, did not present a comprehensive literature review in our Discussion. The Society of Radiologists in Ultrasound Consensus Conference Statement was included as citation number 10 (now number 9) in our References. We also agree that the criteria used by our system overlaps with those used by other strategies and consider the organized application of these criteria in our population to be the main point of the report, not the criteria themselves. We regret that we did not make the objective more clear and have added the following to the Discussion to clarify: "While generally accepted knowledge exists regarding the ultrasound characteristics associated with malignancy, which is reflected in the overlap between our system and other ultrasound-based risk assessment strategies (9, 16-20), few if any prior studies have described applying that knowledge to a community-based population using structured reports. In our view, the ability to optimally care for women with adnexal masses suffers less from a lack of knowledge about the ultrasound characteristics associated with malignancy than a failure to systematically apply that knowledge to every woman's case."

Reviewer #2: Suh-Burgmann and colleagues examined performance of a system the standardized ultrasound reporting for ovarian cancer risk assessment. Comments for the author:

Abstract

1. Recognizing that space is limited, some indication of what the various categories of findings are would be helpful.

Due to the word limitation of the Abstract we are unable to list the criteria for each category. However, we revised the Methods section of the Abstract to include a brief description of the types of ultrasound features used to determine categorization:
"Methods: Prospective community-based cohort study of average-risk women undergoing ultrasound in 2016 using a reporting system that requires adnexal masses to be categorized as 1, 2, 3, or X based on standardized ultrasound criteria including size, presence of solid components and vascularity assessed by Doppler."

2. "Correlated" should be replaced with associated or other similar terminology.
We have replaced "correlated" with "associated" in the abstract and throughout the text.

3. The risk of cancer for a category 1 ultrasound was 0.2% vs. 0.1% for normal/benign findings. It seems that this category would be of little clinical utility.

To clarify the potential clinical implications of our findings, we have added the following sentence to the Discussion: "Our system enabled identification of a higher risk subset (10%) of women with Category 3 or X masses who are more likely to benefit from surgical referral, while identifying 70% of women as having Category 1 masses, which were associated with a risk of cancer similar to that of women with normal studies. The goal of management for these women should be avoidance of harm."

Introduction

4. Introduction is well written.

5. Line 79-80 are difficult to follow and should be reworded.

We have reworded and shortened the sentence to the following: "To address this problem, we created a system designed to standardize ovarian cancer risk assessment for adnexal masses on ultrasound and be usable by radiologists with varying levels of ultrasound expertise."

Methods

6. Clarify whether this was a prospective cohort study or a retrospective review of patients during a 1 year period. Would seem to be the later if patients were not consented and followed in some way prospectively.

The study is a prospective cohort study as it was designed prospectively, with the study population identified at the time of exposure of undergoing ultrasound in 2016, prior to the development of the outcomes of interest. The study population was then followed until December 31, 2017.

7. If a patient with a mass/cyst did not undergo surgical evaluation were they assumed to have benign findings? If so could this bias the results?

Patients who did not undergo surgical removal and were not otherwise diagnosed with malignancy during the follow-up interval (median 18 months, range 12-24 months) involving the adnexa are assumed to have benign disease. We discuss this as a limitation in our Discussion: "Not all cancer outcomes may have been captured in the follow-up period (median 18 months, range 12-24 months). However, high grade ovarian cancers which are responsible for 80-90% of ovarian cancer deaths are generally aggressive (29,30) and would be expected to become clinically evident within short time intervals. Screening trial data support a time to diagnosis of less than 12 months for cancers diagnosed after abnormal ultrasound (31, supplemental tables)."

8. If a patient underwent surgical evaluation at another institution was this captured?

Surgical removal finding cancer at outside institutions within the state would have been captured through our exchanges with the California Cancer Registry. To address this question in the manuscript, we have added the following to the Discussion:"Although some patients may have had surgery at outside institutions, the closed nature of the health care setting reduces the likelihood of undetected surgical procedures. Cancer diagnoses made at outside institutions within California would still have been captured through the organization's participation in the California Cancer Registry."

9. Some description of the training and characteristics of the ultrasound providers need to be included. Given the somewhat subjective nature of some of the criteria this could have an important influence on diagnostic accuracy.

We have added the following sentence to the Methods: "In the organization, reports are read by approximately 300 radiologists, of whom 15-20% have completed fellowship training in either women's imaging or body imaging and 1% in pelvic ultrasound specifically."

Results

10. Correlation should be removed. This is the association between two continuous variables.

We have revised the text to remove the word correlation.

11. How are age-standardized risks for ovarian cancer determined in this context (lines 194-196)?

We describe in our Methods section how age-standardized risks were determined: "Age-standardized risks of ovarian cancer diagnosis were calculated using weights based on the 2000 US standard population from the Census P25-1130 estimates."

12. It would be very useful to report results stratified by age.

We have expanded our discussion of Figures 3a and 3b to the following:
"Figures 3a and 3b show the risk of cancer or borderline tumor stratified by age groups 18-39 years, 40-49 years and 50 years and older. While absolute risk was lower for younger women, Category 3 and X masses were associated with higher risk, compared to Category 1 and 2 masses, of both ovarian cancer

diagnosis (Figure 3a), as well as ovarian cancer or borderline tumor diagnosis (Figure 3b) for women in all three age groups."

13. Should consider including performance characteristics (sensitivity, specificity) for each category of tracing.

In this study, the risk of cancer in each category is equivalent to the specificity, i.e., it is the number of test-positives who are true positives. We now present the number needed to examine for each category, as suggested by the Statistical Editor, in Table 3 and in our discussion of Results, as we agree that this is more clinically meaningful expression of these findings. We cannot compute sensitivity, because the study was not designed to assess every case for cancer, which would be required to achieve a true gold standard. We also do not focus on sensitivity and specificity as we do not consider our standardization system to be a diagnostic test for ovarian cancer, but rather a tool in a diagnostic process that informs further evaluation and management, along with other clinical factors. For many women, management includes repeat interval ultrasound which provides additional data.

Discussion

14. There needs to be a description of how this specific grading system has previously performed in other populations.
This is the first report of the performance of this specific system as it had not been applied to previous populations.

Reviewer #3: I applaud this study. I think it is so important that we devise a system for ovarian cancer risk assessment by ultrasound in a community-based setting.

I feel the revision of Category 0 from 2016 to 2017 (lines 241-246) was appropriate. Although stated in line 243 that this complicated" interpretation of outcomes" which I am not clear on exactly what this means, I think the initial Category 0 was too broad for the community-based radiologist.
Thank you. We agree with your assessment. In the discussions leading to the development of the system, the inclusion of "classic" appearing endometriomas, dermoids and hydrosalpinges in Category 0 was favored primarily by ultrasound fellowship trained radiologists who were comfortable with these definitive assessments but they did not prove to be descriptions that the majority of radiologists were comfortable applying. Ultimately, we felt that their inclusion introduced heterogeneity that complicated the goal of assessing cancer risk associated with specific ultrasound features.

I also think another limitation, which the authors acknowledge, is lack of expert review (lines 274-277). I think if expert review correlated with the community-based U/S findings it would further validate the findings.
We agree that correlation with expert review would be of potential interest. However, expert review for over 40,000 studies was not practicable. Also, we aimed to evaluate the performance of the system in the hands of non-expert community radiologists.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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, as well as subsequent author queries. 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:

   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

We OPT-IN: Please publish our response letter and subsequent email correspondence related to author queries.

2. Based on the forms that have been submitted the following people have not met the criteria for authorship. Elizabeth Suh-Burgman, Tracy Flanagan, Todd Osinski, Mubarika Alavi. On the third page of the agreement form, under the section labeled "Authorship," items #2-4, in addition to either 1a or 1b, MUST be checked off in order to qualify for authorship. These contributors should be moved to the acknowledgments, or they could resubmit a revised author agreement form if they filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

We have uploaded corrected author agreement forms.

3. 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.

The lead author, Elizabeth Suh-Burgmann, 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.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

The study was approved by the Kaiser Permanente Institutional Review Board. This is noted in the Methods section as well.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

We have corrected any inappropriate use of definitions.

6. 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 22 typed, double-spaced pages (5,500 words. Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).
Please limit your Introduction to 250 words and your Discussion to 750 words.

We have revised the Introduction to be limited to 250 words (245 words) and the Discussion to be limited to 750 words (713 words). As two-thirds of the original Discussion was devoted to discussion of limitations, to achieve the word count we substantially shortened the discussion of limitations, including deleting the paragraph describing ultrasound indication: "Our evaluation of ultrasound indication was extracted from the history section of reports which may have variable accuracy. Due to the rarity of cancer outcomes, ovarian cancer and borderline tumor outcomes were combined to enable inclusion of indication in multivariable modelling. With pain as the reference, the only other symptoms associated with cancer or borderline outcome were "mass," "evaluation of other cancer," and "postmenopausal bleeding." We did a detailed evaluation of cases associated with "evaluation of other cancer" and found that approximately a third represented cases of endometrial cancer associated with a dual primary ovarian cancer, which is a well-described phenomenon (32). "

Following edits to respond to reviewer comments and for brevity, the title page, précis, abstract, text and references together comprise 16 pages and 4120 words. The original Tables and Supplemental information initially brought the page count to 27 and 6148 words. To achieve the word and page count limit, we therefore deleted Table 4 (histologic detail of tumors found), citing the key findings in the text, Supplemental Table 1 (ICD-10 codes), listing these instead in the text, Supplemental Table 2 (sensitivity analysis), citing the overall result in the text, and Supplemental Table 3 (revised Category system in use in 2018). We added a new Table 3 to present a clearer presentation of the risk data requested by the Statistical Editor, including absolute counts and risk expressed as number needed to examine. We also shortened the previous Table 3 (multivariable regression, now Table 4), by not displaying the non-significant adjusted odds ratios associated with Charlson morbidity index, outpatient utilization and those ultrasound indications that were both not significantly associated and not clinically expected to be predictive of malignancy.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

We have revised the title to be less than 100 characters (96 characters including spaces).

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

We have added to the Acknowledgements persons who contributed to the early development of the system and persons who critically reviewed the manuscript prior to submission. The study has not been previously presented.

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

We have revised the short title to be under 45 characters (44 characters) including spaces.

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.
In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

The word count of the Abstract is 288 words.

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.
We have corrected the use of any non-standard abbreviations.

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.
We have revised the manuscript to remove these symbols and phrases.

13. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Although we are not aware of a similar analysis of a standardized ovarian cancer risk assessment system implemented for a large population-based cohort, we appreciate the concern and have removed the explicit claim of first report as we feel a literature review to justify the comment would be a poor use of space in the Discussion.

14. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

We have shortened the Discussion to be under 750 words and have reframed the first paragraph to emphasize the clinical implications of our work.

15. 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.

We find no errors to the Table format.

16. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 2: Please upload a high res version of this figure (tiff, eps, jpeg)."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.
When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).
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.

We have converted Figure 2 to the TIFF format and have submitted this as well as the PDF generated directly from SAS.

STATISTICAL EDITOR'S COMMENTS:

1. lines 49-50: Although it is cited in Results, it would be worthwhile to cite the counts among the 36,768 with ovarian cancer (n = 38).

We have changed the sentence to "Among 36,768 (84%) women with normal or benign adnexal findings reported, 38 women were diagnosed with ovarian cancer, for a risk of 0.1% (95% CI, 0.07%-0.14%)."

2. lines 205: The study design allows for associations, not prediction or causation.

We have corrected the sentence to refer to association.

3. Table 3: Should cite the meaning of the estimates (adjusted odds ratios). The odds are a useful metric, but ovarian cancer is relatively rare, so a "number needed to examine" to identify a case of ovarian CA would be useful information, but Categories 2, 3 and X are referenced to Category 1.

We have revised the multivariable regression analysis presented in Table 3 (now Table 4) to use Category 0 as the reference and have added text to cite the adjusted odds ratios in the Results.

We address the recommendation to present risk as "number needed to examine" in the response to the next comment.

5, Suppl table 2: The top row of this deserves citation in the main text.

This data is cited in the Results (lines 188-191 in original submission pdf) in reference to Figure 2a.

However, the format, rather than citing small percentages, should be in terms of reciprocals, including CIs and contrasting the rates of ovarian CA with the Normal/0 group. For example, for the normal U/S group the rate was 1:968, with CI: 1:1367-1:708.
Should also cite whether the rates of the normal/0 group were statistically different from the Category 1 rate. I do not see the actual counts in the text, but using the rates and CIs of Suppl Table 2, I presume the counts of ovarian cancer for categories 1, 2, 3 and X were 8, 18, 15 and 48, for a sum of 89. If the counts are correct, then the rate for category 0 is statistically indistinguishable from Category 1 and those categories comprise the majority of the patients. It is only for Categories 2, 3 and X that the rates are significantly higher than for the other groups, ranging from 1:8 to 1:78 examinations.

We have reorganized the presentation of the risk data in a new Table 3, to show both the absolute counts and risks associated with each category, as incidence rates as well as by "reciprocal" or number needed to examine, with 95% CIs.

We concur that the rate of cancer for Normal/Category 0 is not statistically different than that of Category 1 (P=0.21). However, for the combined outcome of either ovarian cancer or borderline tumor, which is the outcome we evaluated by multivariable logistic regression, there is a statistically significant difference between Category 1 compared to Category 0 (P<0.001).

In the first paragraph of the Discussion we added the following to point out the similarity between risk for Category 1 and Normal/Category 0 for cancer specifically: "…70% of masses were identified as Category 1, which were associated with a risk of ovarian cancer similar to that of women with normal or benign studies."

Unfortunately, Categories 0 and 1 comprised 95% of the exams, while including 46 of 127 cases of ovarian CA. So, the U/S system does satisfactorily stratify risk, it is far from perfect and unfortunately > 1/3 of ovarian CA cases had low risk U/S.

We agree with the observation that while the system overall stratified risk among our low-risk population, many cases of cancer were not captured by high risk categorization at initial ultrasound. As we noted in our Methods: "Cancers diagnosed by cytology or biopsy only were classified as primary ovarian if results indicated adenocarcinoma of likely gynecologic origin and there was no evidence of another primary site," so it is possible that some cancers categorized as "Normal" or Category 0 represented primary peritoneal cancers which are often not associated with adnexal masses. We chose to include these cases as ovarian cancers in order for any bias introduced by this judgement to be against, not in favor, of an association between ovarian cancer diagnosis and the high risk category scores.

As we discussed in our initial cover letter, we do not consider the initial ultrasound categorization to be a stand alone diagnostic test for cancer but rather a tool in the process of diagnosis. A clinical Practice Resource document accompanied the roll-out of the system in which we emphasize the importance of considering other clinical factors such as symptoms, elevated CA 125 level, or abnormal physical exam findings when determining management, and recommend initial follow-up studies at intervals of 6 weeks for category 2 masses and 12 weeks for category 1 masses to observe for interval change for women not having immediate surgery.

We also see the system as enabling its own improvement over time. Because of it, we can now identify and analyze cases of cancer not captured by high risk categorization to identify quality improvement opportunities in radiology as well as inform revisions to improve its performance. Indeed, we have already revised the system twice based on analysis of outcomes and expect this iterative process of improvement to continue.

6. Also, the CIs for the rates in Suppl Table 2 appear to be calculated based on assumption of normality. The counts and percentages are relatively low and the CIs should be based on a binomial or Poisson model, not normality.

The CIs were calculated using the binomial distribution in SAS.

Again, we appreciate the time and attention spent by the Editorial board and Reviewers and feel the changes have strengthened the manuscript. Should additional questions or need for revision remain, we hope to have the opportunity to respond.

Elizabeth Suh-Burgmann, MD
Tracy Flanagan, MD
Todd Osinski, MD
Mubarika Alavi, BS
Lisa Herrinton, PhD

Re: Manuscript Revisions: ONG-18-1193R1

Daniel Mosier

Tue 8/21/2018 12:31 PM

Sent Items

To:Betty J Suh-burgmann ████████████████████

Dr. Suh-Burgmann,

The Journal's Manuscript Editor is finalizing her review of your manuscript. We're currently looking to put this in our November 2018 issue (publishing in October). The proofs will arrive before September 19th. The Manuscript Editor will contact you directly once they are ready.

Sincerely,
-Daniel Mosier

From: Betty J Suh-burgmann ████████████████████
Sent: Tuesday, August 21, 2018 9:38:41 AM
To: Daniel Mosier
Subject: Fwd: Manuscript Revisions: ONG-18-1193R1

Dear Mr. Mosier,
I'm wondering if you could update me on the status if this submission. I'm going to be traveling for the next few weeks and will have limited access to my email for some of that time so am trying to anticipate items that will need attention.
Thanks very much,
Betty Suh-Burgmann, MD

Sent from my iPhone

Begin forwarded message:

> **From:** Betty Suh-burgmann ████████████████████
> **Date:** August 13, 2018 at 1:17:51 PM EDT
> **To:** Daniel Mosier <dmosier@greenjournal.org>, ████████████████████████████
> **Subject:** RE: Manuscript Revisions: ONG-18-1193R1
>
> Dear Mr Mosier,
> Thank you for your message and we thank the Editorial Board for their consideration of our revised manuscript.
>
> We agree with all the suggested edits made by the Editor, including:
> 1. Replacement of "ultrasound" with "ultrasonography" in the title, precis and in the other indicated places in the text.
> 2. Replacement of "ultrasound" with "ultrasonogram" in the indicated places in the text.
> 3. Changes to the attestations regarding conflict of interest, authorship and funding.
> 4. Change of "10%" to "9-10%" in the Abstract and Discussion.

5. Change of heading from "Methods" to "Materials and Methods."
6. Removal of subheadings "Study Design, Participants and Setting" in the Material and Methods section and "Cancer Outcomes" from the Results section.
7. Replacement of the cited ACOG Practice Bulletin No. 83 with PB No. 174. We have reviewed the current Practice Bulletin and the information is still consistent with the citation.

We have attached a revised track changed version in which these changes are made (the submission is not open to editing on the Editorial manager site, but please let us know if we should upload this directly).

Again, thank you for your time and attention to the manuscript.

Elizabeth Suh-Burgmann, MD

From: Daniel Mosier <dmosier@greenjournal.org>
Sent: Monday, August 13, 2018 7:49 AM
To: Betty J Suh-burgmann ███████████████████████████
Subject: Manuscript Revisions: ONG-18-1193R1

Caution: This email came from outside Kaiser Permanente. Do not open attachments or click on links if you do not recognize the sender.

Dear Dr. Suh-Burgmann,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 293: Practice Bulletin No. 83 was replaced with PB No. 174. Please review PB 174 to be sure it supports what you are citing. The Practice Bulletins are available at https://www.acog.org/Clinical%20Guidance%20and%20Publications/Practice%20Bulletins%20List

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Wednesday, August 15th.**

Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology

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Web: http://www.greenjournal.org

Dear Ms Casway,

Thank you for your message and for the editing of the figures and legends. Both myself and my statistician have reviewed them and find no errors or omissions.

Kind regards,
Betty Suh-Burgmann, MD

From: Stephanie Casway <SCasway@greenjournal.org>
Sent: Thursday, August 16, 2018 7:05 AM
To: Betty J Suh-burgmann ████████████████████████████████
Subject: O&G Art Revision: 18-1193

Caution: This email came from outside Kaiser Permanente. Do not open attachments or click on links if you do not recognize the sender.

Good Morning Dr. Suh-Burgmann,

Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Monday, 8/20. Thank you for your help.

Best wishes,

Stephanie Casway, MA
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