OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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.*

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: Jun 14, 2019
To: "George R. Saade" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-966

RE: Manuscript Number ONG-19-966

Mind the (Gestational Age) Gap!

Dear Dr. Saade:

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 Jul 05, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for your work.

In general: I am not sure this is commentary. A modeled analysis is more appropriately a research paper, and would require more explanation of methods and reasoning, hypothesis, etc…

Specific comments:

1. Abstract could be more succinct.

2. Text: Can you define "omics-based" the first time you use it in text.

3. Line 76: this is incorrect format for endnotes

4. Line 81: can you explain what you mean by "at an enriched ratio?"

5. In the methods section of this can you describe why you did a simulation instead of just using your data set to make the example? What was the gain? Are there limitations to this method?

I am not sure the supplementary figures add much to the paper.

Reviewer #2: Review of manuscript ONG-19-966 Mind the (Gestational Age) Gap!

This manuscript describes the test performance characteristics of a commercially available product for prediction of preterm birth. The primary aim of the paper is to describe methodologic differences in definition of comparison groups in prior published studies of similar products, presumably competing products.

I agree with the authors that the methodologic concerns they have raised are valid and accurate. However, the presentation of the data gives this reader the perception that the purpose this study was done was to discredit the science supporting competing products. It gives the impression of industry bias.

The audience who may be most interested in reading this publication might be those with epidemiology/ biostatistics

background (like myself), and perhaps not the primarily clinical audience of this journal.

I did enjoy reading this study, and I think the figures give a clear description of how differing cut offs for exposure group comparisons alter the findings of a test's predictive accuracy. I would suggest the authors consider changing the title to something more scientific.

Reviewer #3: This is a clearly written and important methodological paper concerning diagnostic studies for prediction of preterm birth.

Please pardon this very minor suggestion: Although either might be ok, I think line 94, "Biomarker data was derived..." may be better phrased as "Biomarker data were derived..."

Line 98 - I believe "BMI" here on this line is the first use of this abbreviation, and hence, by convention, may be better spelled out. Or can note abbreviation on line 55 where it is spelled out.

May also consider spelling out the "PAPR" abbreviation for the specified study on line 95 - and/or refer to it specifically on line 87 when it is cited. (I believe that this is the study being referred to here).

Reviewer #4: "Mind the (Gestational Age) Gap!" from Boniface et al is a well-written commentary on a timely topic in the age of increased prevalence of prediction tests to prevent adverse outcomes in obstetrics. The rationale set forth regarding the importance of paying attention to the methods and populations used to develop prediction tests is a valuable reminder to researchers and clinicians as further implementation and clinical use of these tests rise. However, there are some important clarifications/edits that I think are necessary before publication, and would make this commentary more applicable/digestible by the many clinicians who would read this but maybe wouldn't understand/don't have expertise in some of the semantics used in this commentary.

1) Further explanation/clarification of some key concepts would be helpful to make the argument the authors put forth stronger: a brief explanation of what omics-based tests are and their significance (line 59); provide some background about why test developers omitted certain gestational age groups (to help give the other side of the story); provide context on how widely used these tests are today, or what stages of development they are in.

2) The methods section would benefit from more information about what the US PAPR study was, the biomarkers that were used in this commentary/study specifically, and an explanation of what/how the simulations were built. This is unclear in this section, and is necessary to understand the primary outcome of this study.

3) Lines 135-141 belong in the clinical implications section.

4) A clearer explanation of what the harms of choosing the wrong control groups/exclusion of certain GA groups would be in terms of implications for clinical use, cost effectiveness, and patient outcomes/experience would really enhance the discussion section, rather than just simply stating it is the wrong methodology to go about when developing these tests.

5) Additionally, more rationale about appropriate composition of non-case control groups would clarify lines 164-167. It seems to me that excluding patients who develop preeclampsia and have an iatrogenic/induced preterm birth would be appropriate to exclude since these tests are designed to predict spontaneous preterm birth, and not medically indicated/induced. The inclusion of patients who develop pregnancy complications that result in iatrogenic preterm birth seems like it would be a misclassification error of the outcome in the non-case group and would impact the results of the test performance as well.

And as a final point, while I know is not the point of this commentary, Black race is not a risk factor for preterm birth - there is nothing inherently biologic about Black birthing people that increases the prevalence of preterm birth. Instead, the association of Black race with preterm birth is a symptom of structural bias/racism within health care, health care institutions, and society. I suggest the authors reframe this in the introduction (line 54) as we as an OBGYN academic, advocacy, and community work to shift the narrative away from identifying race as a risk factor and instead towards naming racism/bias as the risk factor.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 66-68: Should consider changing this description of AUCs, since "around" and "closer to" are inexact values. Actually, a value of 0.50 represents no improvement compared to random chance, while a value = 1.0 would be perfect prediction in a positive sense, while AUC = 0 would represent a perfectly negative predictive test. Furthermore, the statistical significance of any AUC would depend on its confidence intervals, which in turn depend on the sample sizes. Suggest stating something like: AUC = .50 and 1.0 represent no and perfect predictive ability, respectively.

lines 126-128: For consistency, should round the simulation AUC and its CIs to the nearest .01, not .001.

Would strongly urge including Suppl fig 1 to the main text, since it illustrates the divergence of observed vs predicted risks very well for the gapped analyses.

Fig 1: Should include AUC CIs, either in figure or in fig legend.

Suppl Fig 1: Should state the meaning in the fig legend of the CIs shown on the figure. Also, the term"training" was not used earlier in the text, it is a modeling term and likely not understood (or misunderstood) by many readers. Should use a different term or define it understandably in the main text.

EDITOR COMMENTS:

1. Please add a comment in the disclosure statement on the title page for the two co-authors who are employed by Sera. Please state that Sera is developing a screening test for premature birth.

2. For all manuscripts with corporate funding, we require that the following information be included: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide). Please state this information in paragraph form.

Since you are submitting a Current Commentary, please create a section for this information after your Introduction.

Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:
(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.
(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.
(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:
"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of

it is true, and they should attest to this in the cover letter (see #2, above).

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

3. 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. 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.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

4. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Variance is needed in the following sections:
- Lines 40-47 (“Preterm delivery, defined as….continue to rise in most countries. ”)

6. 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 and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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).

9. 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: Current Commentary articles, 250 words. Please provide a word count.

10. 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.

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

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. 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.

14. Figures

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.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

16. 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 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 Jul 05, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

_____
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

July 12, 2019
RE: Re-submission of manuscript with new title: "Impact of Selective Exclusion of Subjects in Preterm Birth Test Development", for Current Commentary, ONG-18-2234

The Editors
Obstetrics and Gynecology
409 12th Street, SW
Washington, DC 20024-2188

Dear Editors:

Thank you for the review process and consideration applied to our previously submitted manuscript, "Mind the (Gestational Age) Gap!" We have addressed reviewer comments and criticisms comprehensively. These changes have been tracked and listed below in this cover letter. We have expanded our discussion of the clinical impact of these issues raised in this Commentary to make the manuscript more relevant to physicians. We hope that publishing our commentary to the wide readership of the Green journal will alert clinicians and researchers to this important issue and empower them with more insight regarding evaluation of published work.

Each author participated in conceptualizing the ideas in this manuscript, designing the analysis, drafting the manuscript, editing, and approving the final, submitted version. Ms. Burchard performed the statistical analyses. Dr. Boniface and Ms. Burchard are full-time employees by Sera Prognostics. Dr. Saade has no conflicts of interest. The manuscript has not been previously published, is not under consideration elsewhere and will not be submitted to another journal until a final decision is made by the Editors of *Obstetrics and Gynecology*. Each author has attends that GPP3 practices have been maintained. Specifically, the authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed.

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.

Signed by: _____

*The manuscript's guarantor.

If you have any questions about the manuscript, I will be the corresponding author. Thank you for your consideration.

Sincerely,

George Saade, MD

[redacted]

Reviewer #1:

Thank you for your work.

General Comments

In general: I am not sure this is commentary. A modeled analysis is more appropriately a research paper, and would require more explanation of methods and reasoning, hypothesis, etc…

> *Thank you for this comment. In this paper we offer a Commentary on a topic that is often overlooked. The data were only used to illustrate the point we are trying to make. We felt that the commentary might be perceived as more controversial if it were not backed up with actual analyzed data, but felt that the level of data analysis employed did not rise to that of a full research paper.*

Specific comments

1. Abstract could be more succinct.

> *Thank you for this comment. We have deleted as much text as we can. The abstract has been shortened from 250 to 222 words and also includes the addition of an "omics" definition requested below.*

2. Text: Can you define "omics-based" the first time you use it in text.

> *The introductory sentence in the Abstract now reads: The need to reduce the rate of preterm delivery and the recent emergence of technologies that measure hundreds of biological analytes (e.g. genomics, transcriptomics, metabolomics, proteomics; collectively referred to as "omics approaches") have led to proliferation of potential diagnostic biomarkers.*

3. Line 76: this is incorrect format for endnotes

> *We followed the journal's author guide found in url at: 1)https://journals.lww.com/greenjournal/Fulltext/2014/01000/Instructions_for_Authors.34.aspx , or an identical pdf found here: 2) http://edmgr.ovid.com/ong/accounts/authors.pdf. Both state: Use references found published in peer-reviewed publications that are generally accessible. Unpublished data, personal communications, statistical programs, papers presented at meetings and symposia, abstracts, letters, and manuscripts submitted for publication cannot be listed in the references. Information from such sources may be cited, if necessary, in the text with the sources given in parentheses. Manuscripts accepted by peer-reviewed publications but not yet published ("in press") are not acceptable as references.* ***We ask the editor for resolution on how best to handle this.***

4. Line 81: can you explain what you mean by "at an enriched ratio?"

> *Another more subtle form of gapping can also be found in the recent report by Jelliffe et al.(16) where very early preterm deliveries (<32 weeks) were included at unnatural equivalent proportion to late preterm deliveries (32-36 weeks).*

5. In the methods section of this can you describe why you did a simulation instead of just using your data set to make the example? What was the gain? Are there limitations to this method?

> *Thank you for this comment. The limitations of simulations are that they are not the same as a new independent population. We have pointed out in the Methods section that the simulation strategy improved the statistical power, and added clarity to the description of the simulation process as well. The relevant sentence now reads: The simulation process maintained the*

characteristics of the original dataset with respect to GA and biomarker correlation and variability, while increasing statistical power to 80% power for detection of an AUC difference of 0.1 with p<0.05 by DeLong's test(21), a non-parametric approach to compare AUCs.

I am not sure the supplementary figures add much to the paper.

This second figure was added at the request of the Statistical Editor. In his review (below) of our resubmission it is clear he still feels strongly about the analysis. We also agree that it nicely illustrates the impact of gapping on Risk prediction and that it should be moved to a full figure in the text.

Reviewer #2

This manuscript describes the test performance characteristics of a commercially available product for prediction of preterm birth. The primary aim of the paper is to describe methodologic differences in definition of comparison groups in prior published studies of similar products, presumably competing products.

Thanks for sharing your point of view.

I agree with the authors that the methodologic concerns they have raised are valid and accurate. However, the presentation of the data gives this reader the perception that the purpose this study was done was to discredit the science supporting competing products. It gives the impression of industry bias.

Thank you for your concerns regarding industry bias. Dr. Saade, the senior author on this paper, is not in industry nor employed or paid in any way by Sera Prognostics. He was also the one to bring the issue of gapping to the attention of colleagues and Sera. Dr. Saade merely used Sera's data and analytical support to make a point about this important issue that applies to all screening tests, whether supported by industry or not. He and the two authors employed by Sera would like others in the community to be aware of this error that leads to a mis-representation of any test performance.

The audience who may be most interested in reading this publication might be those with epidemiology/ biostatistics background (like myself), and perhaps not the primarily clinical audience of this journal.

We agree that epidemiologists and biostatisticians may appreciate the mechanistic impact of selective exclusion of subjects on test performance. But we feel that ultimately the clinicians who use the test should be able to determine whether a study design was appropriate or not, and should be aware of the clinical impact of this issue. It is in this spirit that we added a checklist for clinicians to use when interpreting the evidence for screening tests.

I did enjoy reading this study, and I think the figures give a clear description of how differing cut offs for exposure group comparisons alter the findings of a test's predictive accuracy. I would suggest the authors consider changing the title to something more scientific.

We thank the reviewer for the compliments. We have changed the title of this manuscript to: "Impact of Selective Exclusion of Subjects in Preterm Birth Test Development"

Reviewer #3

General Comments

This is a clearly written and important methodological paper concerning diagnostic studies for prediction of preterm birth.

Thank you for this comment.

Specific Comments

Please pardon this very minor suggestion: Although either might be ok, I think line 94, "Biomarker data was derived..." may be better phrased as "Biomarker data were derived..."

This has been corrected.

Line 98 - I believe "BMI" here on this line is the first use of this abbreviation, and hence, by convention, may be better spelled out. Or can note abbreviation on line 55 where it is spelled out.

Thank you. We have defined BMI earlier when first used.

May also consider spelling out the "PAPR" abbreviation for the specified study on line 95 - and/or refer to it specifically on line 87 when it is cited. (I believe that this is the study being referred to here).

Thank you. We have defined PAPR on line 95: ....the US-based Proteomic Assessment of Preterm Risk (PAPR) clinical trial.....

Reviewer #4

General Comments

"Mind the (Gestational Age) Gap!" from Boniface et al is a well-written commentary on a timely topic in the age of increased prevalence of prediction tests to prevent adverse outcomes in obstetrics. The rationale set forth regarding the importance of paying attention to the methods and populations used to develop prediction tests is a valuable reminder to researchers and clinicians as further implementation and clinical use of these tests rise. However, there are some important clarifications/edits that I think are necessary before publication, and would make this commentary more applicable/digestible by the many clinicians who would read this but maybe wouldn't understand/don't have expertise in some of the semantics used in this commentary.

Thank you for helping us make this manuscript more clinically relevant and digestible.

Specific Comments

1) Further explanation/clarification of some key concepts would be helpful to make the argument the authors put forth stronger: a brief explanation of what omics-based tests are and their significance (line 59); provide some background about why test developers omitted certain gestational age groups (to help give the other side of the story); provide context on how widely used these tests are today, or what stages of development they are in.

Thank you for making suggestions to improve the manuscript. In response to Reviewer number 1 we have added a brief definition of "omics tests".

2) The methods section would benefit from more information about what the US PAPR study was, the biomarkers that were used in this commentary/study specifically, and an explanation of what/how the simulations were built. This is unclear in this section, and is necessary to understand the primary outcome of this study.

We have defined PAPR and added the biomarker descriptions in the methods section. We have also reworked the description of the simulations to make them more clear.

3) Lines 135-141 belong in the clinical implications section.

These statements have been moved.

4) A clearer explanation of what the harms of choosing the wrong control groups/exclusion of certain GA groups would be in terms of implications for clinical use, cost effectiveness, and patient outcomes/experience would really enhance the discussion section, rather than just simply stating it is the wrong methodology to go about when developing these tests.

Thank you. We have added additional explanation in the Clinical Implications section.

5) Additionally, more rationale about appropriate composition of non-case control groups would clarify lines 164-167. It seems to me that excluding patients who develop preeclampsia and have an iatrogenic/induced preterm birth would be appropriate to exclude since these tests are designed to predict spontaneous preterm birth, and not medically indicated/induced. The inclusion of patients who develop pregnancy complications that result in iatrogenic preterm birth seems like it would be a misclassification error of the outcome in the non-case group and would impact the results of the test performance as well.

Thank you for this question. Because a test to predict spontaneous preterm birth is used before the outcomes of the pregnancy are known, the test will definitely be performed on patients who ultimately deliver preterm for medical indications. It may help to keep in mind that when the test is performed, these patients would not be known, otherwise it would not be a screening test. Therefore, since patients destined for iatrogenic preterm birth (iaPTB) and preeclampsia (PE) are included in the intended use population, it is important to demonstrate a test's performance in the presence of subjects who will later have iaPTB and PE. Thus, the non-case group should include iaPTBs and PEs. Analogously, when developing a test to predict prostate cancer the non-case group should include subjects with benign prostatic hyperplasia and not just perfectly healthy subjects, as the test would be applied to all such subjects.

And as a final point, while I know is not the point of this commentary, Black race is not a risk factor for preterm birth - there is nothing inherently biologic about Black birthing people that increases the prevalence of preterm birth. Instead, the association of Black race with preterm birth is a symptom of structural bias/racism within health care, health care institutions, and society. I suggest the authors reframe this in the introduction (line 54) as we as an OBGYN academic, advocacy, and community work to shift the narrative away from identifying race as a risk factor and instead towards naming racism/bias as the risk factor.

Thank you for this comment. We'd like to communicate that there are identified risk factors and that racial disparities exist. We understand and agree that groups affected by disparities vary by cultural/national context. We have reworded as follows: Although racial disparities and risk factors, such as low socioeconomic status, maternal age and low maternal body-mass index (BMI) have been identified(8, 9), up to 50% of all PTDs occur in women without any evident risk factors(10).

Statistical Editor

lines 66-68: Should consider changing this description of AUCs, since "around" and "closer to" are inexact values. Actually, a value of 0.50 represents no improvement compared to random chance, while a value = 1.0 would be perfect prediction in a positive sense, while AUC = 0 would represent a perfectly negative predictive test. Furthermore, the statistical significance of any AUC would depend on its confidence intervals, which in turn depend on the sample sizes. Suggest stating something like: AUC = .50 and 1.0 represent no and perfect predictive ability, respectively.

Thank you. This statement now reads: The area under the ROC curve (AUC) represents the overall predictive ability of the test, with an AUC of 0.5 indicating no predicitve ability and an AUC of 1.0 representing perfect predictive ability.

lines 126-128: For consistency, should round the simulation AUC and its CIs to the nearest .01, not .001.

This has been corrected.

Would strongly urge including Suppl fig 1 to the main text, since it illustrates the divergence of observed vs predicted risks very well for the gapped analyses.

We have moved the Supplemental Figure to the Main Text as Figure 2.

Fig 1: Should include AUC CIs, either in figure or in fig legend.

We have added the CIs to the Figure.

Suppl Fig 1: Should state the meaning in the fig legend of the CIs shown on the figure. Also, the term"training" was not used earlier in the text, it is a modeling term and likely not understood (or misunderstood) by many readers. Should use a different term or define it understandably in the main text.

The word "training" has been removed from the figure legend. The CIs have been defined in the Figure Legend.

EDITOR COMMENTS:

Thank you for these comments.

1. Please add a comment in the disclosure statement on the title page for the two co-authors who are employed by Sera. Please state that Sera is developing a screening test for premature birth.

This statement now reads: Conflict of Interest/Disclosure Statement: JJB and JB are employees of Sera Prognostics, a company that has developed a screening test for preterm birth prediction and continues to develop such tests.

2. For all manuscripts with corporate funding, we require that the following information be included: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide). Please state this information in paragraph form.

Since you are submitting a Current Commentary, please create a section for this information after your Introduction.

Thank you for this request. We have added the paragraph in Section 4 below to the Cover Letter and after the Introduction and included a description of the contributions of the two authors from Sera Prognostics.

Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

At the end of the Abstract we have added: Funding Source: Sera Prognostics.

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

This has been added.

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

We affirm that this is true and this has been added to the manuscript following the Introduction and the Cover Letter.

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

3. 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. 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.

We opt-in. Thank you.

B. OPT-OUT: No, please do not publish my point-by-point response letter.

4. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Variance is needed in the following sections:

- Lines 40-47 ("Preterm delivery, defined as....continue to rise in most countries. ")

  This statement has been modified to read: Preterm delivery (PTD), which refers to delivery before 37 weeks of gestational age (GA), affects 15 million infants babies born each year and varies from approximately 5%–18% of all births across different geographies worldwide(1).

6. 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 and gynecology data definitions at https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2FAbout-ACOG%2FACOG-Departments%2FPatient-Safety-and-Quality-Improvement%2FreVITALize&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=nBVXIIWVt8e%2BX4LF09Kbyby%2BO0hUnNp4Hb%2Fqx2I88cI%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

We have maintained these space limits.

8. 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.

No additional manuscript assistance was involved.

* 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.

All named persons have given permission.

* 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).

These data have not been presented.

9. 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.

Thank you for this reminder.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Current Commentary articles, 250 words. Please provide a word count.

The abstract includes 222 words and we have checked it carefully.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=RG5RTAJBAtYGDqH2qJH2pFChSCgn7AnljNrTvjmYe08%3D&reserved=0. 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 include abbreviations after properly defining them and when the expanded version would detract from its readability. These include commonly accepted abbreviations in this field such as: gestational age (GA), preterm delivery (PTD), spontaneous preterm delivery (sPTD), receiver operating characteristic (ROC) curve.

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

We have not included any commercial or generic drug names in this 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.

We have corrected the one instance of this.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Ftable_checklist.pdf&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=Ah8qePdqSY4B8SzZVfzF0zAfuRByQtfVADYCOVQdyY0%3D&reserved=0.

14. Figures

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.

We are using EPS.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Flinks.lww.com%2FLWW-ES%2FA48&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=sFG6xQR%2Fz%2FpAr0X2VrN9af70j3FJfuxWa%2BL3pNOJkLw%3D&reserved=0. The cost for publishing an article as open access can be found at https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Facd%2Faccounts%2Fifauth.htm&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=mStxZ2onGkLh8EUDiyHZ5XRuFUYpux%2FM0bN5XCsqiOU%3D&reserved=0.

Thank you.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

Thank you.

16. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com&data=02%7C01%7Cgsaade%40utmb.edu%7C1083292ab96b4e189fda08d6f0cf1874%7C7bef256d85db4526a72d31aea2546852%7C0%7C1%7C636961169602916279&sdata=x0pvmyHkl9JaC9yxVL0GTE3j1PLyvWExlGUv5wtfdQ4%3D&reserved=0. 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.