OBSTETRICS & GYNECOLOGY

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

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

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

Date: Jun 14, 2019
To: "Rebecca Luckett" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-933

RE: Manuscript Number ONG-19-933

Performance of two-stage cervical cancer screening strategies utilizing primary hrHPV testing for women living with HIV

Dear Dr. Luckett:

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:

The authors present their assessment of a two step cervical cancer screening program in a low resource setting in sub-Saharan Africa in HIV. This is an important question for high incidence regions with HIV. There are concerns to the design of this trial that might have influenced the performance outcomes

1) Why did the authors choose cytology as the standard for the HPV negative women?

2) Describe the QC for cytology. There is huge variability in the hrHPV positive women with cytology as a secondary triage- could this be a cytology quality issue? What were the QC measures and standards for the cytology?

3) According to the methodology, the colposcopists were blinded to the hr HPV results- yet all with hrHPV got colposcopy- so this colposcopy is with prejudice- why is blinding important?

4) When colposcopy was done- if the evaluation showed lesser abnormalities- was a biopsy done? What was the QA/QC for colposcopy given that colpo is not 'routine' in Botswana. In other words, how is the colpo quality assessed and how does this assessment affect the performance? Around line 165 it appears all had histopathology, but this is not clearly stated and it is unclear how many biopsies/ECC were performed.

5) Can the authors explain why they think the hrHPV positivity rate was so low in this HIV+ population? Is it that they are all well controlled on ART- this rate is very low compared to other studies in the setting of HIV.

6) In this unscreened population one would expect a higher rate of cancer at the time of first screen. Can the authors comment?

Reviewer #2:

Overall Comments: The authors present results from a prospective cohort study evaluating cervical screening algorithms in women living with HIV in a low resource country. All participants underwent hrHPV screening and participants with a positive screen underwent cytology, visual inspection with acetic acid (VIA), colposcopy and biopsy (hrHPV neg underwent cytology). Histopathology was the reference standard for pre-invasive disease/cervical cancer. Sensitivity, specificity, PPV and NPV of hrHPV-based 2 stage screening approaches were assessed. hrHPV followed by colposcopy resulted in the

highest sensitivity and PPV in detecting high grade cervical dysplasia. This information is of interest as using colposcopy in low resource environments may be a more effective strategy than VIA or cytology, especially in this high risk patient population.

Specific Comments:

1. Title: OK

2. Précis: Good

3. Abstract: Good

4. Introduction: Currently in Botswana, a combination of pap smear and VIA are utilized for cervical screening. Increasingly, hrHPV testing has been used for its increased sensitivity and is planned to be used in the future in Botswana, but the guidelines for managing positive hrHPV are unclear. This study addresses this issue in an HIV+ population which is at high risk for the progression to cervical cancer. The Intro provides a good rationale for the study. Please provide hypothesis.

5. Methods: Consider revising the writing to the third person instead of the "we" perspective. Overall Methods clearly articulate the primary outcome and analysis plan. Sample size calculation reasonable.

6. Results: Well presented. Can you comment on treatments that were then performed in these participants?

7. Discussion: line 217-please spell out LMIC (first time used). Can you please comment on the cost effectiveness of the various treatment algorithms and the plan to implement this strategy. This paper goes to the next level from just looking at prevalence rates of hrHPV subtype prevalence in HIV+ women in Africa to how best to then confirm pathology which will determine treatment.

8. Tables/Figures: good

Reviewer #3:

Overview:
1. This is a prospective study of HIV infected women in Botswana that evaluates the sensitivity, specificity, and PPV and NPV of different screening strategies for cervical cancer screening. The authors performed hrHPV testing on all HIV infected women which will soon become the standard of care per the Botswanan Ministry of Health. However, data is lacking on what the next steps should be if a patient has hr HPV testing. This is a well-designed, discrete study that is useful information that could affect policy.

Background:
2. The authors provide a convincing argument for why the study needed to be done, especially in a country such as Botswana who is starting to adopt HPV screening. The authors used the cytology result as the gold standard which is appropriate.

Methods:
3. It is not clear in the manuscript that the authors used the histopathology results from colposcopy as the gold standard to which VIA, inspection by Colpo and cytology were compared.

Results:
4. Table 3 and Table 4 are hard to read and am wondering if the authors would consider presenting at least some of their data with ROC curves.

Discussion:
5. The authors adequately describe results and address limitations. A cost effectiveness analysis really needs to be performed to further guide policy changes

STATISTICAL EDITOR COMMENTS:

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

1. Line 51: Need to reconcile with Table 3, where the spec is cited as 49%, not 29%,

2. Abstract and results: Comparing sensitivities in terms of arithmetic order does not establish statistical superiority. Need to statistically compare the three methods in terms of sens, spec to show that one method is superior.

3. As can be seen in Table 2 and generally in women with HIV, the prevalence of CIN2+ is not constant. Therefore, metrics such as PPV or NPV are not appropriate measures, since they would not apply to another cohort having a different prevalence rate of CIN2+. Instead, should compute the LR(+) and LR(-), with CIs and compare them to determine whether one method is superior.

4. Table 4, lines 53-54: This was a small sample, with wide CIs 100%(47-100). Is it statistically better, or just arithmetically higher?

EDITOR 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. 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.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA). Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA. Please note that we are awaiting a response from Doreen Ramogola-Masire and Sarah Feldman.

3. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission of your revised manuscript. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

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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,

The Editors of Obstetrics & Gynecology

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

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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.

[redacted]

Attn: Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics & Gynecology

RE: Manuscript Number ONG-19-933, Performance of two-stage cervical cancer screening strategies utilizing primary hrHPV testing for women living with HIV

Dear Dr. Chescheir,

Thank you so much for considering our manuscript for publication and for the helpful input from your Editorial Board and expert referees. We have addressed the issues detailed by the reviewers point-by-point below and have attached the manuscript with tracked changes. We appreciate your consideration of this revised version.

Reviewer #1:

The authors present their assessment of a two-step cervical cancer screening program in a low resource setting in sub-Saharan Africa in HIV. This is an important question for high incidence regions with HIV. There are concerns to the design of this trial that might have influenced the performance outcomes

1) Why did the authors choose cytology as the standard for the HPV negative women?

Cytology was assessed in addition to HPV in all women because current standard-of-care in Botswana according to the national cervical cancer screening strategy is cytology or VIA. In order to ensure all women in the study were screened according to national standard, in addition to the trial algorithms, all participants had cytology evaluated. I have clarified this in lines 145-146.

Because there are no clinical guidelines for management of positive hrHPV results in Botswana, we also collected cytology at the time of hrHPV sample collection to ensure that all participants were screened according to current cervical cancer screening guidelines in Botswana.

2) Describe the QC for cytology. There is huge variability in the hrHPV positive women with cytology as a secondary triage- could this be a cytology quality issue? What were the QC measures and standards for the cytology?

This is a good point. We did receive IRB approval to have external validation performed, however, due to policy at the National Health Laboratory, it was not possible for pathology slides to leave the National Health Laboratory and there was no one in-country with the capacity to perform external validation. That being said, our goal was to evaluate the performance of the algorithm with the current pathology services available. There are internal quality control checks including review of 10% of abnormal cytology results by a second pathologist. I have noted this limitation (lines 353-356).

While the goal of this study was to evaluate screening algorithms that would be possible with pathology services currently available, external validation of cytology and histopathology specimens was not performed and thus accuracy compared to an expert gynecologic cytopathologist and pathologist was not evaluated.

3) According to the methodology, the colposcopists were blinded to the hr HPV results- yet all with hrHPV got colposcopy- so this colposcopy is with prejudice- why is blinding important?

It is true that we expect all of the second stage triage tests to have enhanced performance because they are following a positive hrHPV primary screen. Although they were few, two women with hrHPV negative results did have colposcopy for HSIL cytology (lines 215-216). Additionally, the colposcopist was blinded to hrHPV type (ie HPV16 HPV18/45 or other hrHPV positive) as it was thought that knowing presence of HPV16/18/45 vs other might impact assessment.

4) When colposcopy was done- if the evaluation showed lesser abnormalities- was a biopsy done? What was the QA/QC for colposcopy given that colposcopy is not 'routine' in Botswana. In other words, how is the colpo quality assessed and how does this assessment affect the performance? Around line 165 it appears all had histopathology, but this is not clearly stated and it is unclear how many biopsies/ECC were performed.

All patients who underwent colposcopy had a biopsy performed. I have clarified this in lines 160 – 176.

All participants had a biopsy collected at the time of colposcopy. If there was a visible lesion, a punch biopsy or LEEP was performed according to current best practice in Botswana. If no lesion was visible, a small endocervical excision or an endocervical curettage was performed. All women with cervical intraepithelial neoplasia ≥ CIN2 (CIN2+) on biopsy or endocervical curettage were referred for an excisional procedure. Women with histopathology showing CIN3 with microinvasion or invasive cervical cancer were referred to gynecologic providers for further assessment and treatment.

There was no QA/QC for colposcopic assessment; it was compared to histopathology as the gold standard.

5) Can the authors explain why they think the hrHPV positivity rate was so low in this HIV+ population? Is it that they are all well controlled on ART- this rate is very low compared to other studies in the setting of HIV.

It is true that the literature has shown high rates of HPV prevalence in women living with HIV and I think this is an important point to make in the discussion. The population prevalence in a pilot study validating hrHPV self-swabs amongst 100 women living with HIV who receive care at the same infectious disease clinical center used in our study was also shown to be 30% [data presented at the Botswana HIV conference, 2018]. In another study validating self-swabs amongst both HIV-positive and HIV-negative women, the overall hrHPV positivity rate was 33% and the hrHPV positivity rate in HIV-positive women was 40% [data presented at the Botswana HIV conference, 2018]. I have compared our results to prior literature in the text as follows (lines 331-345):

We found lower rates of hrHPV prevalence amongst women living with HIV than reported in the literature, which may highlight the improvement in HIV management over time with higher antiretroviral therapy utilization and viral suppression.[1,2] Botswana has had continuous access to antiretroviral therapy in the public sector since 2002, with initiation of antiretroviral therapy at graduated CD4 counts over time (initially 200 then 350) until it initiated a test-and-treat policy in 2016. Demographic differences in

study populations may also contribute to this difference. Our study had a higher median age than in studies conducted in the United States, Kenya and Brazil. Additionally, the population in New York had higher risk behaviors, as indicated by high rates of smoking and on-going intravenous drug use.[3] The study population in Brazil was pregnant which may have resulted in increased immunosuppression and higher detection rates.[4] Rates of hrHPV prevalence amongst women living with HIV in the region generally range from 47-57%, however, the prevalence is lower in women aged 40-49.[5,6] In a similarly-aged cohort of women in Zambia, where 90% of participants were on antiretrovirals and only 77% virally suppressed, hrHPV positivity was 47%.[7] On-going evaluation of hrHPV rates in women living with HIV in the modern antiretroviral therapy are necessary to understand if our findings are generalizable.

6) In this unscreened population one would expect a higher rate of cancer at the time of first screen. Can the authors comment?

This is also a very important point. We felt the rate of detection of invasive cervical cancer in our population relatively high at 2%. I have added a comparison to other studies in our discussion as follows:

This study highlights the acute need to improve screening for cervical cancer and raises concern about the frequency of screening in women living with HIV in low- and middle-income countries. Current national strategy in Botswana recommends screening with cytology or VIA in women living with HIV every three years. While many of the participants had been screened before (over 90%), only 11% of women reported a prior abnormal result and 2-3% reported a prior excisional procedure. Our high prevalence of high-grade pre-invasive cervical disease supports the need for frequent screening to ensure diagnosis of disease prior to progression to malignancy. In addition to high rates of pre-invasive cervical disease, the rate of detection of cervical cancer in our screening cohort was relatively high at 2%. This included 3 women enrolled but immediately referred for suspicion for clinical stage IB cervical cancer on examination and 4 women with histopathology concerning for Stage IA cervical cancer (cervical cancer or CIN3 with microinvasion). This rate was similar to another screening cohort in Zambia where 6 of 200 (3%) women living with HIV had invasive cervical cancers detected at the time of screening, but higher than other settings.[8] In a large cervical cancer screening cohort of 79,506 women in India, 238 (0.3%) invasive cervical cancers were detected (Sankaranarayanan, 2009). In a cervical cancer screening cohort of 1128 women living with HIV in India, 5 (0.4%) invasive cervical cancers were detected. [9]

Reviewer #2:

Overall Comments: The authors present results from a prospective cohort study evaluating cervical screening algorithms in women living with HIV in a low resource country. All participants underwent hrHPV screening and participants with a positive screen underwent cytology, visual inspection with acetic acid (VIA), colposcopy and biopsy (hrHPV neg underwent cytology). Histopathology was the reference standard for pre-invasive disease/cervical cancer. Sensitivity, specificity, PPV and NPV of hrHPV-based 2 stage screening approaches were assessed. hrHPV followed by colposcopy resulted in the highest sensitivity and PPV in detecting high grade cervical dysplasia. This information is of interest as using colposcopy in low resource environments may be a more effective strategy than VIA or cytology, especially in this high-risk patient population.

Specific Comments:

1. Title: OK

2. Précis: Good

3. Abstract: Good

4. Introduction: Currently in Botswana, a combination of pap smear and VIA are utilized for cervical screening. Increasingly, hrHPV testing has been used for its increased sensitivity and is planned to be used in the future in Botswana, but the guidelines for managing positive hrHPV are unclear. This study addresses this issue in an HIV+ population which is at high risk for the progression to cervical cancer. The Intro provides a good rationale for the study. Please provide hypothesis.

We have added this as follows (lines 106-108):

We hypothesized that VIA, cytology and colposcopy would perform similarly in women living with HIV who tested positive for hrHPV.

5. Methods: Consider revising the writing to the third person instead of the "we" perspective. Overall Methods clearly articulate the primary outcome and analysis plan. Sample size calculation reasonable.

I reviewed this with co-authors and they preferred the “we” perspective if it is acceptable to the reviewer.

6. Results: Well presented. Can you comment on treatments that were then performed in these participants?

I have clarified this in the methods section as follows (lines 163-176):

All women with cervical intraepithelial neoplasia ≥ CIN2 (CIN2+) on biopsy or endocervical curettage were referred for an excisional procedure. Women with histopathology showing CIN3 with microinvasion or invasive cervical cancer were referred to gynecologic providers for further assessment and treatment.

7. Discussion: line 217-please spell out LMIC (first time used). Can you please comment on the cost effectiveness of the various treatment algorithms and the plan to implement this strategy. This paper goes to the next level from just looking at prevalence rates of hrHPV subtype prevalence in HIV+ women in Africa to how best to then confirm pathology which will determine treatment.

I have written out low- and middle-income countries. We are currently planning a cost-effectiveness analysis of this data and I have added that point in the discussion (line 370-371):

Balancing the cost of these strategies with clinical effectiveness is essential and a cost-effectiveness evaluation of these strategies in Botswana is being explored.

8. Tables/Figures: good

Reviewer #3:

Overview:
1. This is a prospective study of HIV infected women in Botswana that evaluates the sensitivity, specificity, and PPV and NPV of different screening strategies for cervical cancer screening. The authors performed hrHPV testing on all HIV infected women which will soon become the standard of care per the

Botswanan Ministry of Health. However, data is lacking on what the next steps should be if a patient has hr HPV testing. This is a well-designed, discrete study that is useful information that could affect policy.

Background:
2. The authors provide a convincing argument for why the study needed to be done, especially in a country such as Botswana who is starting to adopt HPV screening. The authors used the cytology result as the gold standard which is appropriate.

Methods:
3. It is not clear in the manuscript that the authors used the histopathology results from colposcopy as the gold standard to which VIA, inspection by Colpo and cytology were compared.

I have clarified this in the methods section as follows (lines 179-180):

Using histopathology collected at time of colposcopy as the gold standard, we calculated the sensitivity…

Results:
4. Table 3 and Table 4 are hard to read and am wondering if the authors would consider presenting at least some of their data with ROC curves.
We agree this would have been useful, however, our algorithms only had 2 thresholds for positivity and so we believe an ROC curve is not appropriate.

Discussion:
5. The authors adequately describe results and address limitations. A cost effectiveness analysis really needs to be performed to further guide policy changes

Thank you. I have highlighted the need for a cost effectiveness analysis more clearly in the revision (line 370-371):

Balancing the cost of these strategies with clinical effectiveness is essential and a cost-effectiveness evaluation of these strategies in Botswana is being explored.

STATISTICAL EDITOR COMMENTS:

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

1. Line 51: Need to reconcile with Table 3, where the spec is cited as 49%, not 29%,

Done

2. Abstract and results: Comparing sensitivities in terms of arithmetic order does not establish statistical superiority. Need to statistically compare the three methods in terms of sens, spec to show that one method is superior.

We agree with the comment that our confidence intervals are wide and do not establish statistical superiority. Our understanding is that p-values around sensitivity are not standard and so have highlighted that we have a small sample size with wide confidence intervals and therefore recommend a larger sample size, which may narrow the CIs, to confirm whether the trend in performance is significant.

3. As can be seen in Table 2 and generally in women with HIV, the prevalence of CIN2+ is not constant. Therefore, metrics such as PPV or NPV are not appropriate measures, since they would not apply to another cohort having a different prevalence rate of CIN2+. Instead, should compute the LR(+) and LR(-), with CIs and compare them to determine whether one method is superior.

We prefer to include PPV because our sample size calculation was performed based on PPV and because we believe most lay readers have a better intuitive sense in interpretation of PPV and NPV than LR. We also agree that in diagnostic statistics, LRs are better measures. We have therefore included LRs for the lower threshold for each algorithm in the revised Table 3 and in the results section as follows (lines 228-251):

We compared the performance of the two-stage cervical cancer screening algorithms. hrHPV followed by colposcopy impression had a sensitivity of 83%, specificity of 49%, PPV of 47%, LR+ of +1.6 and LR- of -0.4. hrHPV testing followed by VIA resulted in a reduced sensitivity of 59%, specificity of 49%, PPV of 39%, LR+ of +1.2 and LR- of -0.8 at the low cut-off point of "low-grade impression". hrHPV testing followed by cytology also resulted in a reduced sensitivity of 62%, specificity of 77%, PPV of 60%, LR+ of +2.7 and LR- of -0.5 at the ASC-US threshold (Table 3). Triaging hrHPV positive women with colposcopy impression, VIA and cytology missed CIN2+ diagnoses in 5, 12, and 11 women in our cohort, respectively.

4. Table 4, lines 53-54: This was a small sample, with wide CIs 100%(47-100). Is it statistically better, or just arithmetically higher?

We agree that it is only arithmetically higher and in calculating LRs, we discovered an error in Table 4 which has now been corrected. I have adjusted our comments on the results related to Table 4 as follows (lines 251-252):

Evaluation of the two-stage algorithms stratified by HPV 16/18/45 versus other hrHPV types did not improve the performance of any of the algorithms (Table 4).

EDITOR 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. 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: **I agree to OPT-IN**
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.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA). Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA. Please note that we are awaiting a response from Doreen Ramogola-Masire and Sarah Feldman.
They have signed the eCTA.

3. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely

account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission of your revised manuscript. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.
We have followed the STARD guidelines.

4. 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.
I have reviewed the definitions and adjusted the term “Abnormal lower genital tract cytology” accordingly.

5. 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.
Noted

6. 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.
I have not been able to get the title down to 100 characters when I write out HPV and HIV so I have kept those abbreviations. I have left hrHPV, VIA and PPV because of the number of times it is used in the manuscript even though they are not in the list of approved abbreviations. I am also not clear on what to do with CIN- terminology as it is listed in the reVITALize definitions but not on the approved abbreviations list. I can change what is needed to be in compliance with journal regulations.

7. 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.
Noted

8. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access.

Sincerely,

Rebecca Luckett

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