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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.

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.
RE: Manuscript Number ONG-19-716

Extended HPV Genotyping with Test-of-Cure following Treatment of High-Grade CIN: Systematic Review

Dear Dr. Andrews:

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 May 31, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall: This is a systemic review that describes the use of extended HPV genotyping to discriminate the risk of recurrent disease after treatment for high grade cervical dysplasia.

Other:
Disclosures: This work was supported by Becton, Dickinson and Company, BD Life Sciences - Diagnostic Systems.

Abstract:
1. Line 11 states that the "grey" literature was searched but this was not explicitly defined in the main paper.

Introduction:
2. Good description of the need for this review. PICO is described in detail.
3. Line 60: It may be useful to define "extended genotyping" here.

Sources:
4. Data sources included MEDLINE, Cochrane Database of Systematic reviews, Health Technology Assessment (which includes the required MEDLINE), EMBASE and ClinicalTrials. PRISMA guidelines and IOM standards were followed and the study was registered with PROSPERO.

Study Selection:
5. Procedures for study selection and evaluation of risk of bias are adequately described and enough detail is provided to permit duplication.

Results:
9. The results are provided in great detail. They relate to the main point and answer the research question.

Discussion:
10. A thoughtful discussion is provided. The data support the conclusions and limitations are discussed.

References:
11. Pertinent literature is cited and the limit for references is not exceeded.

TABLES and FIGURES:
12. Figure 1: It might be useful to include the reason for exclusion in the box that describes the second round of exclusions (n= 200).

Reviewer #2: Authors have prepared systemic review following all the guidelines.

1. Extended genotyping demonstrated assertive results in different measure of performance (Sens, Spec, PPV, NPV etc.). However, data did not show that how those measures for extended genotyping translated into prevention of malignant progression compared to pooled assay. It would be interesting to see whether extended genotyping vs pooled assay make any difference in long term outcome as far as progression of malignancy from post treatment persistent ≥ CIN II is concerned.

2. Overall sample size and sample size of some studies incorporated in systemic review are small.

3. Certainly, more information is helpful provided we have an individualized treatment protocol. As per suggested by authors, identification of persistence of same genotype post treatment may require closer follow up. However, as per evidence-based data and per current guidelines, practitioners are already following up those post treatment patients with persistence of high-risk HPV (irrespective of genotype) closely.

4. At present, there is lack of substantial evidence-based data that would recommend different approach for treatment and follow up for individualized genotypes. Therefore, until more data supporting genotype specific approach is available, universal use of extended genotyping is questionable.

5. Last but not least, cost benefit analysis and hazard analysis for implementing extended genotyping protocol would be warranted compared to standard practices.

Reviewer #3: The authors should be congratulated for a well developed systematic review the data available for extended HPV genotyping with Test-of-Cure following treatment of high grade CIN. I have the following comments/questions:

1) Were studies not reported in the English language evaluated for data collection? Of the 233 unique abstracts, why were the 200 initially excluded? Was this also based on the PRISMA flow?

2) In lines 130-137, why is there discussion of LSIL? Is this data relevant given the question in hand is CIN 2 or worse? I understand the HSIL logistic regression was not possible due to sensitivity of 100%, but perhaps best to state this and leave it at that. Unable to draw conclusions from LSIL data as many of these low grade lesions will regress spontaneously.

3) The review addresses negative HPV subtype specific tests after treatment with surgical excision, please comment on risk of re-infection from the same partner or a different partner with the same HPV subtype. Would this impact data or conclusions with regard to surveillance?

4) In discussion the authors outline that a more personalized follow up plan can be created for patients with persistent HPV subtype infection after CIN 2 surgical treatment. Patients with a new strain of HPV are still at risk for these same lesions at a lower rate over the immediate follow up (ie 2 years). How would this new management strategy impact population based follow up if providers will still need to manage/survey patients with new HR HPV strains compared to persistent strains? Does this data decrease or increase the burden of testing? Would consider mentioning this in discussion section on some level.

Overall well done. This will add the literature as new guidelines are developed with patients receiving the HPV vaccine and the HPV genotype specific testing needed to risk stratify.

Reviewer #4: Thank you for allowing me to review this article. Cervical intraepithelial neoplasia is a very interesting topic
in gynecological practice with special interest for prediction/prevention of recurrence that is a considerable risk factor for development of invasive cervical cancer. This makes the current review important piece of knowledge. In general the article is well written with very few typographic mistakes. However, the main problems, as stated by the authors themselves, are the few heterogeneous studies included in the review. Failure of the authors to produce meta-analysis deepens the issue and emphasizes that the review couldn't find usable evidence. In addition, using different packages for extended HPV testing may reflect the variation of accuracy of the kits itself rather than the HPV testing process itself. Considering other risk factors of recurrence that were not clearly controlled by the included studies adds another source of weakness of evidence. Finally, considerable number of the included studies followed their cases for only 6 months. In my opinion this is too short to generate evidence about recurrence of CIN and this concept was supported by the current review. The authors stated with references that clearance of HPV is expected within one year and recurrence is expected within 2 years of successful treatment of CIN. Finally, the authors mixed the concept of "recurrence" with "treatment failure". Despite recurrence of some diseases is considered a type of treatment failure, in systematic reviews, that are pieces of evidence, it is highly preferred to be robust in terminology not to confuse the reader about the outcome. In addition, there are some other issues that should be considered before deciding to publish the review:

Title:
- What is meant by "with test of cure"? Does it mean that extended HPV testing is a test of cure or used with another test for cure? Please explain.

Precis:
- Please replace "cervical disease" with "cervical intraepithelial neoplasia".
- There is inconsistency with the title. In title, it is understood that extended genotype is used in addition to a test of cure, while in precis, it is stated that this test is the test of cure. Please correct.
- The page header contains "Cochrane systematic review". I don't understand this phrase.

Abstract:
- The first sentence is a background not objective and I think has no value to the reader. Please delete.
- The objective is to use extended HPV testing to predict recurrence high grade CIN after treatment. This is inconsistent with both the title and the precis. Please correct.
- Methods of study selection should include the inclusion and exclusion criteria of studies and qualitative assessment. Please correct.
- This is a diagnostic review, how the authors included clinical trails?
- The conclusion is too decisive for the review results.

Sources:
- No search terms, MeSH headings, strategy, or methodology was reported in the "sources" section. The reader can't evaluate the search process.
- In the abstract, the authors state that they searched grey literature, but no details were reported in sources section.
- It is not clear why search started at year 2000. Please clarify.
- It is not clear whether the end of search was at start or end of year 2018. I think update is needed.

Study selection:
- Line 85-86: What are the inclusion and exclusion criteria? Please enumerate in details.
- Newcastle and Ottawa is for observational studies. What was used for trials?

Results:
- Line 121-122: Please specify the study designs rather than describing as prospective or retrospective.
- The second prospective study (Jones et al., 2011) followed up their 98 cases for only 6 months. The authors stated that their review determines the risk after 12 months or greater. Please explain this controversy.
- In the third prospective trial (Kreimer et al., 2012), the authors didn't calculate the diagnostic utility of extended HPV testing in predicting recurrent high grade CIN. They just described the results of the article. Please complete the report.
- In the fourth prospective study (Soderlund-Strand et al., 2014), the authors didn't report the duration of follow up used in calculating the stated sensitivity and specificity. The study started the follow up at 3 months till 36 months.
- Line 181: It is unclear why the authors stated the reference of the PCR technique used by Soderlund-Strand et al., 2014. Please explain.
- The fifth prospective study (Bottari et al., 2018) also followed the cases for an average of 6 months. Thus, 2 out of the 5 prospective studies included in the review are actually not consistent with the inclusion criteria set by the review authors.
- In the fifth prospective study, the authors didn't calculate accuracy of HPV testing in predicting the risk of recurrence.
- Line 216 and following: Please specify the definition of the stated ratio.
- It is unclear why the authors couldn't perform meta-analysis on the accuracy measures of the extended HPV genotype testing. Please explain.
- Table 2: Please add the key for "NR"
- Table 2: It is unclear why the authors didn't report the PPV, LR+ve and LR-ve.
- There is no result regarding the risk of bias for each study.
- There is no result regarding the GRADE overall quality of evidence.
Discussion is very short and is rather comment without real argument or deep analysis.

STATISTICAL EDITOR COMMENTS:

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

Table 1: The variable times of the studies (varied from earliest 1993-2001 to most recent 2011-2015) and the variable follow-up (from 6 months to > 6 years seems problematic in terms of detection of relapse.

Table 2: Need to include CIs with Sens and Spec estimates. Given the rates of CIN2 in these cohorts, NPV is inappropriate. Could include LR(-), with CIs or simply include the AUC with the Sens and Spec estimates.

EDITOR COMMENTS:

Jeff,
I hope this finds you well.

As you will see, we are moving one of the papers you've submitted forward for revision (19-716, the systematic review) and the other paper we are declining. Let me share the Editors’ thinking.

This new technology seems like it will be somewhat disruptive in a setting when there is already a good deal of confusion by practitioners using the pooled DNA lab test. It also doesn’t seem that there are clear guidelines in the Dysplasia world to know how to use this additional information. The study as presented doesn’t really give very much background and frankly is written at a level the presupposes a lot of knowledge about the technology and its implications (or lack of current indications). You will get my comments which may reflect those of a relatively uninformed doc in practice. Write your review for me as that representative and make me understand.

As well, you need to deal with what is an obvious competing interest—BD’s development and marketing of an expanded genotyping test. Yes, you’ve disclosed it but in a test without a clear indication, for which you do not say anything about cost, and with no clear benefit to patient care identified, this needs more than just disclosing it. You will see what needs to be included.

We understand that BD is not the only company developing and marketing this technology so it is coming—and we want our readership to fully understand it and its limits.

Cheers,
NC

1. You are being sent a notated PDF that contains the Editor’s specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

***The notated PDF is uploaded to this submission’s record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenJournal.org.***

- please confirm that this is the correct footer.
- The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.

- The objective for the abstract should be a simple "to" statement without background.

- several of the authors are concerned about use of "recurrent" as of course it could be re-infection or failure to clear the infection with treatment. Mechanistically you need to be more inclusive here.

- please describe source for gray literature search; not mentioned above.

- you can delete highlighted portion.
- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=. ) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4). You have given no data here in the abstract.

- True for each paper?

- perhaps "determined risk of >=CIN2 post treatment to a clinically significant degree".... would be clearer.

- The conclusion is of course of this study; please eliminate highlighted phrase and state your conclusion. Questions I have at the end of this abstract that should be clarified: When and how often is the genotyping that you are studying being done? At time of initial presentation and at follow up visit? WHAT IS being compared here? Extended genotyping, pooled genotyping? You don't say anywhere in abstract. You also have provided no data to suggest any sort of clinical utility beyond follow up screening.

- For all manuscripts with corporate funding, we require that the following information be included in the materials and methods of the manuscript: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide)

- We do not require that initial submissions adhere to the Green Journal publication requirements. Articles for which a revision is requested however, do require that the revised submission adhere to all Green Journal formatting requirements. We strongly recommend that you read the Instructions for Authors to be able to present your revised submission in a format that is likely to allow for a prompt final decision. It is available as a PDF download from the login page for Editorial Manager. It has information for formatting, required elements, word limits, reference style and other necessary items.

- in the ellipse can you state CIN 2,3?

- can you define "conservative treatment"?

- The struck through phrase isn't really needed The interested reader can find time, place of study

- when was TOC done?

- do you mean return to screening every 3-year?

- for clarity, you mean cytology and HPV genotyping when you mean co-testing. Could you state this so that everyone understands what you mean by co-testing?

- can you state what you mean by "pooled HPV assay" for the general reader?

- I am obviously not familiar with this literature, so I'm asking a bunch of questions that I'm hoping other readers may have in order to understand this well. Statement starting on line e 48 to me suggests that a woman who has been treated with excision of some sort should have a negative cytology and then after that at some future time, an HPV test. Is that correct? Of is this an HPV test done as reflex from same specimen as the cytologic exam and sent only if the cytology was negative? Also, just doing the test (implementing that HPV ToC) wouldn't not avert anything. Its the action that follows a positive result, isn't it

- provide the data as you have on line 53 above

- Perhaps this would be clearer with something like the following which links back to prior paragraph. "In order to individualize the post-treatment surveillance, which may reduce patient anxiety, cost, and occurrence of cervical cancer, better identification of women with relevant HPV genotype presence may be a benefit. As such, the purpose of this systematic review is to to compare risk stratification through extended genotyping compared to pooled HPV testing."

- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- Jeff, although you taught me about PICO in 2005, my hunch is that many readers won't recognize it. Can you put a brief statement in about what PICO is?

- Thank you for the attention to PRISMA (including citing it in your paper) and PROPSERO,

- For all manuscripts with corporate funding, we require that the following information be included in the materials and methods of the manuscript: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide).
- what were these criteria? How many people reviewed abstracts? How were differences adjudicated?

- Did each author assess the risk of bias for each paper? If not, how was this done?

- do you mean same-genotype HPV infection detected residual disease? I think you mean it was associated with it. The HPV infection didn't detect it.

- It's not clear to this reader that persistent same genotype HPV testing is the same as extended genotyping. By name only (and perhaps a reason to explain this a bit more) if one is testing for only the same genotype virus as you had before, it wouldn't be "extended" but would really be more focused. From a clinical perspective in your discussion, please make sure you touch on whether getting a result which increases a woman's chance of residual disease by 5 fold alters one's planned surveillance and treatment differently than getting a result which increases her risks 12 fold?

- I don't know what this notation means (>=HSIL)/CIN

- First, the yellow sentence belongs in the discussion section as it an interpretation, not a result. Second, since you found that the majority are NOT same-genotype, this sentence does not seem to make sense

- This is the second brand name being used. Perhaps in a box you could indicate for each of the different tests what HPV genotypes are being tested.

- how long after treatment?

- Still unclear why the same-genotype persistence is so critical? If she had HPV 18 before and now has HPV 16, does that change anything? Aren't you looking for any High risk HPV infection? The issue is whether she is at risk of residual disease, right?


- A lot of this paragraph is redundant. For instances lines 173-4 and lines 177-8 are identical. Please edit.

- what does this notation mean?

- not knowing what onclarity or hc2 tests for makes this not very helpful.

- this sentence is part of discussion; not in results.

- what is a dna chip test?

- as a summary statement, please include what the endpoint is for what your sensitivity and specificity values are relative to.

- please also include a comment on negative association with new genotype.

- Sorry Jeff. I'm not convinced here. Why in particular extended genotyping? Seems to me, what one really needs to know is if the patient has persistence of one of the HPV high risk virus, which doesn't really need "extended" testing. Again, from above: does a relative risk of 5 based on pooled results change your plan any compared to a relative risk of 12? (Or thereabouts) and if so, how?

- you didn't report on other predictors so you can't really say its the "main" predictor.

- I would delete the "as previously reported" phrase. Those previous studies, I assume, are included in this review in part. In addition, given that this is previously reported, defend why a systematic review is needed and what it adds.

- in whom prevalence of what?

- have no clue what PICO heterogeneity is. Please rephrase for reader.

- spell out abbreviations on first use.

2. 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:
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3. 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.

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

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

5. 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 nonfinancial, 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).


6. 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 158-178 ("The role of long-term...post-treatment disease were identified").
- Lines 192-196 ("At baseline, 153 patients tested...tested Onclarity positive at follow-up")
- Lines 215-224: ("HPV testing at 6-months....in the next 24 months.")
- Lines 269-73 ("Relapse of CIN...development of disease recurrence.")
- Lines 315-317 ("...HPV genotyping....same genotype over time").
7. 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. 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.

8. Please include your PROSPERO registration information at the bottom of the abstract.

9. 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.

10. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

11. 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).

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

13. 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: Reviews, 300 words. Please provide a word count.

14. 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.

15. 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.

16. 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.

17. 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.

18. Figure 1: Please submit an editable version with your resubmission.
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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.

20. 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 May 31, 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

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RE: Manuscript Number ONG-19-716

Extended HPV Genotyping with Test-of-Cure following Treatment of High-Grade CIN: Systematic Review

Dear Dr. Andrews:

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 referees 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 May 31, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall: This is a systemic review that describes the use of extended HPV genotyping to discriminate the risk of recurrent disease after treatment for high grade cervical dysplasia.

Other:
Disclosures: This work was supported by Becton, Dickinson and Company, BD Life Sciences - Diagnostic Systems.

Abstract:
1. Line 11 states that the "grey" literature was searched but this was not explicitly defined in the main paper.
   Thank you. This was an error and has been deleted from the manuscript.

Introduction:
2. Good description of the need for this review. PICO is described in detail.
3. Line 60: It may be useful to define "extended genotyping" here.
   Thank you. After reading all of the Reviewer’s responses and the Editor’s comments, we realized that it would be more authentic and better for the reader to refer to ‘genotyping’. All mentions of ‘extended’ were removed except for one place in the Discussion where we define the differences between partial, extended, and full genotyping.
Sources:
4. Data sources included MEDLINE, Cochrane Database of Systematic reviews, Health Technology Assessment (which includes the required MEDLINE), EMBASE and ClinicalTrials. PRISMA guidelines and IOM standards were followed and the study was registered with PROSPERO.

Study Selection:
5. Procedures for study selection and evaluation of risk of bias are adequately described and enough detail is provided to permit duplication.

Results:
9. The results are provided in great detail. They relate to the main point and answer the research question.

Discussion:
10. A thoughtful discussion is provided. The data support the conclusions and limitations are discussed.

References:
11. Pertinent literature is cited and the limit for references is not exceeded.

TABLES and FIGURES:
12. Figure 1: It might be useful to include the reason for exclusion in the box that describes the second round of exclusions (n = 200).
Thank you. We improved the description of this in the Methods, and we modified Figure 1.

Reviewer #2: Authors have prepared systemic review following all the guidelines.

1. Extended genotyping demonstrated assertive results in different measure of performance (Sens, Spec, PPV, NPV etc.). However, data did not show that how those measures for extended genotyping translated into prevention of malignant progression compared to pooled assay. It would be interesting to see whether extended genotyping vs pooled assay make any difference in long term outcome as far as progression of malignancy from post treatment persistent ≥ CIN II is concerned.
Thank you. We realized that we could improve the analysis of genotyping vs pooled assay and these changes were made throughout the manuscript.

2. Overall sample size and sample size of some studies incorporated in systemic review are small.
3. Certainly, more information is helpful provided we have an individualized treatment protocol. As per suggested by authors, identification of persistence of same genotype post treatment may require closer follow up. However, as per evidence-based data and per current guidelines, practitioners are already following up those post treatment patients with persistence of high-risk HPV (irrespective of genotype) closely.

Thank you. Your comment made us realize that we had not adequately analyzed the difference between same genotype persistence and new HPV infection. The manuscript was re-written to provide a more clarity. A systematic review may be useful to guideline panels; but the systematic review should not over-reach to make recommendations for management.

4. At present, there is lack of substantial evidence-based data that would recommend different approach for treatment and follow up for individualized genotypes. Therefore, until more data supporting genotype specific approach is available, universal use of extended genotyping is questionable.

Thank you. We agree that management of women post-treatment with same genotype persistence should Not differ across the genotypes. There could be differing management between same genotype persistence and new HPV infection (these two would appear the same if using a qualitative HPV pooled result). In order to make a determination between same genotype persistence and new HPV infection, a genotyping test would be need on a pre-treatment sample and post-treatment.

5. Last but not least, cost benefit analysis and hazard analysis for implementing extended genotyping protocol would be warranted compared to standard practices.

We agree; but think a guideline panel is the appropriate body for that work, and not a systematic review.

Reviewer #3:
The authors should be congratulated for a well developed systematic review the data available for extended HPV genotyping with Test-of-Cure following treatment of high grade CIN. I have the following comments/questions:

1) Were studies not reported in the English language evaluated for data collection? Of the 233 unique abstracts, why were the 200 initially excluded? Was this also based on the PRISMA flow?

Thank you. We improved the description of this in the Methods, and we modified Figure 1.

2) In lines 130-137, why is there discussion of LSIL? Is this data relevant given the question in hand is CIN 2 or worse? I understand the HSIL logistic regression was not possible due to sensitivity of 100%, but perhaps best to state this and leave it at that. Unable to draw conclusions from LSIL data as many of these low grade lesions will regress spontaneously.

Thank you. We were reporting what the original article reported. Upon re-reading, we agree with you that this introduced unnecessary confusion into the manuscript and did not support the objectives of the systematic review. Interested readers can read the included articles in full text for the study details, if they wish. We deleted this portion.

3) The review addresses negative HPV subtype specific tests after treatment with surgical excision, please comment on risk of re-infection from the same partner or a different partner with the same HPV subtype. Would this impact data or conclusions with regard to surveillance?
Thank you for this interesting question. First, we think this is beyond the scope of our systematic review. Second, none of the included studies contemplated this subject, so we cannot report on any results from our analysis. In the context of this letter, we understand that women who have clearance of an HPV genotype infection (by natural immune response or by excision treatment) do not become re-infected by the same genotype. If a woman was positive, then negative, then positive, the explanations are that the second test was near the clinical cutoff, or that the immune system had suppressed the virus and then it reactivated. Each genotype has different variants. The vaccines seem to be effective against all the variants.

4) In discussion the authors outline that a more personalized follow up plan can be created for patients with persistent HPV subtype infection after CIN 2 surgical treatment. Patients with a new strain of HPV are still at risk for these same lesions at a lower rate over the immediate follow up (ie 2 years). How would this new management strategy impact population based follow up if providers will still need to manage/survey patients with new HR HPV strains compared to persistent strains? Does this data decrease or increase the burden of testing? Would consider mentioning this in discussion section on some level.

Thank you. We added this to our discussion.

Overall well done. This will add the literature as new guidelines are developed with patients receiving the HPV vaccine and the HPV genotype specific testing needed to risk stratify.

Thank you

Reviewer #4:
Thank you for allowing me to review this article. Cervical intraepithelial neoplasia is a very interesting topic in gynecological practice with special interest for prediction/prevention of recurrence that is a considerable risk factor for development of invasive cervical cancer. This makes the current review important piece of knowledge. In general the article is well written with very few typographic mistakes. However, the main problems, as stated by the authors themselves, are the few heterogeneous studies included in the review.

Failure of the authors to produce meta-analysis deepens the issue and emphasizes that the review couldn't find usable evidence.

Thank you. We think that anything can undergo meta-analysis. But just because one could do a meta-analysis does not mean one should do a meta-analysis. We tried to improve our description of why we did not perform a formal meta-analysis. However, we think that the rewriting of this manuscript may lessen your concern that we did not find usable evidence (we think we did).

In addition, using different packages for extended HPV testing may reflect the variation of accuracy of the kits itself rather than the HPV testing process itself.
We agree. We clarified this limitation.

Considering other risk factors of recurrence that were not clearly controlled by the included studies adds another source of weakness of evidence.
Many of the included articles did discuss other factors and did compare HPV and genotyping to other factors. We did not summarize those comparisons because it was beyond the scope of the systematic review and it would have made the manuscript too large. Interested readers could pursue this by referring to the included articles.
Finally, considerable number of the included studies followed their cases for only 6 months. In my opinion this is too short to generate evidence about recurrence of CIN and this concept was supported by the current review. We clarified this data with new table columns that stipulate when the follow-up HPV tests were done, and how long the histopathologic follow-up was for every study.

The authors stated with references that clearance of HPV is expected within one year and recurrence is expected within 2 years of successful treatment of CIN. We deleted the early sentence in the prior Discussion because it was not coherent with the analysis and was not an appropriate opening for the Discussion of these results.

Finally, the authors mixed the concept of "recurrence" with "treatment failure". Despite recurrence of some diseases is considered a type of treatment failure, in systematic reviews, that are pieces of evidence, it is highly preferred to be robust in terminology not to confuse the reader about the outcome. Thank you. We made the mistake of copying each included article terms and definitions. This lead to overlapping terms and confusion. We rewrote the manuscript with ‘one voice’ and selected one set of terms and definitions.

In addition, there are some other issues that should be considered before deciding to publish the review:

Title:
- What is meant by "with test of cure"? Does it mean that extended HPV testing is a test of cure or used with another test for cure? Please explain. Thank you. We agree that test-of-cure is jargon. We removed this, in preference for the Editor’s suggestions (example: posttreatment).

Precis:
- Please replace "cervical disease" with "cervical intraepithelial neoplasia". Done
- There is inconsistency with the title. In title, it is understood that extended genotype is used in addition to a test of cure, while in precis, it is stated that this test is the test of cure. Please correct. Thank you. Upon re-reading, we agree that this was confusing. We eliminated use of the term ‘extended’, and we improved the clarity regarding what tests were done (cytology, qualitative HPV, genotyping).

- The page header contains "Cochrane systematic review". I don't understand this phrase. Thank you. One of us inserted the descriptor ‘Cochrane’, but that was incorrect. We deleted the header.

Abstract:
- The first sentence is a background not objective and I think has no value to the reader. Please delete. Done
- The objective is to use extended HPV testing to predict recurrence high grade CIN after treatment. This is inconsistent with both the title and the precis. Please correct. Thank you. After reading your review and the Editor’s, we rewrote the objective.
- Methods of study selection should include the inclusion and exclusion criteria of studies and qualitative assessment. Please correct.

Added

- This is a diagnostic review, how the authors included clinical trials?

We searched for clinical trials. We did not find any clinical trials. It is possible to conduct and report a diagnostic clinical trial. There are a few notable examples. However, we did not find any clinical trials.

- The conclusion is too decisive for the review results.

Thank you. We revised.

Sources:
- No search terms, MeSH headings, strategy, or methodology was reported in the "sources" section. The reader can't evaluate the search process.

Added

- In the abstract, the authors state that they searched grey literature, but no details were reported in sources section.

Thank you. This was an error and has been deleted from the manuscript.

- It is not clear why search started at year 2000. Please clarify.

Our focus was HPV testing, including genotyping. The first HPV assay (Digene HC2) achieved FDA approval in 1999 and reached the US market in 2000.

- It is not clear whether the end of search was at start or end of year 2018. I think update is needed.

Thank you. The search and results were updated to April 2019.

Study selection:
- Line 85-86: What are the inclusion and exclusion criteria? Please enumerate in details.

Added

- Newcastle and Ottawa is for observational studies. What was used for trials?

There were only observational studies. Had we found a clinical trial, we would have used the Cochrane Risk of Bias form, but we did not find a clinical trial.

Results:
- Line 121-122: Please specify the study designs rather than describing as prospective or retrospective.

Added

- The second prospective study (Jones et al., 2011) followed up their 98 cases for only 6 months. The authors stated that their review determines the risk after 12 months or greater. Please explain this controversy.

Thank you for noticing this. We corrected our error; the timing for post-treatment HPV testing was 6 months or more.

- In the third prospective trial (Kreimer et al., 2012), the authors didn't calculate the diagnostic utility of extended HPV testing in predicting recurrent high grade CIN. They just described the results of the article. Please complete the report.

Thank you. We completely revised the description and reporting of Results for all of the included articles.
- In the fourth prospective study (Soderlund-Strand et al., 2014), the authors didn’t report the duration of follow up used in calculating the stated sensitivity and specificity. The study started the follow up at 3 months till 36 months.

- Line 181: It is unclear why the authors stated the reference of the PCR technique used by Soderlund-Strand et al., 2014. Please explain. Thank you. You alerted us to this inconsistency in our article. After reading the Editor’s comments, we decided to remove all mentions of HPV assay names from the main body and we improved the description of these in one table.

- The fifth prospective study (Bottari et al., 2018) also followed the cases for an average of 6 months. Thus, 2 out of the 5 prospective studies included in the review are actually not consistent with the inclusion criteria set by the review authors Thank you for noticing this. We corrected our error; the timing for post-treatment HPV testing was 6 months or more.

- In the fifth prospective study, the authors didn't calculate accuracy of HPV testing in predicting the risk of recurrence. Thank you. We completely revised the description and reporting of Results for all of the included articles.

- Line 216 and following: Please specify the definition of the stated ratio. Thank you. We were reporting what the original article reported. Upon re-reading, we agree with you that this introduced unnecessary confusion into the manuscript and did not support the objectives of the systematic review. Interested readers can read the included articles in full text for the study details, if they wish. We deleted this portion. Of note, the ratio was a risk ratio.

- It is unclear why the authors couldn't perform meta-analysis on the accuracy measures of the extended HPV genotype testing. Please explain. Thank you. We think that anything can undergo meta-analysis. But just because one could do a meta-analysis does not mean one should do a meta-analysis. We tried to improve our description of why we did not perform a formal meta-analysis. However, we think that the rewriting of this manuscript may lessen your concern.

- Table 2: Please add the key for "NR"
Revised
- Table 2: It is unclear why the authors didn't report the PPV, LR+ve and LR-ve. Thank you for your suggestion. We completely revised the description and reporting of Results for all of the included articles. We added PPV. We did not add LR+ and LR-. To do so would make the tables larger and potentially more confusing; and would lengthen the Results section of the manuscript. If you would like us to report the LRs, we can calculate them and create a supplemental table. Perhaps after reading our revision, you may decide whether this is necessary?

- There is no result regarding the risk of bias for each study. Thank you. We did this work, but it was not in our submission, due to an oversight. We have added the analysis, by table and text.

- There is no result regarding the GRADE overall quality of evidence.
Thank you. We did this work, but it was not in our submission, due to an oversight. We have added the analysis, by table and text.

Discussion is very short and is rather comment without real argument or deep analysis. Thank you. We rewrote the Discussion.

STATISTICAL EDITOR COMMENTS:

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

Table 1: The variable times of the studies (varied from earliest 1993-2001 to most recent 2011-2015) and the variable follow-up (from 6 months to > 6 years seems problematic in terms of detection of relapse.
We agree. However, the endpoint was histopathologic biopsy post-treatment. After treatment of CIN2+, there should not be a finding of CIN2+ - whether we call that treatment failure, residual disease, or recurrence. In clinical practice, if CIN2+ is found, following treatment, we usually re-treat. (exceptions would be CIN2 in a younger woman, pregnancy).

Table 2: Need to include CIs with Sens and Spec estimates. Given the rates of CIN2 in these cohorts, NPV is inappropriate. Could include LR(-), with CIs or simply include the AUC with the Sens and Spec estimates.
Thank you very much. We added CIs for all Sens and Spec results. We kept NPV because the included articles reported NPV. If, after reading our revision, you want us to remove NPV, we will comply. We added the AUC (Figure 2)

EDITOR COMMENTS:

Jeff,
I hope this finds you well.

As you will see, we are moving one of the papers you’ve submitted forward for revision (19-716, the systematic review) and the other paper we are declining. Let me share the Editors’ thinking.

This new technology seems like it will be somewhat disruptive in a setting when there is already a good deal of confusion by practitioners using the pooled DNA lab test. It also doesn’t seem that there are clear guidelines in the Dysplasia world to know how to use this additional information.
Thank you. A common timeline is the publication of primary research, a number of systematic reviews that address specific questions by analyzing primary research, a guideline or revision that utilizes the systematic reviews as a foundation for making recommendations. The fact that a guideline in 2019 does not call for genotyping does not mean that a systematic review reporting on genotyping should not be
published in 2019. You Journal is one way that confusion is decreased, by continuous publication of new science and evolving diagnostics and therapeutics.

The study as presented doesn’t really give very much background and frankly is written at a level the presupposes a lot of knowledge about the technology and its implications (or lack of current indications). You will get my comments which may reflect those of a relatively uninformed doc in practice. Write your review for me as that representative and make me understand.

Thank you. We are very grateful for this insight. Of course, you are right – our group of experts all understood internally what we were analyzing and reporting and the clinical utility, but we did not take care to explain this for the perspective of the average reader. The entire manuscript was rewritten with your points in mind.

As well, you need to deal with what is an obvious competing interest—BD’s development and marketing of an expanded genotyping test. Yes, you’ve disclosed it but in a test without a clear indication, for which you do not say anything about cost, and with no clear benefit to patient care identified, this needs more than just disclosing it. You will see what needs to be included.

Several comments.

- there is no test with clinical claims for post-treatment testing (not cytology, not any HPV test)
- BD has no intention of seeking an FDA approval for post-treatment genotyping
- We have no reason to think that the FDA has any desire to begin regulating post-treatment use of cytology or HPV tests
- For almost 2 decades, USA guidance from ASCCP, SGO, ACOG has recommended both cytology and HPV testing after treatment of CIN2+. Those tests have been done daily, for decades. All of that use is off-label.
- We removed any mention of Onclarity from the main body of text.
- We retained a single mention of Onclarity in the table that provides the names of all the genotyping tests used in all of the studies
- In the USA, cost is set by the AMA – who determine both diagnostic codes and reimbursement, with the input of key organizations like ACOG. In 2019, the code and reimbursement for an HPV test is the same, whether that test provides no genotyping, partial genotyping, extended genotyping, or full genotyping.
- We have tried to clarify what we view as the benefits for the patient in our revised Discussion.

We understand that BD is not the only company developing and marketing this technology so it is coming—and we want our readership to fully understand it and its limits.

Cheers,
NC
Cheers back!

1. You are being sent a notated PDF that contains the Editor’s specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

***The notated PDF is uploaded to this submission’s record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.***
- please confirm that this is the correct footer.

- The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't include statements like "in this study" or "we found". Just state what you found.

- The objective for the abstract should be a simple "to" statement without background. Revised.

- several of the authors are concerned about use of "recurrent" as of course it could be re-infection or failure to clear the infection with treatment. Mechanistically you need to be more inclusive here. We agree and recurrent is no longer used.

- please describe source for gray literature search; not mentioned above. Thank you. This was an error and has been deleted from the manuscript.

- you can delete highlighted portion.

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=. ) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4). You have given no data here in the abstract. Thank you. We revised the main body. We revised the abstract

- True for each paper?

- perhaps "determined risk of >=CIN2 post treatment to a clinically significant degree".... would be clearer. Thank you

- The conclusion is of course of this study; please eliminate highlighted phrase and state your conclusion. Questions I have at the end of this abstract that should be clarified: When and how often is the genotyping that you are studying being done? At time of initial presentation and at follow up visit? Yes, that is the minimum; clarified. WHAT IS being compared here? Extended genotyping, pooled genotyping? You don't say anywhere in abstract. You also have provided no data to suggest any sort of clinical utility beyond follow up screening. You were correct. We did not clearly follow thru on our objective in our presentation of the results and analysis. The entire manuscript was rewritten to correct this.

- For all manuscripts with corporate funding, we require that the following information be included in the materials and methods of the manuscript: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide) Added
We do not require that initial submissions adhere to the Green Journal publication requirements. Articles for which a revision is requested however, do require that the revised submission adhere to all Green Journal formatting requirements. We strongly recommend that you read the Instructions for Authors to be able to present your revised submission in a format that is likely to allow for a prompt final decision. It is available as a PDF download from the login page for Editorial Manager. It has information for formatting, required elements, word limits, reference style and other necessary items.

- in the ellipse can you state CIN 2,3?
done
- can you define "conservative treatment"?
Thank you. We were copying the original article. We’ve revised to use ‘one voice’ and consistent terms and definitions. ‘Conservative treatment’ is no longer in the manuscript

- The struck through phrase isn't really needed The interested reader can find time, place of study
Deleted
- when was TOC done?
We added new columns to the table to make this clear for each included study
- do you mean return to screening every 3-year?
Revised for clarity
- for clarity, you mean cytology and HPV genotyping when you mean co-testing. Could you state this so that everyone understands what you mean by co-testing?
Yes, thanks – we revised all locations to be clear to the reader throughout
- can you state what you mean by "pooled HPV assay" for the general reader?
Yes, thanks – we revised all locations to be clear to the reader throughout
- I am obviously not familiar with this literature, so I'm asking a bunch of questions that I'm hoping other readers may have in order to understand this well. Statement starting on line e 48 to me suggests that a woman who has been treated with excision of some sort should have a negative cytology and then after that at some future time, an HPV test. Is that correct? Of is this an HPV test done as reflex from same specimen as the cytologic exam and sent only if the cytology was negative? Also, just doing the test (implementing that HPV ToC) wouldn't not avert anything. Its the action that follows a positive result, isn't it
Thank you. We needed to make this clearer. The clinical options are: i) cytology only; ii) HPV test only; iii) HPV test with reflex to cytology if positive; HPV test and cytology (cotest); colposcopy with/without any of the preceding at same time. The ASCCP (and ACOG) currently recommend cotest in the USA.

- provide the data as you have on line 53 above
Done
- Perhaps this would be clearer with something like the following which links back to prior paragraph. "In order to individualize the post-treatment surveillance, which may reduce patient anxiety, cost, and occurrence of cervical cancer, better identification of women with relevant HPV genotype presence may be a benefit. As such, the purpose of this systematic review is to to compare risk stratification through extended genotyping compared to pooled HPV testing."
Thank you, very helpful – done.
- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.
Corrected
- Jeff, although you taught me about PICO in 2005, my hunch is that many readers won't recognize it. Can you put a brief statement in about what PICO is?
Thank you. We clarified this by rewriting the segment.

- Thank you for the attention to PRISMA (including citing it in your paper) and PROPSERO,

- For all manuscripts with corporate funding, we require that the following information be included in the materials and methods of the manuscript: The role of the sponsor in the design, execution, analysis, reporting and funding (ie, what did the sponsor provide).
  
  Added
  - what were these criteria? How many people reviewed abstracts? How were differences adjudicated?
  
  Revised description for more detail

- Did each author assess the risk of bias for each paper? If not, how was this done?
  
  Revised description for more detail

- do you mean same-genotype HPV infection detected residual disease? I think you mean it was associated with it. The HPV infection didn't detect it.
  
  Revised
- It's not clear to this reader that persistent same genotype HPV testing is the same as extended genotyping.
  
  You were right! We deleted ‘extended’. We explained genotyping versus qualitative pooled result. Once, in the discussion, we provided the reader with an annotated explanation of qualitative, partial, extended, full genotyping.

By name only (and perhaps a reason to explain this a bit more) if one is testing for only the same genotype virus as you had before, it wouldn't be "extended" but would really be more focused. From a clinical perspective in your discussion, please make sure you touch on whether getting a result which increases a woman's chance of residual disease by 5 fold alters one's planned surveillance and treatment differently than getting a result which increases her risks 12 fold?

Thank you. We addressed this in the new revised discussion. We annotated to the clinical action thresholds published by Katki et al, and currently in use by the ASCCP under the principle of ‘similar management for similar risk’. A PPV of 44.4% is well above the clinical action threshold for colposcopy (repeat, in this case) and is comparable to the risk of HPV-positive and HSIL cytology. A PPV approximating zero would be consistent with ‘cure’ with respect to the setting of post-treatment testing. However, the serendipitous discovery of a new HPV infection means the patient cannot return to routine screening. Currently, women in the USA with a risk above the clinical action threshold for return to routine screening, and below the clinical action threshold for colposcopy are retested after one year. The exact timing of the test and which test would properly be determined by a guideline panel.

- I don't know what this notation means (>=HSIL)/CIN
  
  Deleted

- First, the yellow sentence belongs in the discussion section as it an interpretation, not a result.
  
  Moved
  
  Second, since you found that the majority are NOT same-genotype, this sentence does not seem to make sense.
  
  We revised and clarified.
- This is the second brand name being used. Perhaps in a box you could indicate for each of the different tests what HPV genotypes are being tested.
We removed all brand names from the body of the text and only mention once, in the table of studies that reports which test was used in which study.

- how long after treatment?
Clarified
- Still unclear why the same-genotype persistence is so critical? If she had HPV 18 before and now has HPV 16, does that change anything? Aren't you looking for any High risk HPV infection? The issue is whether she is at risk of residual disease, right?
We hope that this is now clear, after rewriting the whole manuscript. Detecting the same genotype post-treatment that was present pre-treatment confers a >40% risk of CIN2+ (or a >40% risk of treatment ‘failure’) and the patient must be reassessed (by colposcopy & biopsy) to determine if she needs additional treatment. However, a result that the prior genotypes are not present (clearance) and the detection of a new genotype (not present pre-treatment) indicates two things: the treatment was very likely successful because the pre-treatment HPV genotype is cleared; and the woman has contracted a new HPV infection in the interim between the tests. If the post-treatment test interval was 6-12 months, this is not enough time for the virus to have induced CIN (takes years) nor cancer (takes years). Further, more than 90% of infections clear within 24 months. Therefore, this woman should undergo simple retesting after an appropriate interval. The exact timing of the test and which test would properly be determined by a guideline panel. The experience for this latter woman is very different if genotyping is used, compared to a qualitative pooled HPV result. A positive hrHPV result would be interpreted as ‘treatment failure’; she would be brought back for another colposcopy and more biopsies; she would be at risk for over treatment (back for another LEEP); she would be at higher risk for PTB if she had multiple LEEPs; she would be unduly worried. A genotyping result could reassure her (the HPV that caused the CIN2+ is gone) and be informed (you have a new infection that will likely clear by your own immunity; we will retest in 12+ months to verify).

Revised
- A lot of this paragraph is redundant. For instances lines 173-4 and lines 177-8 are identical. Please edit.
Deleted
- what does this notation mean?
Fixed (deleted from main body; described in Table)
- not knowing what onclarity or hc2 tests for makes this not very helpful.
Deleted, and tests explained in table
- this sentence is part of discussion; not in results.
Moved
- what is a dna chip test?
Deleted, and tests explained in table

- as a summary statement, please include what the endpoint is for what your sensitivity and specificity values are relative to.
Thanks. Revised
- please also include a comment on negative association with new genotype.
Thanks. Revised
- Sorry Jeff. I'm not convinced here. Why in particular extended genotyping? Seems to me, what one really needs to know is if the patient has persistence of one of the HPV high risk virus, which doesn't
really need "extended" testing. Again, from above: does a relative risk of 5 based on pooled results change your plan any compared to a relative risk of 12? (Or thereabouts) and if so, how?
Thanks! You were right! We revised.

- you didn't report on other predictors so you can't really say its the "main" predictor.
You were right. Deleted
- I would delete the "as previously reported" phrase. Those previous studies, I assume, are included in this review in part. In addition, given that this is previously reported, defend why a systematic review is needed and what it adds.
Agree. Done.
- in whom prevalence of what?
Corrected
- have no clue what PICO heterogeneity is. Please rephrase for reader.
Agree - poorly phrased and explained. Revised.
- spell out abbreviations on first use.
Done

2. 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.

3. 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.

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

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

5. 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. Done

(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.

The above instruction was completed

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

(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). Added

6. 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 158-178 (“The role of long-term...post-treatment disease were identified”).
- Lines 192-196 (“At baseline, 153 patients tested...tested Onclarity positive at follow-up”)
- Lines 215-224: (“HPV testing at 6-months....in the next 24 months.”)
- Lines 269-73 (“Relapse of CIN...development of disease recurrence.”)
- Lines 315-317 (“...HPV genotyping....same genotype over time”).

We completely rewrote the Results section, and none of these sentences were retained.

7. 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. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=wgu6hzw1MOorcVMSMqu8lcS59mhBvl1Fc7tKn_Em0PVg &r=SjCqaEttTxsIXZXriq59Mc6z2tDNm470HppZDxVi9a8&m=t9bXF MF3dwVY0I0BCKziWwhPaJNOoiUwgtO aPN1we0Y&s=VJ3Ji7tUWxoY3FtUgcy7avBIN9rWX3NhxHySih_Rck&g=. 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.

8. Please include your PROSPERO registration information at the bottom of the abstract.

Added

9. 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://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG- 2DDepartments_Patient-2DSafety-2Dand-2DDQuality-2DImprovement_reVITALize&d=DwlGaQ&c=wgu6hzw1MOorcVMSMqu8lcS59mhBvl1Fc7tKn_Em0PVg&r= SjCqaEttTxsIXZXriq59Mc6z2tDNm470HppZDxVi9a8&m=t9bXF MF3dwVY0I0BCKziWwhPaJNOoiUwgtOaN1we0Y&s=GNK4kU49lMlMMrnRb467Hysom6tT3sfZBX99zvjWDS&g=. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

We cross-checked reVITALize against our manuscript.

10. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.
We conform.

11. 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).

No part of this article was presented at the ACM of ACOG. All of this article has never been presented. As you can tell, the current article is vastly different from the one you initially submitted to you, and nothing from the current submission; no data, no tables, no figures have been ever been presented, because they were just created in response to your review. Some aspects of some of the included articles have been mentioned in a Poster at International Workshop on Lower Genital Tract Pathology, Rome, Italy in April 2018, Poster at ASCCP annual conference, Las Vegas, NV, USA in April 2018; and in 3 brief oral presentations at Oral presentation at IPV conference, Cape Town, South Africa in February 2017, EUROGIN conference, Amsterdam, Netherlands in October 2017, and at SCCPS annual conference, Singapore in March 2019. According to our understanding of the rules, the prior oral presentations were substantially different from this article and do not require inclusion in the acknowledgement that accompanies the article.

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

Done

13. 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: Reviews, 300 words. Please provide a word count.

Word count added

14. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=wgu6hzw1MOrcVMSMqu8IcS59mhBvl1Fc7tKn_EmOPVg&r=SjCqaEttTXsLXXZriq59Mc6z2tDMn470HppZDxVi9a8&m=t9bXFMF3dwVYOI0BCKZiWhxPamoJNOoUlWp4tAPN1we0Y&s=_ScyGnFiZ59GG20M964njFyq2dTKeug39CZGeH7pNM&e=. 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 cross-checked out use of abbreviations and acronyms
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We conform; we removed all commercial names from the body of manuscript.

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Corrected for all tables

18. Figure 1: Please submit an editable version with your resubmission.

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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 May 31, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

Responses were contributed and agreed by all authors; this letter was compiled by Jeff Andrews.