

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

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

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Jul 06, 2018
To: "Mark S. DeFrancesco" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1121

RE: Manuscript Number ONG-18-1121

Hereditary Cancer Risk Assessment and Genetic Testing in the Community Practice Setting

Dear Dr. DeFrancesco:

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 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Abstract

- Objective of the study are not reflect in the conclusions.

Introduction

- Inadequate.
- There is no clear goal stated: are we testing the office process and presenting a quality improvement process or addressing prevalence and failure to provide an adequate testing in the community":
 - o There should be either algorithm for quality improvement;
 - o There should be more specific description of genetic testing and discrimination of different genetic syndromes, as these appears all lumped together;

Material and Methods

- Not well organized and hard to follow
- It would be nice to see the flow of patients seen through patients tested and diagnosed with the mutations. Since the rate of cancer detection in all patients 5.5% but, patients who actually had the test 18%. Is this the system issue that 13% of patients with mutations are not identified; why they have not completed the testing and how these patients are followed in the future.

Results

- As above, the rate of cancer detection in all patients 5.5% but, patients who actually had the test 18%. Is this the system issue that 13% of patients with mutations are not identified .Why they have not completed the testing and how these patients are followed in the future;
- Why all patient s are tested with my risk: if patients are appropriately screened and counseled there should be more selective testing

Discussion

- Authors do need to make a decision of what they actually trying to address; 4% test rate is miserably low.

Tables

- Appropriate.

Figures

- As above: are we talking about process improvement or screening for at risk population?

Reviewer #2:

This work is a novel submission of a prospective process intervention study of community practice OB GYNs researching for publication the feasibility of generalist OB GYNs screening and counseling women for risk of inherited cancer syndromes without initial referral to genetic counseling. This was an industry sponsored study. The work also falls into the realm of the ACCME competency of Practice based Learning and Improvement (PBLI), and the general area of quality improvement in medicine.

1. This work is novel and important to the field of OB GYN because it is a quality improvement work, carried out prospectively and with attention to important factors for ethical publication of practice improvement research.

There are few OB GYN works of this nature to date, and they are often published in the Quality research journals. A quick and informal search finds Dyrkorn et al.'s Norwegian reduction of post-cesarean infections improvement project[1], Burstein et al.'s 2016 paper on standardizing obstetric practice to improve neonatal outcomes in Health Services Research[2] and Powell et al.'s investigation of the effect of HIV-centered OB care on HIV transmission rates.[3]

2. A key feature of the submission is that it was carried out by active clinicians. This is likely to improve its scalability (or generalizability) - it's worthy of publication.

3. Their key finding of eightfold increased completed genetic testing is important, as is their confirmation of a significant amount of risk is conferred by testing for genes and variants not on the usual screening panels.

4. Secondary findings are also important -that same day sampling availability significantly increased patient participation and follow-up should guide other practices choosing to implement projects

5. Abstract - well written, concise and clear

6. Methods - overall understandable Please clarify

a. Is Myriad the testing laboratory?

b. Were the genetics counselor and LEAN professional from a local commercial laboratory or from the sponsor Myriad?

---there is concern of potential conflicts of interest for genetic counselors employed by commercial labs.

7. Methods - It seems really clear results were given to patients by the study clinicians on site (OB GYN providers); but how were the frequent VUS results given, if they were? For patients in the study who got tested, it seems a potential risk is anxiety about uncertain results, and (less likely) stigma or other harm from knowledge of a positive.

a. For Myriad authors - This seems a higher frequency of VUS findings

8. Methods - For Myriad authors -The panels used have 28 genes, but the references are for panels of 25 genes - are there data or references on the effect of adding those three? (all colorectal cancer risk associated: GERM1,POLD1, and POLE)

9. Methods - breast, ovarian and colorectal cancer all have clear prophylactic and screening (breast and colorectal) advantages; but other genes on the panel (melanoma and pancreatic associated) don't - clarify how it is advantageous to the patient to have those on the panel - how were the differences in counseling needed approached?

10. Introduction -Clear and quickly establishes the context.

11. Results - Clearly stated and complete with the supplemental tables - Tables/Figures clear and add to the understanding. Survey tools for satisfaction methods appropriate and referenced.

a. Statistics should be reviewed by journal statistics editor

12. Discussion - Mostly clear (see below for a few more considerations)

13. The authors report adhering to the SQUIRE guidelines for publishing medical quality improvement works, a helpful guide and good supplemental submission for the review. The submission doesn't address limitations (Item 16), and seems weak in Item 18 - the company funding is mentioned on page one (Line 19), but no further discussion of a company role is noted. Yet, it seems possible the sponsor, Myriad, is also the 'testing laboratory' and Myriad is clearly the source of the LEAN engineers who developed the study processes and protocol (Lines 91-97).

14. The source of the 'limited education' for the providers conducting the research (Line257) should be clear - one is left to presume it is the sponsor (testing?) laboratory, Myriad. The authors should clarify the amount and andragogy of the education provided. Simply stating it is likely to be similar to a newly starting ACOG offering which has not met yet (first generalist providers are going through in August sessions) [Submission Reference 29] in content and effectiveness seems insufficient.

15. While study funding was disclosed (Myriad) and sponsor education of clinicians mentioned, individual author conflict(s) of interest were not. The GPP3 guidelines are mentioned as being in action, but Principles 9 (Disclosures) and 10 (full explanation of sponsor role in design and implementation) don't seem completely fulfilled.

16. Line 38 and elsewhere - the plural word 'data' is given a singular verb at other locations the pairing is correct.

-
1. Dykorn OA, Kristoffersen M, Walberg M. Reducing post-caesarean surgical wound infection rate: an improvement project in a Norwegian maternity clinic. *BMJ Quality & Safety*. 2012;21(3):206-210.
 2. Burstein PD, Zalski DM, Edwards JL, et al. Changing Labor and Delivery Practice: Focus on Achieving Practice and Documentation Standardization with the Goal of Improving Neonatal Outcomes. *Health Services Research*. 2016;51 Suppl 3:2472-2486.
 3. Powell AM, DeVita JM, Ogburu-Ogbonnaya A, Peterson A, Lazenby GB. The Effect of HIV-Centered Obstetric Care on Perinatal Outcomes Among a Cohort of Women Living With HIV. *Journal of Acquired Immune Deficiency Syndromes* (1999). 2017;75(4):431-438.

Reviewer #3:

This is a prospective process intervention study to assess the feasibility and impact of incorporating hereditary cancer risk assessment, counseling, and follow-up genetic testing in a community-based OB/Gyn practice without referral to a genetic counselor.

1. Abstract is clear and concise.
2. Lines 44, 49. Discrepancy in the total # of women who completed genetic testing. Line 44 stated 165 and Lines 49-50 stated 169 patients.
3. Materials and Methods: It would be helpful to mention how long the screening took during the post-intervention period to give readers a sense of whether this is feasible in their practice setting
4. Lines 182-183: How were patients with variants of uncertain significance counseled and planned to be followed? If these variants are reclassified, does Myriad contact the patient or ordering physician directly?
5. This is a well written and very relevant paper and nicely designed study. I commend the authors for their hard work in implementing this type of much-needed program which can be an example to other ob/gyn practices around the country. My concern is the post-screening followup specifically of patients who are found to NOT have a pathogenic mutation or to have one of uncertain significance and whether the physicians and NPs/PAs/CNM felt they had adequate training and time to discuss this with patients.
6. Lines 200-201: Why did the 1 provider not feel they could/would continue to use the process to screen and test patients at risk?
7. Discussion of insurance coverage was also much appreciated.

Reviewer #4:

The objective of the manuscript is to find out of the feasibility of including routine hereditary cancer risk assessment and genetic testing in the general obstetrics and gynecology office. The study was conducted in two offices of obstetrics and gynecology practices, one in Syracuse, NY and the other in Waterbury, Connecticut. The study was approved by an independent institutional review board. The staff of these offices were trained and they had a four week period to incorporate the new process and the work out for the program. The post intra-patient period occurred in the two offices at two different times.

The clinical criteria or HBOC Genetic Testing were based on the presence of personal or family history of breast, ovarian, prostate, or pancreatic cancer. Also the study included patients with a history of Lynch Syndrome criteria used on the presence of colorectal, endometrial, gastric, ovarian, uterus and adrenal pelvic, urinary tract, small bowel, pancreatic, brain or sebaceous adenomas.

Patients who met the HBOC and/or Lynch Syndrome Criteria, they were given genetic testing. This was done on the same day or different dates. The genetic testing included 28 gene testing.

Participating patients were surveyed for their subscription to this program. It was clear from the testing that some of the pathogenic variants were found and the patients were taken care of by a specialist. The patient satisfaction survey was at 97.6%.

The study clearly shows that it is possible and of great value to include genetic screening, testing, and counseling for patients that come to the general obstetrics and gynecologists' office for checkups. This also confirms the view of the American College of Obstetrics and Gynecology.

The authors of this article certainly put a large number of data in this study and also did a great organized study.

Reviewer #5:

Nicely sized study evaluating the feasibility of implementing genetic cancer screening in a community setting. The authors were able to markedly increase genetic cancer screening and testing compared to previous practice. The process was well received by providers and patients.

Several authors work for Myriad.

The pre-study site intervention was extensive and supported by industry with both certified genetic counselors and a LEAN engineer. This contradicts the premise put forth in the introduction that this process is necessary because of the dearth of genetic counselors. It also speaks to lack of generalizability with implementation in communities without this support.

Why were some patients referred for delayed testing by a NP? Was this because the original clinician did not have time, training, or inclination or was this to replicate referral to genetic counseling done in previous practice as implied by your discussion. As you note, this process resulted in a marked decrease of actual testing.

Why do you postulate that only 40% of patients offered testing, agreed to it? Is this consistent with prior literature when screening is done by a genetic counselor?

I'm not sure that Tables 4 and 5 of provider and patient satisfaction add to the body of the paper.

STATISTICAL EDITOR:

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

Table 1: The "Total" column has no entries for denominators. To have a consistent format, should include denominators as in the other columns or otherwise indication what denominators were used for various proportions.

Table 2: Should explain VUS in footnote.

Table 3: Since the sample was $n = 15$, no need to cite %s to nearest 0.1%, should round to nearest whole number.

Would be useful to include a flow diagram, beginning with 4107 patients, then number providing family history, number with (+) family history, number offered etc to final number completed testing and number with abnormal findings.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, 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 Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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.

3. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). Script font is not acceptable. Please have each other send us forms with their signatures.

The author agreement form is available online at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

4. 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. For publication purposes, the portions of particular importance to industry-sponsored research are below.* Please indicate whether the following statements are true or false, and provide an explanation if necessary:

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

(b) 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.

(c) 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.

(d) 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.

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

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

5. 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 guidelines, as appropriate.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and appendixes) except for references.

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

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

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

11. The 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.

12. 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.

13. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at <http://www.acog.org/Resources-And-Publications>.

14. To ensure a quality experience for those viewing supplemental digital content, the journal's publisher suggests that authors submit supplemental digital files no larger than 10 MB each. The exceptions to this rule are audio or video files, which are acceptable up to 100 MB. When submitting text files or tables as supplemental digital content with your revisions, please do not submit PDFs.

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir
Editor in Chief Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

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

25 July 2018

Nancy C. Chescheir, MD
Editor
Obstetrics & Gynecology

Dear Dr. Chescheir,

Thank you for your review of our manuscript, "Hereditary Cancer Risk Assessment and Genetic Testing in the Community Practice Setting." We appreciate the opportunity to revise our manuscript and respond to your and the reviewers' comments. We have provided a detailed description of our revisions below.

Thank you for your consideration, and we look forward to hearing from you.

Reviewer #1:

Abstract

- Objectives of the study are not reflect in the conclusions.

***Response:** We have revised the abstract Conclusion to reflect the study objectives, which are to demonstrate feasibility and impact of incorporating routine hereditary cancer risk assessment, counseling/education, and follow-up genetic testing in the community obstetrics-gynecology practice setting.*

Introduction

- Inadequate.
- There is no clear goal stated: are we testing the office process and presenting a quality improvement process or addressing prevalence and failure to provide an adequate testing in the community":
 - There should be either algorithm for quality improvement;
 - There should be more specific description of genetic testing and discrimination of different genetic syndromes, as these appears all lumped together;

***Response:** We thank the Reviewer for this insight and have revised the Introduction to better clarify the aim of this study – to evaluate the feasibility of the process integration and describe the results of screening and testing. In addition, we have incorporated text to frame the importance of these goals and call out that hereditary cancer risk assessment is currently not utilized universally in the OB/GYN setting, despite ACOG recommendations over the past several years. As a result, there is little data describing the prevalence of women at increased hereditary cancer risk in this population and the outcomes of genetic testing.*

We also appreciate the Reviewer's interest in a more specific description of genetic testing and hereditary cancer syndromes. However, we are unable to incorporate more specific text on this topic in the Introduction due to the formatting requirements of the journal, which limit the Introduction to 250 words.

Material and Methods

- Not well organized and hard to follow

Response: *The Materials and Methods section admittedly includes a large amount of information outlining the study design, genetic testing methods, and data collection and analysis. In order to improve the organization and readability of this section, we have made some revisions to the text. In addition, we have incorporated sub-headers to better differentiate the separate components included in the Materials and Methods section. We recognize that the journal recommends against the use of sub-headers, but feel it improves the readability of the paper. We are happy to remove the sub-headers if the Editors feel it is necessary.*

- It would be nice to see the flow of patients seen through patients tested and diagnosed with the mutations. Since the rate of cancer detection in all patients 5.5% but, patients who actually had the test 18%. Is this the system issue that 13% of patients with mutations are not identified; why they have not completed the testing and how these patients are followed in the future.

Response: *We appreciate the interest in a patient flow. We do not believe that a patient flow is appropriate to include in the Materials and Methods section, as the proportion of patients who completed each step of the study is a key Result regarding the feasibility of the process intervention. This data is currently captured in Table 1 and discussed in the Results section.*

The Reviewer has correctly calculated that about 18% (165/906) of patients who met testing criteria completed genetic testing. Of those who completed genetic testing, 5.5% (9/165) had a pathogenic mutation (we did not evaluate cancer detection). The majority of patients who met testing criteria but did not complete testing did not agree to undergo testing. Reasons for why patients did not agree to undergo testing were not captured as part of this study. Among those who agreed to undergo testing, some never submitted a sample for testing and others had their tests cancelled (largely due to insurance reasons). We do not have any concerns about identification of mutations among tested women, but aim to highlight the large number of women at increased risk who are not being tested. This was evaluated here by extrapolating the proportion of women who met testing criteria here to the approximately 100 million women in the US population between the ages of 18 and 64.

Although the Reviewer has raised this point in the Materials and Methods section, we feel this is appropriate for the Discussion section. We have revised the language that discusses this point in order to better clarify the clinical findings and concerns.

Results

- As above, the rate of cancer detection in all patients 5.5% but, patients who actually had the test 18%. Is this the system issue that 13% of patients with mutations are not identified .Why they have not completed the testing and how these patients are followed in the future;

Response: *Please see the response above regarding this comment. We would like to clarify that we did not do any assessment of cancer detection as part of this study. 5.5% of tested patients carried a pathogenic variant that results in significantly increased cancer risk.*

- Why all patients are tested with my risk: if patients are appropriately screened and counseled there should be more selective testing

Response: Historically, hereditary cancer genetic testing focused on specific cancer-risk genes or hereditary cancer syndromes. However, there has been a great deal of data over the last five years demonstrating that there is a large amount of phenotypic overlap between hereditary cancer syndromes and that multi-gene pan-cancer panel testing identifies mutations that would not have been identified with single-syndrome testing (1, 2). In addition, many of the genes more recently incorporated into clinical genetic testing (including tests other than myRisk) are moderate-penetrance genes. Compared to genes like BRCA1 and BRCA2, where cancer risks are up to 80%, families who carry moderate-penetrance genes often have a less obvious clinical presentation. As such, clinical testing practices of both genetic counselors and oncologists are increasingly shifting towards the use of pan-cancer, multi-gene panels rather than more targeted testing in order to avoid missing clinically actionable mutations.

The Results section currently incorporates a discussion of the personal and family cancer history for the nine women with a pathogenic variant identified here. There is a large amount of phenotypic overlap between women with mutations in BRCA1/2 versus other breast cancer-risk genes (CHEK2, PALB2). In addition, there was a large amount of phenotypic overlap among all mutation carriers, with breast, ovarian, and colon cancer being common regardless of the gene in which their pathogenic variant was identified. This highlights that targeted screening based on phenotype alone would likely have resulted in missed mutations or multiple iterations of more selected testing. We have added text to the Discussion to better highlight this finding.

1. Yurgelun MB, Allen B, Kaldete RR, Bowles KR, Judkins T, Kaushik P, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected Lynch Syndrome. *Gastroenterology* 2015;149(3):604-13.

2. Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of breast cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016;34(13):1460-8.

Discussion

- Authors do need to make a decision of what they actually trying to address; 4% test rate is miserably low.

Response: We appreciate the Reviewer's comment and would like to clarify that 4% of all patients seen completed genetic testing. This should not be 100%, as most patients seen will not meet testing criteria. That was the case here, where about 24% of patients met clinical testing criteria. This metric is highlighted early in the Discussion because the proportion of tested patients after the process intervention represents a 400% increase relative to before the process intervention. We view this as a highly relevant metric that highlights the success (and therefore feasibility) of the process intervention here.

In order to better clarify the impact of these findings, we have revised the first paragraph of the Discussion.

Figures

- As above: are we talking about process improvement or screening for at risk population?

Response: As discussed above, the primary aim of this study was to demonstrate the feasibility of the process intervention. We believe the edits described above better highlight this point throughout the manuscript.

Reviewer #2:

This work is a novel submission of a prospective process intervention study of community practice OB GYNs researching for publication the feasibility of generalist OB GYNs screening and counseling women for risk of inherited cancer syndromes without initial referral to genetic counseling. This was an industry sponsored study. The work also falls into the realm of the ACCME competency of Practice based Learning and Improvement (PBLI), and the general area of quality improvement in medicine.

1. This work is novel and important to the field of OB GYN because it is a quality improvement work, carried out prospectively and with attention to important factors for ethical publication of practice improvement research.

There are few OB GYN works of this nature to date, and they are often published in the Quality research journals. A quick and informal search finds Dyrkorn et al.'s Norwegian reduction of post-cesarean infections improvement project [1], Burstein et al.'s 2016 paper on standardizing obstetric practice to improve neonatal outcomes in Health Services Research[2] and Powell et al.'s investigation of the effect of HIV-centered OB care on HIV transmission rates.[3]

2. A key feature of the submission is that it was carried out by active clinicians. This is likely to improve its scalability (or generalizability) - it's worthy of publication.
3. Their key finding of eightfold increased completed genetic testing is important, as is their confirmation of a significant amount of risk is conferred by testing for genes and variants not on the usual screening panels.
4. Secondary findings are also important -that same day sampling availability significantly increased patient participation and follow-up should guide other practices choosing to implement projects
5. Abstract - well written, concise and clear
6. Methods - overall understandable Please clarify
 - a. Is Myriad the testing laboratory?

Response: Yes, all genetic testing was performed by Myriad Genetic Laboratories. This is specified in the Materials and Methods.

b. Were the genetics counselor and LEAN professional from a local commercial laboratory or from the sponsor Myriad? ---there is concern of potential conflicts of interest for genetic counselors employed by commercial labs.

***Response:** The genetic counselors and Lean process engineers were from Myriad Genetic Laboratories; however, we do not believe that this represents a conflict of interest. The process intervention included an evaluation of current practice standards in order to incorporate efficient processes that could be integrated into a busy practice. There was also training on hereditary cancer risk assessment, counseling, and patient follow-up. All processes were based on professional society guidelines and standards and were approved by an independent IRB. All materials used during the process intervention were unbranded. As this was conducted as part of a study where testing was performed through a single laboratory, the process intervention did not include laboratory selection. We have added text to the Materials and Methods to highlight these points.*

7. Methods - It seems really clear results were given to patients by the study clinicians on site (OB GYN providers); but how were the frequent VUS results given, if they were? For patients in the study who got tested, it seems a potential risk is anxiety about uncertain results, and (less likely) stigma or other harm from knowledge of a positive.

***Response:** VUS results were also given to patients and providers counseled patients appropriately. In brief, this included a discussion that there was no known association with cancer. Patients were also told that if this changed as new data became available, the practice would be in touch with them to follow-up. Most patients fully comprehended this counseling, as indicated in the patient surveys. We have revised the Materials and Methods section to include this information.*

a. For Myriad authors - This seems a higher frequency of VUS findings

***Response:** The VUS rate is the cumulative VUS rate for all 28 tested genes. Therefore, the cumulative VUS rate of 26% corresponds with an average VUS rate <1% per gene. This is consistent with or better than previous reports on myRisk testing as well as panel testing from other laboratories.*

8. Methods - For Myriad authors -The panels used have 28 genes, but the references are for panels of 25 genes - are there data or references on the effect of adding those three? (all colorectal cancer risk associated: GERM1,POLD1, and POLE)

***Response:** The Reviewer is correct that the references describe the earlier version of the myRisk test that included 25 genes. However, the overall testing methods described in the included references were used here for all 28 genes. Given the recent incorporation of the three new genes and the absence of any changes in testing methods, there has not been a publication detailing the testing methods for the 28 gene panel.*

9. Methods - breast, ovarian and colorectal cancer all have clear prophylactic and screening (breast and colorectal) advantages; but other genes on the panel (melanoma and pancreatic associated) don't - clarify how it is advantageous to the patient to have those on the panel - how were the differences in counseling needed approached?

Response: *Current practice standards included referral to appropriate specialists based on genetic findings. Although no pathogenic variants were identified in genes associated with only melanoma and/or pancreatic cancer, patients would have been referred to the appropriate specialists. In addition, current peer-reviewed NCCN guidelines recommend screening for these genes. It may be possible to reduce cancer risk for individuals with pathogenic variants in these genes with appropriate medical management, including increased attention to surveillance, other therapeutic options, and lifestyle modifications.*

10. Introduction -Clear and quickly establishes the context.

11. Results - Clearly stated and complete with the supplemental tables - Tables/Figures clear and add to the understanding. Survey tools for satisfaction methods appropriate and referenced.

a. Statistics should be reviewed by journal statistics editor

Response: *Please see below for our responses to the statistics editor.*

12. Discussion - Mostly clear (see below for a few more considerations)

13. The authors report adhering to the SQUIRE guidelines for publishing medical quality improvement works, a helpful guide and good supplemental submission for the review. The submission doesn't address limitations (Item 16), and seems weak in Item 18 - the company funding is mentioned on page one (Line 19), but no further discussion of a company role is noted. Yet, it seems possible the sponsor, Myriad, is also the 'testing laboratory' and Myriad is clearly the source of the LEAN engineers who developed the study processes and protocol (Lines 91-97).

Response: *We have added a limitations section to the discussion, per the Reviewer's suggestion. In addition, we have complied with the journal requirements regarding the disclosure of study funding and have clarified that genetic counselors and LEAN professionals were from Myriad. There are also several authors from Myriad and any additional role of the laboratory is encompassed in the standard role of authors.*

14. The source of the 'limited education' for the providers conducting the research (Line257) should be clear - one is left to presume it is the sponsor (testing?) laboratory, Myriad.

Response: *As described in previous responses, the education provided as part of the process intervention was provided by genetic counselors from Myriad, using ACOG and NCCN materials and other unbranded sources. We have revised the Materials and Methods section to better clarify this point, along with the language in the Discussion.*

The aim of the statement in the Discussion is to highlight that that 1) appropriate education enables OB/GYNs to appropriately implement hereditary cancer risk assessment and testing and 2) education resources are widely available to interested OB/GYNs.

The authors should clarify the amount and andragogy of the education provided. Simply stating it is likely to be similar to a newly starting ACOG offering which has not met yet (first generalist providers are

going through in August sessions) [Submission Reference 29] in content and effectiveness seems insufficient.

***Response:** We would like to clarify that the third offering of the referenced ACOG course will occur in August 2018; however, the course has been available for the past two years. (Information is available at <https://www.acog.org/Education-and-Events/Search-Postgraduate-Courses/Genomics-Counseling-Miami>.) Additional education material has also been available through ACOG Committee Opinions and Practice Bulletins, NCCN guidelines, and multiple references to peer-reviewed literature*

We have also added language to the Materials and Methods to provide more detail about the education portion of the process intervention.

15. While study funding was disclosed (Myriad) and sponsor education of clinicians mentioned, individual author conflict(s) of interest were not. The GPP3 guidelines are mentioned as being in action, but Principles 9 (Disclosures) and 10 (full explanation of sponsor role in design and implementation) don't seem completely fulfilled.

***Response:** We appreciate the Reviewer's comment. As part of the original manuscript submission, individual author forms and disclosures were submitted for all authors. We have added this information to the "Financial Support" section on the title page.*

16. Line 38 and elsewhere - the plural word 'data' is given a singular verb at other locations the pairing is correct.

***Response:** We have made the suggested revision throughout the manuscript.*

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1. Dyrkorn OA, Kristoffersen M, Walberg M. Reducing post-caesarean surgical wound infection rate: an improvement project in a Norwegian maternity clinic. *BMJ Quality & Safety*. 2012;21(3):206-210.
 2. Burstein PD, Zalski DM, Edwards JL, et al. Changing Labor and Delivery Practice: Focus on Achieving Practice and Documentation Standardization with the Goal of Improving Neonatal Outcomes. *Health Services Research*. 2016;51 Suppl 3:2472-2486.
 3. Powell AM, DeVita JM, Ogburu-Ogbonnaya A, Peterson A, Lazenby GB. The Effect of HIV-Centered Obstetric Care on Perinatal Outcomes Among a Cohort of Women Living With HIV. *Journal of Acquired Immune Deficiency Syndromes* (1999). 2017;75(4):431-438.

Reviewer #3:

This is a prospective process intervention study to assess the feasibility and impact of incorporating hereditary cancer risk assessment, counseling, and follow-up genetic testing in a community-based OB/Gyn practice without referral to a genetic counselor.

1. Abstract is clear and concise.
2. Lines 44, 49. Discrepancy in the total # of women who completed genetic testing. Line 44 stated 165 and Lines 49-50 stated 169 patients.

***Response:** We have revised the text to specify that 169 patients who submitted a sample for testing and completed the patient satisfaction survey. Not all of these patients completed genetic testing.*

3. Materials and Methods: It would be helpful to mention how long the screening took during the post-intervention period to give readers a sense of whether this is feasible in their practice setting

***Response:** We appreciate the Reviewer's interest in this point, as the aim of this study was to demonstrate the feasibility of incorporating hereditary cancer risk assessment and testing into routine OB/GYN practice. However, the duration of hereditary cancer risk assessment, counseling, and testing was not documented as part of the study and varied based on whether patients met testing criteria. We could anecdotally include that the process typically took 10-15 minutes, but defer to the journal Editors as to whether this would be appropriate given the lack of data.*

4. Lines 182-183: How were patients with variants of uncertain significance counseled and planned to be followed? If these variants are reclassified, does Myriad contact the patient or ordering physician directly?

***Response:** As described previously, patients with a VUS were counseled in accordance with professional society guidelines. Text has been added to the Materials and Methods on this topic. Myriad does issue an amended report for any change in variant classification as a lifetime component of the testing process.*

5. This is a well written and very relevant paper and nicely designed study. I commend the authors for their hard work in implementing this type of much-needed program which can be an example to other ob/gyn practices around the country. My concern is the post-screening followup specifically of patients who are found to NOT have a pathogenic mutation or to have one of uncertain significance and whether the physicians and NPs/PAs/CNM felt they had adequate training and time to discuss this with patients.

***Response:** We thank the Reviewer for their comments and agree that post-screening follow-up for patients without a pathogenic variant is an important consideration. Clinicians did feel that they had adequate training and time to discuss this with patients, as indicated in the provider survey responses.*

6. Lines 200-201: Why did the 1 provider not feel they could/would continue to use the process to screen and test patients at risk?

***Response:** Fifteen of 16 providers completed the post-intervention survey. All 15 responders reported that they would continue to use the established hereditary cancer risk assessment process to screen and test patients at risk for hereditary cancer. We have revised the text to clarify this point.*

7. Discussion of insurance coverage was also much appreciated.

Reviewer #4:

The objective of the manuscript is to find out of the feasibility of including routine hereditary cancer risk assessment and genetic testing in the general obstetrics and gynecology office. The study was conducted in two offices of obstetrics and gynecology practices, one in Syracuse, NY and the other in

Waterbury, Connecticut. The study was approved by an independent institutional review board. The staff of these offices were trained and they had a four week period to incorporate the new process and the work out for the program. The post intra-patient period occurred in the two offices at two different times.

The clinical criteria for HBOC Genetic Testing were based on the presence of personal or family history of breast, ovarian, prostate, or pancreatic cancer. Also the study included patients with a history of Lynch Syndrome criteria used on the presence of colorectal, endometrial, gastric, ovarian, uterus and adrenal pelvic, urinary tract, small bowel, pancreatic, brain or sebaceous adenomas.

Patients who met the HBOC and/or Lynch Syndrome Criteria, they were given genetic testing. This was done on the same day or different dates. The genetic testing included 28 gene testing.

Participating patients were surveyed for their subscription to this program. It was clear from the testing that some of the pathogens variants were found and the patients were taken care of by a specialist. The patient satisfaction survey was at 97.6%.

The study clearly shows that it is possible and of great value to include genetic screening, testing, and counseling for patients that come to the general obstetrics and gynecologists' office for checkups. This also confirms the view of the American College of Obstetrics and Gynecology.

The authors of this article certainly put a large number of data in this study and also did a great organized study.

Response: We thank the Reviewer for their comments.

Reviewer #5:

Nicely sized study evaluating the feasibility of implementing genetic cancer screening in a community setting. The authors were able to markedly increase genetic cancer screening and testing compared to previous practice. The process was well received by providers and patients.

Several authors work for Myriad.

The pre-study site intervention was extensive and supported by industry with both certified genetic counselors and a LEAN engineer. This contradicts the premise put forth in the introduction that this process is necessary because of the dearth of genetic counselors. It also speaks to lack of generalizability with implementation in communities without this support.

Response: We thank the Reviewer for their comment and would like to clarify that the dearth of genetic counselors is an issue in the current referral model where all patients at increased hereditary cancer risk are referred to genetic counselors for further assessment, counseling, and testing. As part of the process intervention, providers and staff at the OB/GYN practices were appropriately instructed on current ACOG and NCCN information by genetic counselors to ensure appropriate training of the various aspects of the genetic conditions, informed consent, and post result counseling; however, all patient assessments, counseling, and testing were performed by the OB/GYN practice. As such, the resource requirement for

genetic counselors in this process was extremely different than the resource requirement in a traditional referral model.

The Reviewer correctly points out that this process intervention incorporated training and education by genetic counselors; however, the Discussion points out that genetics education, including HBOC and Lynch syndrome, is offered by ACOG. In the absence of a partnership with a testing laboratory, this process would still be achievable using the ACOG- and NCCN-provided resources.

Why were some patients referred for delayed testing by a NP? Was this because the original clinician did not have time, training, or inclination or was this to replicate referral to genetic counseling done in previous practice as implied by your discussion. As you note, this process resulted in a marked decrease of actual testing.

Response: *Reasons for referral for delayed testing by a NP was not documented as part of this study. Anecdotally, this option may have been used if the provider did not have enough time at the visit or if the patient was in a hurry or wanted to think about it. We have included this information in the Discussion. Referral testing was not incorporated here to mimic current practice, but occurred naturally during the course of the study.*

Why do you postulate that only 40% of patients offered testing, agreed to it? Is this consistent with prior literature when screening is done by a genetic counselor?

Response: *The referenced literature regarding referral to a genetic counselor demonstrates that patients often have to wait long periods of time (six months or more) for a referral appointment, and frequently they do not follow up for that referral. (See reference 17 in manuscript, Lauritzen et al.) The take-home message from this body of literature is that referral of all patients to a genetic counselor delays or prevents access to care for patients with increased risk. This is independent of how many patients who see a genetic counselor ultimately decide to go through with genetic testing.*

As stated previously, we did not document why patients who met testing criteria did not want genetic testing. Anecdotally, this may have been due to: (1) fear of results; (2) fear of insurance discrimination; (3) assuming insurance would not cover the cost of the test; or (4) lack of awareness of the benefits of having results, such as proactive prevention, screening, or treatment approaches. Overall, we believe that understanding and adoption of appropriate testing will be increased through a broad approach to education in the general population and to targeted audiences by ACOG. The recent NIH strategy for a comprehensive approach from K-12, graduate and post-graduate health provider education is a good start and can be supported by ACOG and other professional societies. (See <https://www.genome.gov/27568594/genomic-literacy-education-and-engagement-gee-initiative/> for additional information on the NIH strategy.)

I'm not sure that Tables 4 and 5 of provider and patient satisfaction add to the body of the paper.

Response: *We believe that Tables 4 and 5 are important components regarding the feasibility of the process integration. If the majority of patients were screened, but did not understand the information, this would demonstrate that the process integration was not successful. As such, we have kept this data*

in the manuscript. In addition, the corresponding text in the Discussion has been revised to better clarify this point.

STATISTICAL EDITOR:

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

Table 1: The "Total" column has no entries for denominators. To have a consistent format, should include denominators as in the other columns or otherwise indication what denominators were used for various proportions.

Response: We have revised Table 1 to include the denominators for the "Total" column.

Table 2: Should explain VUS in footnote.

Response: We have defined "VUS" in a footnote.

Table 3: Since the sample was $n = 15$, no need to cite %s to nearest 0.1%, should round to nearest whole number.

Response: We believe this comment refers to Table 4. We have revised the table to report percentages to the nearest whole number. The corresponding manuscript text has also been revised.

Would be useful to include a flow diagram, beginning with 4107 patients, then number providing family history, number with (+) family history, number offered etc. to final number completed testing and number with abnormal findings.

Response: As discussed above, this information is currently included in Table 1. We believe inclusion of a flow diagram would be repetitive, but are happy to include if the Editors feel it is necessary.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, 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 Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

Editor's Specific Comments

- 1) 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)

Response: We have added the requested information to the Materials and Methods section of the paper.

2) Abstract

- a) Use of the word "screening" in this context is confusing. We often think of the tests in OB for genetic risk assessment as "screening" so this may be tripping me up. When you says 92.8% were screened for hereditary cancer risk how was that done? 906 "screened positive" by some method and then were offered genetic testing. Can you clarify this somehow?

Response: The word "screening" was used to mean that patients were assessed for hereditary cancer risk. To avoid confusion in this setting, we have replaced "screening" throughout the paper with clearer language.

- b) spell out all abbreviations on first use

Response: We have spelled out "NCCN" in the abstract.

3) Introduction

- a) please replace "dangerously" here and in abstract with a less dramatic term.

Response: We have revised the text as suggested.

- b) The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

Response: We have revised the text as suggested.

4) Materials and Methods

- a) Was the consent to be tested or to be included in this study?

Response: Consent was obtained for inclusion in the study. Also, there was informed consent for clinical genetic testing, as per standard of care. Text has been added to clarify this point.

- b) This would be a good place to include the sponsor information. Thank you for using and referencing GPP3. Please respond to comments by one of the reviewers on some portions of it.

Response: We have included the sponsor information in this section. Please see above for responses to the Reviewer on GPP3.

- c) If I understand it, based on my comments re: use of term "screening" above, each patient was asked in some fashion about the HBOC and Lynch criteria and this was the "screening". Correct?

Response: Correct – each patient completed a family history questionnaire to screen for hereditary cancer risk. We have included the family history questionnaire used by one practice in Appendix 1. As previously stated, we have revised the text to avoid confusion over the use of "screening."

- d) Who provided this counseling?

Response: *The text has been revised to clarify that counseling was provided by the treating clinician (obstetrician-gynecologist, nurse practitioner, physician assistant, or certified nurse midwife).*

- e) Please indicate what cancers each of these genes relate to.

Response: *There is a large amount of overlap in the cancers related to each gene and it is not feasible to incorporate this information in the main text. We have included text to specify that all of the genes included in testing are associated with one or more of the following eight cancers: breast, ovarian, colorectal, endometrial, melanoma, pancreatic, gastric, or prostate cancer. In addition, we have added an Appendix that details the specific cancer associations of each gene.*

- f) Please comment about finances--how were providers trained about this for their discussions with patients? Some insurance carriers may not cover this type of testing, so were providers trained on discussing finances? Is it known if the high rate of women who were eligible for testing but who did not do the testing may have declined due to financial constraints?

Response: *We did not document reasons why women who met testing criteria did not complete testing. We have added this as a limitation of the study.*

5) Results

- a) How was questionnaire administered? (put in materials and methods)--form to fill out? On a tablet? Sent out in advance of visit, etc.

Response: *We have added text to the Materials and Methods to specify that a paper questionnaire was completed by patients during their visit. We have included the family history questionnaire used by one practice in Appendix 1.*

- b) Do you know why about 10% were not offered genetic testing? This seems like a medical-legal issue that needs to be addressed in your paper. If you do the historical screening but don't act on it, what is the risk?

Response: *We did not document why some patients were not offered genetic testing. However, this reflects real life in large community practices, where two things happen: (1) early on in the study, providers are slow to become consistent in integrating the process; and (2) some individual practitioners are more adopting than others*

- c) Why are some offered same day and some offered referral appointments? For the reader to understand how to incorporate this into their practices, this is important. Clearly, it increases cost to the patient to have to come back.

Response: *As discussed previously, reasons for referral appointments were not documented as part of this study. Anecdotally, this option may have been used if the provider did not have enough time at the visit or if the patient was in a hurry or wanted to think about it. We have included this information in the Discussion section of the paper.*

- d) Provide denominators

Response: *The text has been revised as suggested.*

- e) Above (line 162) you said that 467 women were offered same day testing. Here I think you mean "Among those who agreed to testing, only 68.9% (219/318) submitted samples. Sample submission for those offered same-day testing was 98.1% (153/156) and 40.7% (66/162) for those offered a referral appointment. "

Response: *Thank you for pointing out this error. We have revised the text.*

- f) You didn't mention this in the materials and methods. Also, how was this data obtained? From Myriad? Office records? Was Myriad the only lab used?

Response: *This is detailed in the Materials and Methods section (lines 165-170). The Results text has been revised to refer the assessment of two "historical time periods" in order to better mirror the language used in the Materials and Methods section. Myriad was the only lab used for these historical time periods. This has been added to the Materials and Methods.*

- g) Do you have information about whether they attended these appointments?

Response: *This study did not document patient follow-up for referral appointments.*

- h) Please put in parenthesis if not mentioned elsewhere in the sentence what the cancer is associated with individual genes mentioned. Most of the readers won't know other than the BRCA genes and the more we associate them together, the more they are likely to recall later.

Response: *The text in this section details the cancers associated with genes being discussed. This information is also included in Table 3. As mentioned earlier, and Appendix has also been added to detail the cancers associated with all tested genes.*

- i) How did you test understanding?

Response: *Patient understanding was assessed in the survey included in Table 5. We have revised the text to clarify that this data was patient-reported.*

- j) Did you ask about satisfaction w/ same day vs referral? Did you give patient satisfaction questionnaires to those women who agreed to testing but didn't get testing?

Response: *Referral testing was not integrated into the study design and occurred naturally after process integration. As such, there were no specific survey questions regarding same-day or referral testing. Patient satisfaction surveys were offered for those who provided samples for testing. This does not include the majority of women who agreed to test but did not complete testing.*

6) Discussion

- a) Perhaps more pertinent is to give the rate of uptake by those identified by the NCCN criteria to be at risk.

Response: *We believe the 4.0% of patients who completed testing is relevant here, as it enables a comparison to the historical comparison periods. We have added text that also highlights the proportion of patients who met criteria and agreed to test. We believe this highlights the ability of providers to successfully implement the process intervention.*

- b) What do you mean by "in the obstetrics gynecology setting" Clearly, these 100 million women overall and the 24 million identified to be at risk are not all seeing an OB GYN.

Response: *The intention of this statement was to highlight the number of women who should be seeing an OB/GYN, Internal Medicine physician, family practitioner, nurse practitioner, physician assistant, or other women's health provider for well woman or other gynecologic care, and are at increased risk. We agree that this is unclear and have removed that portion of the sentence.*

- c) Perhaps removing financial barriers is as important as improving patient education? There was a 63% denial of insurance wasn't there?

Response: *There was a 63% denial of insurance; however, this was among patients who submitted samples for testing. As stated previously, we did not document why patients who met testing criteria did not agree testing. While this may be due to financial barriers, we do not have data to support this claim.*

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.

Response: *We would like to opt-in.*

3. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). Script font is not acceptable. Please have each other send us forms with their signatures.

The author agreement form is available online at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

Response: *We have supplied the requested forms with physical author signatures.*

4. 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. For publication purposes, the portions of particular importance to industry-sponsored research are below.* Please indicate whether the following statements are true or false, and provide an explanation if necessary:

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

Response: This statement is true.

(b) 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.

Response: This statement is true.

(c) 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.

Response: This statement is true.

(d) 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.

Response: This statement is true.

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

Response: This statement is true.

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

5. 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 guidelines, as appropriate.

***Response:** We have included the SQUIRE 2.0 checklist in our submission.*

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

***Response:** We have reviewed these definitions and believe our use of any relevant terms is consistent with these definitions.*

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and appendixes) except for references.

***Response:** We have ensured that our revised manuscript complies with these length restrictions.*

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

***Response:** The revised draft complies with the overall word limit and the Introduction is less than 250 words. However, the Discussion is over the word limit after incorporating the Reviewer and Editor suggestions. We have cut the word count of this section as best as possible, but feel that the included text is important to the clear presentation of the data and its impact in the field. Because the overall word count complies with the journal requirements, we would like to request an allowance for the Discussion section to exceed the journal limit.*

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the

acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

Response: The acknowledgements section adheres to these requirements.

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

Response: The abstract has been reviewed and complies with the requirements outlined above.

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

Response: All abbreviations are spelled out at the time of first use in the abstract and body of the manuscript.

11. 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.

Response: The text has been revised to remove the use of "and/or."

12. 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.

Response: All tables conform to the journal style.

13. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could

include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at <http://www.acog.org/Resources-And-Publications>.

Response: We have confirmed that all cited ACOG documents are available.

14. To ensure a quality experience for those viewing supplemental digital content, the journal's publisher suggests that authors submit supplemental digital files no larger than 10 MB each. The exceptions to this rule are audio or video files, which are acceptable up to 100 MB. When submitting text files or tables as supplemental digital content with your revisions, please do not submit PDFs.

Response: Our supplemental file has been submitted in the appropriate format.



Subject:

Re: O&G Figure Revision: 18-1121

Date:

Thursday, August 2, 2018 12:31:28 PM

Attachments:

[Redacted attachment list]

Dear Stephanie,

Attached is our final revision of Figure 1. Thank you very much for all your help. I believe you have everything requested, but please let me know if you still need anything else.

Have a great day,

MSD

Mark S. DeFrancesco, MD, MBA, FACOG

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