

# 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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[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org).

**Date:** Nov 09, 2018  
**To:** "Benjamin E. Berkman" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-18-1869

RE: Manuscript Number ONG-18-1869

Views of Pregnant Women on Prenatal Genome Sequencing

Dear Dr. Berkman:

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 Nov 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: This is a survey study which is either paper or electronic offered to women attending 3 clinics in Invona healthcare system in northern Virginia. The response rate was 69%. The participants indicated that they are most likely interested in information regarding serious treatable childhood-onset conditions (90%) and they wanted more firm recommendation by their physician with a clear plan with options.

#### Main issues:

1- The low response rate hampers the validity of the results. What was the measures to identify and address non responder bias? Do you have demographic and clinical information about women who refused participation?

2- The participants are asking for specific guidance from their physician which is currently not present. An important call from our patient to develop clinical guidance from ACOG to address this need. I encourage the authors to make this their main message with detailed next steps best in a table or box format in the discussion.

#### Specific Issues:

1- Abstract: there is a discrepancy between the number of patients approached from 805 (line 41) in the abstract and 605 (line 124) in the method section of the study, please clarify!

2- Introduction: can be shorter

#### 3- Methods:

- (a) Please start the methods with identification of the type of study
- (b) Was a focus group used to develop the survey?
- (c) The authors mention cognitive testing, please include the instrument applied and how the authors utilized this testing in administrating their survey, did you have 2 versions based on participant level of education or cognition??
- (d) Please move any numbers about participants to the result section!
- (e) The authors mentioned "partially completed surveys". I did not see any plan to compute or handle missing data included in the results? Please clarify and add to the method section!
- (f) What was the primary endpoint, please define and report if there was any power analysis included based on that primary endpoint

#### 4- Results:

- a. Response rate: How many women attended those 3 clinics during the study period and met the inclusion criteria for the study and were not approached?
- b. Please add a table comparing clinical and demographic data between responders and non-responders! This can

replace Table 2.

c. First couple of figures are not easily interpreted (there are no figure legends) Please start with a crude rate for % response then report the adjusted analyses! You might need to re-organize your result section to be easier to read and interpret.

5- Discussion:

a. Can be shorter

b. While External validity might be limited to Virginia and similar communities, the main issue is the low response rate and need to be addressed. With this low response rate, the internal validity of the survey is greatly affected!

Reviewer #2: While such survey studies can be challenging, the authors did a good job addressing the data and I learned something reviewing this paper so am extrapolating that there may be other ObGyns/readers of the Green Journal who will feel similarly. I am especially hoping that the clinical genetic laboratory community will access the information as well. Thus, the 'heart' of the paper (methods/results) are credible and can certainly be used for future research on this topic.

My issues, below, are more focused on the introduction/discussion in terms of the current overview of the field. The aim of the study is appropriate. However, the reason this research is necessary is because we are already seeing the entry of WGS. WGS will be used in the same way that we are implementing this test for newborns (when diagnosis remains elusive but anomalies are present). I also was unclear as to whether authors are referring to WGS or WES or both? In addition, as a general overview, the authors should perhaps distinguish better between diagnostics vs broad based screening (further off in the future as for now, the only access to fetal tissue is via diagnostic testing - or are they writing only about the future when we will be able to extract circulating fetal cells from maternal blood and do a genome scan?). Suggest tightening/shortening up the intro and using the space to help the audience with some of these key concepts (esp. sequencing as a technology vs what we mean by WGS vs WES etc.) as I found myself somewhat confused. At the very least, what do the authors mean by 'prenatal genome sequencing'? Furthermore, there is ongoing/current research addressing some of the important concerns raised in this study, although in different, albeit related, settings (e.g. WGS and parents attitudes to NBS in the BabySeq studies which did have a screening component too) that may be relevant. Because of current research regarding integration of WES in to prenatal care, we are seeing studies on parental views - e.g. this recent paper <https://www.ncbi.nlm.nih.gov/pubmed/30035818> where participants are actually undergoing prenatal genomic testing. Finally, as noted below, PGS is used in the obstetric and genetic community to refer to preimplantation genetic screening (another relevant area where we are already starting to sequence embryos - although still targeted) and therefore this particular acronym may confuse.

Page 6; 70: In the ObGyn community, PGS is the usual acronym for preimplantation genetic screening. PGS may be confusing to some readers.

Page 6; 72: This is not quite correct. A recent joint position statement by multiple organizations states that ideally, prenatal WGS should be done in the context of research protocols but "alternatively, sequencing may be performed outside a research setting" when clinically indicated. <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1002/pd.5195>. This statement makes the authors' paper all the more compelling. I respectfully recommend that the rest of the paragraph be altered to reflect the new guidelines (which may also be educational for many readers)

Page 6; 76: ACMG recommends NIPS (noninvasive prenatal screening). I am not sure if the editorial board of the Green Journal has an opinion on this, but language matters to reinforce NIPS as a 'Screening' modality rather than a diagnostic 'test'

Page 6; 85: It may be worth noting either in the intro or discussion that the clinical genetic laboratory community has weighed in on these issues regarding carrier screening that is done using NGS. Not fetal, but conceptually similar. In a prenatal setting, laboratories do not return VUS - rather only report back variants that are pathogenic or likely pathogenic. In addition, even the panels (per ACOG/SMFM) should only include serious disorders. As per the guideline mentioned previously, that seems to be the current general consensus on the medical side. It may be worth noting that the medical community has weighed in on returning only serious, medically relevant information (and why). But again, this makes the current paper an even more interesting read as we move to shared decision making models. And the results of this present paper do seem to confirm the perspective of the medical community to limit non-medical information

Page 6; 88 This is not necessarily the case (as per previous comment) - that these decisions will fall 'primarily' to parents. The phrase 'will fall' denotes a level of certainty that as of yet remains unclear with respect to variant choice to assay and report out (agreed that choice to undergo testing is and will remain a parental option). The laboratory community makes these decisions every day as to what to report out based on internal or external guidelines (see the 'secondary findings' from ACMG with variants that must be reported out) As a rule, prenatal reporting is 'actionable' (LP/P), while even in adult patients, there is hesitancy to report non-medical findings. (Noted that this is not the case with DTC laboratories). Respectfully suggests that the parents undergoing carrier screening now are generally limited to opt for disorders with significant morbidity and mortality so it is a leap to say that there will be looser standards for prenatal WGS. However, are we being presumptuous? With shared decision making models becoming more prevalent, the questions asked in this paper are very important.

Page 7; 93: Strongly suggest rewording this paragraph or providing clarity. (1) For aneuploidy screening and even carrier screening (which is NGS based in many cases), generalist ObGyns will provide a lot of the guidance, but so will NPs, CNMs and other women's healthcare professionals - would not limit to ObGyns. (2) are we talking about screening or diagnostics? When it comes to current prenatal sequencing, that testing currently falls under MFM and ObGyn-geneticists who are better trained. So while there are not nearly enough CGCs for routine screening, sequencing would likely fall under a specialty service. Unless the authors are talking about noninvasive prenatal diagnosis (NIPD) which is now an important area of research - isolating fetal cells in maternal blood could end up being part of routine care in the future? However, if we are talking about the more immediate issue of amniocentesis/CVS based fetal sequencing, that would not happen in a general ObGyn setting and hence the lack of education (which is unfortunately very true) may not be applicable. However, do agree that even when MFMs/geneticist specialists guide/manage care, women still look to their primary ObGyns/midwives etc. to know about these new genetic tests.

Page 7; 98: The PGS issue is highlighted here. PGD means we are looking for a particular variant in the embryo. PGS is a general genetic screen that parents undergoing IVF can opt for to rule out (screen) for potential genetic syndromes/disorders. PGS for embryo screening is not uncommon as the family has already paid a great deal of money for the IVF and PGS adds a few thousand dollars. PGS screens for significant genetic disorders, and not non-medical traits.

Page 7; 104: Preimplantation genetic screening is usually not covered by insurance. Not sure why the authors are sure that genome screening in pregnancy will be covered?

Page 8; 116: Verb 'is' could be helpful.

Page 8; 127: As these women were pregnant at time of the survey, does 'medical' mean ObGyn? Or were they high risk undergoing medical management (e.g. neurology for seizures/ endocrine for diabetes etc.), as that could bias the results. It would be helpful to know if women were average or high risk for maternal/fetal disorders. Once could hypothesize that if a family is already dealing with a genetic/medical disorder, they may be more inclined to consider a genetic test/information as being of benefit. (apologies if I missed this in the paper or appendices)

Page 19; 366: Perhaps the authors would like to address informed consent processes which is required element in genetic testing protocols (clinical as well as research). Options can be provided on the consent document as to how much information a patient would like returned. In other words, the lab community is grappling with this issue presently. Do the authors feel this is a potential opportunity? Is there literature to support this approach?

Page 19; 375: Kudos to the authors for identifying the 'hypothetical' issue re: desire for information. The BabySeq experience is not exactly what is being addressed in this paper, as that study was focused on newborn screening. However, there was a significant gap in uptake when compared to initial interest in the pilot study and those parents who enrolled in the sequencing study. [http://www.genomes2people.org/wp-content/uploads/2018/07/20180912\\_BabySeq\\_GeneticsInMedicine\\_Genetti\\_ParentalInterest.pdf](http://www.genomes2people.org/wp-content/uploads/2018/07/20180912_BabySeq_GeneticsInMedicine_Genetti_ParentalInterest.pdf) - may be a helpful reference on this topic as there was a psychosocial arm in the large NIH funded NBS study looking at interest/views of parents. Confirms authors' concerns that people react differently when confronted with reality compared to 'hypothetical' situation

Reference 9: Please confirm this committee opinion is still available on the ACOG website. I believe it may have been superseded by PB 163.

Reviewer #3:

The survey described in this manuscript is an early step toward understanding the preferences of pregnant women about new prenatal genetic testing technologies. The authors should be commended for recruiting a diverse group of women.

1. I note that the survey document provided to participants calls the testing in question "PWGS" or prenatal whole genome sequencing. I would recommend using PWGS in place of PGS in the document, as PGS is currently known to most obstetric providers as "pre-implantation genetic screening", typically used to screen for chromosomally normal embryos (as contrasted to PGD, pre-implantation genetic diagnosis, used to test for embryos affected with specific conditions such as hemophilia or Tay Sachs.)

2. Line 225.

The discussion here and elsewhere in the paper (line 246, 343, 354 for example) describes the option as "wanting firm recommendations from their doctor". As I read the manuscript, I thought about the risk of inaccurate assumptions or bias on the part of providers attempting to counsel patients with a range of educational, religious and racial/ethnic backgrounds. In reading the actual survey instrument, I see that the language used there is different, "clear recommendations about categories of information that the medical community thinks are most appropriate to test for". I would recommend that the authors be clearer in the manuscript about the language used in the survey, as the implications of consensus based v. individually derived recommendations are potential quite different. Further, the term "clear recommendations" (the language used in the survey) has different implications than "firm recommendations", particularly

in the context of counseling.

3. While the survey instrument stated "recommendations from their doctor", there are many strategies currently in use for counseling patients about prenatal genetic testing. Midwives and nurse practitioners play central roles in this counseling in many clinical settings, and others offer classes or information on line. In some practice setting, most if not all prenatal care is provided by nurses, CNMs and/or NPs, with physicians involved only to address complications. I would urge the authors to acknowledge the role of non-physician professionals in prenatal genetic counseling and prenatal care generally. Too bad they didn't use a more inclusive term in the survey. In the conclusion, the role of the prenatal care team could be acknowledged again when the recommendation for more professional training is made.

4. Line 348 - Replace "tenant" with "tenet"

#### STATISTICAL EDITOR COMMENTS:

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

lines 181-183: Of the 553 (68.7%) who responded, did those individuals complete all questions? If not, what were the response rates to individual questions and how might that have affected the results? Some of the no response are indicated in the figures, but a more complete enumeration should be provided.

Table 2: Should provide description of the non-responders and compare them to the responders to examine if differences in demographic profiles might have affected generalizability of the results. If there were significant differences when comparing the responders to non-responders, how might that have affected the models cited and the responses to statements as shown in figs 2-6?

Fig 1a: Cannot construct CIs from samples of  $n=1$  or  $n=2$  (insufficient degrees of freedom). Should just omit from the comparisons due to small samples.

#### EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

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

2. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the January 2018 issue). Please note:

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; <http://www.icmje.org>):

\* Substantial contributions to the conception or design of the work;

OR

the acquisition, analysis, or interpretation of data for the work;

AND

\* Drafting the work or revising it critically for important intellectual content;

AND

\* Final approval of the version to be published;

AND

\* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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](mailto:obgyn@greenjournal.org).

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

\*The manuscript's guarantor.

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

4. 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>.

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

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

6. 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).

7. 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.

8. 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.

9. 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.

10. Line 110: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

11. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

12. 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](mailto: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>.

13. Figures 1-6 may be resubmitted as-is.

14. 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 Nov 30, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD  
Associate Editor for Gynecology

2017 IMPACT FACTOR: 4.982

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

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In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.





Dear Dr. Chescheir,

We are pleased to resubmit our manuscript entitled “Views of Pregnant Women on Prenatal Whole Genome Sequencing” to be considered for publication in the *Obstetrics & Gynecology*. This manuscript has not been previously published and is not under consideration for publication elsewhere. As the lead author, I affirm 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.

We would like to thank the reviewers and editors for their very helpful comments. Below, we summarize the changes we’ve made in response. Please let us know if there are any additional questions or concerns.

Thank you for your time and consideration.

Sincerely,

Benjamin E. Berkman JD, MPH

[Redacted]

[Redacted]

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[Redacted]



## Reviewer #1:

- Main issue #1 – “The low response rate hampers the validity of the results. What was the measures to identify and address non-responder bias? Do you have demographic and clinical information about women who refused participation?”
  - This issue was raised by a number of reviewers. Unfortunately, we were not able to collect individual demographic information on women who did not enroll in the study (i.e., those who were approached and said no, or who agreed to participate but never filled out the survey electronically). There are a few reasons, however, why we are not acutely concerned about non-response bias. (We deal separately with the issue of partial response bias in a comment below). First, we viewed our response rate of nearly 70% as a positive. While an even higher response rate would have been preferable, patients are known to be difficult to recruit from clinical settings, and given our previous experience with patient surveys we were relatively pleased with the response rate for this project. Second, women were recruited while they were in the waiting room before their appointment. While overall this was a fruitful recruitment location, we knew that the unpredictable timing of their appointment prevented some of them from participating. In fact, “no time” was the most frequent reason given for declining to participate. We considered this to be a neutral explanation that was not likely to have introduced any systematic bias into our data. Third, the research team (ITMI) that collected the data also recruits for a large 4500 family genomic-based longitudinal study in the same facility, using a very similar recruitment procedure. They did not find that the experience of recruiting for this survey was substantially different, or that there was any noticeable systematic difference in people who said yes or no to the survey. Nevertheless, the reviewer concerns are valid, and we have added a sentence acknowledging the potential for non-response bias to the limitations section of the paper (line #673: “Finally, while our response rate was reasonable, there could have been an undetected systematic difference between people who enrolled and those who did not, introducing a non-response bias.”). If it would be helpful, we could also add an analysis comparing our population to that of the larger ITMI study.
  - Main issue # 2 – “The participants are asking for specific guidance from their physician which is currently not present. An important call from our patient to develop clinical guidance from ACOG to address this need. I encourage the authors to make this their main message with detailed next steps best in a table or box format in the discussion.”
    - This is an excellent suggestion. We have added a sentence to the discussion to emphasize the need for ACOG guidance on this issue. (line #604: “Given this clear patient desire for guidance, there is a vital opportunity for ACOG to provide leadership and recommendations as PWGS is adopted into clinical practice.”) If the editors are interested in a pull-out box to further highlight this point, we would be happy to write some additional text.
  - Specific issues #1 – “Abstract: there is a discrepancy between the number of patients approached from 805 (line 41) in the abstract and 605 (line 124) in the method section of the study, please clarify!”

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[REDACTED]

- We have deleted the 605 number from the methods section, to reflect a reviewer comment to only put numbers about participants in the results section. However, to clarify, per the existing text at line #314, we “invited 805 people to take the survey, 605 agreed and 553 returned a survey that was at least partially completed.” We calculated our response rate as 553/805 people.
- Specific issue #2 – Introduction: can be shorter
  - We have edited the introduction to comply with the 250-word limit.
- Specific issue #3 – Methods:
  - (a) Please start the methods with identification of the type of study
    - We have updated the methods to indicate that this was a quantitative survey.
  - (b) Was a focus group used to develop the survey?
    - We did not use a formal focus group to develop the survey, but it was built on questions that had been used in a previous survey of obstetricians about their views about PWGS. We also utilized cognitive testing (see next response) and the survey was run through multiple reviews at the NIH Department of Bioethics Empirical Research Lab, which provides expert scientific review of empirical bioethics studies. We are happy to add details about the survey development process if the editors think it would be helpful.
  - (c) The authors mention cognitive testing, please include the instrument applied and how the authors utilized this testing in administering their survey, did you have 2 versions based on participant level of education or cognition?
    - We only had one final version of the survey. We utilized cognitive testing to test a draft of the survey. Our colleagues at Inova administered the draft survey to women from the clinics where we would be recruiting, as well as physicians in those clinics. They were then interviewed about their experience with the survey. For example, we asked them to point out questions or terms that were unclear, and whether or not the skip patterns were easy to follow. From this feedback, we made edits to the survey in an attempt to eliminate potential confusion.
  - (d) Please move any numbers about participants to the result section!
    - We have moved numbers about participants from the methods to the results section.
  - (e) The authors mentioned "partially completed surveys". I did not see any plan to compute or handle missing data included in the results? Please clarify and add to the method section!

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[REDACTED]

- Please see our response to the statistical editor below addressing how we clarified our approach to partially completed surveys.
- (f) What was the primary endpoint, please define and report if there was any power analysis included based on that primary endpoint
  - The primary endpoint for the survey was the average information-seeking preference score, which we calculated as an average of the preference score reported by each respondent across all category of genetic information. A sample size calculation was conducted based on a two-sided confidence interval for one proportion with assumed point estimate equal to 50% (most conservative) and a desired confidence interval width of  $\pm 4\%$ . At the 90% confidence level, the resulting sample size was 446, and at the 95% confidence level, it was 623. We have added this information to the methods section of the paper at line #210: “The primary endpoint for the survey was the average preference score for seeking PWGS information. A sample size calculation was conducted based on a two-sided confidence interval for one proportion with assumed point estimate equal to 50% (most conservative) and a desired confidence interval width of  $\pm 4\%$ . At the 90% confidence level, the resulting sample size was 446, and at the 95% confidence level, it was 623.”

○ Specific issue #4 – Results:

- a. Response rate: How many women attended those 3 clinics during the study period and met the inclusion criteria for the study and were not approached?
  - We do not have an exact count of the number of women that attended those clinics during the time that the survey was in the field. It should be noted that the research coordinators who were recruiting subjects for this study weren’t in the clinics every day and were sometimes recruiting for different studies. When they were in the clinics and were actively recruiting for our study, they approached all potentially eligible women, thus the denominator for our response rate should conservatively capture the number of women who could have been recruited for our study.
- b. Please add a table comparing clinical and demographic data between responders and non-responders! This can replace Table 2.
  - As indicated above in our response to Main Issue #1, we did not gather this information. However, if the editors wish us to, we could add an analysis comparing our population to that of the larger ITMI study that is representative of the clinic.
- c. First couple of figures are not easily interpreted (there are no figure legends) Please start with a crude rate for % response then report the adjusted analyses! You might need to re-organize your result section to be easier to read and interpret.

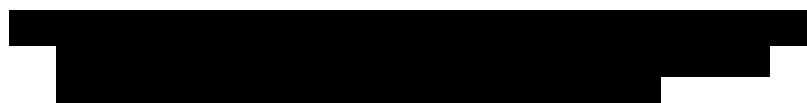
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[REDACTED]

- We believe that we did provide captions for the figure that would be included should it be published. The editor comments instruct us to resubmit all figures as-is, but we would be happy to start with the crude response rate if the editors wish us to make this change.
- Specific issue #5 – Discussion:
  - a. Can be shorter
    - We have shortened the discussion to comply with the 750-word limit.
  - b. While External validity might be limited to Virginia and similar communities, the main issue is the low response rate and need to be addressed. With this low response rate, the internal validity of the survey is greatly affected!
    - This point is well taken. Through our analysis of non-responders and partial responders, we hope that we have alleviated concerns about internal validity. Additionally, while we always hope for a higher response rate, given our experience with empirical bioethics projects, and patient surveys in particular, we were quite pleased with a response rate that approached 70%.

➤ Reviewer #2:

- I also was unclear as to whether authors are referring to WGS or WES or both? In addition, as a general overview, the authors should perhaps distinguish better between diagnostics vs broad based screening (further off in the future as for now, the only access to fetal tissue is via diagnostic testing - or are they writing only about the future when we will be able to extract circulating fetal cells from maternal blood and do a genome scan?). Suggest tightening/shortening up the intro and using the space to help the audience with some of these key concepts (esp. sequencing as a technology vs what we mean by WGS vs WES etc.) as I found myself somewhat confused. At the very least, what do the authors mean by 'prenatal genome sequencing'?
- We have edited the introduction to better explain what we mean when we are talking about PWGS. Specifically, we've specified that there is good evidence to suggest that in the near future, it will be possible to efficiently extract sufficient circulating fetal DNA from maternal blood and then sequence it. We clarify that we mean both WES and WGS, since in either case they would generate information well beyond that which is currently available. See line #2: "Non-invasive prenatal testing (NIPT) is now widely offered to test for fetal aneuploidies,<sup>1,2</sup> and although professional societies have differing recommendations about when to use NIPT as a first-line screening test,<sup>3,4</sup> clinical uptake is increasing rapidly.<sup>5</sup> The next step in prenatal testing will be to use cell-free fetal DNA from maternal blood<sup>6</sup> to sequence the entire fetal genome. Non-invasive prenatal whole genome sequencing (PWGS) will significantly increase access to fetal genetic information, raising ethical concerns regarding which categories of information should or



should not be offered, how these results will be returned, and what parents will do with the results.<sup>7</sup>”

- Furthermore, there is ongoing/current research addressing some of the important concerns raised in this study, although in different, albeit related, settings (e.g. WGS and parents attitudes to NBS in the BabySeq studies which did have a screening component too) that may be relevant. Because of current research regarding integration of WES in to prenatal care, we are seeing studies on parental views - e.g. this recent paper <https://www.ncbi.nlm.nih.gov/pubmed/30035818> where participants are actually undergoing prenatal genomic testing.
  - This is very helpful, and we have added a citation to highlight this analogous work.
- Page 6; 70: In the ObGyn community, PGS is the usual acronym for preimplantation genetic screening. PGS may be confusing to some readers.
  - To avoid any such confusion, we have changed the term used to “Prenatal Whole Genome Sequencing” (PWGS).
- Page 6; 72: This is not quite correct. A recent joint position statement by multiple organizations states that ideally, prenatal WGS should be done in the context of research protocols but "alternatively, sequencing may be performed outside a research setting" when clinically indicated. <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1002/pd.5195>. This statement makes the authors' paper all the more compelling. I respectfully recommend that the rest of the paragraph be altered to reflect the new guidelines (which may also be educational for many readers)
  - We thank the reviewers for pointing out these timely new guidelines. We have included a citation in the revised introduction. As a point of clarification, we were not suggesting that PWGS *must* be done in the context research protocols, but rather, that research protocols are where it is most commonly performed with the exception of the rare circumstances that these guidelines outline (i.e. clinicians are unlikely to offer PWGS as standard of care to healthy pregnant women for the foreseeable future).
- Page 6; 76: ACMG recommends NIPS (noninvasive prenatal screening). I am not sure if the editorial board of the Green Journal has an opinion on this, but language matters to reinforce NIPS as a 'Screening' modality rather than a diagnostic 'test'
  - We used NIPT (as opposed to NIPS) in accordance with the Green Journal's list of preferred abbreviations but are happy to use NIPS if the editors would prefer.
- Page 6; 85: It may be worth noting either in the intro or discussion that the clinical genetic laboratory community has weighed in on these issues regarding carrier screening that is done using NGS. Not fetal, but conceptually similar. In a prenatal setting, laboratories do not return VUS - rather only report back variants that are pathogenic or likely pathogenic. In addition, even

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[REDACTED]

the panels (per ACOG/SMFM) should only include serious disorders. As per the guideline mentioned previously, that seems to be the current general consensus on the medical side. It may be worth noting that the medical community has weighed in on returning only serious, medically relevant information (and why). But again, this makes the current paper an even more interesting read as we move to shared decision making models. And the results of this present paper do seem to confirm the perspective of the medical community to limit non-medical information

- We certainly agree that the ACMG guidelines, among others, currently suggest that only serious, medically actionable results be returned after clinical genetic laboratory testing. Similarly, we are not suggesting that variants of unknown significance (VUS) be returned. Instead, we are referring to categories of scientifically valid genetic results that are not serious and medically actionable (i.e., actionable, but not serious; non-medical; non-actionable, etc.). We believe there is far less consensus about how (and if) to return results that fall into these categories. We designed this survey to gather patient perspectives on prenatal genome sequencing results that fall into these additional categories.
- Page 6; 88 This is not necessarily the case (as per previous comment) - that these decisions will fall 'primarily' to parents. The phrase 'will fall' denotes a level of certainty that as of yet remains unclear with respect to variant choice to assay and report out (agreed that choice to undergo testing is and will remain a parental option). The laboratory community makes these decisions every day as to what to report out based on internal or external guidelines (see the 'secondary findings' from ACMG with variants that must be reported out) As a rule, prenatal reporting is 'actionable' (LP/P), while even in adult patients, there is hesitancy to report non-medical findings. (Noted that this is not the case with DTC laboratories). Respectfully suggests that the parents undergoing carrier screening now are generally limited to opt for disorders with significant morbidity and mortality so it is a leap to say that there will be looser standards for prenatal WGS. However, are we being presumptuous? With shared decision making models becoming more prevalent, the questions asked in this paper are very important.
  - We agree that the phrase “will fall” is perhaps too strong when we are speculating about the future state of the field and have changed it to “With access to a plethora of scientifically valid fetal genetic information, parents might have to make difficult decisions about whether to undergo PWGS and which results to learn.” (line #14) However, the reviewer raises an interesting point. While parents would not have any say on whether or not certain genetic results are deemed scientifically valid, or medically actionable, much like how adults can elect to be tested for genetic conditions that fall outside of the ACMG’s list of medically actionable results that they recommend be returned, parents might elect to receive results for some types of non-actionable genetic information. In shortening our discussion, we find we have less room to sufficiently discuss the nuances of this situation and have reserved such important analyses for future normative projects.
- Page 7; 93: Strongly suggest rewording this paragraph or providing clarity. (1) For aneuploidy screening and even carrier screening (which is NGS based in many cases), generalist ObGyns



will provide a lot of the guidance, but so will NPs, CNMs and other women's healthcare professionals - would not limit to ObGyns. (2) are we talking about screening or diagnostics? When it comes to current prenatal sequencing, that testing currently falls under MFM and ObGyn-geneticists who are better trained. So while there are not nearly enough CGCs for routine screening, sequencing would likely fall under a specialty service. Unless the authors are talking about noninvasive prenatal diagnosis (NIPD) which is now an important area of research - isolating fetal cells in maternal blood could end up being part of routine care in the future? However, if we are talking about the more immediate issue of amniocentesis/CVS based fetal sequencing, that would not happen in a general ObGyn setting and hence the lack of education (which is unfortunately very true) may not be applicable. However, do agree that even when MFMs/geneticist specialists guide/manage care, women still look to their primary ObGyns/midwives etc. to know about these new genetic tests.

- In this section of the introduction, we were speculating about a near future scenario where NIPT is used to gather fetal DNA to perform whole genome sequencing. This future scenario is different from any current practices of using amniocentesis/CVS for many prenatal tests. We do acknowledge that ObGyns are not the only clinicians who might be involved in these decision-making processes. We cited ObGyns specifically because we believe, based in part on the results of a past survey (conducted by some of this paper's authors) that ObGyns will play a vital gatekeeper role should non-invasive PWGS become incorporated into routine clinical care. However, all clinicians involved in providing PWGS to patients are important, and as this technology is integrated into prenatal care, it will be vital to understand how different types of clinicians provide different types of care. In rewriting the introduction, we sought to clarify this issue. We also plan future empirical work to examine some of these other provider groups (e.g., genetic counselors, midwives, general practitioners, etc.).
- Page 7; 98: The PGS issue is highlighted here. PGD means we are looking for a particular variant in the embryo. PGS is a general genetic screen that parents undergoing IVF can opt for to rule out (screen) for potential genetic syndromes/disorders. PGS for embryo screening is not uncommon as the family has already paid a great deal of money for the IVF and PGS adds a few thousand dollars. PGS screens for significant genetic disorders, and not non-medical traits.
  - We wish to clarify that we were using the acronym "PGS" to refer to Prenatal Genome Sequencing (rather than, as we believe this reviewer thought, Prenatal Genetic Screening). Based on the comments of several reviewers, we have removed all uses of the acronym PGS from the paper, and replaced them with PWGS, to clarify what we mean. To shorten the introduction, we've also removed the paragraph concerning PGD.
- Page 7; 104: Preimplantation genetic screening is usually not covered by insurance. Not sure why the authors are sure that genome screening in pregnancy will be covered?
  - Due to space constraints, we have removed the discussion of insurance coverage.
- Page 8; 116: Verb 'is' could be helpful.





- We have added the verb, to address this typographical mistake.
- Page 8; 127: As these women were pregnant at time of the survey, does 'medical' mean ObGyn? Or were they high risk undergoing medical management (e.g. neurology for seizures/ endocrine for diabetes etc.), as that could bias the results. It would be helpful to know if women were average or high risk for maternal/fetal disorders. Once could hypothesize that if a family is already dealing with a genetic/medical disorder, they may be more inclined to consider a genetic test/information as being of benefit. (apologies if I missed this in the paper or appendices)
  - Yes, we used the word “medical” to refer to general ObGyn appointments. These women were selected based on the clinic populations—there was no inclusion requirement that they be at high risk for maternal/fetal disorders, and we did not collect this information from their medical providers (or any other medical information). However, the survey did ask women to report if they had a child or close relative with a genetic disorder, and this variable was included in our list of candidate explanatory variables for statistical modeling. Very few of our respondents indicated that they had experience with a genetic disorder, and it did not appear to be predictive of information seeking or desire for guidance, so we did not focus on this variable in the discussion (but would be happy to expand if the editors would like).
- Page 19; 366: Perhaps the authors would like to address informed consent processes which is required element in genetic testing protocols (clinical as well as research). Options can be provided on the consent document as to how much information a patient would like returned. In other words, the lab community is grappling with this issue presently. Do the authors feel this is a potential opportunity? Is there literature to support this approach?
  - This is an extremely interesting and important issue, but a detailed discussion of informed consent challenges and opportunities is beyond the scope of this paper. One of the authors is part of a prominent group of bioethicists, medical geneticists and obstetricians exploring this problem, and our hope with this paper is to provide empirical data to support development of future recommendations.
- Page 19; 375; Kudos to the authors for identifying the 'hypothetical' issue re: desire for information. The BabySeq experience is not exactly what is being addressed in this paper, as that study was focused on newborn screening. However, there was a significant gap in uptake when compared to initial interest in the pilot study and those parents who enrolled in the sequencing study. [http://www.genomes2people.org/wp-content/uploads/2018/07/20180912\\_BabySeq\\_GeneticsInMedicine\\_Genetti\\_ParentalInterest.pdf](http://www.genomes2people.org/wp-content/uploads/2018/07/20180912_BabySeq_GeneticsInMedicine_Genetti_ParentalInterest.pdf) - may be a helpful reference on this topic as there was a psychosocial arm in the large NIH funded NBS study looking at interest/views of parents. Confirms authors' concerns that people react differently when confronted with reality compared to 'hypothetical' situation
  - Thank you for this helpful comment. We've added a citation to that paper to support our claim that it is important to study why women may not want to learn genetic information.

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[REDACTED]

- Reference 9: Please confirm this committee opinion is still available on the ACOG website. I believe it may have been superseded by PB 163.
  - We have updated the reference to reflect the most recent ACOG guidance.

**Reviewer #3:**

- 1. I note that the survey document provided to participants calls the testing in question "PWGS" or prenatal whole genome sequencing. I would recommend using PWGS in place of PGS in the document, as PGS is currently known to most obstetric providers as "pre-implantation genetic screening", typically used to screen for chromosomally normal embryos (as contrasted to PGD, pre-implantation genetic diagnosis, used to test for embryos affected with specific conditions such as hemophilia or Tay Sachs.)
  - We agree with this comment and have changed all mentions of PGS to PWGS, to reflect the current terminological standards.
- 2. Line 225. The discussion here and elsewhere in the paper (line 246, 343, 354 for example) describes the option as "wanting firm recommendations from their doctor". As I read the manuscript, I thought about the risk of inaccurate assumptions or bias on the part of providers attempting to counsel patients with a range of educational, religious and racial/ethnic backgrounds. In reading the actual survey instrument, I see that the language used there is different, "clear recommendations about categories of information that the medical community thinks are most appropriate to test for". I would recommend that the authors be clearer in the manuscript about the language used in the survey, as the implications of consensus based v. individually derived recommendations are potential quite different. Further, the term "clear recommendations" (the language used in the survey) has different implications than "firm recommendations", particularly in the context of counseling.
  - We thank this reviewer for highlighting this important point about terminology. The text of the response choice in the survey is "a. Firm Recommendations: I would like my doctor to present clear recommendations about the categories of information that the medical community thinks are most appropriate to test for." We agree that "clear recommendations" is the more accurate term and have changed the text accordingly.
- 3. While the survey instrument stated "recommendations from their doctor" there are many strategies currently in use for counseling patients about prenatal genetic testing. Midwives and nurse practitioners play central roles in this counseling in many clinical settings, and others offer classes or information on line. In some practice setting, most if not all prenatal care is provided by nurses, CNMs and/or NPs, with physicians involved only to address complications. I would urge the authors to acknowledge the role of non-physician professionals in prenatal genetic counseling and prenatal care generally. Too bad they didn't use a more inclusive term in the survey. In the conclusion, the role of the prenatal care team could be acknowledged again when the recommendation for more professional training is made.

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[REDACTED]

- Thank you for this comment. We acknowledge the importance of other medical providers and have edited the introduction and conclusion to broaden the scope of the paper. As we discussed above, we focused on ObGyns because we believe that they will likely be a key gatekeeper for this information. We also have future surveys planned to study the views of some of these additional provider groups.
- 4. Line 348 - Replace "tenant" with "tenet"
  - We have addressed this error.

**STATISTICAL EDITOR COMMENTS:**

- lines 181-183: Of the 553 (68.7%) who responded, did those individuals complete all questions? If not, what were the response rates to individual questions and how might that have affected the results? Some of the no response are indicated in the figures, but a more complete enumeration should be provided.
  - We do not feel that non-responses significantly affected the results because the vast majority of respondents completed all questions (65.3%) or only skipped one (23.3%) or two (7.2%). Furthermore, the missing data were distributed fairly evenly across all questions, with most questions missing just a handful of responses. We've provided a table below to summarize the missing data and added a sentence to the results section to clarify (Line #316: "The vast majority of respondents completed all questions (65.3%) or only skipped one (23.3%) or two (7.2%); missing data were distributed evenly across all questions.")

<i>Question</i>	<i>Missing (count)</i>	<i>Missing (percent)</i>
<i>Information-seeking average score</i>	<i>14</i>	<i>2.5%</i>
<i>Non-medical traits: want info</i>	<i>7</i>	<i>1.3%</i>
<i>Non-medical traits: reason</i>	<i>12</i>	<i>2.2%</i>
<i>Common Untreatable Conditions: want info</i>	<i>5</i>	<i>0.9%</i>
<i>Common Untreatable Conditions: reason</i>	<i>10</i>	<i>1.8%</i>
<i>Fatal Adult-Onset Conditions: want info</i>	<i>8</i>	<i>1.4%</i>
<i>Fatal Congenital Conditions: reason</i>	<i>12</i>	<i>2.2%</i>
<i>Serious Treatable Adult-Onset Conditions: want info</i>	<i>7</i>	<i>1.3%</i>
<i>Serious Treatable Childhood-Onset Conditions: reason</i>	<i>16</i>	<i>2.9%</i>



<i>Common Treatable Conditions: want info</i>	6	1.1%
<i>Common Treatable Conditions: reason</i>	10	1.8%
<i>Developmental Delays/Learning Disabilities: want info</i>	6	1.1%
<i>Developmental Delays/Learning Disabilities: reason</i>	12	2.2%
<i>Fatal Congenital Conditions: want info</i>	6	1.1%
<i>Fatal Congenital Conditions: reason</i>	11	2.0%
<i>Serious Treatable Childhood-Onset Conditions: want info</i>	5	0.9%
<i>Serious Treatable Childhood-Onset Conditions: reason</i>	10	1.8%
<i>Views on abortion</i>	4	0.7%
<i>It is appropriate for physicians to provide their opinion about the kinds ...</i>	14	2.5%
<i>The state or federal government should decide what categories of fetal ...</i>	17	3.1%
<i>How much help would you want from your doctor?</i>	30	5.4%
<i>Genetic Literacy Score</i>	0	0.0%
<i>Receiving scientifically uncertain genetic information about autism</i>	7	1.3%

- Table 2: Should provide description of the non-responders and compare them to the responders to examine if differences in demographic profiles might have affected generalizability of the results. If there were significant differences when comparing the responders to non-responders, how might that have affected the models cited and the responses to statements as shown in figs 2-6?
  - Please see our first response to Reviewer #1 where we discuss the non-responder issue in detail.
- Fig 1a: Cannot construct CIs from samples of n=1 or n=2 (insufficient degrees of freedom). Should just omit from the comparisons due to small samples.
  - We have updated Figure 1a to remove groups where n=1 or n=2. We have included an updated Figure 1a in the resubmission.

#### **EDITOR COMMENTS:**

- 1. OPT-IN:



- Yes, please publish my response letter and subsequent email correspondence related to author queries.
- 2. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the January 2018 issue). Please note: 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.
  - We have included this language in this cover letter and have uploaded author agreement forms for all authors.
- 4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.
  - We have endeavored to follow these definitions where appropriate.
- 5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes). Please limit your Introduction to 250 words and your Discussion to 750 words.
  - We have edited the manuscript to comply with these word limits. The introduction is 250 words, and the discussion is 750 words. We are below the 5,500 overall word limit.
- 6. 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.
    - This project was supported entirely by the NIH intramural research program. We have edited the acknowledgments to clarify this point.

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[REDACTED]

- \* 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 parts of this project were done by authors or acknowledged research assistants.
- \* 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).
  - N/A
- 7. 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.
  - This paper's abstract is 295 words long. We have reviewed the abstract for consistency with the revised manuscript.
- 8. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.
  - We have removed all non-standard abbreviations, with the exception of Prenatal Whole Genome Sequencing (PWGS), which we retained to reflect the comments of reviewers.
- 9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.
  - We have removed the symbol (/) from the paper, with the exception of several variable names and demographic categories where we retained the symbol to reflect the language

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[REDACTED]

used in the original survey. These exceptions are “race/ethnicity” “Hispanic/Latino” and “Developmental Delays/Learning Disabilities.”

- 10. Line 110: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
  - We have removed any mention of this study being the first of its kind.
- 11. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).
  - We have followed the journal style to the best of our ability but are happy to make any additional edits.
- 12. 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](mailto: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>.
  - We have checked the ACOG documents cited in our manuscript and have only included ones that are currently valid. (We have removed Committee Opinion 640).
- 13. Figures 1-6 may be resubmitted as-is.
  - We have resubmitted the figures as-is, with the exception of a slight change to Figure 1 per a reviewer comment, and Figure 4, to use the replace the term “firm recommendations” with “clear recommendations” per another reviewer comment.

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[REDACTED]



## Daniel Mosier

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**From:** Berkman, Benjamin (NIH/NHGRI) [E] [REDACTED]  
**Sent:** Monday, December 17, 2018 11:22 AM  
**To:** Daniel Mosier  
**Cc:** Stephanie Casway  
**Subject:** Re: Manuscript Revisions: ONG-18-1869R1  
**Attachments:** 18-1869R1 ms (12-14-18v4).docx

Daniel,

Here is the updated manuscript. We've moved Figures 3, 5, and 6 to the Supplemental Digital Content and we've renumbered everything accordingly. I kept tracked changes on, and I've dropped comment boxes throughout to mark these changes. Please let me know if you have any questions.

Ben Berkman

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**From:** Daniel Mosier <dmosier@greenjournal.org>  
**Date:** Friday, December 14, 2018 at 12:25 PM  
**To:** "Berkman, Benjamin (NIH/NHGRI)" [REDACTED]  
**Cc:** Stephanie Casway <SCasway@greenjournal.org>  
**Subject:** RE: Manuscript Revisions: ONG-18-1869R1

Dr. Berkman,

Thank you for responding in a timely manner. The editor on your manuscript has reviewed your latest revision and has one additional request:

1. Please move half of the figures in your manuscript to the Supplemental Digital Content portion of the paper. Please rename those figures "Appendix X" (numbering them based on their order of appearance in the manuscript), and amend all citations accordingly.

When revising, please use the attached version of the manuscript. Leave the track changes on, and do not use the "Accept all Changes" function prior to re-submission.

Please let us know if you have any questions or concerns.

Sincerely,  
-Daniel Mosier

**Daniel Mosier**  
Editorial Assistant  
*Obstetrics & Gynecology*  
Tel: 202-314-2342

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**From:** Berkman, Benjamin (NIH/NHGRI) [E] [REDACTED]  
**Sent:** Wednesday, December 12, 2018 5:02 PM  
**To:** Daniel Mosier <dmosier@greenjournal.org>  
**Subject:** Re: Manuscript Revisions: ONG-18-1869R1

Daniel,

I'm attaching some documents in response to these queries. Attached, you will find:

- An updated manuscript with a few minor tracked edits responding to the issues raised by the editors.
- A cover memo explaining our responses.
- Sara Hull's signed author form.
- A Microsoft Word version of Appendix 1.

Please let me know if you have any additional questions or concerns. I received a separate email from Stephanie Casway with edited figures. I am gathering some feedback on those and will send that response tomorrow.

Thanks,

Ben Berkman

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**From:** Daniel Mosier <[dmosier@greenjournal.org](mailto:dmosier@greenjournal.org)>

**Date:** Tuesday, December 11, 2018 at 10:43 AM

**To:** "Berkman, Benjamin (NIH/NHGRI) [E]" [REDACTED]

**Subject:** Manuscript Revisions: ONG-18-1869R1

Dear Dr. Berkman,

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

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 9: Three questions about Dr. Hull:
  - a. 1) If your paper is accepted, should Dr. Hull's name be indexed as [REDACTED] or [REDACTED]?
  - b. 2) Please ask Dr. Hull to respond the authorship confirmation email we sent. We sent an email from [em@greenjournal.org](mailto:em@greenjournal.org). The message contains a link that needs to be clicked on. We emailed Dr. Hull at [REDACTED] – is this the correct address?
  - c. 3) AQ: Please provide a completed author agreement forms for Dr. Hull using the latest version of our author agreement form, which can be found at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.
3. LINE 39: Please say where- E.g., "in practices affiliated with a large, tertiary care maternity hospital"
4. LINE 44: Do you mean respondents were queried about their demographics and their genetic literacy
5. LINE 45: Please provide dates.
6. LINE 73 : I noticed that reference 12 isn't cited. Reference 12 is an outdated ACOG document that has no clear replacement. Did you intend to omit reference 12? If so, please renumber your subsequent references, both in the text and the References list.
7. LINE 77: This refers to births. Please either say births or give an estimate for pregnancies
8. LINE 98: Please move info on dates to Results
9. LINE 106: Please provide a Microsoft Word version of Appendix 1.
10. LINE 168: Please throughout manuscript truncate P values to 3 places beyond the decimal point
11. LINE 185: Please express this p-value and all the p-values in your paper to no more than three decimal places.

12. LINE 243:

- a. Why is this italicized
- b. What does "were wanted" mean here?

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Thursday, December 13<sup>th</sup>**.

Sincerely,

-Daniel Mosier

**Daniel Mosier**

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**From:** [REDACTED]  
**To:** [Stephanie Casway](#)  
**Subject:** Re: O&G Figure Revision: 18-1869  
**Date:** Thursday, December 13, 2018 10:56:57 AM

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Stephanie,

Here are our comments about the figures. Please let me know if you have any questions or concerns.

Ben Berkman

Figure 1:

- To be consistent between 1a and 1b, would it be possible to remove the number of people in the group from the labels for 1a (e.g., delete 188 for Hispanic or Latino, delete 160 for White, etc.)?
- A question: Is it important to make sure both charts have the same y-axis scale? 1a goes to -0.2 but 1b goes to 0.0. Maybe it is necessary to have different scales since one of the confidence intervals in 1a goes to just below 0. We are flexible on this issue but wanted to point out the slight difference.

Figure 2:

- Can we change the label “Prepare financially, medically” to “Prepare financially, medically, psychologically”?
- There was an edit to change one category label to be “nonmedical”. In the paper, however, we use “non-medical” with a hyphen. Can we make this consistent?

Figure 3:

- Formatting comment: We’re not sure if this is the final version of the figure, but would it be possible to align the x-axes on figures 3A and 3B? Right now, figure 3B is slightly lower than figure 3A.

Figure 4:

- The x-axis label should not be “respondent agreement.” What we are measuring is patient response to the question “In making a decision about which categories of information to choose, how much help would you want from your doctor?” This is currently in the figure legend text. A shortened x-axis label could be “decision making preferences”

Figure 5:

- In the legend, “Firm recommendations” and “Firm recommendations, all options” should be “Clear recommendations” and “Clear recommendations, all options.” This was our error; we did not change this graph when we adjusted this wording in response to a reviewer comment.
- Formatting comment: Similar to our comment for figure 3, all these graphs have the same y-axis scale. Is it possible that the third part of the figure can be given the same dimensions as the first two? We do not want to give the impression that we are trying to exaggerate the scale to skew interpretation of data. But we are fine keeping it as is if the editors think that shrinking it would make it too hard to read.
- The editors asked us to remove reference to 5a/5b/5c, and just refer to this whole image as figure 5. Can we remove the a/b/c from the figure?

Figure 6:

- Looks good.

Figure Legends:

- Figure 1
  - Can the first sentence be changed to “Least-squares means with 95% CIs for significant explanatory variables in the model of information seeking behavior for race or ethnicity (A) and views on abortion (B).”

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**From:** Stephanie Casway <SCasway@greenjournal.org>

**Date:** Tuesday, December 11, 2018 at 12:56 PM

**To:** [REDACTED]

**Subject:** O&G Figure Revision: 18-1869

Good Afternoon Dr. Berkman,

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

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

To avoid a delay, I would be grateful to receive a reply no later than Friday, 12/14. Thank you for your help.

Best wishes,

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