OBSTETRICS & GYNECOLOGY

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

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

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

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Feb 06, 2020
To: "Julia Sage O'Hara" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2331

RE: Manuscript Number ONG-19-2331

Executive Summary of the ACOG/CDC Early Onset Breast Cancer Evidence Review Conference

Dear Dr. O'Hara:

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 Feb 27, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: I appreciate the thoroughness of this executive summary and the attention to research gaps. I especially appreciate the review of socioeconomic barriers to care and determinants of health and how they disproportionately effect diagnosis and survival in minority women. Are there groups within these communities working to reduce these disparities that can be highlighted as a resource for practitioners (much like the black-led efforts towards maternal mortality)?

line 126: The table in appendix 10 includes only information for women under 49, and deaths to 45. The fields are also unlabeled as to what is contained (n, percentage, etc... especially in the first two sections). I was expecting a complete demographics table, and if available would like to see that in the publication, not appendix as I think it is a good reference for clinicians.

When you refer to the risk modeling, you introduce several different risk estimation models and talk a bit about the output they give, can you include slightly more about which models perform best in which populations (this is somewhat more clear in the paragraph on cancer risk than the BRCA paragraph), and who these models were validated in?

Reviewer #2: This is a very well written and thorough executive summary on early onset breast cancer. The methods are nicely outlined.

Major comments
- Line 595-597: This line is confusing about who the overall risk reduction of 44% is in (besides women younger than age 50 - is this BRCA1, BRCA2, prior chest radiation; anyone with a certain risk score?). Would clarify.

Minor comments
- Because ten separate research questions were asked; it could be nice to frame each section as a question and perhaps even number the sections, both of which would make it more "interactive" to the reader
- In the section "Effect of health history on early onset breast cancer" it would be useful to have a subheading for each of the individual risk factors that the authors address
- Lines 498-500, Lines 506-510. While I think I understand why the authors are providing this information about other decision aids, these seem out of place and very confusing. It might be nice to group these other examples of decision aids together in one paragraph and to explain that these represent other examples of how decision aids are used in cancer screening and ?thrombolysis (I think this example was being used to show that decision aids could be integrated into the

EMR; being more clear about the purpose of these examples would be helpful)

Reviewer #3: The authors present a review of the literature summarizing recommendations for prevention, diagnosis, and supportive care related early onset breast cancer. The manuscript is well organized. I have the following comments/questions:

1) Thermograms are not recommended for routine breast cancer screening, however patients, especially younger patients, often ask about this testing modality. Would recommend adding in the primary manuscript a short sentence with guidance on this for providers.

2) There is no definition of "breast self-awareness" in the primary manuscript (line 309). It is referred to and there is an annotation in the tables section. Would a recommend adding this definition to the primary manuscript.

3) There is no comment on self breast exams. While many organizations no longer endorse these exams, with the intent of this document, would consider adding a brief summary stance on the topic of breast self exams in the primary manuscript.

4) In the genetic risk factors section and discussion of genetic testing, would consider adding that there are many different panels of gene tests. Insurance companies may only pay for one test, and the incorporation of a genetic counselor can help determine which panel is most appropriate. This seems to best fit near lines 250-258.

5) Lines 180-103 which direct to Table 3, mention common genes associated with panel testing. Would indicate that table 3 is current, however these guidelines are constantly being updated and it is important for providers to reference the most recent recommendations through the National Comprehensive Cancer Network (or other such organizations).

6) Lines 507 includes the term "thrombolysis" please double check this and confirm if this is the correct word as it does not fit in the sentence. The authors may have meant to say "chemoprophylaxis."

7) Lines 652 - 664 contain many summative statements about survivorship and breast cancer. Would rework this paragraph or consider adding to it. The entire manuscript is dedicated to diagnosis and prevention with this last section dedicated to management strategies in early breast cancer. The other option is to remove this section. For instance lines 654-655, "Treatment with gonadotropin-releasing hormone agonist should be considered when ovarian oocyte/embryo cryopreservation is not possible...." Usually this management is employed during chemotherapy. Do the authors mean to indicate someone should be on this indefinitely with early onset breast cancer? It needs clarification. Lines 659-660 involving prenatal diagnosis should not be restricted to only BRCA mutation carries. Would clarify this statement to include women with documented germline mutations or something similar. Ovarian tissue harvesting is controversial with no clear data this will be helpful in the future. It is considered experimental and should be identified as such. Lines 662-665 have conflicting statements. The first sentence says pregnancy does not impact recurrence and the second sentence says conception and influence on recurrence is unknown.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 71: include units for age (18-45 years)

Line 78: Is it Patient material or materials? Maybe clear “Content for patients, Bring your Brave, is available…? Patient material just sounds awkward.

As you paper is quite long, judicious use of abbreviations is warranted. Please abbreviate CDC and ACOG and other organizations you reference more than once (such as the USPSTF) after first use with these fully spelled out. In order to help shorten some the paper, I will make a few suggestions for wording modification. These are suggestions only and should be considered only if they do not change your meaning or emphasis. I’ve given a few specific recommendations along with line numbers for areas that need to be made more concise.

Line 82-86: “ACOG convened an expert panel to identify and the best evidence and practices from the literature, existing

relevant society guidelines and available validated specific or generalizable clinical tools. The developed provider educational materials and full reviews are available on line (give URL). “

Lines 89-90 essentially repeats what you have in lines 82-85. Perhaps it is better here in the methods section rather than in the introduction, but either way it needs to be consolidated.

How were these 10 research questions developed? Move the information about how the panel was identified and its characteristics to before a description of what the panel did. It might read something like: “Methods: ACOG convened an expert panel to identify and the best evidence and practices from the literature, existing relevant society guidelines and available validated specific or generalizable clinical tools. The developed provider educational materials and full reviews are available on line (give URL)."

A physician panel was recruited from the Society for Academic Specialists in General Obstetrics and Gynecology to review and summarize the evidence. Panel members were required to have expertise in evidence review and synthesis. Subspecialty expertise in breast disease was also sought. Several of the panel members had completed subspecialty fellowship training in breast disease. The panel developed ten separate research questions and used the PICO criteria (P=patient, problem or population;…….) to frame the literature review. These questions form the organizing basis for this executive summary”

Line 101: You could just say “A primary reviewer was assigned….” As it can be assumed that the person was a panel member. On line 109, similarly you could just say “A secondary reviewer….” And line 116 “Tertiary reviewer”.

Line 105: Units for age here and throughout.

Line 113 Delete the parenthetic.

Line 116: unclear what you mean by author/primary reviewer. Do you mean the first author of this article or are the author/primary reviewer the same people? If it’s the primary reviewer for the specific question, I would just call it primary reviewer.

Line 119: Is Epidemiology, etc the first of the 10 questions?

Line 124 : Is this data specific to deaths of women in this age group? So its “per 100,000 women ages 18-45 with breast cancer”? Later in the paragraph you included death rates in women over 75 so this is all unclear to me. Please be very clear what population you are addressing.

Line 159: What is 3-site testing?

Line 156 and line 160 both mention that routine genetic testing is not recommended. Please consolidate.

Line 176: Can undergo or should undergo?

Line 199: please point out that this is a non significant finding and should not be considered an “increased risk”. The very wide confidence intervals, which cross 1 should be noted.

By line 206, I’m unclear if breast density makes a difference in this age group. Please be explicit for the reader about how patients should be counseled on this issue.

Line 231 paragraph mentions the mandatory breast density reporting laws, but you mentioned them on line 192 already. Please consolidate

Line 287 or thereabouts: Could you contrast this information with recommendations for when to initiate mammographic screening in the general population?

Lines 291-294 seem to contain conflicting information re: atypical lobular hypoplasia. Is close monitoring enough given < 5% risk or is there are 4x increased risk so it should be excised?

Line 298: What are radial scars? Is that a pathologic finding seen on excised tissue?

Line 302: Breast MRI specifically in this population?

Line 312, 313: Include 95% CI’s.

Line 323: Please give the actual rate for excess cancer deaths related to hormonal contraception including the articulation of what the denominator represents (100,000 women on hormonal contraception, presumably).

Line 395 paragraph: Not necessary to add this, but did you find anything about reminders or prompts in EHR’s for offering screening?

Line 400: It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow.

Line 473: Where are these tools available

Lines 498-500 comes out of the blue. Does this belong up in the se tion where you introduce decision aids? Its wedged in here in a list of tools for breast cancer topics. Similarly, lines 506-510. It seems like you need to have a more robust section on the use of decision tools and aids (is there evidence that they work, and if so under what circumstances?) then list the ones available for this topic. Maybe this could be included at the beginning of this section in the context of describing shared decision making?

Section starting on line 525: Would you consider moving this up to follow the section starting on line 136 about genetic risks? That would seem to flow well and would allow you to consolidate some of the information in this section.

Line 581: Is this BSO or just oophorectomy?

Line 586: Somewhere earlier (although I can't find it right now) I think you said that a 20% risk was considered a high risk; here you say 1.7% risk or higher. Please make this clear. Maybe the 20% was a life time risk? Either way, to this reader the information seems to be conflicting.

Line 594: again, the CI crosses 1 and this would not be a signficiant decrease. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.

Line 620: do no organizations recommend maintaining a health (normal) weight as a strategy?

Line 653 The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.

Line 658: What is EOBC? Not a standard abbreviation—please spell out

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Permission for Figures 1 and 2: Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was

convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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

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

7. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

8. 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.

9. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

10. Figures 1–2: Please upload as high res figure files on Editorial Manager.

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

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

12. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 27, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

February 23, 2019

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

RE: Manuscript Number ONG-19-2331

Dear Dr. Chescheir,

Thank you for your review of our manuscript entitled 'Executive Summary of the Early Onset Breast Cancer Evidence Review Conference' by David Chelmow, MD, Mark D. Pearlman, MD, Amy Young, MD, Laura Bozzuto, MD, MS, Sandra Dayaratna, MD, Myrlene Jeudy, MD, Mallory E. Kremer, MD, Dana Marie Scott, MD, and Julia Sage O'Hara, MPH.

Please find a response to each point raised by the reviewers below. The revised manuscript indicates the position of all changes made using the tracked changes feature in Microsoft Word.

The lead author and corresponding author have read the Instructions for Authors. This revision has been developed in consultation with our co-authors and each author has given approval to the final form of the revision.

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.

Sincerely,

Julia S. O'Hara, MPH
American College of Obstetricians and Gynecologists
409 12th Street SW, Washington, DC 20024
[redacted]

REVIEWER COMMENTS:

Reviewer #1: I appreciate the thoroughness of this executive summary and the attention to research gaps. I especially appreciate the review of socioeconomic barriers to care and determinants of health and how they disproportionately effect diagnosis and survival in minority women. Are there groups within these communities working to reduce these disparities that can be highlighted as a resource for practitioners (much like the black-led efforts towards maternal mortality)?
Thank you. We added a sentence to Line 498 to highlight the Black Women's Health Imperative: "Groups such as the Black Women's Health Imperative are at the forefront of working to reduce these disparities, and can serve as a resource for both patients and providers."

line 126: The table in appendix 10 includes only information for women under 49, and deaths to 45. The fields are also unlabeled as to what is contained (n, percentage, etc... especially in the first two sections). I was expecting a complete demographics table, and if available would like to see that in the publication, not appendix as I think it is a good reference for clinicians.
Table 1 on Line 65 of Appendix 10 has been updated as requested with labels and more complete demographics. We separated the information into two tables: Table 1. Breast Cancer Incidence Rates by Age at Diagnosis, 2012-2016 by Race and Ethnicity; Table 2. Breast Cancer Mortality Rates by Age at Diagnosis, 2012-2016 by Race and Ethnicity. Although we agree that it is a good reference for clinicians, we respectfully decline to include it in the manuscript, citing the editor's feedback below requesting that we be mindful of paper length. Line 139 of the manuscript currently directs the reader to Appendix 10 to view the tables.

When you refer to the risk modeling, you introduce several different risk estimation models and talk a bit about the output they give, can you include slightly more about which models perform best in which populations (this is somewhat more clear in the paragraph on cancer risk than the BRCA paragraph), and who these models were validated in?
Clarified as requested by editing Lines 520-545: "The three most widely used tools for predicting BRCA gene carrier probability are BRCAPRO, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), and Penn II (103). BRCAPRO and BOADICEA also provide cancer risk estimates in addition to estimates of likelihood of genetic mutations. These models might be useful to direct women to genetic testing and counseling who are at increased risk of genetic mutations that pose a high risk of early onset disease. BRCAPRO is a validated statistical program to estimate individual carrier probabilities on the basis of family history. It is not specific to any age range and does not directly estimate the risk of early onset cancer, but rather the risk of carrying a BRCA1 or BRCA2 mutation. BOADICEA likewise was developed using population data from families in the United Kingdom to create a model based on family history and requires detailed family pedigree. The Penn II model uses clinical questions based on family history to reach a carrier probability, but does not calculate cancer risks. Once a BRCA1 or 2 mutation is identified the Stanford risk assessment tool for BRCA carriers may aid in decision making for preventive measures based as it provides age-related risk of cancer and compares multiple intervention strategies (104).

Additional widely validated models to assess cancer risk include the Tyrer-Cuzick, modified Gail, and Breast Cancer Surveillance Consortium models. None specifically assess risk of early onset or premenopausal breast cancer, although most provide estimated 5- or 10-year cancer risk as well as lifetime risk of breast cancer. No models used validation cohorts with patients younger than 20. The modified Gail model has been validated in women 35 and older to assess 5-year invasive cancer risk (105). The Tyrer-Cuzick model has been studied in women older than age 20 years to assess 10-year

cancer risk and has been shown to perform better in women with a family history of breast cancer (106). The Breast Cancer Surveillance Consortium risk calculator is validated for women older than age 35 years to provide 5- and 10-year risks and includes family history factors as well as breast density in the calculation (107). There are limited data on the use of these models to specifically address cancer risk reduction in young women."

Reviewer #2: This is a very well written and thorough executive summary on early onset breast cancer. The methods are nicely outlined.
Thank you.

Major comments
- Line 595-597: This line is confusing about who the overall risk reduction of 44% is in (besides women younger than age 50 - is this BRCA1, BRCA2, prior chest radiation; anyone with a certain risk score?). Would clarify.
Clarified as requested by editing Lines 706-709: "While other European studies have shown mixed effects, this overall reduction is supported by a systematic review of randomized controlled prevention trials across all studied populations showing a 44% decrease in the risk of breast cancer for women younger than 50 (hazard ratio: 0.66, 95% CI: 0.52–0.85) (133)."

Minor comments
- Because ten separate research questions were asked; it could be nice to frame each section as a question and perhaps even number the sections, both of which would make it more "interactive" to the reader
We respectfully decline to make this change, citing the editor's feedback below requesting that we be mindful of paper length. Each appendix is framed by the research questions, should readers be interested in additional details.

- In the section "Effect of health history on early onset breast cancer" it would be useful to have a subheading for each of the individual risk factors that the authors address
The following subheadings were added for each of the individual risk factors addressed in this section:
Line 368: History of Proliferative Breast Disease
Line 395: Past or Present Use of Hormonal Contraception
Line 420: Past or Present Use of Fertility Treatments
Line 431: History of Radiation Exposure
Line 448: Prior Breast or Ovarian Cancer

- Lines 498-500, Lines 506-510. While I think I understand why the authors are providing this information about other decision aids, these seem out of place and very confusing. It might be nice to group these other examples of decision aids together in one paragraph and to explain that these represent other examples of how decision aids are used in cancer screening and ?thrombolysis (I think this example was being used to show that decision aids could be integrated into the EMR; being more clear about the purpose of these examples would be helpful)
We agree that the sudden broadening of the scope needs a better transition. We have addressed this by adding a new sentence on Line 604: "Because we anticipated that a literature search would find limited information specific to communicating risk of early onset breast cancer, we deliberately conducted a broad search encompassing other aspects of breast cancer and other cancers and health care conditions." We also consolidated the content into one paragraph as suggested (Lines 604-620).

Reviewer #3: The authors present a review of the literature summarizing recommendations for prevention, diagnosis, and supportive care related early onset breast cancer. The manuscript is well organized. I have the following comments/questions:
Thank you.

1) Thermograms are not recommended for routine breast cancer screening, however patients, especially younger patients, often ask about this testing modality. Would recommend adding in the primary manuscript a short sentence with guidance on this for providers.
Studies on thermograms, which are not recommended for routine breast cancer screening, did not come up in our literature search. While the reviewer may get frequent questions in their practice, this has not been the experience of any of the panel or stakeholder organization representatives. Given the length of the manuscript, we do not think it worthwhile to add information about thermograms, which could also serve to give an unproven technology undue attention.

2) There is no definition of "breast self-awareness" in the primary manuscript (line 309). It is referred to and there is an annotation in the tables section. Would a recommend adding this definition to the primary manuscript.
Definition of breast self-awareness added to Line 393: "Engage in breast self-awareness (women should be familiar with their breasts and report changes to their health care provider promptly)."

3) There is no comment on self breast exams. While many organizations no longer endorse these exams, with the intent of this document, would consider adding a brief summary stance on the topic of breast self exams in the primary manuscript.
Added comment regarding breast self exams at Line 738: "Breast self examination is no longer part of major society guidelines for average risk women given the high number of false positives and absence of supportive evidence for benefit (2, 12, 104). Our literature review found no evidence for its use in women at risk for early onset breast cancer. Breast self examination is not recommended, but women should be counseled to be familiar with their breasts and promptly report changes to their breasts to their health care provider."

4) In the genetic risk factors section and discussion of genetic testing, would consider adding that there are many different panels of gene tests. Insurance companies may only pay for one test, and the incorporation of a genetic counselor can help determine which panel is most appropriate. This seems to best fit near lines 250-258.
Added the suggested information to Line 332: "Genetic counselors can help determine which of the many available panels of genetic testing are most appropriate and cost-effective."

5) Lines 180-103 which direct to Table 3, mention common genes associated with panel testing. Would indicate that table 3 is current, however these guidelines are constantly being updated and it is important for providers to reference the most recent recommendations through the National Comprehensive Cancer Network (or other such organizations).
Lines 1276-1278 state: "To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available."

6) Lines 507 includes the term "thrombolysis" please double check this and confirm if this is the correct word as it does not fit in the sentence. The authors may have meant to say "chemoprophylaxis."

Use of the term "thrombolysis" is intended. Lines 604-618 have been updated for clarity: "Because we anticipated that a literature search would find limited information specific to communicating risk of early onset breast cancer, we deliberately conducted a broad search encompassing other aspects of breast cancer and other cancers and health care conditions […] A decision analytic model was used to improve estimation of benefits and risks for patients undergoing thrombolysis, with the added benefit that this computerized decision aid can be embedded in an electronic health record (129)."

7) Lines 652 - 664 contain many summative statements about survivorship and breast cancer. Would rework this paragraph or consider adding to it. The entire manuscript is dedicated to diagnosis and prevention with this last section dedicated to management strategies in early breast cancer. The other option is to remove this section.
Management strategies and special considerations in early onset breast cancer were part of our literature search at CDC's request. We would like to leave this section in after addressing the specific concerns detailed below.

For instance lines 654-655, "Treatment with gonadotropin-releasing hormone agonist should be considered when ovarian oocyte/embryo cryopreservation is not possible...." Usually this management is employed during chemotherapy. Do the authors mean to indicate someone should be on this indefinitely with early onset breast cancer? It needs clarification.
Added "during chemotherapy" after "Treatment with gonadotropin-releasing hormone agonist" on Line 773 for clarity.

Lines 659-660 involving prenatal diagnosis should not be restricted to only BRCA mutation carries. Would clarify this statement to include women with documented germline mutations or something similar.
Revised Lines 778-780 as requested for clarity: "Prenatal genetic diagnosis should be considered in women with BRCA mutations or other documented germ line mutations undergoing in vitro fertilization procedures."

Ovarian tissue harvesting is controversial with no clear data this will be helpful in the future.
It is considered experimental and should be identified as such.
The revised 2019 ASRM Committee Opinion states that ovarian tissue banking is an acceptable fertility-preservation technique and is no longer experimental: Replaced reference 149 (Line 1253) with the 2019 revised ASRM Committee Opinion and cited it in Line 781.

Lines 662-665 have conflicting statements. The first sentence says pregnancy does not impact recurrence and the second sentence says conception and influence on recurrence is unknown.
Updated Lines 782-786 for clarity: "Pregnancy after a diagnosis of early onset breast cancer has not been shown to increase the risk of recurrence (150). When considering timing, pregnancy occurring at least 10 months after breast cancer diagnosis was not found to be harmful and may even contribute to survivorship (151). When breast cancer is diagnosed in pregnancy, chemotherapy can be safely instituted in the second and third trimesters (150)."

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The

instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.
Thank you. We have reviewed the Author Instructions and this revision adheres to the requirements.

Line 71: include units for age (18-45 years)
Added units for age on Line 72 and throughout.

Line 78: Is it Patient material or materials? Maybe clear "Content for patients, Bring your Brave, is available…? Patient material just sounds awkward.
Updated Line 79 to address comment. Sentence now reads: "The educational material geared towards patients, Bring Your Brave, is available on the Centers for Disease Control and Prevention website…"

As you paper is quite long, judicious use of abbreviations is warranted. Please abbreviate CDC and ACOG and other organizations you reference more than once (such as the USPSTF) after first use with these fully spelled out. In order to help shorten some the paper, I will make a few suggestions for wording modification. These are suggestions only and should be considered only if they do not change your meaning or emphasis. I've given a few specific recommendations along with line numbers for areas that need to be made more concise.
Thank you. Organizations referenced more than once (CDC, ACOG, USPSTF, NCCN, NICE, ASCO) have been abbreviated after first use fully spelled out. Responses to your specific recommendations are listed below.

Line 82-86: "ACOG convened an expert panel to identify and the best evidence and practices from the literature, existing relevant society guidelines and available validated specific or generalizable clinical tools. The developed provider educational materials and full reviews are available on line (give URL). "
Per this comment and the comment below, we rearranged and consolidated. The introduction section now ends with Lines 82-89: "The CDC awarded ACOG a grant to develop accompanying provider material, available on line at www.acog.org/eobc."

Lines 89-90 essentially repeats what you have in lines 82-85. Perhaps it is better here in the methods section rather than in the introduction, but either way it needs to be consolidated.
Per this comment and the comment above, we rearranged and consolidated. The beginning of the methods section, starting on Line 91, now reads: "ACOG convened an expert panel to identify the best evidence and practices from the literature, existing relevant society guidelines, and available validated specific or generalizable clinical tools."

How were these 10 research questions developed? Move the information about how the panel was identified and its characteristics to before a description of what the panel did. It might read something like: "Methods: ACOG convened an expert panel to identify and the best evidence and practices from the literature, existing relevant society guidelines and available validated specific or generalizable clinical tools. The developed provider educational materials and full reviews are available on line (give URL)."
A physician panel was recruited from the Society for Academic Specialists in General Obstetrics and Gynecology to review and summarize the evidence. Panel members were required to have expertise in evidence review and synthesis. Subspecialty expertise in breast disease was also sought. Several of the panel members had completed subspecialty fellowship training in breast disease. The panel developed

ten separate research questions and used the PICO criteria (P=patient, problem or population;…….) to frame the literature review. These questions form the organizing basis for this executive summary"
Updated and condensed the first two paragraphs of the methods section (Lines 91-99) as requested: "ACOG convened an expert panel to identify the best evidence and practices from the literature, existing relevant society guidelines and available validated specific or generalizable clinical tools. The panel was recruited from SASGOG to review and summarize the evidence. Panel members were required to have expertise in evidence review and synthesis. Subspecialty expertise in breast disease was also sought. Several of the panel members had completed subspecialty fellowship training in breast disease. The panel developed ten separate research questions and used the PICO criteria (P=patient, problem, or population; I=intervention; C=comparison, control, or comparator; O=outcome[s]) to frame the literature review. These questions form the organizing basis for this executive summary."

Line 101: You could just say "A primary reviewer was assigned…." As it can be assumed that the person was a panel member. On line 109, similarly you could just say "A secondary reviewer…." And line 116 "Tertiary reviewer".
Updated as suggested on Line 114, Line 122, and Line 129.

Line 105: Units for age here and throughout.
Updated as requested (see Line 118) and throughout to include units for age.

Line 113 Delete the parenthetic.
Updated as requested: Removed parenthetic (see Line 126).

Line 116: unclear what you mean by author/primary reviewer. Do you mean the first author of this article or are the author/primary reviewer the same people? If it's the primary reviewer for the specific question, I would just call it primary reviewer.
Author/primary reviewer is intended to mean the primary reviewer for the specific question. Updated Line 129 to say "primary reviewer" as suggested.

Line 119: Is Epidemiology, etc the first of the 10 questions?
Epidemiology was searched as part of question 10 during the literature search, but is listed first in the executive summary to provide background and context for the subsequent topics.

Line 124 : Is this data specific to deaths of women in this age group? So its "per 100,000 women ages 18-45 with breast cancer"? Later in the paragraph you included death rates in women over 75 so this is all unclear to me. Please be very clear what population you are addressing.
This data is specific to deaths of all women in the age group. Lines 137-140 have been updated for clarity: "Black women had the highest death rate at 28.1 per 100,000 persons. While 5-year relative survival rates were largely similar across age groups, women below age 45 had among the lowest rates, second only to women aged 75 and older (1,4)."

Line 159: What is 3-site testing?
Removed "3-site" for clarity. Line 174 now reads: "[…] consensus guidelines recommend offering routine testing for the three specific mutations."

Line 156 and line 160 both mention that routine genetic testing is not recommended. Please consolidate.

Deleted the following sentence from Line 175 to consolidate: "Routine genetic testing is not currently recommended for any other group." Line 171 remains unchanged: "Currently, population-based screening for BRCA genes in the absence of other risk factors is not broadly recommended, given their rarity and the uncertain benefit of large-scale testing (12)."

Line 176: Can undergo or should undergo?
We feel the word "can" is more appropriate as while there are a number of potential options, none has adequate supportive evidence or acceptance as a preferred recommendation to merit "should."

Line 199: please point out that this is a non significant finding and should not be considered an "increased risk". The very wide confidence intervals, which cross 1 should be noted.
Revised sentence starting on Line 258 as requested: "In a more recent case-control study of 213 Korean women with breast cancer, women who had the highest breast density, described as 50% density or higher, had a non-significantly elevated odds ratio for breast cancer (OR 2.98, 95% CI: 0.99–9.03) compared with those with the lowest mammographic density after adjusting for multiple variables."

By line 206, I'm unclear if breast density makes a difference in this age group. Please be explicit for the reader about how patients should be counseled on this issue.
Added clarifying text in two places:
Line 296: "Neither of these organizations specifically address dense breasts in younger women."
Line 306: "Younger women with dense breasts and no other risk factors can be counseled that dense breasts are very common in this age group, and supplemental screening methods are available. However, they are not specifically recommended, have significant risk of false positives, and have not been shown to change outcome."

Line 231 paragraph mentions the mandatory breast density reporting laws, but you mentioned them on line 192 already. Please consolidate
Consolidated into one paragraph starting on Line 298: "Mandatory breast density reporting has been enacted as legislation in an increasing number of states. Many patients receive letters notifying them of their breast density, and interpretation of these letters can be challenging for patients and providers. In early 2019, Congress authorized the U.S. Food and Drug Administration to amend the Mammography Quality Standards Act of 1992 to include mandatory breast density reporting at the federal level. The public comment period for the proposed changes to the legislation ended in June 2019, and final regulations should be forthcoming. ACOG recommends that health care providers comply with state laws that require disclosure of breast density in mammogram reports (39)."

Line 287 or thereabouts: Could you contrast this information with recommendations for when to initiate mammographic screening in the general population?
Added as requested to Line 364: "This is in contrast to screening recommendations for average risk women, which all recommend screening with mammography alone, starting at age 40 to 50, depending on the source (22)."

Lines 291-294 seem to contain conflicting information re: atypical lobular hypoplasia. Is close monitoring enough given < 5% risk or is there are 4x increased risk so it should be excised?
Revised for clarity on Lines 374-377: "When atypical lobular hyperplasia is an incidental finding and there is concordance between radiologic and pathological findings regarding the targeted biopsied

lesion, it is less likely to be associated with a concurrent malignancy, so close monitoring is usually appropriate (48).”

Line 298: What are radial scars? Is that a pathologic finding seen on excised tissue?
Updated Line 380-383 for clarity: “Radial scars are characterized microscopically by a fibroelastic core with radiating ducts and lobules. Radial scars and complex sclerosing lesions carry an 8–15% risk of DCIS or invasive malignancy at the time of excision (47,53–57). Radial scars are usually managed by excisional biopsy (38).”

Line 302: Breast MRI specifically in this population?
Correct. Added “in this population” to the end of Line 386 for clarity.

Line 312, 313: Include 95% CI’s.
Revised on Line 397: “A large meta-analysis in 1996 revealed a small increased risk of breast cancer among women with current or recent oral contraceptive use (RR: 1.07, SD 0.02, p=.0.00005) (59).” Added 95% CI to Lines 400-401: “(RR: 1.20, 95% confidence interval [CI]: 1.14–1.26) (60).” The study on line 397 did not report CI in the original publication.

Line 323: Please give the actual rate for excess cancer deaths related to hormonal contraception including the articulation of what the denominator represents (100,000 women on hormonal contraception, presumably).
Changed Lines 410-413 to: “The maternal mortality rate in the United States in 2015 was 26.4 deaths per 100,000 pregnancies, which is comparable to the rate of excess breast cancer diagnoses (13 (95% CI 10-16) per 100,000 person years) related to hormonal contraception suggested by the 2017 cohort study (60,66).”

Line 395 paragraph: Not necessary to add this, but did you find anything about reminders or prompts in EHR’s for offering screening?
We did not find anything about reminders or prompts in EHRs for offering screening, however this topic was not a specific part of our literature search.

Line 400: It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow.
Noted. We replaced the word impact throughout:
Changed “impact” to “improve” in Line 495.
Changed “impact” to “effect” in Line 460, Line 493, and Line 748.
Changed “impact to “affect” in Line 470.
Changed “impacts” to “affects” in Line 487.
Changed “impactful” to “important” in Line 473.

Line 473: Where are these tools available
These tools are all available online, and links can be found in the references section of this manuscript.

Lines 498-500 comes out of the blue. Does this belong up in the se tion where you introduce decision aids? Its wedged in here in a list of tools for breast cancer topics. Similarly, lines 506-510. It seems like you need to have a more robust section on the use of decision tools and aids (is there evidence that

they work, and if so under what circumstances?) then list the ones available for this topic. Maybe this could be included at the beginning of this section in the context of describing shared decision making?
We agree that the sudden broadening of the scope needs a better transition. We have addressed this by adding a new sentence before Line 604: "Because we anticipated that a literature search would find limited information specific to communicating risk of early onset breast cancer, we deliberately conducted a broad search encompassing other aspects of breast cancer and other cancers and health care conditions." To make the section more robust would likely involve making the section longer than space allows. We also consolidated Lines 604-620 into one paragraph as suggested.

Section starting on line 525: Would you consider moving this up to follow the section starting on line 136 about genetic risks? That would seem to flow well and would allow you to consolidate some of the information in this section.
We moved the understanding genetic counseling and testing section to immediately follow the genetic risk section at Line 199 and updated the order of the references accordingly.

Line 581: Is this BSO or just oophorectomy?
Changed Line 691 to: "We found no evidence to support oophorectomy for the purposes of preventing early onset breast cancer. The use of bilateral salpingo-oophorectomy to prevent lifetime risk of breast cancer has been estimated to be as high as 50% for BRCA1 and BRCA 2 carriers, although more recent publications question these results (131)."

Line 586: Somewhere earlier (although I can't find it right now) I think you said that a 20% risk was considered a high risk; here you say 1.7% risk or higher. Please make this clear. Maybe the 20% was a life time risk? Either way, to this reader the information seems to be conflicting.
Line 355 states that the 20% lifetime risk is the generally accepted level for "high risk." 1.7% is now just stated as the threshold for starting tamoxifen. Changed the sentence on Line 696 for clarity: "Tamoxifen is the only agent indicated for use in premenopausal women at increased risk of breast cancer, and is recommended for women with 5 year risk of 1.7% or higher."

Line 594: again, the CI crosses 1 and this would not be a signficiant decrease. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.
Inserted the word "nonsignificant" before "62% decrease" on Line 705.

Line 620: do no organizations recommend maintaining a health (normal) weight as a strategy?
Added "maintaining a healthy weight" to the list of strategies on Line 736.

Line 653 The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.
Noted. Removed virgule throughout. Exceptions include URLs and references.

Line 658: What is EOBC? Not a standard abbreviation—please spell out
EOBC stands for early onset breast cancer. Since it is not a standard abbreviation, we have spelled early onset breast cancer out in Line 778 as requested.

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https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
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Understood, thank you. Financial support acknowledged on Lines 21-23.

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Understood, thank you. Lines 48-50 note that authors are scheduled to present on the material in this manuscript at the 69th American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting in Seattle, Washington, on April 25, 2020.

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Removed virgule from throughout. Exceptions include URLs and references.

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