OBSTETRICS & GYNECOLOGY

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

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

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

Date: Oct 30, 2020
To: "Mariam M. AlHilli" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2577

RE: Manuscript Number ONG-20-2577

Controversies in Hereditary Cancer Management

Dear Dr. AlHilli:

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 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a Clinical Expert series article on Controversies in Hereditary Cancer Management. This is a welcome addition to the series. I have some minor suggestions.

1. Line 27 Obstetrician Gynecologist, no "and".
2. Line 34: Who should be referred for genetic testing. I feel like Table 1 should be referenced in this section as well. Readers are going to be looking for the recommendations of who should be referred.
3. Line 65: How does this section differ from the previous section on Who Should be Referred for Genetic Testing? Perhaps combine these two sections or at least this section should go before Testing in Breast Cancer patients.
4. Line 113 Lynch Syndrome screening: what does "systematic clinical screening with family history" mean and what does "molecular screening" mean? Please clarify for the reader or rephrase? Clarify molecular screening is on pathology specimens.
5. Line 286: You don't mention what to do about people with low ovarian cancer penetrance genes. Should they also have RRSO?
6. Line 321: Here it states that NBN screening is similar to CHEK2 and ATM and says start at age 30 but Line 308 doesn't mention a specific age to start or says age 40 which is different. Please clarify.
7. Line 401: what is the frequency of this MRI based pancreatic cancer screening?
8. Line 503: The first line of the paragraph states that OCPs reduce the risk of ovarian cancer by 50%, so why then is there insufficient evidence to recommend their use?
9. Line 504: The 2nd paragraph says studies are conflicting but then states 2 meta-analyses show no risk, which is also mentioned in the paragraph above, so it is confusing to the reader. Line 505, please cite these 2 meta-analyses.
10. Line 507: Emergence of what studies besides the Morch study (citation 75) which has some flaws...this sentence makes it sound like there are many studies that have emerged but you have cited just one.
11. Line 530: Taken back for surgery for what procedures?
12. Line 535: Use of the term OB/GYN specialists...are you referring to general OB/GYNs or gyn oncologists in this title?
13. Line 645: Age of natural menopause? 51? 55?
14. Line 713: Is Hereditary Cancer psychologist an actual job description? How many exist?
15. Table 1: If you have a known mutation for a breast cancer gene, wouldn't you have already been referred for genetic testing? Please clarify in Row #2 what kind of relatives ?first degree ?2nd degree? Also in Row #3, close blood relatives, what degree? Please clarify.
16. Table 2: Please add what pancreatic cancer screening consists of.

Reviewer #2:

The authors provide a well written review of controversies in hereditary breast and ovarian cancer. I have the following comments/questions:

1) Starting at line 47 with the subject heading: "Universal testing in breast cancer" would consider adding a more summative statement with regard to recommended approach. The section identifies that universal testing has been put forth but is controversial. The reader would benefit from a path forward (ie recommend shared decision making with patients on an individual basis, or use the NCCN guidelines)
2) Line 114 would define SGO (Society of Gynecologic Oncology)
3) Starting at line 163 with subject heading: "Understanding genetic testing results" would add a brief description of the role of genetic counselors and how they may be incorporated into this process. Many insurance companies will not pay for genetic testing unless a patient has had some type of meeting with a genetic counselor, which can be important for general OB/GYN's to be aware.
4) Starting at line 286 with subject heading: "Management of women with low (ovarian cancer) penetrance genes" would add a summative statement with recommendations (ie Lynch Syndrome patients should have risk reducing surgery, and/or shared decision making with patients with other gene mutations).

Reviewer #3:

This review article is very well written and very comprehensive, focusing on genetic testing associated with breast and ovarian cancer. Overall, it covers many of the common high yield questions with regard to genetic testing, controversies with salpingectomies vs salpingo-oophorectomies, role of hysterectomy in risk reducing surgery and risks associated with the various genetic mutations detected on multigene panels.

Would suggest the following:
1) The areas with regard to ovarian cancer are very well written. I do not have breast cancer screening and management in my practice, therefore critique of these sections should be done with someone with this particular academic expertise. Additionally, breast cancer screening is not done by general OB/GYNs where I practice - if this is something of high yield in practice in the United States, then this review article would be pertinent. However, if not, then potentially a journal with broader readership (to include general practitioners, family physicians, general surgeons) may be of value.

2) Lines 104-106 - guidelines with regard to genetic testing for all patients with epithelial ovarian cancer regardless of histology - clarify if should be all non-mucinous epithelial ovarian cancers? Or include mucinous due to risk of Lynch?

3) Lines 270-271 - "women at risk can be offered screening with transvaginal ultrasound and serum CA-125 starting at age 30-35 years" - Remove this statement, or provide a strong reference to back this up, as this statement is controversial.

4) Given the title of this review article is on Controversies in Hereditary Cancer Management, in a ob/gyn journal, should include recommendations of when to do hysterectomy for patients with lynch syndrome and recommendations with regard to endometrial biopsies.

5) Would suggest adding a section on tumor testing for somatic mutations - and the controversies whether tumor testing only is sufficient, or does the patient need both somatic and germline testing if somatic test is negative? Cost-effectiveness of doing both somatic and germline testing or is somatic testing sufficient and only do germline test if somatic positive. Provide percentage of patients who will have a positive mutation in germline testing when somatic test negative.

6) Also would be helpful to add if any data on genetic testing of family members who do not have the disease in question when the original patient with the cancer has already died or not available for genetic testing.

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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. 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. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

5. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. 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); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Conundrums articles should not exceed 6 pages (1,500 words); Questioning Clinical Practice articles should not exceed 6 pages (1,500 words); Research Letters articles should not exceed 2.5 pages (600 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. 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).

8. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

9. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

12. 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.

13. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

14. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

15. 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.

16. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

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

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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. Do not omit your responses to the Editorial Office or Editors' comments.

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 Nov 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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November 20, 2020
Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics and Gynecology

Dear Dr. Chescheir,

Many thanks for the invitation to submit our 'clinical expert series' paper on the topic "Controversies in the Hereditary Cancer Management". We are very excited and honored to be able to contribute to the journal and *Obstetrics and Gynecology* readership through this publication. Please find enclosed a copy of the final edited manuscript and figures for consideration for publication in *Obstetrics and Gynecology.* We are also enclosing a copy of the marked paper and point by point response to reviewers attached to this letter.

Our paper is focused on issues pertaining to "previvors", survivors of predisposition to cancer but who haven't had the disease. We address several controversial issues that arise in the management of women with hereditary cancers including genetic counseling and testing, communication of genetic testing results, breast and ovarian cancer screening, and considerations regarding risk-reducing surgery. We further address psychosocial issues women with cancer predisposition may deal with including sexuality, body image and coping.

Both Dr. Holly Pederson and myself contributed to the writing/editing, structure and development of the manuscript. We appreciate the efforts undertaken in the editorial review process and thank you for considering our paper for publication in *Obstetrics and Gynecology*. 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.

Sincerely,

Mariam AlHilli, MD

REVIEWER RESPONSES

Reviewer #1:
This is a Clinical Expert series article on Controversies in Hereditary Cancer Management. This is a welcome addition to the series. I have some minor suggestions.

1. Line 27 Obstetrician Gynecologist, no "and".

Response: Line 27 changed to Obstetricians/Gynecologists to improve flow of sentence.

Line 27:. ..important for the Obstetrician/Gynecologist and other women's health providers to recognize.

2. Line 34: Who should be referred for genetic testing. I feel like Table 1 should be referenced in this section as well. Readers are going to be looking for the recommendations of who should be referred.

Response: We agree with the reviewer's suggestion. Table 1 has now been referenced earlier in the section "Who should be referred for genetic testing".

Line 45: General recommendations for testing are highlighted in Table 1.

3. Line 65: How does this section differ from the previous section on Who Should be Referred for Genetic Testing? Perhaps combine these two sections or at least this section should go before Testing in Breast Cancer patients.

Response: We appreciate the reviewer's suggestion. The section on "testing in special populations" has been moved to and combined with the section "who should be referred for genetic testing".

Lines 46-63: section on screening in special population moved up and combined with prior section.

4. Line 113 Lynch Syndrome screening: what does "systematic clinical screening with family history" mean and what does "molecular screening" mean? Please clarify for the reader or rephrase? Clarify molecular screening is on pathology specimens.

Response: This statement has been clarified further in lines 115-118 and the sentence

Lines 114- 117: The Society of Gynecologic Oncology (SGO) endorses screening for Lynch syndrome among all women diagnosed with endometrial cancer preferably through universal tumor testing for microsatellite instability or immunohistochemistry staining (or both) such that patients with Lynch syndrome can be identified.

5. Line 286: You don't mention what to do about people with low ovarian cancer penetrance genes. Should they also have RRSO?

Response: Statement inserted lines 294 to clarify recommendations for risk-reducing surgery in women with low penetrance genes.

Lines 295- 301: Patients with Peutz Jeghers syndrome should have annual pelvic examinations with PAP smears from the age of 18 years. There are no formal guidelines for DICER1 or SMARC1 carriers at this time. Risk-reducing surgery can be considered based on family history, but is not required as part of risk-reducing strategies for Peutz Jeghers Syndrome. The NCCN recommends referral of these patients to a specialized team for risk management and education on symptoms that might be associated with development of ovarian cancer and other gynecologic cancers [39].

6. Line 321: Here it states that NBN screening is similar to CHEK2 and ATM and says start at age 30 but Line 308 doesn't mention a specific age to start or says age 40 which is different. Please clarify.

Response: The statement has been clarified for NBN screening to state that there no evidence for increased risk for other mutation carriers (than 657del5) and no sufficient evidence to define risk groups.

Lines 337-341: In fact, current data suggests that breast cancer risks are not increased for pathogenic /likely pathogenic variants other than 657del5, for which there is mixed evidence for increased risk. There is insufficient data to define absolute risk in this group, and patients should be managed based on family history.

7. Line 401: what is the frequency of this MRI based pancreatic cancer screening?

Response: The frequency of MRI and MRCP for pancreatic screening is now clarified to state that annual screening is recommended.

Lines 421: Screening consists of annual contrast-enhanced MRI/magnetic resonance cholangiopacreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have worrisome abnormalities on screening.

8. Line 503: The first line of the paragraph states that OCPs reduce the risk of ovarian cancer by 50%, so why then is there insufficient evidence to recommend their use?

Response: We agree with the reviewer's comment. Clarification has been made to explain that formal recommendations cannot be made for or against the use of OCPs for primary prevention due to conflicting data.

Lines 525-529: At this time, there are no formal recommendations for or against the use of OCPs for primary prevention of ovarian cancer as there have been case control studies showing increased risk [75], [78]. However, larger prospective trials are needed to elucidate the impact of oral contraceptives on cancer risk in carriers of BRCA mutations.

9. Line 504: The 2nd paragraph says studies are conflicting but then states 2 meta-analyses show no risk, which is also mentioned in the paragraph above, so it is confusing to the reader. Line 505, please cite these 2 meta-analyses.

Response: We agree with the reviewer's comment and that the statements described are conflicting. We have made modifications and removed the sentence "Studies on the safety of oral conceptive use among BRCA1/2 mutation carriers have yielded conflicting results" as OCP use is generally recommended for ovarian cancer risk reduction. New statement included to clarify the controversy. The sentence "At least two meta-analyses have shown that oral contraceptive use is not associated with increased cancer risk in women who carry BRCA1 or BRCA2 mutations" has also been removed as it is previously explained.

Lines 537-541: At this time, there are no formal recommendations for or against the use of OCPs for primary prevention of ovarian cancer as there have been case control studies showing increased risk for the development of breast cancer. Larger prospective trials are needed to elucidate the impact of oral contraceptives on cancer risk in carriers of BRCA mutations.

10. Line 507: Emergence of what studies besides the Morch study (citation 75) which has some flaws...this sentence makes it sound like there are many studies that have emerged but you have cited just one.

Response: We agree with the reviewer's comment. Additional references are now included and paragraph modified to explain the controversy.

Lines 520-522: Cohort studies have demonstrated a potential increase in breast cancer risk; however the largest meta-analysis to date demonstrated no increase in risk compared to the general population [75]–[77]'.

Line 526-529: At this time, there are no formal recommendations for or against the use of OCPs for primary prevention of ovarian cancer as there have been case control studies showing increased risk. However, larger prospective trials are needed to elucidate the impact of oral contraceptives on cancer risk in carriers of BRCA mutations.

11. Line 530: Taken back for surgery for what procedures?

Response: Clarification made to state that if carcinoma is diagnosed, patients are taken back to for staging surgery.

Line 553: If carcinoma is detected postoperatively, the patient is taken back for surgical exploration and staging.

12. Line 535: Use of the term OB/GYN specialists...are you referring to general OB/GYNs or gyn oncologists in this title?

Response: We appreciate this suggestion. Clarification has been made and reference to Gynecologic Oncologists made.

Line 558: Title of section changed to "Role of Gynecologic Oncologists in screening and performing risk-reducing procedures"

13. Line 645: Age of natural menopause? 51? 55?

Response: Clarification made regarding age of natural menopause when HT can be discontinued (age 50-52).

Lines 676-678: Women undergoing risk-reducing surgery should be reassured that menopausal symptoms, sexual function and quality of life can be improved with HT use and it is likely safe until the time of natural menopause (age 50-52)

14. Line 713: Is Hereditary Cancer psychologist an actual job description? How many exist?

Response: We thank the reviewer for this point. We are fortunate to have a dedicated health psychologist embedded into the breast center with focus on hereditary risk and counseling. There is a second who also does general psychological counseling. Having a health psychologist as part of our hereditary management team has been an invaluable resource.

Line 736-727: Health psychologists with expertise in caring for patients with hereditary cancers embedded into hereditary programs are important members of the management team when available.

15. Table 1: If you have a known mutation for a breast cancer gene, wouldn't you have already been referred for genetic testing? Please clarify in Row #2 what kind of relatives ?first degree ?2nd degree? Also in Row #3, close blood relatives, what degree? Please clarify.

Response: We appreciate the reviewer's comment and recommendation for clarification of relative status. An addition has been made to table to describe first degree relatives: siblings and children. Second-degree relatives include half-siblings, grandparents, aunts/uncles, nieces/nephews, and grandchildren. Close blood relatives include first, second or third degree relatives on either the maternal or paternal side of the family.

Table 1 modified with above recommendations to clarify relative status

16. Table 2: Please add what pancreatic cancer screening consists of.

Response: Intervention for pancreatic cancer screening with annual MRCP and or endoscopic ultrasound has been added to the table based on NCCN guidelines.

Table 2 modified with above recommendations

Reviewer #2:

The authors provide a well written review of controversies in hereditary breast and ovarian cancer. I have the following comments/questions:

1) Starting at line 47 with the subject heading: "Universal testing in breast cancer" would consider adding a more summative statement with regard to recommended approach. The section identifies that universal testing has been put forth but is controversial. The reader would benefit from a path forward (ie recommend shared decision making with patients on an individual basis, or use the NCCN guidelines)

Response: We appreciate the reviewer's recommendation for including a summative statement regarding universal testing and shared decision-making.

Lines 80-84: Third party payer reimbursement is largely governed by eligibility for testing per NCCN guidelines in conjunction with formal genetic counseling; many patients, however, are opting for affordable clinical grade options now available for personal use (also in conjunction with genetic counseling). However, the overall debate of guidelines-based testing versus a more generalized testing approach continues.

2) Line 114 would define SGO (Society of Gynecologic Oncology)

Response: defined in previous paragraph and redefined in line 114 again for clarity.

Line 114: The Society of Gynecologic Oncology (SGO) endorses screening for Lynch syndrome among all women diagnosed with endometrial cancer

3) Starting at line 163 with subject heading: "Understanding genetic testing results" would add a brief description of the role of genetic counselors and how they may be incorporated into this process. Many insurance companies will not pay for genetic testing unless a patient has had some type of meeting with a genetic counselor, which can be important for general OB/GYN's to be aware.

Response: We agree with the reviewer's suggestion. Statement added to clarify the role of genetic counselors and insurance company reimbursement.

Lines 166-168: Prior to proceeding with genetic testing, a patient is encouraged to pursue pre-test genetic counseling with either a licensed genetic counselor or another genetics professional. Many insurance companies will not pay for genetic testing without genetic counseling as performed by a licensed genetic counselor.

4) Starting at line 286 with subject heading: "Management of women with low (ovarian cancer) penetrance genes" would add a summative statement with recommendations (ie Lynch Syndrome patients should have risk reducing surgery, and/or shared decision making with patients with other gene mutations).

Response: we thank the reviewer for this suggestion. Paragraph has been modified to summarize recommendations for lynch syndrome screening and risk reducing surgery.

Lines 303-312: Genetic mutations in the mismatch repair genes MSH2, MSH6, MLH1 carry an increased risk of ovarian cancer (10-25%) associated with Lynch Syndrome (insufficient evidence for PMS2-associated ovarian cancer risk) and an increased risk of synchronous endometrial and ovarian carcinoma. Since there is no effective screening for ovarian cancer, women should be educated on symptoms that might be associated with the development of ovarian cancer, and that risk-reducing bilateral salpingo-oophorectomy may reduce the incidence of ovarian cancer. Hysterectomy with bilateral salpingo-oophorectomy is recommended for patients with Lynch syndrome. The timing of risk-reducing surgery in patients with Lynch syndrome is individualized based on whether childbearing is complete, comorbidities, menopausal status and Lynch Syndrome pathogenic variant, as risks for endometrial and ovarian cancer vary by gene [39].

Reviewer #3:

This review article is very well written and very comprehensive, focusing on genetic testing associated with breast and ovarian cancer. Overall, it covers many of the common high yield questions with regard to genetic testing, controversies with salpingectomies vs salpingo-oophorectomies, role of hysterectomy in risk reducing surgery and risks associated with the various genetic mutations detected on multigene panels.

Would suggest the following:

1) The areas with regard to ovarian cancer are very well written. I do not have breast cancer screening and management in my practice, therefore critique of these sections should be done with someone with this particular academic expertise. Additionally, breast cancer screening is not done by general OB/GYNs where I practice - if this is

something of high yield in practice in the United States, then this review article would be pertinent. However, if not, then potentially a journal with broader readership (to include general practitioners, family physicians, general surgeons) may be of value.

Response: We thank the reviewer for this suggestion. Breast cancer screening is performed by general OB/GYNs in the United States and there is general interest in breast health and screening within the field of general OB/GYN and primary care.

2) Lines 104-106 - guidelines with regard to genetic testing for all patients with epithelial ovarian cancer regardless of histology - clarify if should be all non-mucinous epithelial ovarian cancers? Or include mucinous due to risk of Lynch?

Response: Statement included to clarify histologic subtypes at risk of ovarian cancer including mucinous ovarian cancer and genetic testing.

Lines 110-113: Although mucinous epithelial ovarian cancer is not associated with BRCA1/BRCA2 and related gene mutations, it can be associated with p53 or KRAS mutations. Therefore multigene panel testing may be of value even among patients with mucinous ovarian carcinoma (NCCN guidelines)

3) Lines 270-271 - "women at risk can be offered screening with transvaginal ultrasound and serum CA-125 starting at age 30-35 years" - Remove this statement, or provide a strong reference to back this up, as this statement is controversial.

Response: The statement has been clarified and an addition made to state" at the discretion of managing physician". Evidence for this statement has been described in prior sentences "In gene carriers at risk for ovarian, fallopian tube and primary peritoneal cancers, targeted multimodal screening using an ultrasound and CA125-based model has been shown to be potentially promising with more women being diagnosed at an earlier stage with lower volume disease based on large population-based studies [36], [37]."

Line 289-300: Women at risk can be offered screening with transvaginal ultrasound and serum CA-125 starting at the age of 30-35 years at the discretion of managing physician [6].

4) Given the title of this review article is on Controversies in Hereditary Cancer Management, in a ob/gyn journal, should include recommendations of when to do hysterectomy for patients with lynch syndrome and recommendations with regard to endometrial biopsies.

Response: A specific section addressing Lynch Syndrome management has been added under Screening and Prevention to address endometrial cancer screening and management. The role of endometrial biopsy and hysterectomy are now discussed.

Lines 316-326: Women with Lynch Syndrome have a 20-60% lifetime risk of endometrial cancer. Surveillance and prevention of endometrial cancer in women with a diagnosis of Lynch syndrome consists of annual gynecologic examinations and education on symptoms, specifically abnormal uterine bleeding or postmenopausal bleeding that would prompt evaluation with endometrial biopsy. Although there is no strong evidence regarding endometrial cancer screening in this population, NCCN guidelines recommend consideration of endometrial biopsy every 1-2 years starting at age 30-35 given the high sensitivity and specificity of diagnostic endometrial biopsies [39]. Transvaginal ultrasound is not recommended as an endometrial cancer screening tool in premenopausal women with Lynch syndrome due to variation in endometrial thickness with menstrual cycle. Hysterectomy can potentially reduce the incidence of endometrial cancer in this patient population [39].

5) Would suggest adding a section on tumor testing for somatic mutations - and the controversies whether tumor testing only is sufficient, or does the patient need both somatic and germline testing if somatic test is negative? Cost-effectiveness of doing both somatic and germline testing or is somatic testing sufficient and only do germline test if somatic positive. Provide percentage of patients who will have a positive mutation in germline testing when somatic test negative.

Response: We appreciate the reviewer's recommendation for including information regarding somatic mutation testing. A sentence has been added to address this in the paper under the section "Universal Testing for Ovarian Cancer". However, we feel that a full discussion of this topic is beyond the scope of the paper.

Lines 110-112: Somatic tumor testing is recommended if germline DNA sequencing is negative, as an additional 5% of women will have a somatic mutation in BRCA or related genes

6) Also would be helpful to add if any data on genetic testing of family members who do not have the disease in question when the original patient with the cancer has already died or not available for genetic testing.

Response: It is recommended that patients with a family history of cancer, including those whose' relatives with cancer have already died, be screened and those who meet criteria (based on Table 1- Who Needs Breast or Ovarian Cancer Genetic Testing) be referred to a licensed genetic counselor or other genetics professional for genetics assessment as discussed in lines 190-197. Based on this assessment and discussion of implications of genetics testing results, testing is conducted.

Date: Dec 14, 2020
To: "Mariam M. AlHilli"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2577R1

RE: Manuscript Number ONG-20-2577R1

Controversies in Hereditary Cancer Management

Dear Dr. AlHilli:

The revised manuscript was evaluated and it needs additional editing before it can be considered. The latest version of the manuscript will be sent to you to work on by email, it is called "20-2577R1 ms (12-11-20v2)". This is the version you should edit, not through Editorial Manager. Please find the Editorial Comments below to respond to in your revision. 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 Dec 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

EDITORIAL COMMENTS:

1. The manuscript needs to be shortened. Please see Editor suggestions to shorten.

2. Provide a précis for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). Please avoid phrases like “This paper presents” or “This case presents.

3. Provide a one-paragraph abstract of not more than 300 words that summarizes your paper. All statements in the abstract must also be contained in the body text for consistency.

4. The paragraph "Testing in special populations..." was crossed out. Do you agree with this change?

5. On page 11, it's hard to justify a paragraph on men and it has been deleted. Do you agree with this change?

6. Line 202: Please reword for clarity.

7. Line 329: Please clarify intent here: DICER1 and STK11 are s/w both Sertoli-Ley and (?) a type of germ cell tumor; or are the author suggesting S-L are a type of germ cell tumor (which would not be accurate).

8. Line 348: Earlier, in line 153 this was described as 16-70%: please be consistent with risk estimates throughout manuscript.

9. On page 28, paragraph "Technical considerations...:" To which guidelines are you referring? Those should be cited here. Add to the References list if needed and renumber the subsequent references in the body text and References list.

10. Conclusions on page 37: Deleted due to overall length of submission and page limit. Do you agree with this change?

11. Box 1: Would you describe how you used these sources to create this table? Was the table reprinted elsewhere?

When 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 Dec 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals
