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)*
- Email correspondence between the editorial office and the authors*

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

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

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

obgyn@greenjournal.org.
RE: Manuscript Number ONG-18-1581

Nomogram Predicting Individual Survival Following Recurrence in Advanced Stage High Grade Ovarian Cancer from NRG/GOG Randomized Trials of Platinum and Paclitaxel

Dear Dr. Rose:

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 Oct 15, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This paper is a retrospective analysis of multiple GOG protocols for stage III and IV ovarian/peritoneal/tubal cancer with the objective "To analyze clinical prognostic factors for survival following recurrence of high grade, advanced stage ovarian/peritoneal/tubal carcinoma and to develop a nomogram to predict individual survival following recurrence." The authors do meet their objective, including the nomogram and details as to how they developed it. The paper, to appeal to general ob/gyn clinicians, should have a stronger focus on clinical implications for patients. As written, the paper is for a gyn one readership. Objective is clearly stated in the abstract and should be stated as clearly in the introduction.

1. Line 35 - what stages of ovarian cancer achieve a complete response? All?
2. Line 37-38 - recur within what time frame
3. Line 39 - please define early stage
4. Line 41 - please define late stage
5. Line 44-46 - reference here please
6. Lines 49-50, 51-53 - references here please also
7. Line 54-59 - please clearly state objective here as it is in the abstract (lines 2-4)
8. Line 65 - what stages were included in trial 182?
9. Line 65-66 - please briefly describe these trials
10. Line 83 - please define what performance status means
11. Line 136 - please explain the difference between a complete clinical response and a pathologic complete response
12. Line 138-141 - please define what is meant here as statistically younger
13. Line 139-140 - why did such a small number of patients receive intraperitoneal chemotherapy
14. Line 155 - what are the % of survival in this range of 9.8-48.5 months?
15. Line 162-163 - Please expand this sentence with more detailed discussion of findings
16. Line 174-175 - please define advanced age
17. Lines 187-188 and 188-189 - references please
18. Line 189-190 - please explain further - is this for all types of ovarian cancer?
19. Line 191-192 - reference please
20. Line 194-195 - reference here and please provide more detail in this sentence
21. Line 195-196 - reference here also
22. Line 198-199 - did patients who recurred >6 months have a DNA repair mutation?

REVIEWER #2:

Thank you for the opportunity to review the manuscript by Rose et al entitled "Nomogram predicting individual overall survival in patients with advanced stage high grade ovarian cancer from NRG/GOG randomized trials of platinum and paclitaxel. The authors utilize a large cohort of patients with ovarian cancer with extended follow up to evaluate the impact of time to recurrence after initial chemotherapy as well as other prognostic variables. A nomogram is developed to predict survival after recurrence in patients treated with platinum and taxane. Overall, data on the incremental increase in survival with longer time to recurrence is well illustrated in this study. Clarifications regarding methodology and use of prognostic factors in the study is needed to make the data more generalizable.

Comments and suggestions:
1. Abstract line 15- specify "time to recurrence following initial treatment/ chemotherapy"
2. Abstract line 17-19- clarify what is meant by "prognostic information". Since creation of the nomogram was an important objective of the study, comment on validity and accuracy of the nomogram in results (i.e. c-index).
3. Introduction Line 37-38: acknowledge that stage is only one of several other well described prognostic factors
4. Line 39 (paragraph) refers to studies on early stage ovarian cancer patients, while the manuscript addresses advanced stage disease. I believe the authors are highlighting the importance of chemotherapy treatment-free interval in early stage disease. Would suggest clarifying this and emphasizing the statement that even in early stage disease, survival may approximate that of advanced stage disease if chemotherapy is not administered.
5. Methods: Line 83-85- delete the word "and" before "tumor histology" and "race"
6. Results line 126: delete "following recurrence" from this line
7. Table 1: will require reformatting as it is unclear in its current form. If data is available for residual disease =0, this data should be included as a subcategory. Recurrence site does not seem to take into account patients who had more than 1 site of recurrence. please clarify
8. Table 2: This table would benefit from reformatting. Specify units for time to recurrence (months). Would also suggest
replacing "x" with " time to recurrence (months). results can be simplified to N, median (95%CI) in 1 or 2 columns

9. Nomogram: histology variable includes other, mixed and clear cell/mucinous only. please clarify how patients with endometrioid or serous histology would be plotted on the current nomogram

10. Discussion/methods: please explain the rationale for using GOG218 control arm as validation cohort?

11. Recommend including residual disease= 0 as a variable in the nomogram and discussion of the relatively low adequacy index/ significance in this model given the importance of this factor and impact on survival.

12. Discussion line 183-184 needs clarification. It appears that intraperitoneal chemotherapy and second look laparotomy were analyzed individually and not included in the actual survival nomogram model (authors state a model was used with fewer patients). Please explain why intraperitoneal chemotherapy and second look laparotomy were not included in the model used to develop the final nomogram (i.e. covariate adjusted Cox survival nomogram).


14. Lines 211-212: change germ-line to gremline

15. Discussion: a comment on the applicability of the nomogram to all patients with ovarian cancer would be important as well as a suggestion for future external validation outside of a clinical trial, since this data is reflective of clinical trial information (selected group of patients with potentially good performance status etc). In addition, discussion of the significance of the nomogram/ model's c-index of 0.67 relative to other prediction models in important.

REVIEWER #3:

Rose et al have retrospectively reviewed the data from multiple ovarian cancer trials to develop a nomogram for survival prediction. Overall the manuscript is very well written, statistical analysis is top-notch and the results/discussion section are very good. However, I have following concerns with the paper:

1- Applicability: I have tried to apply this nomogram to several of the patients in my practice, but according to this nomogram, they should have all been dead long ago. A common scenario of a 65 yo with stage IIIC HGSOC with no residual disease and recurrence at 14 months and a performance status of 0 yields a score of 108 (28 for age, 0 for performance, 0 for histology, 0 for stage, 0 for gross disease and 70 for recurrence interval). According to the nomogram, her median survival time from there on is 15 months. This is clearly an underestimation based on my clinical experience. I would urge the authors to go back to their own practice and try to apply this nomogram to some of their own patients and see if it works. It is correctly developed from the data with great statistical tactic, but not sure if the answer we are getting is the right one.

2- There could be several reasons for this discrepancy. Recent uptake of PARP-I is one cause. In patients with BRCA mutation (~20% of total) we will see 15 months added and in those with HRD (~30-35% of total) at least 9 months. This is not accounted for in these trials.

3- Statistical analysis by its nature, is regression to mean. So many patients who did not do well, are pulling the overall survival down for everyone else. There is an over-reliance on one parameter in this model (recurrence time), measurement of which is very different in trials (multiple scans and frequent CA-125) compared to general clinical practice (q 3months scans are not a norm). So how do we take that into account?

4- Validation Cohort: The authors chose GOG 218 as the validation cohort. A study where initial enrollment only include sub optimally debulked patients (therefore lower overall survival). This study validates the nomogram which underestimates the survival, because of its high-risk patients.

STATISTICAL EDITOR’S COMMENTS:

1. This is a thorough evaluation of a large data set of women who had a recurrence of ovarian cancer to better predict individual survival after recurrence.

2. lines 129-132: Since the time to recurrence offered the most information re: survival, should provide a table of concordance indices that correspond to the full model, then the model with successive removal of age, stage, residual disease, histology and performance status. In other words, although the full model was statistically the best fit, how much practical value was added by each of those variables?

3. I would also strongly suggest an additional figure that I believe would help to show the utility of the model for prediction of individual survival. That is, a calibration plot, as in fig 8 of "Transparent Reporting of a multivariable prediction model for

4. My main objection is the interpretation of the data as showing that the model "can be used to predict subsequent survival with high accuracy" (lines 22-23). The concordance indices, (0.67 on line 147 for the initial data set and 0.65 on line 150-151 for the validation data set) are statistically significant, but offer only moderate ability to predict an individual prognosis. I think that this can be readily seen in Fig 4 by noting the confidence intervals. The analysis certainly is a substantial contribution to understanding the survival following recurrence, but to apply it in an individual case, there must be confidence intervals along with each point estimate, to put them in context.

ASSOCIATE EDITOR - GYN:

Two points came up in collating the comments:

1 - Rev #3 points out the need to scale back some of the more sweeping statements such as line 224 where it is suggested that use of the nomogram can 'accurately predict' survival following recurrence.

2 - That STAT Editor points out that since 86% of the model is based on time to recurrence, what if the nomogram was simplified to just that? Would it be meaningfully different than the current, more complicated model of additional less impactful variables.

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, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Examples of statements can be found online at http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf.

3. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the January 2018 issue). Please note:
   a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.
   b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.
   c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.
   d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

   * Substantial contributions to the conception or design of the work; OR the acquisition, analysis, or interpretation of data for the work; AND
   * Drafting the work or revising it critically for important intellectual content; AND
   * Final approval of the version to be published; AND
   * Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of
any part of the work are appropriately investigated and resolved.

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

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

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

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

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). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

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

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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

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

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

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

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

11. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

12. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com
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.

13. 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.

14. 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.

15. The Journal's Production Editor had the following to say about the figures in this manuscript:

"Figure 1: Please upload a high resolution version of this figure.
Figure 2: Is this available in color and at a higher resolution? The gray line will likely not be legible in print.
Figure 3: Please remove the graph paper background from the figure.
Figure 4: Please upload a high resolution version of this figure.
Figure 5: Please upload a high resolution version of this figure.
For all figures: Please upload as a tiff, eps, or jpeg file. Items pasted into Word often lose resolution and do not reproduce well."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 15, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In response to the EU General Data Protection Regulation (GDPR), you have the right to request that your personal information be removed from the database. If you would like your personal information to be removed from the database, please contact the publication office.

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
October 23, 2018

RE: Manuscript Number ONG-18-1581
Nomogram Predicting Individual Survival Following Recurrence in Advanced Stage High Grade Ovarian Cancer from NRG/GOG Randomized Trials of Platinum and Paclitaxel

Dear Editors of Obstetrics & Gynecology

Thank you for reviewing our manuscript entitled “Nomogram Predicting Individual Survival Following Recurrence in Advanced Stage High Grade Ovarian Cancer from NRG/GOG Randomized Trials of Platinum and Paclitaxel”. In the revised version of the manuscript the authors have addressed the reviewer’s concerns and changes are made in a tracked format. Additionally, this cover letter includes a point by point response to the reviewer’s comments.

REVIEWER COMMENTS:

REVIEWER #1:

This paper is a retrospective analysis of multiple GOG protocols for stage III and IV ovarian/peritoneal/tubal cancer with the objective "To analyze clinical prognostic factors for survival following recurrence of high grade, advanced stage ovarian/peritoneal/tubal carcinoma and to develop a nomogram to predict individual survival following recurrence." The authors do meet their objective, including the nomogram and details as to how they developed it. The paper, to appeal to general ob/gyn clinicians, should have a stronger focus on clinical implications for patients. As written, the paper is for a gyn onc readership. Objective is clearly stated in the abstract and should be stated as clearly in the introduction.

1. Line 35 - what stages of ovarian cancer achieve a complete response? All?
Response: This is clarified in the revised version of the manuscript.

2. Line 37-38 - recur within what time frame
Response: This is clarified in the revised version of the manuscript.

3. Line 39 - please define early stage
Response: In the revised version of the manuscript I have replaced early stage with stage I and stage I and II respectively for the studies that I discuss.

4. Line 41 - please define late stage
Response: In the revised version of the manuscript this is defined on line 35.
5. Line 44-46 - reference here please  
Response: Per the editorial manager “Okay as is; don’t need to repeat citation”.

6. Lines 49-50, 51-53 - references here please also  
Response: Per the editorial manager “Okay as is; don’t need to repeat citation”.

7. Line 54-59 - please clearly state objective here as it is in the abstract (lines 2-4)  
Response: This is more clearly stated in the revised version of the manuscript.

8. Line 65 - what stages were included in trial 182?  
Response: Stage III and IV ovarian cancer. This is clarified in the revised version of the manuscript.

9. Line 65-66 - please briefly describe these trials  
Response: Because of length I don’t think it would be possible to briefly describe these trials and the best thing to do would be to provide table describing these trials as a supplement to the article available electronically Table S1.

10. Line 83 - please define what performance status means  
Response: Performance status is frequently used clinical trials dealing with cancer. In order to make sure the readership is aware of the meaning of performance status I have included (measure of independent functionality) to help describe its role.

11. Line 136 - please explain the difference between a complete clinical response and a pathologic complete response  
Response: I have included definition of complete clinical response as (absence of disease by physical and radiologic exams and biochemical markers) and the definition of a complete pathologic response as (no pathologic evidence of persistent disease on surgical specimens).

12. Line 138-141 - please define what is meant here as statistically younger  
Response: When comparing the ages of 2 groups of patients 1 group of patients was significantly younger which was greater than would be expected by chance alone.

13. Line 139-140 - why did such a small number of patients receive intraperitoneal chemotherapy  
Response: Only 3 of the 8 trials in our study used intraperitoneal chemotherapy and only half the patients of each study were randomized intraperitoneal therapy.

14. Line 155 - what are the % of survival in this range of 9.8-48.5 months?  
Response: The survival in this patient population ranged from 9.8-48.5 months. The median survival which is the point in time where 50% of the patients are alive is 21.4 months.
15. Line 162-163 - Please expand this sentence with more detailed discussion of findings
Response: Hopefully, by adding the word individual to both sentences this is clarified in the revised version of the manuscript.

16. Line 174-175 - please define advanced age
Response: Each decade of life above age 50 is associated with a 6% increase in mortality. (Winter et al. 2007 in References)

17. Lines 187-188 and 188-189 - references please
Response: Per the editorial manager “Okay as is; don’t need to repeat citation”.

18. Line 189-190 - please explain further - is this for all types of ovarian cancer?
Response: There are three primary types of ovarian cancer. Ovarian carcinoma the epithelial component of ovarian cancer is the most common comprising 90%. Other ovarian cancers are germ cell tumors and stromal tumors. This manuscript deals exclusively with epithelial ovarian cancer. Therefore to clarify this in the manuscript I have referred throughout the manuscript to ovarian carcinoma which is the epithelial component of ovarian cancer.

19. Line 191-192 - reference please
Response: This is included please

20. Line 194-195 - reference here and please provide more detail in this sentence
Response:
Authors do need to cite a reference for the sentence, “While the survival for the primary “platinum resistant” patient has been well defined, the survival for patients who recur later is more variable.”

Enclosed is a table from a reference which has now been inserted in the revised version of the manuscript. In the platinum resistant population survival varies by only 3 months while in the platinum sensitive population the variability is 12 months.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Comments</th>
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<tr>
<td>Platinum-free interval</td>
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<td>Platinum-refractory</td>
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<td>Platinum-resistant</td>
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<td>Platinum-sensitive</td>
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</tbody>
</table>

PF= progression free interval OS = overall survival.
Response: Per the editorial manager “No reference needed for the sentence, “This is likely due to the fact that the primary platinum resistant patient is less likely to have a BRCA mutation.” This sentence introduces the next point, which does include a citation.”

22. Line 198-199 - did patients who recurred >6 months have a DNA repair mutation? Response: DNA repair mutations were not evaluated in this clinical trial. However, the study by Allsop suggests that patients who had BRCA mutations or less likely (disease progression within 6 months 14.9% compared to 31.7% for those who do not carry mutations).

REVIEWER #2:

Thank you for the opportunity to review the manuscript by Rose et al entitled "Nomogram predicting individual overall survival in patients with advanced stage high grade ovarian cancer from NRG/GOG randomized trials of platinum and paclitaxel. The authors utilize a large cohort of patients with ovarian cancer with extended follow up to evaluate the impact of time to recurrence after initial chemotherapy as well as other prognostic variables. A nomogram is developed to predict survival after recurrence in patients treated with platinum and taxane. Overall, data on the incremental increase in survival with longer time to recurrence is well illustrated in this study. Clarifications regarding methodology and use of prognostic factors in the study is needed to make the data more generalizable.

Comments and suggestions:

1. Abstract line 15- specify "time to recurrence following initial treatment/ chemotherapy"
Response: This is corrected in the revised version of the manuscript.

2. Abstract line 17-19- clarify what is meant by "prognostic information". Since creation of the nomogram was an important objective of the study, comment on validity and accuracy of the nomogram in results (i.e. c-index).
Response: This is included in the revised version of the manuscript.

3. Introduction Line 37-38: acknowledge that stage is only one of several other well described prognostic factors
Response: This is corrected in the revised version of the manuscript.

4. Line 39 (paragraph) refers to studies on early stage ovarian cancer patients, while the manuscript addresses advanced stage disease. I believe the authors are highlighting
the importance of chemotherapy treatment-free interval in early stage disease. Would suggest clarifying this and emphasizing the statement that even in early stage disease, survival may approximate that of advanced stage disease if chemotherapy is not administered.

Response: This is corrected in the revised version of the manuscript.

5. Methods: Line 83-85- delete the word "and" before "tumor histology" and "race"
Response: This is corrected in the revised version of the manuscript.

6. Results line 126: delete "following recurrence" from this line
Response: Does the reviewer mean “The median survival following recurrence stratified by time to recurrence” I want to keep the following recurrence in to clarify that is not the total survival from the original diagnosis.

7. Table 1: will require reformatting as it is unclear in its current form. If data is available for residual disease =0, this data should be included as a subcategory. Recurrence site does not seem to take into account patients who had more than 1 site of recurrence. Please clarify
Response: We’ve redone the model to include R0 residual disease; it doesn’t change the results much, but it adds a new choice to the nomogram. It is important to note that the adequacy indices do not add up to exactly 1.00 because of correlation between some of the variables. “Recurrence site” means site of primary recurrence, since some studies only had that data available. We’ve corrected the name to “Primary recurrence site” in Table 1.

8. Table 2: This table would benefit from reformatting. Specify units for time to recurrence (months). Would also suggest replacing "x" with "time to recurrence (months). Results can be simplified to N, median (95%CI) in 1 or 2 columns
Response: X is replaced with time to recurrence of months and the table has been reformatted according to your suggestions.

9. Nomogram: histology variable includes other, mixed and clear cell/mucinous only. Please clarify how patients with endometrioid or serous histology would be plotted on the current nomogram
Response: In the current manuscript they would be listed as other. In the revised manuscript other has been changed to serous or endometrioid histologies.

10. Discussion/methods: please explain the rationale for using GOG218 control arm as validation cohort?
Response: We chose to obtain a population of patients treated with standard chemotherapy with carboplatin and paclitaxel which were not part of our original study cohort. The control arm of GOG 218 met these criteria.
11. Recommend including residual disease= 0 as a variable in the nomogram and
discussion of the relatively low adequacy index/ significance in this model given the
importance of this factor and impact on survival.
**Response:** As mentioned in #7, we’ve added R0 to the model & nomogram.

12. Discussion line 183-184 needs clarification. It appears that intraperitoneal
chemotherapy and second look laparotomy were analyzed individually and not included
in the actual survival nomogram model (authors state a model was used with fewer
patients). Please explain why intraperitoneal chemotherapy and second look laparotomy
were not included in the model used to develop the final nomogram (i.e. covariate
adjusted Cox survival nomogram).
**Response:** Patients who received intraperitoneal chemotherapy and second look
laparotomy were included in the original nomogram. The impact of
intraperitoneal chemotherapy and second look laparotomy were analyzed to see
what impact they would have on the nomogram and there was no significant
impact.

13. Discussion line 189-191: Germline (one word). Also suggest including reference by
Walsh et al, PNAS, 2011 for specific gene mutations. "Homologous DNA repair
mutations" should be replaced with homologous recombination mutations for technical
correctness.
**Response:** This is corrected in the revised version of the manuscript.

14. Lines 211-212: change germ-line to germline
**Response:** This is corrected in the revised version of the manuscript.

15. Discussion: a comment on the applicability of the nomogram to all patients with
ovarian cancer would be important as well as a suggestion for future external validation
outside of a clinical trial, since this data is reflective of clinical trial information (selected
group of patients with potentially good performance status etc). In addition, discussion
of the significance of the nomogram/ model's c-index of 0.67 relative to other prediction
models in important.
**Response:** This is included in the current version of the manuscript.

**REVIEWER #3:**

Rose et al have retrospectively reviewed the data from multiple ovarian cancer trials to
develop a nomogram for survival prediction. Overall the manuscript is very well written,
statistical analysis is top-notch and the results/discussion section are very good.
However, I have following concerns with the paper:

1- Applicability: I have tried to apply this nomogram to several of the patients in my
practice, but according to this nomogram, they should have all been dead long ago. A
common scenario of a 65 yo with stage IIIC HGSOC with no residual disease and
recurrence at 14 months and a performance status of 0 yields a score of 108 (28 for
age, 0 for performance, 0 for histology, 0 for stage, 0 for gross disease and 70 for recurrence interval). According to the nomogram, her median survival time from there on is 15 months. This is clearly an underestimation based on my clinical experience. I would urge the authors to go back to their own practice and try to apply this nomogram to some of their own patients and see if it works. It is correctly developed from the data with great statistical tactic, but not sure if the answer we are getting is the right one.

Response: The manuscript’s nomogram was internally and externally validated.

2- There could be several reasons for this discrepancy. Recent uptake of PARP-I is one cause. In patients with BRCA mutation (~20% of total) we will see 15 months added and in those with HRD (~30-35% of total) at least 9 months. This is not accounted for in these trials.

Response: It’s true that we haven’t accounted for a number of factors that could affect survival, but unfortunately we’ve aggregated here older trials with a more or less standard set of clinical data that doesn’t include the factors you’ve mentioned. We’ve made every effort, however, to use all the data we have as effectively as possible. This weakness is added to the discussion.

3- Statistical analysis by its nature, is regression to mean. So many patients who did not do well, are pulling the overall survival down for everyone else. There is an over-reliance on one parameter in this model (recurrence time), measurement of which is very different in trials (multiple scans and frequent CA-125) compared to general clinical practice (q 3months scans are not a norm). So how do we take that into account?

Response: We would characterize this not as over-reliance, but rather as a legitimate result of the modeling process on our data. The final model does include a number of other clinical variables, and it attempts to account for trial differences with a trial stratification variable.

4- Validation Cohort: The authors chose GOG 218 as the validation cohort. A study where initial enrollment only include sub optimally debulked patients (therefore lower overall survival). This study validates the nomogram which underestimates the survival, because of its high-risk patients.

Response: The data set used to create the models includes 65% optimally debulked (R0 & R1) patients, so we are able to model both optimal and suboptimal debulking; that is to say, we’re able to account for R0, R1, & R2 (> 1 cm) so that survival isn’t underestimated for any group. Though the 218 cohort was initially all suboptimally debulked patients, it later added optimal patients; the modeled survival should be accurate for its patients (in the context of the data used to create the model).

STATISTICAL EDITOR’S COMMENTS:

1. This is a thorough evaluation of a large data set of women who had a recurrence of ovarian cancer to better predict individual survival after recurrence.

Response: Thank you.
2. lines 129-132: Since the time to recurrence offered the most information re: survival, should provide a table of concordance indices that correspond to the full model, then the model with successive removal of age, stage, residual disease, histology and performance status. In other words, although the full model was statistically the best fit, how much practical value was added by each of those variables?

Response: We've attempted to convey similar information in lines 140–43 using the so-called adequacy index, which is "useful for quantifying the predictive information contained in a subset of the predictors compared with the information contained in the entire set of predictors" (Harrell 2015 in References): "The 'adequacy index' for time to recurrence alone was A = 0.86, which means time to recurrence accounted for 86% of the prognostic information, with the other factors accounting for much less. In decreasing order of significance were performance status, histology, residual disease, stage and age, which had adequacy indices of 0.061, 0.059, 0.054, 0.037, and 0.032, respectively."

3. I would also strongly suggest an additional figure that I believe would help to show the utility of the model for prediction of individual survival. That is, a calibration plot, as in fig 8 of "Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and Elaboration" by K.G.M. Moons, D.G. Altman, J.B. Reitsma, J.P.A. Lonnidis, P. Macaskill, E.W. Steyerberg, A.J. Vickers, D. F. Ransohoff and G.S. Collins, Annals of Internal Medicine 2015:162:W1-W73.

Response: We've actually included a calibration plot as Figure 4, which I'll reproduce here:
Caption: Calibration curve for the OS nomogram model. The dotted line represents an ideal nomogram; the solid line, the observed nomogram. The vertical bars are 95% CIs, and the ×’s are bias-corrected estimates.

(And thank you for the TRIPOD reference, which I was unaware of until now.)

4. My main objection is the interpretation of the data as showing that the model "can be used to predict subsequent survival with high accuracy" (lines 22-23). The concordance indices, (0.67 on line 147 for the initial data set and 0.65 on line 150-151 for the validation data set) are statistically significant, but offer only moderate ability to predict an individual prognosis. I think that this can be readily seen in Fig 4 by noting the confidence intervals. The analysis certainly is a substantial contribution to understanding the survival following recurrence, but to apply it in an individual case, there must be confidence intervals along with each point estimate, to put them in context.

Response: We agree that that language is somewhat too sanguine about the model’s predictive ability; it’s toned down in the corrected version of the MS.

ASSOCIATE EDITOR - GYN:

Two points came up in collating the comments:
1 - Rev #3 points out the need to scale back some of the more sweeping statements such as line 224 where it is suggested that use of the nomogram can 'accurately predict' survival following recurrence.
Response: We agree that some of this language is over-enthusiastic, and have toned it down the current version of the MS.

2 - That STAT Editor points out that since 86% of the model is based on time to recurrence, what if the nomogram was simplified to just that? Would it be meaningfully different than the current, more complicated model of additional less impactful variables.
Response: We think that we've created the best model using the available data, a process that included removing the least significant factors so as to simplify the nomogram as much as possible. While we could promote a model created with only the time to recurrence, the results are different and not so good a fit as the reduced model. Since the clinical factors included in the model are typically readily available, we think we should promote the best-fit model available from the data.

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, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.
Response: OPT-IN

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Examples of statements can be found online at http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf.
Response: The Data sharing agreement is on the NRG web site.

"To outline the general policies for sharing data from National Cancer Institute (NCI) funded trials conducted by NRG Oncology for an investigator's independent use without involvement of
NRG Oncology support of any type. The procedures outlined in this policy do not apply to requests from the NCI or the Food and Drug Administration (FDA). Those requests are handled administratively and as expeditiously as possible. This policy only covers requests for existing data, not requests for use of tissue or for the collection of additional data.”

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

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.
   Response: None exist.

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

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.
   Response: This is included as an attachment.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):
   Response: All authors have met requirements and have completed the disclosure forms.

* Substantial contributions to the conception or design of the work; OR the acquisition, analysis, or interpretation of data for the work; AND
* Drafting the work or revising it critically for important intellectual content; AND
* Final approval of the version to be published; AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

Response: This is included in the cover letter.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

Response: The manuscript conformed to these standard definitions.

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). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

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

Response: The manuscript conformed to these requirements.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

Response: The manuscript conformed to these requirements.

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

Response: The manuscript conformed to these requirements.

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.

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

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.
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In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words Please provide a word count.
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11. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.
Response: The manuscript conformed to these requirements.

12. 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.
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15. The Journal's Production Editor had the following to say about the figures in this manuscript:

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Figure 3: Please remove the graph paper background from the figure.
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Figure 4: Please upload a high resolution version of this figure.
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Figure 5: Please upload a high resolution version of this figure.
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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.

Hopefully, the revised version of the manuscript is more acceptable. Please do not hesitate to contact us if you have any further questions.

Sincerely,

Peter G. Rose, M.D.

James Java, Ph.D.
Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
The American College of Obstetricians and Gynecologists

Please see the letter of response regarding this manuscript which is attached to this email.

Please don’t hesitate to contact me if you have any further questions.

Peter Rose M.D.

-----Original Message-----
From: Daniel Mosier <dmosier@greenjournal.org>
To: rosepeterg@aol.com
Sent: Fri, Nov 2, 2018 3:51 pm
Subject: Manuscript Revisions: ONG-18-1581R1

Dear Dr. Rose,

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

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 1: The title is quite long. Are you okay with this shortened version? Our guideline for titles is 100 characters.
3. LINE 3: The following authors have not responded to the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed each author at the corresponding addresses below– are these the correct email addresses?
   • James J Java:
   • Ritu Salani:
   • Angeles Alvarez Secord:
   • Linda Van Le:
   • Larry J Copeland:
4. LINE 5: The Author Agreement form for Linda Van Le is incomplete. She did not indicate that she drafted the work, nor did she indicate she agrees to be held accountable for all aspects of the work. If this was an error, submit an updated Author Agreement with the correct boxes checked. If this was not an error, she doesn’t meet the requirements for authorship. Her name should be removed from the byline and added to an acknowledgment (“The authors thank…”).
5. LINE 8: Please submit an Author Agreement form for Larry J Copeland with both the “Disclosure of Potential Conflicts of Interest” and “Authorship” sections completed.
6. LINE 128: Did you receive IRB approval? If so, please add that information here.

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the “Accept all Changes” function in Microsoft Word.
Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Wednesday, November 7th.**

Sincerely,
Daniel Mosier

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**Daniel Mosier**  
Editorial Assistant  
*Obstetrics & Gynecology*  
The American College of Obstetricians and Gynecologists  
409 12th Street, SW  
Washington, DC 20024  
Tel: 202-314-2342  
Fax: 202-479-0830  
E-mail: dmosier@greenjournal.org  
Web: [http://www.greenjournal.org](http://www.greenjournal.org)
Stephanie

The nomogram figure 3 should be edited to replace R0 with none, R1 with ≤ 1 cm, R2 to > 1 cm. And serous and endometrioid needs to be shifted to the left. Otherwise figures as edited are OK. I have cc my co author but if you're able to do this please text me at [redacted]. In this case he will not need to do this. Thank you for your help.

Peter Rose

-----Original Message-----
From: Stephanie Casway <SCasway@greenjournal.org>  
To: [redacted]  
Sent: Tue, Oct 30, 2018 8:15 am  
Subject: O&G Figure Revision: 18-1581

Good Morning Dr. Rose,

Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes. In addition, please see our query below.

AQ1: The symbol indicating bias-corrected estimates in the legend for Figure 4 didn’t come through in our version of Word. Please confirm that “open circles” is correct.

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

To avoid a delay, I would be grateful to receive a reply no later than Thursday, 11/1. Thank you for your help.

Best wishes,

Stephanie Casway, MA  
Production Editor  
Obstetrics & Gynecology  
American College of Obstetricians and Gynecologists  
409 12th St, SW  
Washington, DC 20024  
Ph: (202) 314-2339  
Fax: (202) 479-0830  
scasway@greenjournal.org