PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Molecular classification and future therapies for endometrial cancer
AUTHORS	Corr, Bradley; Cosgrove, Casey; Spinosa, Daniel; Guntupalli, Saketh

VERSION 1 - REVIEW

REVIEWER 1	Erickson, Britt, University of Minnesota System. Competing Interest: Research funding from Clovis Oncology. Consulting fees from Natera
REVIEW RETURNED	07-Jun-2022

GENERAL COMMENTS	Very thorough manuscript with attention to detail. Strong and relevant discussion of the TCGA categories and the potential clinical/therapeutic implications. Some big points to consider: 1. In general, the title “Advances in the Management of Endometrial Cancer” does not quite capture what is written. This paper seems more to be about the molecular classifications of endometrial cancer and targeted (biomarker driven) therapy. Consider changing the title to reflect that the focus of this manuscript is on targeted therapy based on molecular classification. However, if the goal of the manuscript is to truly describe advances in management , then some acknowledgement of surgery (namely sentinel LND) should be mentioned. I would also consider discussion of things such as fertility preservation, ovarian preservation, etc. 2. Given that uterine cancer is a cancer with such alarming racial disparities, I think it is imperative to at least mention this in the manuscript . The question remains – do molecular differences drive these disparities or not? And if so, what should we do and if not, what should we do? Until we improve the notable difference in outcome between white and non-white (namely, Black) women, we are not making ‘advances’. It would be worth mentioning the representation (or lack there of) of non-white patients in the TCGA data set. One recent publication to consider is https://pubmed.ncbi.nlm.nih.gov/35490034/ although there are many others. 3. I would strongly consider limiting the detailed text regarding future trials and just references the very nice tables you have developed. This will help the ‘ongoing/future’ trials read better but still have all the necessary information available to the reader. 4. The organization could improve to improve readability. For example, I would recommend discussing HRD/PARP and HER2/trastuzumab in one place in the manuscript, you have it

	mentioned in multiple places which is a bit redundant. I think the best place would be after your description of the 4 subtypes. 5. The TCGA has done a separate molecular analysis of carcinosarcoma, as these were not included in the original subset. I think a quick discussion on carcinosarcoma, its possible molecular drivers and future therapy (there are MMMT specific trials currently ongoing) is warranted in order to be comprehensive regarding endometrial cancer. Specific points to consider: Abstract: Consider changing “endometrial cancer analysis” – unclear what ‘analysis’ means here. Consider also mentioning endocrine/hormonal treatment too. (along with chemo, radiation, surgery) Background: - Consider replacing ‘Western World’ with the regions you are actually referring to. - Consider a worldwide incidence for this journal. - Seems to be lacking any mention of histologic types – at least something simple like endometrioid is the most common histology and then at least list the other subtypes (or refer to a table) would be informative and appropriate here. Uterine Histopathologic Status: Consider shortening this section and not mentioning the details of the studies here. This is less relevant to your manuscript (if the focus is truly future molecular driven therapies). A brief summary of the ‘traditional’ risk factors that drive adjuvant decision is all you really need here. Page 5: MMR-deficient tumors section. Probably worth at least mentioning the benefits seen in colorectal cancer with PDL1/PD1 therapy and that endometrial cancer seems to be following along and is being studied in upfront strategies as well (especially given the recent NEJM data regarding the 100% CR rate for locally advanced dMMR rectal cancer). You could also discuss this in the future trials section Would also mention that dMMR tumors, although they respond to IO, do have a worse prognosis and have higher recurrence rates. Despite similar mechanisms for PD1 efficacy (high neoantigens), dMMR have a much worse prognosis compared to POLE. Page 5, Consider parenthesis line 44-46 when describing MOA of lenvatinib COPY NUMBER HIGH (page 6) Lines 17-22: Simplify/clarify. I think what you are saying is that this molecular category extended beyond histologically ‘serous’ tumors (aka the TCGA broke down traditional histologic silos) and included 14 endometrioid tumors The discussion about HER2 targeted therapy and PARPi here seems a little bit out of place, and the information about HER2 is

	duplicated. Consider introducing the concepts of targeted therapy within the CNH subtype in a way that helps this 'flow' better For example, HRD and HER2 could be subheadings within CNH (or PARP-i and HER2 targeting agents) HER-2/Neu: Consider changing to "HER2" throughout. Change Trastuzumab to trastuzumab Regarding phase II data, would also mention that patients received trastuzumab maintenance therapy. Page 8, line 8: Would change "amplification" to "overexpression/amplification" or just "positive". Would change "this combination" to "chemotherapy plus HER2 targeting agents", given that this trial also has a pertuzumab/trastuzumab arm. If time/space allows could mention that ADCs are being studied in recurrence disease and may be another option for HER2+ recurrent disease. NSMP: Line 21, would reference Figure 1 again to demonstrate how this becomes the default NOS type category. Line 25: 'largely' is confusing here. Large tumors? Or primarily lower grade tumors. Lines 24-14: Consider removing/limiting phrases such as "For Instance" "As such" "Furthermore" "Similarly" "Additionally" Lines 43-46: Consider simplifying this, very wordy as written. Briefly make the point that this class of tumors may have more susceptibility to hormone/endocrine therapy Change "hormone therapy" to "endocrine therapy" when discussing AIs. Final paragraph line 6-13 is a bit contradictory. On one hand you are saying that we need better (and new) stratification given that some NSMP tumors have poor prognosis, then you mentioned the continued importance of the 'traditional…risk factor'. I would argue that treating with these traditional clinical/path risk factors has actually not been particularly effective. The Future of Molecular analysis Page 9, Line 21: delete "as described above" delete "our" Page 9, Line 35: change "along this pathway" to "targeting this pathway" Page 9, Line 36: Delete "which is a" Page 10, Line 7 Delete "but in the meantime could influence counseling" Unclear what is different between the heading "The Future of Molecular Analysis" and "Future Therapies" . I would consider changing "The Future of Molecular Analysis" to something like "Additional biomarker directed therapies". Consider including the discussion of HER2/trastuzumab and HRD/PARP in this section and removing it from the CNH section. FUTURE THERAPIES: What is this section trying to say? These first 2 paragraphs do not add anything and stylistically are concerning. Consider shortening this to 1-2 sentences to introduce the concepts of ongoing clinical trials.

	Primary adjuvant therapy: I would recommend careful review and style editing of this section. Many things can be shortened and condensed for easier reading. Additionally, some of the language is too colloquial. For example: Page 10 line 45: delete “to understand if this therapy is advantageous” Page 10 line 46: for example, could change to “GY020 evaluates the addition of one year of pembrolizumab in addition to radiation therapy in patients with early stage dMMR tumors. The trial addresses the distant recurrence risk of the HIR population in addition to the potential synergistic and abscopal effects of pembrolizumab and radiation therapy” This could be a place to also mention the encouraging data in dMMR rectal cancers Page 10, line 53. Delete the sentence “The largest question to be answered…” as this is really just an opinion. GY018 has 5 years of pembro? I think it is only about 14 cycles, so please double check this. Also, this is too much detail for this manuscript, I would just note that times of maintenance IO vary among trials and/or refer to tables. Page 11 Line 11: Change “adds in” to “includes” Page 11, line 14. Would not ask a question here. Just state “Multiple ongoing trials are challenging the paradigm of adjuvant chemotherapy in endometrial cancer”, or something to that effect. Page 11, line 17. Rewrite sentence “The eligibility criteria for this trial…” In general, this paragraph could be a much quicker summary of LEAP-001, GOG3064. Maintenance therapy: Page 11 Line 36, delete “relatedly” Page 11 Line 42: Delete “SOC” Page 11 line 51: Lower prevalence of what? Page 12 Line 5: I would consider deleting the line about “first approved” Conclusions: remove first person language. Last line is confusing. Our ability? Change to something about now having more options and likely will have more options in the future.

REVIEWER 2	Slomovitz, Brian, Mount Sinai Medical Center, Gynecologic Oncology. Competing Interest: None
REVIEW RETURNED	09-Jun-2022

GENERAL COMMENTS	very well written. no comments to the information in the article may want to comment on the Paleo study and Panos' study on cdk 4/6 also may want to expand on the Siendo data now that it is availablee there is longer term follow up on Garnet that you may want to include re: future therapies, may consider adding GY-026, ADC-Her2, SERDs, Zentalis wee-1

REVIEWER	Eskander, Ramez. Competing Interest: None
REVIEW RETURNED	06-Jul-2022

GENERAL COMMENTS	I would like to thank the editorial office for their kind invitation to review the manuscript submitted by Corr et al. The authors provide a comprehensive review of endometrial cancer treatment and evolving treatment approaches that are biomarker based. In the POLE section of the manuscript, would the authors advocate that immune checkpoint inhibitors replace chemotherapy as the standard of care? We are currently exploring this in dMMR patients, but POLE is distinct from dMMR…perhaps this should be mentioned. In the copy number high section, the authors may want to discuss the GOG 86P publication reporting on concordance of p53 IHC and NGS assessments (88% concordance; Thiel et al. J Clin Oncol 2022). In the Her2 section, I would also comment on the potential frequency of Her2+ in clear cell and carcinosarcomas (~15% each)…given limited therapeutic options for these patients. If the authors think it would be of interest, I would also discuss hormonal combination treatments including exploration of cdk4/6 inhibtors in the NSMP section. This may be particularly relevant given the PALEO data as well as the data shared by Dr. Konstantinopolis et al at SGO 2022 (low grade, p5S wt, endometrioid histology). I know this is mentioned in the future directions section, but may fit nicely into the NSMP. Kudos to the authors for an excellent and well written review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Very thorough manuscript with attention to detail. Strong and relevant discussion of the TCGA categories and the potential clinical/therapeutic implications.

Some big points to consider:

1. In general, the title “Advances in the Management of Endometrial Cancer” does not quite capture what is written. This paper seems more to be about the molecular classifications of endometrial cancer and targeted (biomarker driven) therapy. Consider changing the title to reflect that the focus of this manuscript is on targeted therapy based on molecular classification. However, if the goal of the manuscript is to truly describe advances in management , then some acknowledgement of surgery (namely sentinel LND) should be mentioned. I would also consider discussion of things such as fertility preservation, ovarian preservation, etc.

- Thank you, the authors agree and the initial title of this manuscript was “Molecular classification and future therapies for endometrial cancer.” This was changed by BMJ and we will reopen the conversation with them to accurately reflect the manuscript.

2. Given that uterine cancer is a cancer with such alarming racial disparities, I think it is imperative to at least mention this in the manuscript . The question remains – do molecular differences drive these disparities or not? And if so, what should we do and if not, what should we do? Until we improve the notable difference in outcome between white and non-white (namely, Black) women, we are not making ‘advances’. It would be worth mentioning the representation (or lack there of) of non-white patients in the TCGA data set. One recent publication to consider is https://pubmed.ncbi.nlm.nih.gov/35490034/ although there are many others.

- Thank you for this excellent comment. Racial disparities in uterine cancer, and specifically related to molecular analysis of disparities and outcomes is an extremely important topic. However, we respectfully feel that this topic does not fit into the scope of this paper. While we do discuss TCGA outcomes, we feel our manuscript does not rely solely on the TCGA and is also more related to the molecular classifications and potential therapies, rather than outcomes populations.

3. I would strongly consider limiting the detailed text regarding future trials and just references the very nice tables you have developed. This will help the ‘ongoing/future’ trials read better but still have all the necessary information available to the reader.

- Thank you, the scope of this review paper from the requesting journal was to largely focus on future therapies.

4. The organization could improve to improve readability. For example, I would recommend discussing HRD/PARP and HER2/trastuzumab in one place in the manuscript, you have it mentioned in multiple places which is a bit redundant. I think the best place would be after your description of the 4 subtypes.

- Thank you for this comment on readability. We appreciate your comments and have adjusted the manuscript per your recommendations.

5. The TCGA has done a separate molecular analysis of carcinosarcoma, as these were not included in the original subset. I think a quick discussion on carcinosarcoma, its possible molecular drivers and future therapy (there are MMMT specific trials currently ongoing) is warranted in order to be comprehensive regarding endometrial cancer.

- Thank you, we agree that a review of uterine carcinosarcoma molecular analysis and related treatment specific trials would be a more comprehensive analysis of uterine cancers. However, due to spacial constraints and consideration that our manuscript is organized on molecular subtypes instead of histological subtypes we have elected to exclude this from the manuscript.

Specific points to consider:

Abstract: Consider changing “endometrial cancer analysis” – unclear what ‘analysis’ means here. Consider also mentioning endocrine/hormonal treatment too. (along with chemo, radiation, surgery)

- Thank you for this comment, the abstract has been updated with your suggestions

Background:

- Consider replacing ‘Western World’ with the regions you are actually referring to.

- Consider a worldwide incidence for this journal.

- Seems to be lacking any mention of histologic types – at least something simple like endometrioid is the most common histology and then at least list the other subtypes (or refer to a table) would be informative and appropriate here.

- Thank you for these comments and suggestions. We have incorporated the global statistics as well as adjusted several of your language points

Uterine Histopathologic Status: Consider shortening this section and not mentioning the details of the studies here. This is less relevant to your manuscript (if the focus is truly future molecular driven therapies). A brief summary of the ‘traditional’ risk factors that drive adjuvant decision is all you really need here.

- Thank you, this section has been shortened as recommended

Page 5:

MMR-deficient tumors section. Probably worth at least mentioning the benefits seen in colorectal cancer with PDL1/PD1 therapy and that endometrial cancer seems to be following along and is being studied in upfront strategies as well (especially given the recent NEJM data regarding the 100% CR rate for locally advanced dMMR rectal cancer). You could also discuss this in the future trials section

- While clinically interesting, we feel incorporating other tumor type responses are not as relevant in this manuscript.

Would also mention that dMMR tumors, although they respond to IO, do have a worse prognosis and have higher recurrence rates. Despite similar mechanisms for PD1 efficacy (high neoantigens), dMMR have a much worse prognosis compared to POLE.

- Thank you, while the prognostic implications of the 4 molecular subgroups is highly important, we have chosen to focus our limited space without diving significantly into prognosis.

Page 5, Consider parenthesis line 44-46 when describing MOA of lenvatinib

- This has been added

COPY NUMBER HIGH (page 6)

Lines 17-22: Simplify/clarify. I think what you are saying is that this molecular category extended beyond histologically ‘serous’ tumors (aka the TCGA broke down traditional histologic silos) and included 14 endometrioid tumors

- This has been edited and we agree. We hope clarity has been provided in the edits

The discussion about HER2 targeted therapy and PARPi here seems a little bit out of place, and the information about HER2 is duplicated. Consider introducing the concepts of targeted therapy within the CNH subtype in a way that helps this ‘flow’ better For example, HRD and HER2 could be subheadings within CNH (or PARP-i and HER2 targeting agents)

- We have adjusted the order to improve readability as noted in the above comment

HER-2/Neu: Consider changing to “HER2” throughout. Change Trastuzumab to trastuzumab

Regarding phase II data, would also mention that patients received trastuzumab maintenance therapy.

- These have been corrected

Page 8, line 8: Would change “amplification” to “overexpression/amplification” or just “positive”. Would change “this combination” to “chemotherapy plus HER2 targeting agents”, given that this trial also has a pertuzumab/trastuzumab arm.

- These have been corrected

If time/space allows could mention that ADCs are being studied in recurrence disease and may be another option for HER2+ recurrent disease.

- We also agree this is a promising new drug class being evaluated, but due to limitations in space we hope to incorporate this into future publications.

NSMP:

Line 21, would reference Figure 1 again to demonstrate how this becomes the default NOS type category.

Line 25: ‘largely’ is confusing here. Large tumors? Or primarily lower grade tumors.

Lines 24-14: Consider removing/limiting phrases such as “For Instance” “As such” “Furthermore” “Similarly” “Additionally”

Lines 43-46: Consider simplifying this, very wordy as written. Briefly make the point that this class of tumors may have more susceptibility to hormone/endocrine therapy

Change “hormone therapy” to “endocrine therapy” when discussing AIs.

Final paragraph line 6-13 is a bit contradictory. On one hand you are saying that we need better (and new) stratification given that some NSMP tumors have poor prognosis, then you mentioned the continued importance of the ‘traditional…risk factor’. I would argue that treating with these traditional clinical/path risk factors has actually not been particularly effective.

- Thank you, your comments/edits have all been incorporated

The Future of Molecular analysis

Page 9, Line 21: delete “as described above” delete “our”

Page 9, Line 35: change “along this pathway” to “targeting this pathway”

Page 9, Line 36: Delete “which is a”

Page 10, Line 7 Delete “but in the meantime could influence counseling”

- Thank you, your comments/edits have all been incorporated

Unclear what is different between the heading “The Future of Molecular Analysis” and “Future Therapies” . I would consider changing “The Future of Molecular Analysis” to something like “Additional biomarker directed therapies”. Consider including the discussion of HER2/trastuzumab and HRD/PARP in this section and removing it from the CNH section.

- Thank you for this comment. We would like to keep the current section headings as is and prefer to keep the HER2/trastuzumab data in CNH group as it is currently a therapeutic agent

widely used for advanced stage disease, while this section is dedicated more to molecular analysis beyond the TCGA without current widely used agents.

FUTURE THERAPIES:

What is this section trying to say? These first 2 paragraphs do not add anything and stylistically are concerning. Consider shortening this to 1-2 sentences to introduce the concepts of ongoing clinical trials.

Primary adjuvant therapy: I would recommend careful review and style editing of this section. Many things can be shortened and condensed for easier reading. Additionally, some of the language is too colloquial. For example:

Page 10 line 45: delete “to understand if this therapy is advantageous”

Page 10 line 46: for example, could change to “GY020 evaluates the addition of one year of pembrolizumab in addition to radiation therapy in patients with early stage dMMR tumors. The trial addresses the distant recurrence risk of the HIR population in addition to the potential synergistic and abscopal effects of pembrolizumab and radiation therapy” This could be a place to also mention the encouraging data in dMMR rectal cancers

Page 10, line 53. Delete the sentence “The largest question to be answered…” as this is really just an opinion.

GY018 has 5 years of pembro? I think it is only about 14 cycles, so please double check this. Also, this is too much detail for this manuscript, I would just note that times of maintenance IO vary among trials and/or refer to tables.

Page 11 Line 11: Change “adds in” to “includes”

Page 11, line 14. Would not ask a question here. Just state “Multiple ongoing trials are challenging the paradigm of adjuvant chemotherapy in endometrial cancer”, or something to that effect.

Page 11, line 17. Rewrite sentence “The eligibility criteria for this trial…”

In general, this paragraph could be a much quicker summary of LEAP-001, GOG3064.

- Thank you, your comments have been implemented and this section has been edited and we hope it improves the readability.

Maintenance therapy:

Page 11 Line 36, delete “relatedly”

Page 11 Line 42: Delete “SOC”

Page 11 line 51: Lower prevalence of what?

Page 12 Line 5: I would consider deleting the line about “first approved”

- Thank you, these edits have been incorporated

Conclusions: remove first person language. Last line is confusing. Our ability? Change to something about now having more options and likely will have more options in the future.

- Thank you, these edits have been incorporated

Reviewer: 2

Comments to the Author

very well written. no comments to the information in the article

may want to comment on the Paleo study and Panos' study on cdk 4/6

also may want to expand on the Siendo data now that it is availablee

there is longer term follow up on Garnet that you may want to include

re: future therapies, may consider adding GY-026, ADC-Her2, SERDs, Zentalis wee-1

thanks for allowing me to review

- Thank you for your thoughtful review and recommendations. Updated data from ASCO2022 has been added to lines *** regarding the SIENDO trial. We have also added information regarding the PALEO study as well as the Abameciclib/letrozole trial presented at SGO 2022 as recommended by you and reviewer 3 in the NSMP section. We have also acknowledged GY026 in the HER2 section. In the interest of space we have acknowledged that other wee1 inhibitors are in trial, but have elected to describe the information on adovosertib due to there being more published data with this agent. We hope we have addressed your recommendations adequately.

Reviewer: 3

Comments to the Author

I would like to thank the editorial office for their kind invitation to review the manuscript submitted by Corr et al. The authors provide a comprehensive review of endometrial cancer treatment and evolving treatment approaches that are biomarker based.

In the POLE section of the manuscript, would the authors advocate that immune checkpoint inhibitors replace chemotherapy as the standard of care? We are currently exploring this in dMMR patients, but POLE is distinct from dMMR…perhaps this should be mentioned.

- Thank you for this comment. Our current manuscript describes reports of immunotherapy being used to salvage recurrent cases but not as replacement of chemotherapy. While this is an interesting idea in POLE, we respectively do not want to inject this into this manuscript with little data to present. We prefer to focus on the exciting trials of deescalating care for POLE mutated tumors.

In the copy number high section, the authors may want to discuss the GOG 86P publication reporting on concordance of p53 IHC and NGS assessments (88% concordance; Thiel et al. J Clin Oncol 2022).

- Thank you for this additional information. The data has been added to the manuscript.

In the Her2 section, I would also comment on the potential frequency of Her2+ in clear cell and carcinosarcomas (~15% each)…given limited therapeutic options for these patients.

- Thank you for this comment, we have added the data supporting expression in clear cell carcinomas. We have respectively left out data on uterine carcinosarcomas. While we believe this to be an important tumor of uterine origin, we believe it likely warrants its own individual section, which unfortunately due to space constraints are not within the realm of this manuscript.

If the authors think it would be of interest, I would also discuss hormonal combination treatments including exploration of cdk4/6 inhibtors in the NSMP section. This may be particularly relevant given the PALEO data as well as the data shared by Dr. Konstantinopolis et al at SGO 2022 (low grade, p5S wt, endometrioid histology). I know this is mentioned in the future directions section, but may fit nicely into the NSMP.

Thank you for this comment. In agreement with you and reviewer #2, this information has been updated in the NSMP section. We hope we have adequately addressed your recommendation.