We want to thank the Reviewers for their constructive comments and efforts towards improving our manuscript. We are grateful for insightful comments on our paper and we have been able to incorporate changes to reflect most of the suggestions provided. Please find below a detailed point-by-point response to the comments of the Reviewers. The main corrections made in the manuscript text have been highlighted in blue.

Comments to Authors: Zilvic reported two cases of synchronous endometrial and ovarian cancer (SEOC) and performed review of the literature. After reading this manuscript, I think that this review is well organized and informative. Meanwhile, it is unclear what these case series add to the relevant field. The authors should clearly specify the novel findings and/or lessons obtained from their experience.

Answer: Our cases report aimed to detect whether uterine lavage is suitable and specific for SEOC detection through ctDNA mutation analysis. In present study, next generation sequencing of 10 genes in DNA from uterine lavage and ovarian tissue samples from two cases with SEOC was performed aiming at improved understanding of the molecular profile of these rare tumors and evaluation of rationality of uterine lavage based genetic in SEOC diagnostics. The sentence describing main aim of the study was added in the Introduction. While the main lessons obtained are described in the Conclusion part.

Comments to Authors: 1. (p. 1, l.30) Also, OC with Endometrioid histology diagnosed under the sge og 50 …: Loss of mismatch repair, i.e., Lynch syndrome, is also associated with endometrial cancer. Authors should mention it.

Answer: We agree with the reviewer's comment and mentioned it in the introduction.

Comments to Authors: 2. (p.3, l.3) Next-generation sequencing was performed using uterine lavage and ovarian tissue samples. Please explain why endometrial cancer tissue was not used for sequencing.

Answer: We aimed to test uterine lavage as diagnostic method for possible SEOC diagnostics and evaluate molecular profile of SEOC. Uterine lavage shows molecular profile of endometrial as well as and ovarian cancer. During surgery, we had an opportunity to take extra biopsies from ovarian tissues for next-generation sequencing in order to compare them with uterine lavage. We didn't have possibility to take extra biopsies from uterine cancer tissue for NGS, as tumors were very small and patients didn't signed informed consent for extra biopsies from uterine tumors.

Comments to Authors: 3. (p.5, Table 1) Mutation profiles of two SEOC cases: This must be "Mutation profile of Case 2." Mutation profiles of ovarian tissue and uterine lavage should be listed separately.

Answer: We are thankful for this correction

Comments to Authors: 4. (p.5, l.21) ovary and uterus and still alive more than 2 years after treatment: more than 3 years.

Answer: We agree with the reviewer's comment and corrected accordingly.

Comments to Authors: 5. (p.6) SEOC is misspelled as SEO at 3 places.

Answer: We are thankful for the comments, corrections were done accordingly.

Comments to Authors: 6. (p.7, l.2) GSK3beta/Axin complex is required for beta-catenin stabilization and translocation to nucleus: This is wrong. GSK3beta/Axin complex is required for beta-catenin phosphorylation and degradation.

Answer: We agree with the reviewer's comment and corrected accordingly

Comments to Authors: 7. (p.7, Figure 6) Arrow beneath AKT1 should be replaced with block, since AKT1 inhibits GSK3beta.

Answer: We are thankful for this correction.

Comments to Authors:8. Mild grammar and spell check will be needed.

Answer: We are grateful for insightful comments on our paper. The language checking was carefully performed.

Round 2:

-------This manuscript was improved to some degree in the revised version, but there remain some problems to be settled. We want to thank the Reviewer again for their constructive comments and efforts towards improving our manuscript.

---We are grateful for insightful comments on our paper and we have been able to incorporate changes to reflect most of the suggestions provided. Please find below a detailed point-by-point response to the comments of the Reviewer.

Major point:

1.In response to my previous comment, “Next-generation sequencing was performed using uterine lavage and ovarian tissue samples. Please explain why endometrial cancer tissue was not used for sequencing,” you replied, “We didn’t have possibility to take extra biopsies from uterine cancer tissue for NGS, as tumors were very small and patients didn’t signed informed consent for extra biopsies from uterine tumors.” However, I can read that at least case 1 underwent hysterectomy and NGS can be performed using pathological sample of the uterine corpus cancer.

Answer: Thank you for your comment. Both patients underwent hysterectomy, but in our country after surgery we send histology to special pathology center, we do not perform histology in our clinics and the pathology center routinely do not perform NGS, as it is expensive diagnostic test. Both patients before surgery signed informed consent to take uterine lavage and extra ovarian biopsy for a trial to perform NGS at National Cancer Center genetic laboratory.

2. In your reply to my comments, I found a description, “Uterine lavage shows molecular profile of endometrial as well as an ovarian cancer.” Did you analyze molecular profiling of uterine lavage to investigate gene mutations in not only endometrial cancer but also ovarian cancer simultaneously? If so, analysis of uterine lavage may not be useful for the differential diagnosis between SEOC and metastatic cancer.

Answer: We are thankful for this correction. Uterine lavage can show molecular profile of endometrial cancer, also ovarian cancer, but usually it is appliable for type II ovarian cancer (according to pathogenesis theory), when precursor lesion starts at fallopian epithelial.

Endometrial ovarian cancer is type I ovarian cancer, so for these type of OC uterine lavage can hardly show molecular profile, we agree with the reviewer.

3. Please explain clearly why no mutations found in ovarian cancer and uterine lavage can lead to the diagnosis of SEOC in case.

Answer: Thank you for your comment. Our cases aimed to detect whether uterine lavage is suitable and specific for SEOC detection through ctDNA mutation analysis. In present study, next generation sequencing of 10 genes in DNA from uterine lavage and ovarian tissue samples from two cases with SEOC was performed aiming at improved understanding of the molecular profile of these rare tumors and evaluation of rationality of uterine lavage based genetic in SEOC diagnostics. While the main lessons obtained are described in the Conclusion part. We do not think that no mutations found in ovarian cancer and uterine lavage can lead to the diagnosis of SEOC in case. Our two cases do not show that uterine lavage is a good diagnostic test for SEOC. In our conclusion we say: SEOC predominantly occurs in younger premenopausal women. The identification of SEOC or metastatic endometrium/ovarian disease have great clinical significance, as the disease management, prognosis and overall survival differ. Precise diagnosis of SEOC may require additional molecular or IHC testing in addition to routine histopathologic assessment. According to literature review testing of vimentin, molecular analyses of gene mutation of CTNNB1, PAX8, β-catenin expression may be helpful to categorize SEOC in cases where clinical and pathological parameters are inconclusive. Our two cases do not show that uterine lavage was suitable diagnostic test for SEOC, but further investigation is needed, and additional disease-specific biomarkers have to be discovered. Will be added to the conclusion (marked in red).

1. Minor points: 1. (p.3, l.12) Results: In our report patients with SEOC had an endometroid type histology with: endometrioid

Answer: We agree with the reviewer's comment and will be changed.

2. (p.5, l.7) criteria by Ulbright and Roth for SEOC diagnostics may not always be appliable . When: applicable

Answer: We agree with the reviewer's comment and will be changed.

3. (p.5, l.23) A 54-year-old, menopausal (gravida 0, para 0) women presented with lower abdominal: woman

Answer: We agree with the reviewer's comment and will be changed.

4. (p.6, l.4) Hysterosocpy was performed because endometrial polyp was detected by ultrasound: Hysterescopy

Answer: We agree with the reviewer's comment and will be changed.

5. (Figures 1 to 4) Site of cancer (endometrioid or ovarian) should be specified in figure captions.

Answer: We agree with the reviewer's comment and will be added. Figure 1 shows hematoxylin-eosin stains of the endometrial and Figure 2 shows ovarian tumor specimens. Peritoneal cytological washing and additional peritoneal biopsies, as well as lymph nodes, were negative for malignant cells. Figure 3 shows hematoxylin-eosin stains of the endometrial and Figure 4 shows ovarian tumor specimens.

6. (p.9, l.17) endometrial and Figure 4 shows ovarian tumor specimens. Peritoneal cytological: endometrium

Answer: We agree with the reviewer's comment and will be changed.

7. (p.10, l.1) The patient underwent surgical staging: Please specify surgeries which this patient (case 2) underwent. Was the diagnosis of uterine corpus cancer without myometrial invasion possible without hysterectomy? Did the case 2 really not undergo hysterectomy?

Answer: We agree with the reviewer's comment and will be added. She underwent hysterectomy with bilateral salpingo-oophoarectomy, peritoneal biopsy, pelvic and para-aortic lymph node dissection.

8. (p.10, ll.13-15) In ovarian tissue sample, somatic mutations of PIK3CA and PTEN were detected. Moreover, tumor sample had a mutation in β-catenin gene CTNNB1: Do these two sentences mean these three genes were mutated in ovarian cancer tissue? If so, it should be described as follows: Somatic mutations of PIK3CA, PTEN, and CTNNB1 were detected in the ovarian cancer. Furthermore, in Table 1, "tissue mutation" should be replaced with "ovarian cancer mutation" in the headline.

Answer: We agree with the reviewer's comment and will be changed as the reviewer suggested.

9. (p.11, l.19) different clinical characteristics compared to patients with to EC or OC alone. SEOC is: different clinical characteristics compared to patients with EC or OC alone. SEOC is

Answer: We agree with the reviewer's comment and will be changed.

10. (p.11, l.22) low-grade disease. The endometroid subtype of the primary tumors is the most: endometrioid

Answer: We agree with the reviewer's comment and will be changed.

11. (p.11, l.26) The importance of distinguishing SEOC from either isolated endometrium or: endometrioid **Answer:** We agree with the reviewer's comment and will be changed.

12. (p.12, l.4) metastatic disease [1, 2, 4, 13]. Both patients in our report were diagnosed with low grade of: Delete "of." **Answer:** We agree with the reviewer's comment and will be changed.

13. (p.12, l.28) sequencing (NGS). Pairedbox gene 8 (PAX8) is a marker that can be useful in: Paired box **Answer:** We agree with the reviewer's comment and will be changed.

14. (p.13, l.12, l.21, l.23) SEO: SEOC **Answer:** We agree with the reviewer's comment and will be changed.

15. (p.13, l.17) and ARID1A gene mutations can be helpful for diagnostic of SEOC [16, 22-28]. Reijnen et al study: The study by Reijnen et al **Answer:** We agree with the reviewer's comment and will be changed.

16. (p.14, l.7) Figure 6: Figure 5 **Answer:** We agree with the reviewer's comment and will be changed.

17. (p.14, ll.11-13) The numbers indicate TCGA published mutation data form uterine (right side data) and ovarian (left side data) cancers. Figure generated using PathwayMapper tool [22]: According to this explanation, ovarian cancer in case 1 represented mutations in PTEN, PIK3CA, and CTNNB1 genes which are reported to be very rare in SEOC according to the TCGA data (0.0%, 3.7%, and 1.2%, respectively). Is my speculation right? **Answer:** Overall, CTNNB1, PTEN, PIK3CA mutations in ovarian cancer are not frequent, however they are enriched in less frequent non-high-grade-serous types of ovarian cancer e.g. endometrioid type, which is not reflected in overall ovarian cancer mutation count in the figure. As described in the discussion, Case 1 with mutation in all 3 genes consisted of both endometrioid endometrial and ovarian cancers that are known for these mutations.