Dear Reviewers and Editors:
We are grateful that you took the time to read and provide constructive criticism on our manuscript. We appreciate your comments and have revised the manuscript accordingly. The adjustments are outlined below.

Reviewer #1

1. The suggestion regarding MPE was well received. Based on the literature suggested, we have discussed how utilizing the MPE research approach could help us to further understand the etiology and epidemiology of prostate cancer. Specifically, we considered that MPE research could help to establish clearer associations between circRNAs, cancer risks (genetic mutations, environmental, lifestyle, microbiome, etc.), molecular markers/ tumour characteristics, and disease outcome in prostate cancer patients. Moreover, we highlighted that it would be interesting to see whether these potential associations could also help create predictive models for screening individuals, and tailoring treatment.

2. The authors also discoursed some strengths of MPE, and mentioned a few challenges as advised.

Reviewer #2

Thanks for reviewing our manuscript and deeming it acceptable as is.

Reviewer #3

1. Thank you for pointing out that our explanation of the backsplicing models required more clarity. We amended this by explaining that exon-skipping is a model that facilitates backsplicing, and that backsplicing and exon-skipping are different. Moreover, we also clarified that exon-skipping can occur independent of lariat formation by means of direct backsplicing.

2. As it relates to biogenesis, we do recognize that the mechanisms may be different in viruses and mammalian cells. Our limitation in this regard is that our primary focus was on circRNAs originated from prostate cancer cells that can be served as diagnostic or prognostic markers. Thus, we did not include much mention of circular virus RNA biogenesis in our review.

   As advised, we noted that exonucleases, and not endonucleases, are the more predominant nucleases in RNA host cells (references were cited). As such, the accumulation and detection of circRNAs is favored over linear transcripts,

due their increased resistance to exonucleases. We also took heed in mentioning that circularization generally increases the stability of RNA molecules, but in circular molecules such as circular HDV RNAs, larger molecules are more susceptible to degradation by nucleases, but are stabilized by RBPs.

3. In regards to ascribed functionality of circRNAs, we are in agreement that more doubt should be inferred within our manuscript. We established this by highlighting that the proposed functions have only been investigated in a handful of molecules- it is not to be assumed that all circRNAs exhibit all or any of the functions mentioned in our manuscript. In future directions, we have highlighted that further investigations of their functionality is critical in establishing their roles in tumorigenesis.

4. Though the need to establish the legitimacy of proposed methods for detecting HDV-like RNA circles is valid, our focus is on detecting eukaryotic circRNAs that can be used as biomarkers for prostate cancer. However, we did include that future studies should validate and standardize detection methods.

Many thanks for considering our manuscript for publication in your journal. We hope that you are pleased with our revision. We look forward to your feedback.

Best regards,

The Authors