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Peer Review File

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Reviewer A
Comment 1: First, the title is not very clear.
Reply 1: Thank you. In line with your comment, title has been changed to, “Advances in molecular medicine for breast cancer practice.” We have modified the title as advised.

Comment 2: Second, the abstract is also not informative. I cannot see the main findings summarized from the literature review, research limitations on this topic, and possible research topics to address unaddressed issues. The authors should briefly argue why a review on this topic is needed or its clinical significance.
Reply 2: Following the comment we have redrafted the abstract by summarizing the literature used, research topics covered along with the limitations and clinical significance. Redrafted abstract can be found between lines 45-74.

Comment 3: Third, at the beginning of the main text, the authors may consider to have an overview of this review, i.e., the need for a review and focuses of the review. I also would like to see a brief introduction on the methodology of this review, i.e., the literature search strategies, keywords used, and the end date of the search. This would help readers assess whether this review is up-to-date or not.
Reply 3: To address comment 3, we have included further details in the below lines of the text.
Introduction: Lines 79-83; Lines 92-105
Methodology: Lines: 114-120

Comment 4: Fourth, at the end of this part, please consider to use a paragraph to discuss limitations of the evidence reviewed and have some comments on future research topics to address unaddressed problems.
Reply 4: Limitations have been mentioned and how integrating different ethnic groups in international consortia studies and use of big data could help address this has been mentioned in “lines 440-446”.

Reviewer B
Comment 1: The authors have made efforts to review the literature and studies but the manuscript does not have a structure.
Reply 1: Structure of the review started with early use of IHC, and how omics technology has led to more advanced multi gene signatures. Then the multigene expression signatures and relevant studies were reviewed as part of showing the importance of such signatures and limitations. Subsequently with HER2DX study we reviewed how integration of machine learning could help advance multigene signatures accuracy & usefulness. Following that, improving use of immunotherapy in breast

cancer treatments, prognostic ability of immune signatures in breast cancer has been addressed. Since multigene signatures also involve genes with pathogenic variants, we presented how the recent studies have shed light on the role of pathogenic germline variants in breast cancer patient risk stratification. And owing to the significance of liquid biopsy in gene signatures and use as noninvasive we presented its historical use and advanced application like in CancerSEEK, TARGET and plasmaMATCH studies (based on somatic mutations) for progression free survival (PFS), overall survival (OS), response and benefit to breast cancer treatment.

Comment 2: Is not clear when they discuss early stage compared to advanced tumors. I would suggest to focus on early stage Breast Cancer and elaborate what will be the use of genomic tools in this setting.
Reply 2: We presented the review focusing on the advance use of multigene signatures in breast cancer risk stratification, prognostic and predictive ability of signatures and their applications in escalation and de-escalation of treatments.

Comment 3: They partially mentioned the intrinsic subtypes but is not well defined the impact for treatment selection.
Reply 3: We agree that we only presented limited updates on the impact of treatment selection among the intrinsic subtypes. However, as also mentioned in the text, a recent review in Cell by Qian Y presented a detailed view on this. Hence, to avoid repetition and any overlap, in this review we presented selective and recently reported clinical trials and their outcomes.

Comment 4: Please clarify if IMpassion130 showed OS benefit.
Reply 4: Thank you. We clarified that IMpassion130 trial did not show a significant overall survival benefit in “line 420-421”. In lines 425-429 IMpassion130 trial limitations have been mentioned and the need for further validation was pointed out.