

WJG manuscript number 18623 point-by-point responses to reviewer.

We greatly appreciate the comments and suggestions from the reviewers, which helped improve the clarity of the paper. Please see our point-by-point responses below.

Reviewer 1:

Excellent and comprehensive review. I only have two issues that need to be addressed by the authors to increase the significance of this manuscript. 1. The authors should discuss the issue of molecular intratumoral heterogeneity, and also the potential heterogeneity between different tumor nodules in the same patient. This is important in practical terms regarding their proposed application of molecular profiling for patient prognosis and molecular therapies.

We agree with this important point, although the focus of our review is not molecular classification of HCC. We have amended our text as follows (page 10, paragraph 1, line 10 in revised manuscript):

“In patients with HCC, another application of molecular analysis is the subclassification of HCC into distinct molecular subtypes linked to different clinical and pathological characteristics [73, 74], although intratumoral molecular heterogeneity within a tumor nodule or between nodules in a patient remains a challenge that must be resolved before applying the molecular classification to therapeutic decision-making, especially for selective molecular targeted agents [75].”

2. A brief description of the most adequate technological platforms that in the opinion of the authors could be used in the clinical setting to achieve a robust molecular profiling of tumors and liver tissues.

We agree with the reviewer that this is a key point and we have discussed it as below (page 10, paragraph 2, line 5 from the bottom in revised manuscript):

“Although many modern biomarkers are developed using a variety of technologies, a key factor for implementation in clinical practice is the choice of assay technology for clinical laboratory use [83]. Reproducibility and robustness of the measurement, complexity of the assay, and cost are the major determinants of the assay selection. Historically, immunohistochemistry, including fluorescent in-situ hybridization, and quantitative PCR-based nucleic acid assays have been the dominant technologies employed to deploy molecular biomarkers. However, subjectivity in the quantification and experimental artifact in the process of target amplification, for example, are the major limitation to provide reliable results. Recently developed technologies such as digital transcript counting without target amplification [81, 84] are expected to overcome the issue by providing more objective and robust readout. Genome-wide sequencing of germline DNA variants has posed ethical issues regarding incidental findings [85].”

Minor. In page 10, second paragraph, the words "of successful clinical translation" are repeated twice in the same sentence.

The text has been corrected.

Reviewer #2

The review by Goossens et al on “Molecular prognostic prediction in liver cirrhosis” is a well written report on clinical and molecular markers determining prognosis for disease progression and HCC occurrence or recurrence in cirrhotic patients. However I have a point to make. In liver cirrhosis IGF-I

synthesis drops in parallel to hepatocellular insufficiency and its levels reflect the decline in liver function more precisely than albumin, INR or bilirubin values. In addition IGF-I expression in the cirrhotic peritumor tissue is on top of the molecular signature prognosticating HCC recurrence after resection. Thus, IGF-I is a marker that needs to be included and commented in this review

We appreciate the reviewer's suggestion, and have acknowledged that IGF-1 is an interesting biomarker for degree of liver failure and risk of HCC as below (page 9, paragraph 1, line 7 in revised manuscript):

“Insulin-like growth factor one (IGF-1) has been shown to reflect hepatocellular dysfunction possibly due to a loss of hepatocyte synthesis and a decrease in growth hormone receptors [56], and serum levels of IGF-1 reflect liver failure and risk of HCC [57, 58]. Consistent with these findings, IGF1 is a member of the good prognosis-correlated genes in the 186-gene prognostic liver signature [52, 54]”