

To the Editor,  
World Journal of Gastroenterology  
Rozzano, 28<sup>th</sup> July 2021

Dear Sir,

We thank you and the reviewers for your comments, and the very careful evaluation of our study.

The point-by-point replies are included below.

We think that the manuscript has been improved and we hope that you will find it appropriate for the readership of your journal.

Gratefully yours,

Luca Viganò, for the authors.

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**Reviewer #1:**

- 1. The definition of biomarkers may be added in terms of Figure 1.*

We thank the reviewer for this suggestion. The definition of biomarkers has been added to Figure 1

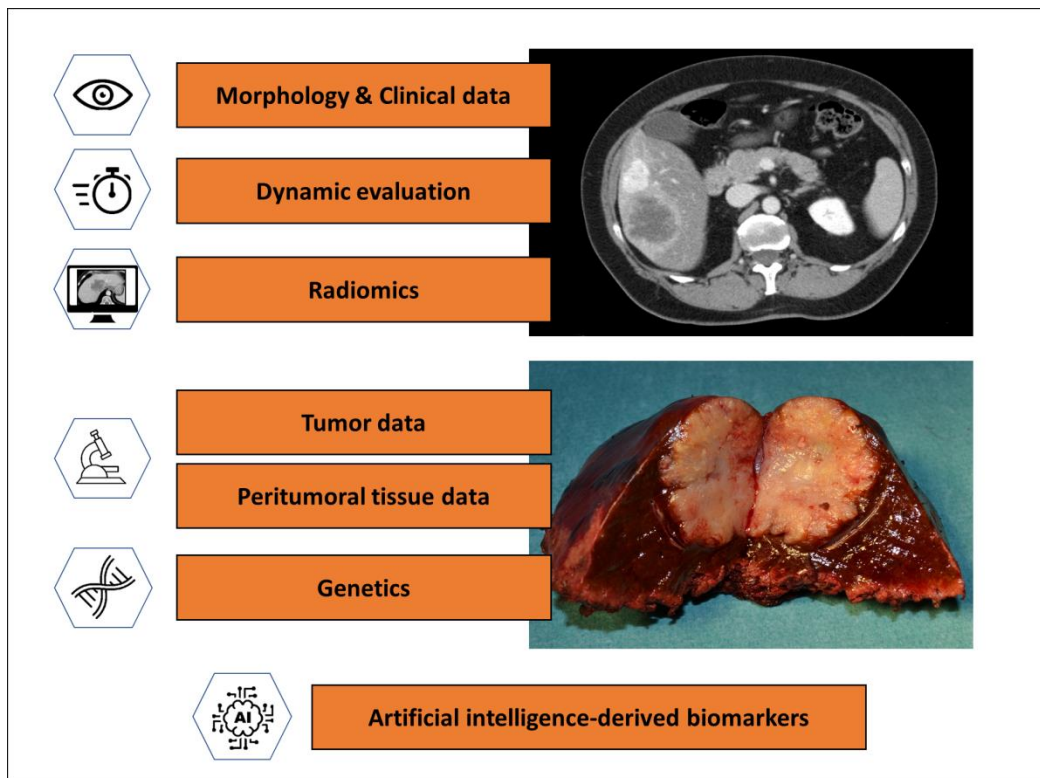
The legend to this Figure now reads as follows:

**“Figure 1.** Available biomarkers for patients affected by colorectal liver metastases. **A biomarker is defined as any parameter (molecular, cellular, clinical, imaging or identified by an artificial intelligence process) having a clinical role in narrowing or guiding treatment decisions and contributing to the estimation of the overall patient prognosis (prognostic biomarker), the clinical outcome after a treatment (predictive biomarker), or the properties of a clinical condition /disease (diagnostic biomarker).”**

- 2. More detailed explanation for application of AI as a biomarker shown in Figure 1 may be clarified.*

Again, we thank the reviewer for this comment. The concept of AI-based biomarker was not adequately explained and was unclear. We modified the Figure 1 and the text about the AI.

The Figure 1



The text about AI now reads as follows:

“In medicine, AI is expected not only to optimize the prediction of an outcome by combining all available variables but also to continuously update and improve prediction according to the experienced results (**Figure 2**). AI can represent a major support to the decision-making processes, especially in the clinical scenarios with several therapeutic and strategical options and lack of consensus among experts, exactly as occurs for colorectal metastases [24]. **In this sense, AI is not per se a biomarker but maximizes the profitability of all available data. However, AI may also have an additional role. It can be applied to medical imaging to identify new patterns that can contribute to diagnosis or prediction [127]. Such patterns, extractable from any type of imaging modality in a completely unbiased and unsupervised way, can be considered AI-derived biomarkers, subject to clinical validation [128]. Analogously, AI can identify biomarkers from any source of data, including clinical charts, medical reports, and images scan.”**

The following references were added:

127. Erickson BJ, Korfiatis P, Akkus Z, Kline TL: *Machine Learning for Medical Imaging*. *Radiographics* 2017, 37(2):505-515.
128. Waldstein SM, Seeböck P, Donner R, Sadeghipour A, Bogunović H, Osborne A, Schmidt-Erfurth U: *Unbiased identification of novel subclinical imaging biomarkers using unsupervised deep learning*. *Scientific Reports* 2020, 10(1):12954.