Responses to Reviewers

Stylistic, typographical, grammatical, and other minor revisions:

We have revised the main manuscript to correct grammatical errors and clarify points we believed required revision for clarity. We have also consolidated references and conformed them to the journal's citation style. Furthermore, we have addressed the remarks addressed by the reviewers below.

Reviewer #1:

- Line 209 Development of diagnos3c tools could be a main heading.

o **Done**

Major Revisions

Some comments by Reviewer #1 required more extensive revisions to the manuscript. Below are our responses.

Reviewer #1:

- Introduc3on (Line 26…): The regulatory impact of tumor microenvironment (TME), as described in the first paragraph, is not clearly related to the microbiome or linked to the founda3onal concepts of Oncobiomics, as subsequently presented. Additional informa3on could be added or the paragraph could be transferred to the section on Impact of Microbes on Immunosurveillance. Lines 35- 75 are more than sufficient as the Introduction.

o **Thank you for your suggestion. We have moved this paragraph from the Introduction to the opening paragraph of the "Impact of Microbes on Immunosurveillance" section.**

- The review is too tightly written and demands intense study; subjects are abruptly changed, conclusions are merged with data presentation, and weighed down with references. For example, Line 156-161, 'Although sequencing methods' should start a new paragraph.

o **Per the reviewer's suggestion, we have started a new paragraph at Line 156. Furthermore, we have revised the language in the (now) preceding paragraph to improve clarity and readability. Furthermore, the citations have been changed to the journal's required citation format, which should additionally improve readability in heavily sourced sentences. We've also removed some citations that ultimately seemed unnecessary (e.g., web-link citations associated with NTC codes for clinical trials) and consolidated duplicates of any citations.**

- The authors should consider using subheadings (cancer-associated microbial neoantigens, intratumoral microbiota, taxonomic biomarkers). Lines 169 and following: The studies of intratumoral microbiota are highly interesting and could be discussed under separate heading that includes TME.

o **We have combined the sections entitled "Impact of microbes on immunosurveillance" and "The clinical relavence of extraintestinal microbiota" into one section, which was then broken into several subheadings to highlight the key themes.**

- Line 222: Comments on toxicity and effects on metabolic pathways could be expanded and explained

o **Noted. We have expanded the discussion about these effects as follows:**

Additionally, gut microbiota composition has been correlated with toxicity to both CAR-T cell therapies [90] and ICI [91,92], specifically the incidence and severity of IrAEs. Moreover, dysbiosis has been characterized by metabolic disruptions, notably reduced produc3on of SCFAs, elevated levels of

inflammatory cytokines, and compromised gut barrier integrity.
- The section on Comedications could be improved with tables for ATB and FMT to set the context and use of precise comments in the text.
o **Thank you for the suggestion. We have incorporated a graphical table into a new Figure 2 that should add clarity to this section.**
- Lines 435: "Given the influence that β-adrenergic signaling-mediated stress has on microbial health in a cancer setting, the use of β-blockers has been proposed as a poten3al therapeutic strategy." What effect? Which cancer?
o **We have added text and clarified the paragraph to better explain this point.**
Sections on Next-generation probiotics (NGP), Live biotherapeutic products (LBP) and Diet, prebiotics, and metabolites are overly discursive and need compression. Some material if compressed could be integrated into previous sections. Example: Line 582 and following: "Other preclinical evidence shows promising results of metabolic modulation in oncology"
o **We have moved the sentences about antibiotic effects on bile acid metabolism to a section that focuses on the discussion on MAdCAM-1. We've also focused and expanded the discussion about prebiotics at the end of the section.**