

## Manuscript No. 75148 - Response to Reviewers suggestions

We thank the reviewers for their feedback. To summarize:

- Reviewer #1 liked the manuscript and had no suggestions.
- Reviewer #2 had no comments other than that it was too long.
- The Science Editor also recommended reduction in size and cleanup of the writing. (Reviewer #3 also had the same concern about the writing, which we have cleaned up and streamlined significantly, reducing repetition).
- The Editor-in-Chief recommended shortening the title to  $\leq 18$  words, and the addition of a figure/table.
- Reviewer #3's comments were the most detailed. They are a strict superset of those stated by the Editor-in-Chief and Science Editor. We found them very valuable and agree with all of them, and we state how we have tackled these issues.
- It is worth noting that Reviewer # 3 had also requested for a deepened discussion, which we have done in the relevant imaging sections.
- It is pertinent to note that in the Invite sent to me it was clearly stated "NO WORD LIMIT"; and hence we spent a lot of time in collating data and preparing this manuscript. However, keeping the overall requests in mind we have reduced the manuscript text by around 1/3<sup>rd</sup> (one third). Any further reduction will reduce the quality of this vital manuscript.

### Summary of Revisions to the Manuscript

Below, we state the points made by Reviewer #3, and describe how we have addressed each concern.

1. Shorten the title to 18 words or less. Include a figure or table.

Our shortened, revised title is "THE TUBERCULOSIS CONUNDRUM - Current and Future Scenarios: A proposed comprehensive approach combining Laboratory, Imaging, and Computing Advances" (17 words). We have included several figures (12 sets of figures, including one Cardiac MRI video).

2. Abstract is too long, should be in 250-350 words only and focused on the main purpose of this review.

The Abstract has been shortened to 298 words from an original 727 words.

3. Abbreviations should be written after full words.

We have now consistently applied the standard practice of defining an abbreviation at first use.

4. Manuscript should be shortened and focused.

This has been done.

5. Scientific writing must be improved.

The same has been done.

6. Format of this review should be reconstructed to make the review clearer.

The same has been done using the “Outliner function of WORD”.

7. Header of manuscript should be added or revised to be easily observed. And the paragraphs in each header should be rewritten to focus on the title of header.

All headers have been revised and marked and can be easily observed and the paragraphs rewritten/rearranged accordingly.

8. What field of Tuberculosis do the authors focus to discuss?

We propose to focus upon current and future scenarios in Tuberculosis (under various headings as stated in the title), especially a comprehensive holistic approach and other strategies to tackle the scourge of TB.

9. The manuscript was written in too broad area but not deep discussion. All manuscript must be rearranged and rewrote based on the manuscript title as “TUBERCULOSIS CONUNDRUM - Current and Future Scenarios - New proposed comprehensive approach & Molecular Imaging, Artificial Intelligence, Quantum Computing perspectives”.

- We have made appropriate changes accordingly. The body of the paper has been reduced to around 65% of its original length; from about 11K words to about 7.5 K words, without any significant loss of content. The shortening - achieved in large part by eliminating repetition, and rephrasing the same points using fewer words, has, we believe, improved the paper’s focus vastly. As requested, a more detailed discussion has been done in the relevant imaging sections.
- In addition, we have used Microsoft Word’s “Outlining” feature to impose a hierarchical structure on the paper, with Headings and Subheadings that are outline-numbered using a decimal notation (e.g., 1.1). Visualizing this hierarchy allowed us to recognize misplaced blocks of text that logically belonged elsewhere, and to subsequently reposition these blocks of text into their appropriate position in the hierarchy.

10. Where is the perspective of “New proposed comprehensive approach & Molecular Imaging, Artificial Intelligence, Quantum Computing”?

The manuscript has been rearranged and each section is marked clearly; thus, making it easy to read/review, including the sections mentioned above (please refer to the Manuscript ‘Outline’ below).

We reproduce below the outline for the Reviewer's benefit:

- ✦ **1→Introduction**
- ✦ **2→Diagnosis of TB**
  - ✦ **2.1MDR-TB: Advances in Laboratory Diagnosis**
- ✦ **3→Imaging Methods in Tuberculosis**
  - ✦ **3.1Conventional Chest radiography (CXR)**
  - ✦ **3.2Ultrasound (US)**
    - ✦ 3.2.1 → Micro-Bubbles (MB): Theragnostics
    - ✦ 3.2.2 → High-Resolution US
  - ✦ **3.3Dark Field Radiography (DFR)**
  - ✦ **3.4Computed Tomography (CT)**
  - ✦ **3.5Magnetic Resonance Imaging (MRI)**
  - ✦ **3.6Nuclear Imaging**
  - ✦ **3.7Advances in Ex Vivo Molecular Imaging and Microscopy**
    - ✦ 3.7.1 → Fluorescence Life-time Imaging Microscopy (FLIM)
    - ✦ 3.7.2 → Multiphoton intravital microscopy (MP-IVM)
    - ✦ 3.7.3 → Matrix assisted Laser desorption/Ionization Mass Spectroscopy Imaging (MALDI/MSI)
- ✦ **4→Molecular Mechanisms in TB**
  - ✦ **4.1Role of Vitamin D**
  - ✦ **4.2The Epigenetics Perspective**
- ✦ **5→Advances in Computing**
  - ✦ **5.1Artificial Intelligence (AI) Applications in TB**
  - ✦ **5.2Augmented Reality (AR) and Virtual reality (VR)**
  - ✦ **5.3Distributed Computing (DC)**
    - ✦ 5.3.1 → Federated Machine Learning
  - ✦ **5.4Quantum Technology**
    - ✦ 5.4.1 → Quantum Entanglement Microscopy
    - ✦ 5.4.2 → Quantum Computing
- ✦ **6→Summary and Conclusions**
- ✦ **7→Bibliography**

11. Please check all manuscript carefully. For example, in abstract section, MDR and XDR TB in 1st sentence?

Thank you for pointing this out. We have addressed this and similar concerns throughout the paper.

12. The authors mentioned about vitamin D for treatment, but the paragraph about vitamin D is in diagnosis section? Please recheck all manuscript and revise it carefully.

Thank you. As stated previously, the use of Outlining helped us to recognize and reposition this and other misplaced blocks of text.

13. Although there are too many techniques of diagnosis or molecular imaging, artificial intelligence, quantum computing; there is no figure that illustrates the techniques or summarizes the diagnostic technique, the future approach of AI. I recommend the authors to add some figures of each section to make the manuscript more interesting and observable.

We have done so, introducing 12 key figure sets (many with multiple images in each set) and includes

a video of 3Tesla Cardiac MRI. The same are inserted in the text based on the outline headers.

