Reviewer Comments

Reviewer A

Comment 1: The setup of this paper is wrong. In line 111-112 (but also in other words in line 117-118 and the abstract) you state that "this review aims to elucidate the pivotal role of clinical laboratories within the evolving landscape of PM", so you already assume that the role is "pivotal". It would be better to write a review to find out what the role is of clinical laboratories in PM. If then, by assessing the literature, you conclude that this role is very important, this is a proper result of your review.

Reply 1: Corrected/amended as per instruction.

Comment 2: I would be more reluctant to use words such as "crucial", "pivotal", "paramount" etc. The abstract almost reads like a commercial for clinical laboratories.

Reply 2: Keeping the opinion of the respected reviewer these words could be changed as per further instructions.

Secondly, the abstract encapsulates a comprehensive exploration of the promising role that clinical laboratories play in the realm of precision medicine. It is important to note that the article is rooted in a thorough examination of the existing literature and a detailed write-up on the subject matter. The abstract, therefore, serves as a succinct summary of the extensive research, presenting a condensed overview of the pivotal insights uncovered regarding the significant contribution of clinical laboratories to the advancement of precision medicine.

If the well-learned want us to amend the abstract, detailed instructions are requested.

Comment 3: line 107/108: "The more data and information that is collected and thus connected, the better scientists will understand health" -> "thus" feels out of place here, as the connection does not always follow collection. The connection (or integration) of data is actually a crucial step that is often forgotten or undervalued.

Reply 3: As there was some pause in the sentence and now has been corrected, hence

the reviewer may now find it appropriate, please refer to comment number 7 as well.

Comment 4: paragraph 2.2.3: AI can indeed play a large role in laboratory medicine. What is crucial to understand, is that with increasing data size, it will be more difficult to analyze data with "traditional" methods. AI is much more suitable for handling multimodal "big data". See e.g. https://www.degruyter.com/document/doi/10.1515/cclm-2022-1096/html

Reply 4: The authors agree with the honorable reviewer that in the context of laboratory medicine, it is evident that AI holds substantial potential. It is imperative to recognize that as the volume of data expands, the conventional methods of analysis face growing challenges. The complexity and diversity inherent in multimodal "big data" necessitate a more sophisticated approach, and AI emerges as a highly suitable solution for navigating and extracting meaningful insights from such expansive datasets. The utilization of AI in laboratory medicine thus becomes not only advantageous but increasingly essential for effective and comprehensive data analysis in the face of expanding data dimensions. Moreover, addressing the challenges of handling big data in laboratory medicine will require the implementation of specialized tools or systems designed to accommodate and streamline the complexities associated with large-scale data sets.

Comment 5: line 575: should be Figure 3. This figure is not referenced anywhere.

Reply 5: Corrected as per instructions and referenced in the text before conclusion

Comment 6: line 107: "The more data and information that is collected" -> "are collected".

Reply 6: Corrected as per instructions

Comment 7: line 108-110: "Further ensuring that patients receive adequate treatment, monitoring, and care for many generations, increasing patient satisfaction and prolonging expected lifespans." -> Not a full sentence.

Reply 7: The authors are grateful for the meticulous review of the manuscript by the

reviewer. This sentence shall be read as "The more data and information that are collected and thus connected, the better scientists will understand health, further ensuring that patients receive adequate treatment, monitoring, and care for many generations, increasing patient satisfaction and prolonging expected lifespans".

Comment 8: line 231-234: "Moreover, AI has facilitated the progression of personalized patient treatment plans, by analyzing an individual's genetic and molecular profiles while cross-referencing an already available databank (Figure 2)" -> The figure does not show the databank, which is actually the crucial difference here.

Reply 8: Thank you very much for raising a point. Please note the following explanation. This illustration encompassing genetic, environmental, physical, and dietary factors depicted on the screen not only contribute to the formulation of personalized treatment plans but also underscore the integral role of data storage and utilization within the realm of precision medicine. It is within this amalgamation of diverse elements that the true differentiator emerges, emphasizing the holistic approach adopted by AI in tailoring patient-centric interventions

Reviewer B

Comment 1: Consider providing a brief definition or explanation of "precision medicine" for readers who may not be familiar with the term.

Reply 1: The depiction of precision medicine (PM) has been expanded in accordance with the reviewer's recommendation; for further details, kindly refer to lines 53 through 61.

Comment 2: Clarify the meaning of "narrative review reporting checklist" mentioned at the end of the introduction.

Reply 2: Referring to the honorable reviewer's query, the inclusion of the "narrative review reporting checklist" at the conclusion of the introduction stems from the imperative for authors to meticulously fulfill a comprehensive set of criteria during the article's preparation, underscoring the commitment to precision and thoroughness in the

scholarly discourse.

Comment 3: Rationale of the Study:

The section effectively emphasizes the pivotal role of clinical laboratories in PM, elucidating their contribution to collecting relevant patient information for personalized treatment plans. The link between funding, increased tests, and subsequent data analysis is well-established.

Consider briefly addressing potential challenges or limitations associated with the reliance on extensive data from clinical laboratories.

Reply 3: Added as per instructions at the end of subheading 2.2.3 artificial intelligence.

Comment 4: Objective:

The objectives are clearly stated, focusing on the rapid advancements in PM technologies, such as next-generation sequencing (NGS) and data integration tools. The emphasis on how these innovations contribute to the discovery of disease-related genetic markers is well-articulated.

Provide more specific details on the intended audience of the review, such as healthcare professionals, researchers, or policymakers.

Reply 4: Added as per reviewer's instructions, please refer to lines 132 to 144.

Comment 5: Consider integrating the objectives into the broader context of precision medicine's impact on patient care.

Reply 5: The authors appreciate the insightful feedback provided by the esteemed reviewer. While we acknowledge the raised point, we contend that the impact on patient care has been extensively elucidated, bolstered by illustrative examples. Should further clarification or additional details be deemed necessary, we sincerely welcome and value your guidance in enhancing the comprehensiveness of the manuscript.

Comment 6: Methods:

The methodology section outlines the literature search approach, including databases and study designs. The inclusion of an inclusive approach and English language criteria enhances the comprehensiveness of the review.

Specify any inclusion or exclusion criteria applied during the literature search.

Reply 6: For inclusion criteria, a thorough search encompassed articles specifically addressing precision medicine and personalized medicine. The articles were searched using precision medicine, personalized medicine, individualized medicine stratified medicine targeted therapy, biomarkers, pharmacogenomics, and genomic medicine. The selected articles were required to provide in-depth insights into the principles, applications, and advancements within the field. Publications not available in the English language were excluded to ensure accessibility for a wider audience.

Comment 7: Provide a rationale for the choice of databases and how they contribute to the comprehensiveness of the review.

Reply 7: Please refer to line 147 to 157 page 7.

Comment 8: Early Developments in Precision Medicine:

This section provides a historical context for precision medicine, highlighting major milestones such as the Human Genome Project. The evolution of healthcare from traditional approaches to precision medicine is well-documented.

Consider integrating visual elements, such as a timeline or figures, to enhance the reader's understanding of historical developments.

Reply 8: The authors acknowledge the point raised by the honorable reviewer. However, we believe that it is deemed unnecessary to delve into intricate details of the historical evolution of technologies and laboratory instruction within the context of the review. The primary focus remains on contemporary advancements and their implications for precision medicine.

Comment 9: Address potential biases in historical narratives, providing a balanced

perspective on the challenges faced during early developments.

Reply 9: In response to the thoughtful feedback raised by the reviewer regarding addressing potential biases in historical narratives, it is respectfully considered that delving into such nuances may divert the focus from the core objectives of the review article. While acknowledging the importance of a balanced perspective, providing a comprehensive exploration of historical challenges faced during early developments might extend beyond the intended scope of elucidating the role of laboratories in precision medicine. The emphasis remains on maintaining relevance to the central themes of the article and ensuring a clear and focused narrative for the readers.

Comment 10: Emerging Technologies in Precision Medicine:

The subsections on NGS, mass spectrometry (MS), artificial intelligence (AI), and proteomics are comprehensive and well-explained. The review effectively demonstrates how these technologies are transforming clinical laboratories.

Provide a brief overview of each technology at the beginning of its respective subsection.

Reply 10: In response to the query suggesting a brief overview of each technology at the beginning of its respective subsection, it is acknowledged that concise introductory sentences have been provided. However, the inclusion of extensive technical details at this juncture may be deemed unnecessary for the targeted audience. If deemed crucial and in alignment with the recommendation of the Editor-in-Chief, further elaboration on each technology's overview can be considered for enhancement while ensuring it complements the overall flow and comprehensibility of the article.

Comment 11: Consider emphasizing the potential limitations or challenges associated with the implementation of each technology.

Reply 11: While it was initially deemed unnecessary to delve into extensive details regarding the limitations of each method, these subtle considerations have now been thoughtfully incorporated at the conclusion of each respective method as per directives of the honorable reviewer.

Comment 12: Applications of Precision Medicine in Clinical Laboratories:

The section effectively explores various applications of precision medicine, including genetic testing, diagnostic test development, monitoring responses to targeted therapies, and its role in cancer care.

Consider providing real-world examples or case studies to illustrate the practical application of precision medicine in clinical laboratories.

Reply 12: While the article does incorporate some general examples, such as cystic fibrosis and the critical role of tumor and germline genetic testing in breast cancer management, it has been deliberately focused on illustrating the broader role of clinical laboratories in PM. Introducing additional real-world examples or case studies, while valuable, may divert the article's focus towards specific diseases or conditions. The current approach aims to maintain a comprehensive exploration of the overarching contributions of clinical laboratories to PM without overshadowing the central theme with disease-specific illustrations.

Comment 13: Include a brief discussion on potential ethical considerations associated with genetic testing and personalized treatment plans.

Reply 13: Added at the end of the genetic testing section.

Comment 14: Challenges and Opportunities for Clinical Laboratories in Precision Medicine:

The review appropriately addresses challenges such as rapid technological advancements, the multidisciplinary nature of precision medicine, and potential cost implications. The opportunities for clinical laboratories to enhance patient outcomes are well highlighted.

Elaborate on potential ethical, legal, and social implications associated with the widespread adoption of precision medicine.

Reply 14: A paragraph has been added to the challenges section as per instructions.

Comment 15: Discuss the potential role of regulatory bodies in guiding the integration of precision medicine technologies into clinical practice.

Reply 15: The authors acknowledge the significance of the potential role of regulatory bodies in guiding the integration of precision medicine technologies into clinical practice. However, the focus of the article is intentionally tailored to delve into the pivotal role of clinical laboratories within the realm of precision medicine. While regulatory considerations undoubtedly play a crucial part in the broader landscape, the article meticulously explores and emphasizes the unique contributions of clinical laboratories, providing an in-depth analysis of their functions, challenges, and advancements within the specific context of precision medicine.

Comment 16: Conclusion:

The conclusion effectively summarizes the key points discussed throughout the review, emphasizing the crucial role of clinical laboratories in the evolving landscape of precision medicine.

Consider providing a brief outlook on the future developments or trends in precision medicine and the potential impact on clinical laboratories.

Reply 16: A paragraph has been added to the challenges and opportunities section as per instructions.

Comment 17: Reiterate the importance of collaboration between clinical laboratories and healthcare stakeholders for the successful implementation of precision medicine.

Reply 17: A paragraph has been added to the challenges and opportunities section as per instructions.

Reviewer C

Comment 1: As an evolution from proteomics, the authors might want to discuss metabolomics and its role in the field of personalized medicine.

Reply 1: The authors express gratitude to the reviewer for highlighting this aspect. However, incorporating additional literature at this stage poses challenges, considering

the already comprehensive coverage of the article on the pivotal role of clinical laboratories in precision medicine

Comment 2: As a prerequisite for laboratories to be able to provide personalized medicine/diagnostics collaboration with bioinformatics, data, scientists, and AI specialists, as well as Financial support for acquiring hardware and software would be necessary to mention. in my humble opinion, I think this should be discussed and also included in the conclusion.

Reply 2: We appreciate the raised point. The manuscript has undergone revisions, including the addition of extra material following the guidance of other reviewers. Kindly review the Challenges and Opportunities section, and we trust it meets the satisfaction of the esteemed reviewer. Should further writing be necessary, we are more than willing to incorporate it with your guidance.

Comment 3: Page 7: Please change the term medicines to medications or treatment options.

Reply 3: Corrected as per instructions

Comment 4: Please change the term databank to a database.

Reply 4: Corrected as per instructions

Comment 5: Protein biomarkers can be measured by other methods than immunoassays or mass spectrometry, such as nephelometric or colorimetric methods.

Reply 5: As per instructions few more methods have been added.

Comment 6: The last two figures are both titled Figure 2 and the last figure (figure 3?) Is not referenced within the text.

Reply 6: Corrected and added in text before conclusion section.