PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

The impact of Comprehensive Genomic Profiling and Molecular Tumor Board on Costs and Access to Tailored Therapies: real-world observational study

Authors

De Micheli, Valentina; Agnelli, Luca; Conca, Elena; Rabsiun Aramburu, Victoria Lucia; Baggi, Anna; Vingiani, Andrea; Duca, Matteo; Perrone, Federica; Tamborini, Elena; Piccolo, Alberta; Lorenzini, Daniele; Busico, Adele; Capone, Iolanda; Niger, Monica; Proto, Claudia; Vernieri, Claudio; Manoukian, Siranoush; Gancitano, Giovanni; Ferrario, Matteo; Franzini, Jean Marie; De Braud, Filippo; Pruneri, Giancarlo; Jommi, Claudio

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Furukawa, Toru**
Affiliation	**Tohoku University Graduate School of Medicine, Investigative Pathology**
Date	**19-Feb-2025**
COI	**None**

In this study, 1) patients' eligibility to personalized therapies based upon genomic data obtained using targeted somatic NGS panels; 2) MTB cost and the overall diagnostic journey cost; and 3) The cost to find a patient eligible to access personalized treatments were retrospectively analyzed in 676 oncological patients evaluated by the INT MTB from April 2020 to September 2021 including 458 NSCLC, 65 CCA, 77 PC and 77 GEC patients. Results indicated that Tumor profiling with comprehensive NGS panels improved patients' eligibility to personalized therapies compared to small panels (NSCLC: 39% comprehensive panel vs. 37% small panel; CCA: 43% vs. 17%; PC: 35% vs. 3%; GEC: 40% vs 0%). The overall diagnostic journey cost per patient was between 3.2K and 7.4K (NSCLC: 7.4K comprehensive panel vs. 6.4K small panel; CCA: 4.9K vs. 3.7K; PC: 5.8K vs. 4.5K; GEC: 4.2K vs 3.2K). MTB discussion accounted for only 2-3% of the diagnostic journey cost per patient (around 113€/patient). The cost to find patient eligible to personalized treatments varied significantly according to panel size and tumor setting (NSCLC: 5K comprehensive panel vs. 2.8K small panel; CCA: 4.4K

vs. 4.4K; PC: 5.5K vs. 27K; GEC: 5.2K vs. not measurable since none of the patients analyzed with small NGS panels were eligible). The authors concluded that MTB discussion of genomic data obtained with NGS comprehensive panels significantly increase patient eligibility to targeted therapies and optimize the cost to find a patient eligible to personalized treatments, mainly for CCA, PC and GEC patients.

This study proved the overall eligibility to personalized treatment by CGP, enhancement of patients' accessibility to targeted therapies, the average MTB cost, the cost to find a patient eligible to access personalized medicines, and preferability of the comprehensive panel for CGP compared to the small panel to find targeted therapies for patients with CCA, PC and GEC. A concern is as follows:

The authors should show what genes were tested in the small and comprehensive panels, respectively. The result implied that the small panel may be adapted/optimized for lung cancer rather than pancreatic cancer or gastroesophageal cancer. It is highly curious whether the eligibility of patients to targeted therapies would be increased if the small panel is adapted for each cancer type.

Reviewer	**2**
Name	**Prajapati , Bhupendra**
Affiliation	**Ganpat University, Pharmaceutics**
Date	**25-Feb-2025**
COI	**None**

This study provides valuable insights into the economic impact of using comprehensive genomic profiling (CGP) and molecular tumor boards (MTB) for personalized cancer treatments. The findings highlight improved patient eligibility for targeted therapies and cost optimization, particularly for certain cancers. Further exploration of long-term clinical benefits and broader healthcare implications would strengthen the study. The comment to improve the manuscript are :

1. Briefly describe, Explain why comparing small vs. comprehensive NGS panels is important in cancer treatment.

2. The introduction should better highlight the computation biology and genomics, refer recent work like : https://doi.org/10.25259/Cytojournal_47_2021, https://doi.org/10.1038/s42003-024-06488-9, https://doi.org/10.25259/cytojournal_47_2021, https://doi.org/10.1093/nar/gkae1008, https://doi.org/10.1016/j.stem.2024.04.021 etc

3. The eligibility improvement is significant, particularly for PC and GEC. However, discussing potential reasons for these differences would strengthen the findings.

4. Provide a clearer breakdown of how costs were calculated, especially regarding the cost of identifying eligible patients across different tumor types.

5. tabular data not clearly visible as its cut off..arrange appropriately

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VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:
In this study, 1) patients' eligibility to personalized therapies based upon genomic data obtained using targeted somatic NGS panels; 2) MTB cost and the overall diagnostic journey cost; and 3) The cost to find a patient eligible to access personalized treatments were retrospectively analyzed in 676 oncological patients evaluated by the INT MTB from April 2020 to September 2021 including 458 NSCLC, 65 CCA, 77 PC and 77 GEC patients. Results indicated that Tumor profiling with comprehensive NGS panels improved patients' eligibility to personalized therapies compared to small panels (NSCLC: 39% comprehensive panel vs. 37% small panel; CCA: 43% vs. 17%; PC: 35% vs. 3%; GEC: 40% vs 0%). The overall diagnostic journey cost per patient was between 3.2K and 7.4K (NSCLC: 7.4K comprehensive panel vs. 6.4K small panel; CCA: 4.9K vs. 3.7K; PC: 5.8K vs. 4.5K; GEC: 4.2K vs 3.2K). MTB discussion accounted for only 2-3% of the diagnostic journey cost per patient (around 113€/patient). The cost to find patient eligible to personalized treatments varied significantly according to panel size and tumor setting (NSCLC: 5K comprehensive panel vs. 2.8K small panel; CCA: 4.4K vs. 4.4K; PC: 5.5K vs. 27K; GEC: 5.2K vs. not measurable since none of the patients analyzed with small NGS panels were eligible). The authors concluded that MTB discussion of genomic data obtained with NGS comprehensive panels significantly increase patient eligibility to targeted therapies and optimize the cost to find a patient eligible to personalized treatments, mainly for CCA, PC and GEC patients.
This study proved the overall eligibility to personalized treatment by CGP, enhancement of patients' accessibility to targeted therapies, the average MTB cost, the cost to find a patient eligible to access personalized medicines, and preferability of the comprehensive panel for CGP compared to the small panel to find targeted therapies for patients with CCA, PC and GEC. A concern is as follows:
The authors should show what genes were tested in the small and comprehensive panels, respectively. The result implied that the small panel may be adapted/optimized for lung cancer rather than pancreatic cancer or gastroesophageal cancer. It is highly curious whether the eligibility of patients to targeted therapies would be increased if the small panel is adapted for each cancer type.

We thank the Reviewer for this suggestion. The list of genes tested in small and comprehensive panel has been included as Supplementary Data. *Undoubtedly, the use of customized small panels*

investigating the biomarkers for which on-label drugs are available might significantly increase the chance to select patients for personalized therapies, e.g. in virtue of faster analyses or less demanding computational efforts. On the other hand, customizing different panels for each tumor cancer subtype would be costly and time consuming and would require significant additional workload (and adequate cohorts) for internal validation. Furthermore, given the steady incorporation of new biomarkers in clinical practice, this would compel to frequently adapt the customization.
These considerations have been added to the discussion section of the revised version.

Reviewer: 2
Dr. Bhupendra Prajapati, Ganpat University, Silpakorn University
Comments to the Author:
This study provides valuable insights into the economic impact of using comprehensive genomic profiling (CGP) and molecular tumor boards (MTB) for personalized cancer treatments. The findings highlight improved patient eligibility for targeted therapies and cost optimization, particularly for certain cancers. Further exploration of long-term clinical benefits and broader healthcare implications would strengthen the study. The comment to improve the manuscript are :
1. Briefly describe, Explain why comparing small vs. comprehensive NGS panels is important in cancer treatment.

We thank the Reviewer for highlighting the need to discuss this aspect in greater depth. The following consideration has been added to the discussion section.
In the management of oncological patients, the therapeutic approach should not be limited to the use of on-label drugs but should necessarily extend to the rational and scientifically supported utilization of off-label treatments, as well as to the access to targeted clinical trials. This paradigm reflects the growing need for precision medicine, which, through a synergistic integration of emerging evidence, advanced genomic profiling, and multidisciplinary assessments, allows optimizing therapeutic efficacy in the context of real-world clinical practice. Consequently, this approach inherently drives the preference for large DNA/RNA sequencing panels over small panels, exploiting personalized therapeutic opportunities.

2. The introduction should better highlight the computation biology and genomics, refer recent work like: https://doi.org/10.25259/Cytojournal_47_2021, https://doi.org/10.1038/s42003-024-06488-9, https://doi.org/10.25259/cytojournal_47_2021, https://doi.org/10.1093/nar/gkae1008, https://doi.org/10.1016/j.stem.2024.04.021 etc

In accordance with the Reviewer's suggestion, we provided reference to highly-impacted review manuscripts that discuss the state-of-the-art of the wet-lab and bioinformatics pipeline for genomic/transcriptomic target identification in cancer: https://www.mdpi.com/2073-4425/15/8/1036, https://www.nature.com/articles/s41568-025-00795-x, https://www.nature.com/articles/s41571-023-00824-4

3. The eligibility improvement is significant, particularly for PC and GEC. However, discussing potential reasons for these differences would strengthen the findings.

We thank the Reviewer suggestion for his valuable suggestion and discussed this aspect in more detail in the revised version of the manuscript.

Other reasons prompt to sustain the advantages described by the eligibility improvement, particularly for PC and GEC. Among these, Copy Number Variations (CNVs) are emerging as a promising biomarker for treatment stratification, particularly in cancer settings in which on-label treatments are scarce. This dynamic scenario underscores the necessity for more comprehensive genomic analysis beyond standard sequencing panels, to achieve a more thorough molecular dissection capable of capturing clinically relevant CNVs.

4. Provide a clearer breakdown of how costs were calculated, especially regarding the cost of identifying eligible patients across different tumor types.

According to Reviewer's suggestion, these data have been moved from supplementary section to Methods in the revised version of the manuscript.

5. Tabular data not clearly visible as its cut off. arrange appropriately

In the revised version of the manuscript, all tables and images are properly arranged and fully visible, with each one uploaded individually for clarity.