Peer Review File

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Reviewer A

Authors conducted a narrative review to investigate the value of nutrition support therapy in patients with gastrointestinal malignancies with focus on the health economic analysis of impact on clinical outcomes in the United States. From eight studies were found with clinical outcomes and health cost savings data, 2 of those had the strongest level of evidence and were used for Value Analysis calculations. Nutrition interventions such as oral diet modifications, enteral nutrition supplementation, and parenteral nutrition have been studied especially in the peri-operative setting. Specifically, perioperative immuno-nutrition administration and utilization of enhanced recovery pathways after surgery have been associated with significant improvement in postoperative complications and decreased length of hospital stay. Utilizing economic modeling of Medicare claims data from GI cancer patients, potential annual cost savings of $242 million were projected by the widespread adoption of these interventions. In summary, they concluded that the application of nutrition intervention provides a positive clinical and economic value proposition to the healthcare system for patients with gastrointestinal cancers. The results seems interesting and appealing; however, there are a lot of criticisms and have several issues that the authors need to address before the manuscript is suitable for publication.

Major Compulsory Revisions:

1. In Methodology section: This search was conducted using PubMed and Google Scholar in 5-year look-back period, for human trials and papers in English, published in both her US & International. Authors have to provide the exact keywords for the literature search here.
   Reply: We appreciate the comments from the reviewers. The list of search terms that we used added to the manuscript as Table 2. We also added clarity on the text for the literature review methods as follows:

   Page 5ln 27 up to page 6line 9. "A literature assessment rubric that was developed by the ASPEN Value Project group was used to evaluate each article identified in the search to select publications for inclusion in the final analysis.[24] The rubric, consisted of 4 domains with a point-based scoring system: A. Level of evidence using the GRADE evidence scale (1to 5), B. Outcomes of interest (0 to 3), C. Type of nutrition intervention (0-4) D. Scalability (1-4). [24] The initial ASPEN Value Project search 2012-2018 yielded 10 qualifying studies in this population, 7 of which used oral nutrition supplements (ONS), enteral nutrition (EN), or parenteral nutrition (PN), as nutrition support.[2423] The additional search in 2019 yielded one additional clinical trial[25] (Figure 2). Narrative analysis of the qualifying papers was performed. Of the eleven papers only 2 received the highest marks across the 4 domains and were selected to be used in the Medicare claims data analysis described below."

2. In Methodology section: The initial ASPEN Value Project search 2012-2018 yielded 10

qualifying studies in this population, 7 of which used oral nutrition supplements (ONS), enteral nutrition (EN), or parenteral nutrition (PN), as nutrition support. The additional search in 2019 yielded one additional clinical trial (Figure 2). The papers with the strongest evidence for cost savings were then selected to be used in the Medicare claims data analysis described below. Please explain in more details how authors select 2 papers with the strongest evidence for potential cost savings. Two studies are relatively few to have a powerful conclusion.

Reply: Thank you for this comment we added additional details of the value analysis cost as expressed by our previous paper reference 24. And modified the text for the Value analysis methodology:

Page 6 ln14 to page 7 ln5 : "An analysis of potential cost savings of nutrition interventions for the Medicare population was conducted using the methodology published previously by our group;[24] initially the papers with the strongest evidence for cost savings were selected and analyzed. The objective of the analysis was to model the effects of the specific nutrition interventions studied on the specific GI cancer population. This modeling exercise consisted on identifying the cost and healthcare resource utilization implications on the GI cancer population, with the goal of determining the impact of nutrition support on reducing these costs as reflected in the summary of the evidence, and identify the maximum potential savings to the Medicare program as demonstrated by modeling the findings described in the studies if all patients with the diagnoses of GI cancers received the beneficial nutrition intervention, annualized savings were projected.[24] The Medicare data Source was Avalere Health, a Washington, DC-based health policy firm who on behalf of ASPEN obtained the appropriate human participant approvals to analyze the Medicare fee-for-service Parts A and B claims 5% sample dataset according to Medicare requirements.[24] These claims include information on procedures, diagnoses, and payments organized by individual beneficiary. The 5% sample is recognized as being statistically representative of the entire Medicare population and can be roughly adjusted to the full 100% population by multiplying raw results by 20.[24] Relevant ICD-10 codes were used for the different GI cancer diagnosis. For each included study, findings were applied to the defined population and savings associated with reduced adverse outcomes or healthcare resource utilization were measured (such as, shorter LOS or reduced complications)."

3. In Results section: The literature is presented based on three types of nutrition interventions, oral nutrition (ONS), enteral nutrition (EN), and parenteral nutrition (PN). Patients also received nutrition in the pre-operative period, post-operative, or both. The above 3 types of nutrition interventions were administrated to different patient populations, of which it would lead to some bias to put them together.

Reply: The authors agree 100% with the reviewer regarding the fact that nutrition interventions were varied and in different types of gastrointestinal cancers. And our intent was not to endorse one route for perioperative nutrition nor one specific intervention but to provide an economic frame were nutrition intervention in these complex patients can be discussed. We have added language in the discussion section to bring clarity.

Page 9 line24: we added "Although is beyond our analysis to exhaustively review specific interventions"

4. No Figures or Tables were accompanied with the text.
   Reply :We apologize for this formatting failure.

5. Table 1. Factors Associated with Malnutrition in Cancer Patients. Therefore, it is confusing that authors wish to investigate the value of nutrition support therapy in non-malnourished patients with gastrointestinal malignancies or malnourished patients with investigate the value of nutrition support therapy in patients with gastrointestinal malignancies? Furthermore, the target population of nutrition interventions were only for the subsequent surgery or including other intensive therapy, for example, radiotherapy or chemotherapy?
   Reply: Thank you for the comment, our intent with this table was to highlight the multifactorial etiology of malnutrition in patients with gastrointestinal cancers. We clearly understand that the nutritional status is a fluid condition in cancer patients, and they can go from having adequate nutrition, to being at risk of malnutrition and finally becoming malnourished. Our hope is that by recognizing the risk factors and etiologies for malnutrition we can prevent patients developing this devastating problem, therefore, different types of nutrition interventions will be adequate for different patients at different stages of their disease or therapy

Reviewer B

This manuscript claims to report on an economic analysis of the effect of nutrition interventions in the United States. In the present form, it is impossible for me to judge the value of this manuscript.

1. The manuscript frequently refers to tables and figures which are not provided with the file available for review.
   Reply: we apologize for the problems with the paper formatting we have added the figures and tables to the text

2. The Abstract provides inadequate information on the methodology used and no information on the quality of the single numerical data given in the Results section. Thus, the conclusions presented appear unwarranted.

Specifically:

2. Somewhere the authors explain the review to be a “narrative”; however, I do not find this word in the ms; the ms only refers to a “targeted” review (p5 ln20). What kind of review does this specify?
   Reply: We appreciate the reviewer comment and have clarified the terms utilized for the search by adding Table 2. Additionally, we have added the following text to the methods to clarify the literature review.

   Page 5ln 27 up to page 6line 9. “A literature assessment rubric that was developed by the ASPEN Value Project group was used to evaluate each article identified in the search to select publications for inclusion in the final analysis.[24] The rubric, consisted of 4 domains with a point-based scoring system: A. Level of evidence using the GRADE evidence scale (1to 5), B. Outcomes of interest (0 to 3), C. Type of nutrition intervention (0-4) D. Scalability (1-4). [24] The initial ASPEN Value Project search 2012-2018 yielded 10 qualifying studies in this population,

7 of which used oral nutrition supplements (ONS), enteral nutrition (EN), or parenteral nutrition (PN), as nutrition support.[2423] The additional search in 2019 yielded one additional clinical trial[25] (Figure 2). Narrative analysis of the qualifying papers was performed. Of the eleven papers only 2 received the highest marks across the 4 domains and were selected to be used in the Medicare claims data analysis described below."

3. Even if the authors refer for methodology to another paper (P5 ln 24), the Methodology should be explained in more detail to enable the reader to understand the procedure.
   Reply: Thank you very much for the comment we have modified the text for the Value analysis methodology for clarity.

   Page 6 ln14 to page 7 ln5 : "An analysis of potential cost savings of nutrition interventions for the Medicare population was conducted using the methodology published previously by our group;[24] initially the papers with the strongest evidence for cost savings were selected and analyzed. The objective of the analysis was to model the effects of the specific nutrition interventions studied on the specific GI cancer population. This modeling exercise consisted on identifying the cost and healthcare resource utilization implications on the GI cancer population, with the goal of determining the impact of nutrition support on reducing these costs as reflected in the summary of the evidence, and identify the maximum potential savings to the Medicare program as demonstrated by modeling the findings described in the studies if all patients with the diagnoses of GI cancers received the beneficial nutrition intervention, annualized savings were projected.[24] The Medicare data Source was Avalere Health, a Washington, DC-based health policy firm who on behalf of ASPEN obtained the appropriate human participant approvals to analyze the Medicare fee-for-service Parts A and B claims 5% sample dataset according to Medicare requirements.[24] These claims include information on procedures, diagnoses, and payments organized by individual beneficiary. The 5% sample is recognized as being statistically representative of the entire Medicare population and can be roughly adjusted to the full 100% population by multiplying raw results by 20.[24] Relevant ICD-10 codes were used for the different GI cancer diagnosis. For each included study, findings were applied to the defined population and savings associated with reduced adverse outcomes or healthcare resource utilization were measured (such as, shorter LOS or reduced complications)."

4. Who is the "GI cancer workgroup (P5, ln 26)?
   Reply: We appreciate the comments and apologize for the lack of clarity. We have clarified in page 5 line 20 that the GI cancer group is a multidisciplinary working group within the ASPEN Value project team.
5. Instead of "high impact" the authors most probably want to refer to e.g. "high evidence" papers (P5, ln27). Standard agreement is that systematic reviews are of a different evidence level than narrative reviews.
   Reply: we appreciate the reviewer comment and have change the word, Thank you
6. What does the sentence on "strongest evidence for cost savings" refer to (P6, ln 6)? How was the ranking performed?
   Reply: Thank you for your question we have added the following in page 5 and 6

Page 5ln 27 up to page 6line 9. "A literature assessment rubric that was developed by the ASPEN Value Project group was used to evaluate each article identified in the search to select publications for inclusion in the final analysis.[24] The rubric, consisted of 4 domains with a point-based scoring system: A. Level of evidence using the GRADE evidence scale (1to 5), B. Outcomes of interest (0 to 3), C. Type of nutrition intervention (0-4) D. Scalability (1-4). [24] The initial ASPEN Value Project search 2012-2018 yielded 10 qualifying studies in this population, 7 of which used oral nutrition supplements (ONS), enteral nutrition (EN), or parenteral nutrition (PN), as nutrition support.[2423] The additional search in 2019 yielded one additional clinical trial[25] (Figure 2). Narrative analysis of the qualifying papers was performed. Of the eleven papers only 2 received the highest marks across the 4 domains and were selected to be used in the Medicare claims data analysis described below."

7. I do not understand the concept of the procedure referred to on P6 ln 12-13: "... findings were analyzed and modeled..." Please explain.
   Reply: Thank you for your comments we have clarified the methods section for clarity (page6)
8. Why are the results of 2 selected papers referred to as either reporting "cost savings" (P6 ln6) or as "potential cost savings" (P6 ln13)?
   Reply: Cost savings was used for the ones reported by the literature (line6), potential refers to the calculated savings based on the economic modeling (ln13). We have removed the word potential in ln 13, thank you for catching this
9. The sentences on P6 ln 16-19 are difficult to understand: how was Medicare claims data analyzed? The remainder of the sentence is to complex for my simple mind.
   Reply r: Thank you for your comments we have clarified the methods section for clarity (page6)
10. How were "relevant ICD-10 code sets" generated? Which sets?
    Reply: We have clarified the wording in the methods section (page6)
11. Is there a contradiction, when first it is reported that articles were excluded if dealing with mortality (P7 ln 11) and later trials are reported showing a decrease in mortality (P7 ln 24)?
    Reply: Thank you for pointing this out, and sorry we did not make it clear enough. Papers that reported mortality, nonspecific complications or quality of life were excluded of the Medicare Value analysis (Figure 2), but not of the narrative analysis. We added clarity in page 8 ln 7
12. Similarly, it is first stated that trials comparing EN vs PN were excluded (P7 ln 13) but later it is stated that EN was compared to PN (P7 ln 25).
13. Reply: Thank you for pointing this out, and sorry we did not make it clear enough. Papers that compare head to head nutrition interventions were excluded of the Medicare Value analysis but not of the narrative analysis we added clarity in page 8 ln 7