Peer-review Comments and Author Responses

Reviewer 1

1. *Redundancy in the Definition of PROMs: "When dealing with ETD, PROMs can be valuable tools for evaluating how the condition affects patients' quality of life and guiding treatment decisions. PROMs have the potential to complement objective measures by capturing patients' personal experiences and functional limitations. This helps healthcare professionals gain a comprehensive understanding of the illness and its impacts. PROMs refer to validated tools or questionnaires that gather insights about patients' health and quality of life from their own perspectives. These tools serve various purposes, such as aiding in treatment choices, enhancing communication between patients and healthcare providers, assessing the quality of healthcare services, and supporting research (Johnston et al., 2022; Agarwal et al., 2021)."*

Response: I agree that these definitions of PROMs are redundant. Reviewer #1 pointed out redundant text in these definitions and recommended a more compact approach.

To avoid repeating these definitions, the corresponding text on page 9 has been modified. The content is now more concise, focusing on the use of PROMs in ETD without reiterating previously stated facts, as follows:

> "PROMs are critical for assessing the impact of vertigo on patient well-being in the management of ETD. They provide a patient-centered perspective, which is essential for determining how vertigo affects quality of life and informs treatment decisions. This approach is especially important in ETD since the subjective nature of vertigo necessitates an evaluation that goes beyond clinical criteria to ensure treatments are aligned with patients' feelings and needs."

2. *References in the Conclusion: "ETD is a common condition that can significantly affect the quality of life of patients. The development of BMs and COAs can increase the accuracy of the diagnosis and assessment of the severity of ETD and treatment efficacy. However, less focus has been placed on incorporating vertigo as a symptom in recent COAs for ETD, necessitating further research in this area. Some studies have added vertigo as an outcome measure, rendering it a potential symptom for inclusion in future COAs for ETD. Based on recent research, new COAs for ETD can be improved by adding objective measures, considering such comorbidities as LPR and vegetative symptoms, and using digital health technologies (Kim, 2015; Roland, 2004; Rosenberg et al., 2023; Sánchez-Manso et al., 2022; Thompson & Amedee, 2009) (Table 1)."*

Response: Reviewer 1 has advised avoiding using references or tables in the conclusion section for a clearer and more focused conclusion.

As advised, I have deleted references and Table 1 from the conclusion section. The updated conclusion is now independent of these parts and focuses more on describing the study's findings and implications, as follows:

> "ETD is a common condition that can significantly affect the quality of life of patients. The development of BMs and COAs can increase the accuracy of the diagnosis and assessment of the severity of ETD and treatment efficacy. However, less focus has been placed on

incorporating vertigo as a symptom in recent COAs for ETD, necessitating further research in this area. Some studies have added vertigo as an outcome measure, rendering it a potential symptom for inclusion in future COAs for ETD. Based on recent research, new COAs for ETD can be improved by adding objective measures, considering such comorbidities as LPR and vegetative symptoms, and using digital health technologies."

Reviewer 2

3. *Some of the major suggestions regarding this review are regarding the formatting and language flow of the review. The manuscript requires adjustments in terms of grammar, language, spelling, consistency, and readability. I have added comments to the document to bring this to your attention.*

Reviewer #2 recommended improvements to grammar, language, spelling, consistency, and readability. The work has been edited extensively to correct grammatical errors and enhance readability. Special care has been taken to ensure consistency in vocabulary and style. I believe I have adequately addressed the reviewer's comments.

4. *Some sections of the document appear to be repetitive, such as the discussions on the limitations of MEP as a BM and the limitations of the ETDQ-7 as a PROM. Consider consolidating these sections for a more concise presentation.*

As highlighted by Reviewer #2, some sections of the text appear to be redundant, such as explanations on the limitations of MEP as a BM and the constraints of the ETDQ-7 as a PROM, and it was suggested that these sections be combined to present the material more concisely. I integrated the sections "Limitations and challenges of using MEP as a biomarker for ETD" and "Limitations and challenges of using the ETDQ-7 as a PROM for ETD," and I included a new section, termed "Integrating Objective and Subjective Measures: Understanding the Limitations of MEP and ETDQ-7 in ETD Diagnosis." To minimize repetition and present the text more clearly and succinctly, the sections on the limits of MEP as a BM and the ETDQ-7 as a PROM have been combined, as follows:

Integrating objective and subjective measures: Understanding the limitations of MEP and the ETDQ-7 in diagnosing ETD

MEP

Although MEP has been proposed as a BM for ETD, its implications are not always easy to determine. A type C tympanogram that shows a negative MEP at rest and tympanic insufflation that reveals active negative pressure (Hamrang-Yousefi et al., 2022) do not necessarily indicate ETD (Bluestone, 2018; Smith et al., 2019). Despite a clear tympanic membrane and no signs of an ME infection, the function of the ET must be checked (Bluestone, 2018), primarily due to the emergence of symptoms that might be attributed to ETD. For example, an MEP above -50 daPa [BPS1] [HYK2] does not always reflect a normally functioning ET. For instance, an asymmetrical

MEP case could simply indicate balance problems (Kim, 2021; Kim, 2023b). If the MEP values are considered normal solely because they do not dip below -50 daPa, bias has clearly been introduced—a systematic error that leads to an incorrect measurement of a dependent variable and, as a result, a false conclusion (Fregni & Illigens, 2018).

ETD is usually treated by inserting a ventilation tube to bypass the ET, restoring ambient MEP, preventing inflammation of the ME, draining effusions, and improving hearing (Bluestone, 2018; Kim, 2023a; Kim, 2023b; Teixeira, 2020). Asymmetrical MEPs are a potential cause of ABV, and it can be challenging to distinguish between unilateral and bilateral ETD (Bluestone, 2018; Kim, 2017; Kim, 2021; Kim, 2023b). Thus, combining tympanometry, acoustic reflex testing, and MEP measurements can help one diagnose ETD more accurately (Teixeira, 2020).

Testing ET function is the first step toward understanding that ETD is more than just being "too closed" or "too open" and in fact comprises a spectrum of disorders with varying causes and effects (Teixeira, 2020). The state in which vestibular functions are perfectly equalized is referred to as balance. This status requires the pressure in the ME to be equal bilaterally. Only tympanometry results of 0 daPa for MEP on both sides should be considered normal, and ranges in MEP should be classified as mild, moderate, or severe. By learning how ETD symptoms behave, we realize that the normal range and commonly used types of tympanometry are ineffective. Only by changing the normal criteria for tympanometry can a new method be developed for validating MEP as a surrogate BM for ETD and the results after ETC. This new tympanometric approach uses normal criteria with an MEP of only 0 daPa.

ETDQ-7

Similarly, the ETDQ-7 has several drawbacks. Many symptoms of ETC, particularly those that are less typically reported, are not captured by the ETDQ-7—most notably, vertigo—reducing the tool's comprehensiveness (Bluestone, 2018; Bluestone et al., 2012; Mallen & Roberts, 2019). Further, voice disturbance, a sign of LPR that can develop from ETD, should be considered a possible symptom in the ETDQ-7 (Brown & Shermetaro, 2022; Kim, 2015); its neglect could result in insufficient portrayal of the patient's experience. The ETDQ-7 also suffers from a lack of precise criteria for what defines normal and abnormal responses. This ambiguity might complicate the distinction between levels of ETD severity, influencing therapy options and patient management techniques.

That the ETDQ-7 is not an objective measure of ET function (Andresen et al., 2021) is particularly significant, given the varied and complex nature of ETD symptoms and their potential impact on quality of life (Teixeira, 2020). Responses on the ETDQ-7 may be influenced by factors that are unrelated to ETD, such as emotional state and other concurrent health issues, perhaps skewing the results and impacting the accuracy of the diagnosis. Thus, its subjective nature requires careful interpretation and consideration of additional corroborative diagnostic instruments. Although it excels at capturing patient-reported outcomes, it can not replace the objective metrics that are required for a complete ETD assessment. More study is needed to increase the validity, reliability, and inclusivity of the ETDQ-7 as a supplement to objective diagnostic measures, such as MEP (Andresen et al., 2021).

Complementation of measures

The testing criteria for understanding ET function are constantly expanding through research using objective measures (Alper et al., 2019; Smith et al., 2018b). In this pursuit, we must use multiple tests and conduct research to develop more accurate and reliable methods of measuring ET function to improve the diagnosis and treatment of ETD-related conditions, such as ABV. PROMs are useful in validating BMs, particularly for such conditions as ETD, in which subjective symptoms carry significant weight alongside objective measurements. Although BMs provide objective data, the human experience of a disease is multifaceted. PROMs consider the patient's perspective, ensuring that validated BMs are scientifically valid and clinically relevant. By combining these aspects, we can gain a comprehensive understanding of ETD and the value of BMs, like MEP. To improve patient care, it might be advantageous to first recognize the patient's viewpoint through PROMs.

5. *In terms of content, kindly consider adding insight into the anatomical and physiological aspects of ET function, as it will create a flow into how it's presented.*

Reviewer #2 suggested including information on the anatomical and physiological aspects of ET function. I agree that adding content on "Anatomical and Physiological Insights into Eustachian Tube Function" to the manuscript is an effective strategy. This information has been added to the subsection "Definition of biomarkers in the "Biomarkers for ETD" to improve the reader's understanding of the study's context and significance as follows:

Understanding the anatomical and physiological properties of the ET is crucial for understanding its role in ear health and the repercussions of its failure. The ET, which connects the middle ear to the nasopharynx, is essential for regulating middle ear pressure, increasing air ventilation, and protecting the ear from nasopharyngeal secretions and viruses. It is roughly 35 mm long, with a bony section near the middle ear and a flexible cartilaginous section towards the nasopharynx, providing for excellent pressure equalization and fluid outflow. The ET equalizes air pressure on both sides of the eardrum, which is essential for optimal hearing, and protects the middle ear from infections. Dysfunction of the ET can cause symptoms such as ear pain, fullness, tinnitus, and hearing loss, and persistent ETD can progress to more severe disorders such as middle ear effusions or otitis media.

6. *Limitations:*

   According to Reviewer #2, although it discusses the available biomarkers and patient-reported outcome measures (PROMs), this review does not explain how to differentiate the three forms of ETD using these tools. This omission was due to the absence of literature, which Reviewer 2 suggested mentioning in the limitations section to this end, the following subsection was added to the manuscript:

Limitations and future directions in ETD research

A notable gap exists in the literature regarding the lack of methods that differentiate the 3 types of ETD using BMs (e.g., MEP) and PROMs (e.g., ETDQ-7). Current diagnostic methods are more concerned with detecting the presence and severity of ETD than with classifying its types. Addressing this gap is critical for customizing treatment regimens in ETD.

Future research should strive to identify and validate biomarkers and PROMs that can properly classify ETD types, perhaps examining specific symptom patterns and objective findings that are unique to each type. Further, advances in digital health may affect more efficient collection and processing of data, providing new insights into the diagnosis of ETD.

7. *Provide information about the demographic characteristics of the established biomarkers and the patient-reported outcome measures that have been the subject of discussion in this paper, particularly in terms of their applicability.*

Reviewer #2 recommended providing information on the demographics of the established biomarkers and patient-reported outcome measures, particularly in terms of their applicability. The manuscript now provides a full discussion of the demographics that are pertinent to the biomarkers and PROMs under examination, highlighting their usefulness and limitations as follows:

Demographic considerations of BMs and PROMs for diagnosing ETD

When evaluating BMs and PROMs for ETD, it is critical to consider their effectiveness across demographic groups. The dependability of MEP can fluctuate by age and gender, due to physiological differences and changes, whereas the ETDQ-7 requires cultural and linguistic adjustments to ensure accuracy across populations. Further, for ePROMs, such factors as digital literacy and accessibility can influence their adoption in various socioeconomic circumstances. As a result, ensuring that these instruments are verified over a broad demographic spectrum is crucial for their general application in clinical and research settings.

To this end, PROMIS (Patient-Reported Outcomes Measurement Information System) was created to assess self-reported physical, mental, and social health. It has shown strong reliability and validity across varied populations, demonstrating its comparability with heritage instruments as a measure of generic symptoms and functional reports (Cella et al., 2010).

8. Reviewer #2 made a recommendation as follows: *"Please specify the prevalence of the condition and the specific age group or demographic your review is targeting. Additionally, provide information about the demographic profile of the existing biomarkers and the currently utilized patient-reported outcome measures discussed in this paper can be used for."*

Response: I agreed with this suggestion and inserted the following in the "Introduction" section. However, we believe that these statistical epidemiological data will shift as the diagnostic criteria for ETDs evolve.

“ETD affects adults and children, with its prevalence varying by age group. ETD affects approximately 1% of the adult population, underscoring its clinical relevance, whereas children have a higher incidence, with a significant 0.77 adult-to-pediatric visit ratio, highlighting this condition's importance in pediatric care. By school age, nearly all children (90%) may develop otitis media with effusion, which is frequently associated with ETD. Gender differences also arise, with males being diagnosed with ETD before age 20 years, whereas females are more likely to develop the disorder as they age. The prevalence of ETD does not appear to vary by season, indicating a constant risk throughout the year. These findings are critical for developing age-specific and gender-specific biomarkers and patient-reported outcome measures to effectively assess and manage ETD (Hamrang-Yousefi, Ng, & Andaloro, 2022).”

Reviewer 3

9. *Comment 1: "MEP has been proposed as a surrogate endpoint BM of ET function and can be used to measure the efficacy of treatments for ETD (Aronson, 2005; Bluestone et al., 2012; Schilder et al., 2015). “*

The following questions were posed to me by Reviewer 3: What were the findings of these primary studies? What do they conclude, and who was studied? I need information on the major studies that proposed Middle Ear Pressure (MEP) as a surrogate endpoint biomarker (BM) of Eustachian Tube (ET) function and its application in determining the efficacy of treatments for Eustachian Tube Dysfunction (ETD).

Response: Ideally, to cite specific research that has explored MEP in this context, I added the following articles:

- Llewellyn, G. Norman, M. Harden, A. Coatesworth, D. Kimberling, A. Schilder, and C. McDaid (2014). A systematic review of adult Eustachian tube dysfunction treatments. Health Technology Assessment, 18(46). https://doi.org/10.3310/hta18460

- Kim, H-Y. (2023b). A case report on ground-level alternobaric vertigo due to Eustachian tube dysfunction with the assistance of conversational generative pre-trained transformer (chatgpt). Cureus. https://doi.org/10.7759/cureus.36830;

These studies examined several ETD-related procedures, including surgical and pharmaceutical treatments. The success of these therapies was assessed in terms of symptom intensity, quality of life, and middle ear function, which includes MEP as an important metric.

10. *Was the ETDQ-7 tool validated for many populations/languages? I was wondering if it could be indeed considered a biomarker if the tool is not validated yet for large populations... Again, I missed here results from studies showing associations between ETDO-7 and clinical outcomes.*

Reviewer #3 mentioned the following: “Was the ETDQ-7 tool validated for many populations and languages? I was wondering if it could indeed be considered a biomarker if the tool has not been

validated yet for large populations. Again, I missed the results from studies showing associations between ETDO-7 and clinical outcomes."

Response: Several studies have validated the ETDQ-7 across multiple languages and cultures, ensuring its global applicability as a tool for diagnosing Eustachian tube dysfunction. However, such an opinion is not acceptable to me. I have an opinion regarding the construction of new PROMs for ETD. I believe that the ETDQ7 was validated for the sole purpose of ET balloon tuboplasty. I recommend the following articles: 1. FDA-NIH Biomarker Working Group (2017a). BEST (Biomarkers, Endpoints, and Other Tools) Resource [Internet] Silver Spring (MD): Food and Drug Administration (US); 2016–. Validation. 2017 Sep 25 [Updated 2021 Nov 29]. Co-published by the National Institutes of Health (US), Bethesda (MD). Available from https://www.ncbi.nlm.nih.gov/books/NBK464453/ ; 2. McCoul, E. (2020, July 31). Eustachian tube dysfunction: evidence and controversies. AAO-HNS Bulletin. https://bulletin.entnet.org/home/article/21247953/eustachian-tube-dysfunction-evidence-and-controversies; 3. McCoul, E. D., Anand, V. K., & Christos, P. J. (2012). Validating the clinical assessment of eustachian tube dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7) Laryngoscope, 122(5), 1137–1141. https://doi.org/10.1002/lary.23223

11. Relevance of specific sections: Reviewer #3 mentioned *"What is the relevance of the section 'A step-by-step guide to creating PROMs for vertigo in ETD,' considering that the aim of the article was to examine the current state of BMs and COAs in ETD, including the methods by which they have been evaluated historically and their potential clinical applications?" the same for Table 1, what is its relevance?"*

Response: The section's goal was to validate the new PROMs. The subheading title should be changed from "A step-by-step approach to developing PROMs for vertigo in ETD" to "A step-by-step guide to validating PROMs for vertigo in ETD." The section "A step-by-step guide to creating PROMs for vertigo in ETD" has been clarified and made more concise. Table 1's significance in the context of the article's purpose has also been examined.

12. Reviewer #3 stated, *"In general, the review is well-written, but I think that results from original studies in all sections would increase the link between clinical practice and the use of these new biomarkers."*

Response: It is difficult to comprehend what Reviewer 3 desires, but I have included the following two articles as original studies : 1. McCoul, E. D., Anand, V. K., & Christos, P. J. (2012). Validating the clinical assessment of eustachian tube dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7). Laryngoscope, 122(5), 1137–1141. https://doi.org/10.1002/lary.23223; and 2. Bluestone, C. D., Swarts, J. D., Furman, J. M., & Yellon, R. F. (2012). Persistent alternobaric vertigo at ground level. The Laryngoscope, 122(4), 868–872. https://doi.org/10.1002/lary.22182

The revised manuscript, as well as a clean copy with all tables and figures, is attached. I hope that the adjustments that I have made sufficiently address the reviewers' concerns and suggestions, and I look forward to the prospect of my work being published in PPCR Journal.

Thank you for your insightful criticism and the opportunity to polish my manuscript once more.

Sincerely,

Hee-Young Kim, MD, PhD