Peer Review File

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Reviewer Comments

Reviewer A

Abstract

The majority of the background section is copied from the authors' previously published abstract (Am J Clin Pathol 2022;158:S1-S29 DOI: 10.1093/ajcp/aqac126.) and could be considered plagiarism. Conclusions are not fully supported by evidence provided.

Editorial Note: The editorial office has checked and confirmed that the previous publication of the conference abstract is acceptable. Therefore, please move on to other helpful comments.

Response: Thank you for this feedback. We have reworded the abstract to more faithfully reflect a number of the improvements described below, with a focus on limiting the conclusion to only highlight findings directly supported by data in the paper.

Introduction:

Line 72-74. The authors state that PTHrP is a cause of >80% of all malignancy-related hypercalcemia based on the ref1. However, in this reference the percentage based on that data is actually only 77% (41/49). In addition discussion in ref 4 describes the contribution to be a lot less, with in region of 20-30%. The utility of this test needs to be discussed in light of this and whether it adds anything to the management of the patient.

Response: Thank you for highlighting this inconsistency. We have altered the language to read "a common cause of" to avoid making an estimate of incidence.

Line 77-78. No evidence provided that PTHrP is ordered in first round testing.

Authors need to discuss the limitations of the specialist test, the availability and methodology involved.

Response: Thank you for bringing this detail to our attention. We agree that relevant methodological details regarding collection and performance of the test were missing from the first draft. This line has been removed and replaced with a more thorough explanation of the testing methodology in the introduction and methods, including the transition away from PPACK tubes and towards a less specialized workflow (lines 222-230).

Authors need to introduce the basis of machine learning and how it can be applied.

Response: A paragraph of introductory concepts in machine learning and how we sought to apply it in this setting has been added (lines 136-141).

Methods:
Line 106. No manufacturer details are provided for R 4.1.2

Response: R core team has been added and credited.

Results:
Line 145-149. This should either in introduction or method, but not results.

Response: We have removed this sentence from the results as it is redundant with the methods.

Line 150. Authors need to describe the patient numbers first before launching into result including demographics of patient group.

Response: We have included a brief summary of the demographic details to which we have access prior to summarizing the results (lines 269-271).

Line 161. ML abbreviation not previously mentioned.

Response: ML abbreviation added to its first use in the introduction (line 136).

Line 166 MCC abbreviation not previously mentioned.

Response: MCC abbreviation added to its first use in line 288.

Line 175-195. Authors haven't demonstrated an understanding of how this test is used in normal practice, it's inherent stability issues that require a planned collection with the appropriate specialist tube etc. They are advised to review this and reflect it's utility. The conclusions they draw are not valid as the test is not routinely available and isn't a first line test.

Response: Thank you for highlight this very important procedural detail. A major part of the rationale for including only those results that had been performed after 2019 is that this date will exclude all results prior to the Mayo Clinic's transition away from the PPACK tube and towards a new assay that only requires the specimen to be collected on ice. We completely agree that the process considerations of the older workflow would have made this approach less valid, and it may certainly be the case that some of the discordance between the performance of the result predictors and the cancellation predictors may be attributed to providers having this prior workflow in mind. We have added this keen insight into the discussion section in lines 331-342.

Line 191. Expand CDS

Response: Thank you, we have made this change.

Reviewer B

I think this is a valuable paper to publish with an interesting use case. This can provide ideas to other researchers on how to utilize machine learning algorithms to help with some of the tasks currently done manually.

Comments to the authors:

A very interesting approach and use case of machine learning to automate some of the work done in the lab. It does show the resistance to cancel orders is harder to predict – which is possibly also due to some people not ready to cancel more than others. It would also be interesting to see if there is any relation between who the ordering/cancelling provider is or if it's a trainee or the attending. Well written paper as well.

Response: Thank you for this kind feedback and for the very interesting idea. We unfortunately have limited access to the training level of the ordering provider, but with a pending switch to a new LIS system in the coming years, we look forward to probing that issue further.