Project Name: A Systematic Review on RedPathTG® Diagnostics

Project ID: GEND0308

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	Overall, this TA is well-written and comprehensively addresses the limitations of this test, as well as the methodologic flaws in the studies. The important points were made: there is no evidence that this test will impact clinical decision-making in a way that will lead to a net health benefit as defined by clinical outcomes. Nor is there evidence of incremental value when compared to existing alternatives. The results need to be shown to be reproducible with application of the test (with a priori defined cut-offs) to independent samples for validation.	*We agree with the reviewer's summation of the Technology Assessment.*
1	General	Just a few suggestions on clarity: a more simplified explanation of LOH may be helpful for the reader who is not familiar with molecular testing. Also, it might help to clarify how LOH is used for the different PF indications: i.e. different panels are used to "diagnose malignancy" by detecting a level of LOH with a panel tailored to an organ (for example pancreas); comparing LOH profiles between two tumors to determine if they are separate primaries or a metastasis, etc.	*We followed the reviewer's suggestion and rephrased the pertinent section adapting some of the proposed wording.*
1	General	One additional study that I thought might meet the inclusion criteria: Khalid A et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol 2005; 3:967-73.	*We reviewed this study. We exclude this study based on our eligibility criteria. The reason is that –according to the description of the biochemical analyses in the Methods Section of said paper– topographic genotyping was not used for the LOH-based molecular analyses. For these analyses DNA was extracted from the cystic fluid. For the same reason we excluded the 2009 report of the PANDA study by Khalid et al.*

2	General	The report is clear and easy to read.	*Thank you.*
2	Introduction	The scope of the report is clearly defined. All clinically important issues were considered. No deficiencies.	*Thank you.*
2	Methods	1. The inclusion and exclusion criteria are appropriate. 2. There is published literature/work in progress that was missing from the report. 3. The report did not include materials that ought to be excluded or down-weighted. 4. The method for grading the quality of individual studies was not appropriate. 5. The method for analyzing data is not appropriate, nor is it clearly explained.	1. *Thank you.* 2. *We have assessed for eligibility all papers suggested by all reviewers. We accepted 5 additional papers that were published electronically or in print after our last literature search. We believe that the reviewer refers to these 5 papers.* 3. *Thank you.* 4. *We are unclear on what is problematic in the grading of the individual studies. We have rephrased the methods section to enhance clarity.* 5. *Please, see our reply to the previous comment of the reviewer.*
2	Methods	The report is thorough.	*Thank you.*
2	Results	The results are stated clearly and the figures and tables are clear. The tables and references support the conclusions of this report.	*Thank you.*
2	Discussion	The major findings are clear and accurate. The report is concise, thorough, and I concur with the conclusions presented in the Discussion section.	*Thank you.*
3	General	This is a comprehensive and well grounded review of existing public data on the use of this technology. I am in agreement with both the methodologies used and the conclusions reached by this systemic review.	*Thank you.*
3	General	The only additional note of caution that I would add is that implicit in the lack of evaluation of analytical validity of this system is the fact that there have obviously been no reports on preanalytical issues that might confound the diagnostic signal. I think this weakness is so important that it is worth emphasizing in the final discussion with a caveat related to	*We followed the reviewer's suggestion and rephrased the pertinent section adapting some of the proposed wording.*

		clinical use of this assay.	
3	General	I would suggest an edit as follows to the last sentence: "However, all studies are small, have no information on analytical performance or on preanalytical variables that might affect performance, have important methodological limitations, and do not address patient-relevant outcomes. At this point in time it would be most appropriate to characterize this as an investigational use test."	*We appreciate the reviewer's rationale in proposing this modification. However, we would prefer to avoid characterizing the methodology in such an explicit way. This summation statement is not part of the evidence review, and constitutes an interpretation of the presented evidence.*

[1] Peer reviewers are not listed in alphabetical order.

[2] If listed, page number, line number, or section refers to the draft report.

[3] If listed, page number, line number, or section refers to the final report.