Response to reviewers:

Reviewer #1: This manuscript by Durkin & Krishna is a good, concisely , coherently organized and presented, and effective review manuscript describing current literature on confocal endomicroscopy and cyst fluid molecular analysis for evaluation of pancreatic cyst. As promising adjuncts to existing standard of care for management of pancreatic cysts with the potential to improve diagnostic accuracy and ultimately patient outcomes. The title reflects the main subject of the manuscript as well as the abstracts correctly summarizes the main points of the review and key words reflect the focus of the manuscript. The manuscript's sections are well defined and structured. Discussion and conclusions clearly fpocus on progresses challenges and .. of the issue addressed. Figures and tables are sufficient, good quality and appropriately illustrative of the paper contents Issues that remain to be solved (involving bothe imaging and molecular techniques) are clearly indicated.

Comment: We greatly appreciate the positive comments by the reviewer.

Minor issues In the section on molecular analysis, reference is made to VHL screening as if NGS could not technically resolve it , and therefore Sanger should be used. This a little misleading quotation of a sentence in ref 37, which actually better describes the issue. "Due to technical issues, we were unable to include VHL within this panel, but assessed the entire coding sequence of VHL by Sanger sequencing with the understanding that the sensitivity of Sanger sequencing is known to be lower than NGS" I would suggest to clarify and check references (37) on this sentences to avoid misinterpretation of the sensitivity of the techniques.

Comment: The following changes were made:

The Sanger sequencing technique is not able to detect the entire loss of the *VHL* gene but can detect deletions and insertions within exons or complete loss of an exon. Hence Sanger sequencing has low sensitivity for the detection of *VHL* mutation which is otherwise commonly observed in SCAs

Reviewer #2: The authors made a good review of confocal endomicroscopy and cyst fluid molecular analysis in evaluation of pancreatic cysts. I have the following comments:

(1) About the learning curve of performing confocal endomicroscopy, how many cases should the doctors encounter before being a skilled operator?

Comment: The following changes were made:

Procedural expertise for optimal image acquisition during EUS-nCLE can be obtained by directly observing an expert EUS-nCLE in dedicated workshops and subsequently performing at least 10 cases. Since there are no formal studies to address

high-quality image acquisition, the limited case requirement is only an opinion among experts.

(2) Please summarize the methods mentioned in this manuscript in a table and list the sensitivity, specificity, benefits and disadvantages.

Comment: While we have summarize the sensitivity and specificity, a new table has been included summarizing the benefits and disadvantages. Following table was added:

Table 5: Benefits and drawbacks of EUS-nCLE and molecular analysis of cyst fluid[21, 30, 36, 41, 42]

Molecular Analysis of PCL fluid (DNA analysis)	**EUS-nCLE of PCLs**
High sensitivity and specificity for the diagnosis of mucinous PCLs	High sensitivity and specificity for the diagnosis of mucinous PCLs
Markers can detect advanced neoplasia in IPMNs; need validation in multicenter studies	Need further studies to address role of EUS-nCLE in the identification of advanced neoplasia in PCLs
Lower sensitivity for the detection of KRAS mutations in MCNs	Detection of flat epithelium in MCNs can be difficult for early adapters of EUS-nCLE
Need large multicenter prospective studies with confirmed histopathology to replicate single center results	Need large multicenter prospective studies with confirmed histopathology to replicate single center results
Lack of established markers for cystic-NET and squamous lined cysts	EUS-nCLE reveals specific image patterns for different PCL types. Unable to differentiate between cystic-NET and SPN
During EUS-FNA, 5-10% of PCLs may not yield DNA for molecular analysis	There is a 2-5% risk of technical and procedural issues with failure of image acquisition during EUS-nCLE
Low sensitivity for the detection of VHL mutations in SCAs	EUS-nCLE identifies characteristic 'fern-pattern' of vascularity for diagnosing SCAs

Reviewer #3: This is a very interesting article with regard to advanced diagnostics for pancreatic cysts. Nevertheless, several issues have been raised and revisions are implemented.

1. The Introduction section is too long. Clinical evidence as well as guidelines should be re-arranged in a separate chapter. The aim of the article is not clear.

This issue is now addressed in the revision.

This review aims to summarize current literature on confocal endomicroscopy and cyst fluid molecular analysis for the evaluation of pancreatic cysts.

2. In the second part additional information about confocal laser endomicroscopy should be added. Indications and contra-indications of the method are also missing.

Commment: The following is included –

As per expert opinion, the indication for EUS-nCLE is the evaluation of a PCL which is ≥ 2 cm in size. EUS-nCLE is contraindicated in patients with allergic reactions to fluorescein.

3. Grammatical errors should be corrected.

Multiple grammatic errors have been corrected.