The authors thank the Editor and the reviewers for their hard work and useful suggestions. The manuscript has been amended accordingly. All the changes are highlighted in red through the text.

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Good effort with general overview of the topic Authors to highlight the role of fine needle biopsy (FNB) in EUS for tissue acquisition to improve the tissue yield for molecular analysis. Can authors discuss the role of culture of PDAC tumoroids and its clinical utility? Authors need to demonstrate/ elaborate how this bench data translate into real world clinical practice.

The authors thank the reviewer for the suggestions. The manuscript has been amended accordingly.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This manuscript is a nice, comprehensive and informative review about the molecular alterations in pancreatic tumors. Authors have benefited from 116 references. Some small typewriting errors such as IMPN in the abstract and LOF in Table 3 should be corrected as IPMN and LOH, respectively.

Manuscritpt typos have been revised

On the other hand, authors mention MSI in Acinar cell carcinoma section, but not in PDAC in general. Although it was very low (0.8 %) in PDAC (*), NCCN recommends MSI and/or MMR testing in metastatic disease (**). I recommend adding this latest information to the manuscript to increase its quality. (*): Hu ZI, et al. Clin Cancer Res. 2018 Mar 15;24(6):1326-1336. (**): Pancreatic adenocarcinoma. NCCN Guidelines Version 1. 2021

Authors thank the reviewer for this suggestion. A paragraph about MSI in PDAC has now been added in the main manuscript.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Visani et al have written a nice review on molecular alterations in pancreatic tumors. The 3 tables give an overview of the most important genetic alterations identified in the most common types of pancreatic tumors. My comments are minor. -Correct IMPN to IPMN on page 3 and 5. -Use the term Serous Cystic Neoplasm (SCN) and not SCA. -In the abstract: "e.g., pancreatic ductal

adenocarcinomas, IMPN, Cystic Neoplasms, solid pseudopapillary tumors". IPMN and SPN are cystic neoplasms. I suggest to remove cystic neoplasms from this sentence.

Manuscript has been extensively revised and amended according to reviewers' suggestions.

-Ref 55 and 56. I suggest to replace these two references with Goggins et al, Gut 2020, "Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium". In these recommendations; for BRCA2 germline mutated individuals an agreement of 93 % for surveillance was reached if at least one affected FDR, or at least two affected relatives of any degree, whereas for BRCA1 germline mutated individuals an agreement of 69.6 % for surveillance was reached if at least one affected FDR. Moreover, surveillance with EUS and/or MRI is recommended to be performed in a research setting by multidisciplinary teams in centres with appropriate expertise. Please modify the sentence regarding annual screening of individuals with BRCA1/2 mutations.

Paragraph about BRCA germline mutation in pancreatic cancers have been amended according to 2020 CAPS recommendations, as suggested.

-The authors state: "The presence of a KRAS mutation in EUS-FNA material may support a re-evaluation of the original cytopathology report (especially if doubtful), an indication for a second FNA or surgery, and allows to a significant reduction of false-negative diagnoses". Is a cytology specimen as good as a biopsy to identify the different molecular alterations in pancreatic tumors. (EUS-FNAC (cytology) versus EUS-FNAB (biopsy)). Please add some comments to this point in the last part of the paper.

Authors thank reviewer for this right consideration. This aspect has now been discussed in the last part of the manuscript

-Are any of the molecular alterations presented currently used in routine diagnostics? Is it possible to add a table on molecular alterations routinely used in the clinic?

The authors thank the reviewer for this useful suggestion. Possible role of molecular alterations in routine diagnostics has now been added in Tables 1-2-3

Reviewer #4:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors have done a great work to systematize modern knowledge about genetic alterations in pancreatic tumors. In general, the article is written at a very high level. The reviewer has only one principal ("fundamental") comment and two technical ones.

1) The article refers mainly to the genre of basic science. However, in my opinion, it would be correct to bring the work a little closer to clinical practice by adding to each paragraph devoted to a particular mutation, a small summary of the preferred chemotherapy option for such a mutation, if these data are available in the literature.

The influence of the different mutations in therapeutic approaches has now been added to the manuscript, wherever possible.

2) The field of research, namely molecular oncology, involves a huge number of abbreviations, mainly related to the names of genes. However, the work contains a number of other abbreviations that are not explained when they first appear in the text (IPMN, PDAC, MCN, LOH), or are not explained at all (GTP, WNT, TRK, ACC, NGS). Two times (Abstract and Introduction, page 5) IPMN was misspelled as IMPN.

"Uncommon" abbreviations have been now spelled out and typos amended through the manuscript

3) The titles of the journals in the Reference section should be presented in abbreviated form as in PubMed (see Guidelines for Manuscript Preparation and Submission).

References were amended accordingly

Science editor: Reviewer's Code: 03262127: Dear Editor, I have already submitted my review but I want to add a minor comment. As it is written in "Guidelines...", designation of co-first authors and co-corresponding authors is not permitted. In a reviewed paper, there are two so-called senior authors (GT and DdB share senior authorship). I do not know how to define the term "senior author" but think that this statement can be incorrect.

If the co-senior authorship is not allowed, we can avoid it