Marseille July 8, 2019

To the editorial office,

Thank you very much for reviewing our article and for the comments of the reviewers.
Please find hereunder the answers to the reviewers' comments.
All the corrections requested by the reviewers have been made in the main text in RED except all the spelling and grammar corrections. The spelling and grammar corrections (performed by American journal experts) have been directly integrated in black into the NEW main text because of their very high number. Tables, figures and legend have also been reviewed and changed, so please take the entire new article into consideration before editing.
Once again thank you very much for your interest in our article
Remaining to your disposal for any further information,
Best regards.
A LAQUIERE and co-authors

Answers to reviewers

Number ID	Review Info	Specific Comments To Authors	Specific Comments To Authors (File)
03388124	**Conclusion:** Minor revision **Scientific Quality:** Grade C (Good) **Language Quality:** Grade B (Minor language polishing)	This study performed NGS sequencing in pancreatic fluid and neoplastic tissue and found that there was high concordance in genomic profiles between these types of specimens. 1. This is a very nice study; however, it is severely limited by the small number of specimen (17) which precludes statistical analysis, thus the conclusion is also limited. This should be clearly stated in the manuscript. 2. Although the aim of this study was to compare fluid with tissue, which matters most is whether the genomic profiles from fluid analysis predict a malignant diagnosis thus indication for surgical resection. This should be stressed in the discussion. 3. The manuscript also stated "... various proportions of mutated alleles but generally higher in CF-DNA than in NT-DNA". This also needs some explanation.	1. We agree with this comment and have added a paragraph in the discussion about this limitation *"The main limitation of this study lies in the small number of patients. As a result, the final diagnosis and the resulting sensitivity and specificity calculations may lack precision. This pilot study was a first step, and a multicenter study on a larger scale is ongoing."* 2. We agree with this comment and have added a paragraph in the discussion *"Although the aim of this study was to compare fluid with tissue, the most important issue was to determine whether the genomic profiles from fluid analysis could predict a malignant diagnosis and thus indicate surgical resection. Despite the fact that 15/17 patients presented the same genomic profile between CF and NT, the specificity and sensitivity observed in this study were not satisfactory because the mutations were not systematically present in all patients with cancer.* *In our study, 3 patients with cancer had mutations in neither CF nor NT.* *The predictive effect of CF mutations on malignity needs to be further analyzed with some additional mutations. This analysis has been planned in a future larger-scale study."* 3. We agree with this comment and have added a supplement file with raw data (supplement 4) to confirm this statement see page 11 : *"Concordant genotypes were found in 15 of 17 paired DNAs, with various proportions of mutated alleles but generally a higher proportion in CF-DNA than in NT-DNA, as shown in supplement* 4".

		4. This study requires extensive pathology expertise. It is unclear whether any of the coauthors is a pathologist. 5. The meaning of some of the sentences is unclear and requires further clarification: (1) Page 8, under "DNA extraction", "... except for 3 points". (2) Page 11, last sentence, "... collected by EUS-FNA was positive and negative for 5/8 benign pancreatic cyst." (3) Page 12, line 6, "... collected by surgery or EUS-FNA was positive and negative for 6/8 benign pancreatic cyst". 6. Regarding the grammar, there appears to be excessive short paragraphs - some of them can be combined into the same paragraph. Some of the words also requires further polishing.	*Furthermore, table 2 has been totally reorganized in order to make the results easier to understand. The data have been double checked using a second algorithm and some modification have been made in his table without any incidence on the final results of the article.* 4. We have added the pathologist who provided its expertise as an author of the publication: see "*Jean Pascal Buono" in the author list (page 1, a new copyright agreement has also been updated and downloaded with his signature.* 5. Those sentences have been corrected to be more clear : -Page 8: "except for 3 points": deleted. Please see supplement 1 for details. -page 11: the paragraph "*KRAS and/or GNAS mutation in CF and NT"* has been clarified. *"a) CF (figure 2/A)* *Of the 9 patients who had a cancerous cyst, CF mutations were found in 7 patients (# 10-13-14-15-17-18-19). Regarding the 2 patients who did not have CF mutations, one had no NT mutation (# 1), whereas the second had a NT mutation (# 9) (see table 2).* *Finally, the sensitivity and specificity of the KRAS/GNAS mutations in the CF collected by EUS-FNA to indicate surgical resection (or to predict the risk of cancer) were 0.77 (7/9) and 0.62 (5/8), respectively."* (3) Page 12, line 6 : the paragraph KRAS and GNAS mutation in NI has been clarified : *"b) NT (figure 2/B)* *Of the 9 patients who had a cancerous cyst, only 6 patients had NT mutations (# 9-13-14-15-17-18).* *Of the 8 patients without cancer, 2 patients had mutations (# 5, 20).* *These 2 patients had IPMN with low grade dysplasia.* *Finally, the sensitivity and specificity of the KRAS/GNAS mutations in the CF collected by surgery or EUS-FNA to predict the risk of cancer (or to indicate surgical resection) were 0.66 (6/9) and 0.75 (6/8), respectively."* 6. The grammar and spelling in the entire document (including tables and figures) have been corrected by professional "American Journal Experts" as suggested in the guidelines for authors (https://www.aje.com/) a certificate is attached. The corrections of revision have not been added in red in the text because they were too many, but please consider the whole text as tolatty corrected in spelling and grammar.

Number ID	Review Info	Specific Comments To Authors	Specific Comments To Authors (File)
03492099	**Conclusion:** Major revision **Scientific Quality:** Grade D (Fair) **Language Quality:** Grade C (A great deal of language polishing)	1. Sensitivity = Number of true positive / (Number of true positive+ Number of false negative)*100%. Thus, in Table 3, Sensitivity = 7/(7+2)*100% = 77.8%. It is NOT 8/9! 2. 2. The sensitivity and specificity in Figure 2 and Figure 3 is redundant!	1. We agree with this comment and have corrected the sensitivity to 0.78 accordingly : a. In the abstract b. In the core tip c. Page 12: *"Finally, the sensitivity and specificity of the KRAS/GNAS mutations in the CF collected by EUS-FNA to indicate surgical resection (or to predict the risk of cancer) were 0.78 (7/9) and 0.62 (5/8), respectively"* d. *In the figure 2/A* 2. The figure 3 has been deleted

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03252981	**Conclusion:** Major revision **Scientific Quality:** Grade C (Good) **Language Quality:** Grade B (Minor language polishing)	The study was conducted to elucidate the correlation of genetic alteration in pancreatic cystic fluid and resected neoplastic tissue. The genotypes in cystic fluid and resected tissue were comparable. Mutation analysis of cystic fluid by next generation sequencer appears to be useful for the assessment of malignancy. There are a couple of critical issues. 1. Tre results of mutations in cystic fluid and resected tissue should be separated. 2. The authors presented the mutation data with "discordant" and "concordant" genotypes. This is interpreted data not raw data. The best way to show the data is to show raw data of mutation status hierarchically in cystic fluid and resected tissue. 3. It is strongly recommended that the cytological diagnoses of cystic fluid are shown in the results. The cytological description was found in Studied population in Method, but the findings were not well shown. The cytological diagnosis itself is important to predict neoplastic or malignant nature, but more importantly, it would certify that genetic data come from neoplastic cell. 4. The excluded three cases should be excluded from the study. Inclusion of the cases will not give any result. 5. In Table 2, the order of the cases appears random. As mentioned above, the order and the presentation of genetic data need to be revised. 6. There are many grammatical errors. In addition, there are many strange sentences and wordings. There are also misspellings. The manuscript needs thorough revision.	1. The results of mutations in cystic fluid and resected tissue have been been separated. See page12 and 13 2. Raw data have been added in supplement 4. Page 12 (results): *"- Concordance between the genomic profiles of CF and NT:* *Concordant genotypes were found in 15 of 17 paired DNAs, with various proportions of mutated alleles but generally a higher proportion in CF-DNA than in NT-DNA, as shown in the raw data detailed in supplement 4."* *3.* Cytological analysis of cystic fluid was not systematically performed, and do not appear in the results a sentence has been added in the methods: *"-Cystic fluid and neoplastic tissue collection:* *Pancreatic CF samples were collected at the time of EUS. CF samples were aspirated under EUS control using 22-gauge needles (Boston Scientific) and studied for biochemical markers in the systematic preoperative evaluation; 1.5 mL was preserved for molecular analysis in 2 mL of ATL Buffer (Qiagen, Germany). Cytological analysis of cystic fluid was not systematically performed because of its poor diagnostic performance in the presence of poor cellularity"* 4. The excluded three cases have been deleted from the tables and the results. 5. The table 2 has been completely reviewed regarding the presentation of genetic dada. 6. The grammar and spelling in the entire document (including tables and figures) have been corrected by professional "American Journal Experts" as suggested in the guidelines for authors (https://www.aje.com/) a certificate is attached. The corrections of revision have not been added in red in the text because they were too many, but please consider the whole text as tolatty corrected in spelling and grammar.

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00646357	**Conclusion:** Minor revision **Scientific Quality:** Grade B (Very good) **Language Quality:** Grade B (Minor language polishing)	1. Add the unique of this study compared to other studies discuss the same issue. 2. Add more on the basic of this disease in the introduction 3. Discus role of imaging using these ref Razek AAKA, Elfar E, Abubacker S. Interobserver agreement of computed tomography reporting standards for chronic pancreatitis. Abdom Radiol 2019; doi: 10.1007/s00261-019-01979-4.	1. A sentence has been added int the discussion: *"The unique feature of this study lies in the fact that, for all patients, the profile of the genetic mutations in CF and NT was systematically compared."* 2. The introduction has been completed with the sentences in red *"Cystic neoplasms of the pancreas are frequent in the general population, with an estimated prevalence ranging from 5 to 15% in those over the age of 70[1,2]. Pancreatic cysts can be divided into mucinous and nonmucinous. Their distinction is important because mucinous cysts, which comprise mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN), are considered premalignant. Indeed, the risk of pancreatic adenocarcinoma developing from main-duct intraductal papillary mucinous neoplasm (IPMN) is high, at 40-90% within 5 years of diagnosis [3,4]. For branch-duct IPMN, the risk is moderate, ranging between 6 and 46% within 5 years [5–8]. This risk considerably decreases for mucinous cystadenoma (MCN) to under 15%[8] and is quite rare for serous cystadenoma (SCA)[2]. The clinical management of patients with pancreatic cysts is unfortunately imperfect, and distinguishing between different cystic tumors and their risks of malignant evolution can be challenging. A few guidelines based on clinical features and cystic tumor morphology were published to help set intervals of follow-up and define criteria for surgical resection [9–13]. However, in a meta-analysis, the pooled sensitivity and specificity for malignancy in Sendai-positive lesions were 56% and 74%, respectively, and under the Fukuoka criteria, they were 83% and 53%[14]. Worrisome features in those guidelines are not sufficient to correctly select patients for surgery[10,12]. Currently, 75% of resected IPMNs harbor only low- or intermediate-grade dysplasia, which could have been safely observed[15]. Similarly, in a retrospective multicentric study, 96.5% of patients presenting an IPMN with worrisome features who did not undergo surgery were still alive 5 years later without having developed pancreatic cancer[16]. Other tests that can help in cystic lesion diagnosis and management include cytology and biochemical tests of cystic fluid, such as carcinoembryonic antigen (CEA). However, those tests are also limited: cytology had a sensitivity for malignancy of 42% in a meta-analysis of 12 articles [17] and there are varying cut-off values for CEA. This is why molecular analysis was developed in the last decade, with new techniques of advanced sequencing becoming available to help in pancreatic cyst differential diagnosis. DNA mutational analysis of the different types of pancreatic cysts involves several specific alterations, each cyst type having different mutational profiles. IPMN and mucinous cysts harbor KRAS mutations at diagnosis, in addition to GNAS mutations in IPMN, while PTEN, CDKN2A and TP53 mutations are mostly found in cancerous lesions[18]. In contrast, SCA contains a mutation in the Von Hippel Lindau gene, and a mutation in the CTNNB1 gene is described in solid pseudopapillary neoplasms."* 3. The role of imaging including the cited reference have been added in the discussion: *"In this series, all patients had precancerous or cancerous cysts. No patient had a pseudocyst or dilatation of the main pancreatic duct in relation to chronic calcific pancreatitis because morphological criteria are now well defined in imaging [26]".*

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00043819	**Conclusion:** Minor revision **Scientific Quality:** Grade C (Good) **Language Quality:** Grade B (Minor language polishing)	Authors evaluated the genomic profile concordance between pancreatic cyst fluid and neoplastic tissue: 20 patients were enrolled in the study. finally, mutational analyses of in cyst fluid and in neoplastic tissue were highly concordant. 1. The study is interesting, but the small number of patients included in the analisys limits any definitive conclusion. 2. In table 2 clinical-pathological findings of twenty patients are detailed, but only 17 patients had pathological confirmation after surgery; so, three patients should be excluded.	1. We agree with this comment and have added a paragraph in the discussion about this limitation *"The main limitation of this study lies in the small number of patients. As a result, the final diagnosis and the resulting sensitivity and specificity calculations may lack precision. This pilot study was a first step, and a multicenter study on a larger scale is ongoing."* 2. The excluded three cases have been deleted from the tables and the results.