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Dear Reviewer,

Thank you for your comments. We have addressed all comments below.

Comment #1: The discussion (section IV) attempted to organize this knowledge but lacks some important elements of summarizing current research and draw attention to other factors affecting the expression of miRNAs, which limits the diagnostic value of these tests. The discussion should included (briefly discussed) other factors which may alter the expression of miRNAs in patients with pancreatic cancer (this applies to the intra- and extracellular miRNAs expression).

We agree with the reviewer that there should be discussion of factors which affect expression of miRNA. We have added text describing the factors that affect miRNA expression, including transcriptional deregulation, epigenetic alterations, mutations, DNA copy number abnormalities, and defects in the miRNA biogenesis pathway and described them in more detail on page 15.

Comment #2: For example, an important component associated with cancer (especially with pancreatic cancer) are disorders of nutritional status. Reduction of nutrients and metabolic changes significantly modulates the expression of miRNAs. Extensive surgical trauma (pancreatectomy) and accompanying inflammatory response and malnutrition can also change the expression of miRNAs. It is a further limitation of early diagnosis of recurrence after surgery.

We agree with the reviewer that nutritional status affects expression of miRNAs and have included text on page 16 discussing specific deficiencies and the effect of cancer cachexia in pancreatic cancer.

Comment #3: The discussion also lack a brief reference to the basic mechanisms associated with cancer (e.g. impaired apoptosis), which can regulate the expression of miRNAs.

We agree with the reviewer that there should be some discussion of mechanisms associated with cancer that regulate the expression of miRNA and have added text to page 16.