The EUS molecular evaluation of pancreatic cancer: A prospective multicenter cohort trial

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ABSTRACT

Background and Objectives: Patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (A-PDAC) are not candidates for surgical resection and are often offered palliative chemotherapy. The ready availability of a safe and effective tumor sampling technique to provide material for both diagnosis and comprehensive genetic profiling is critical for informing precision medicine in A-PDAC, thus potentially increasing survival. The aim of this study is to examine the feasibility and benefits of routine comprehensive genomic profiling (CGP) of A-PDAC using EUS-FNA material. Methods: This is a prospective cohort study to test the clinical utility of fresh frozen or archival EUS-FNA samples in providing genetic material for CGP. The results of the CGP will be reviewed at a molecular tumor board. The proportion of participants that have a change in their treatment recommendations based on their individual genomic profiling will be assessed. Correlations between CGP and stage, prognosis, response to treatment and overall survival will also be investigated. This study will open

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INTRODUCTION

Pancreatic duct adenocarcinoma (PDAC) is one of the leading causes of cancer mortality worldwide\(^1\) and is projected to become the second deadliest cancer in the United States by 2030.\(^2\) Despite recent developments in treatment strategies, the median 5-year survival for all stages of the disease has remained low.\(^3\) Surgery is the main therapeutic modality in early PDAC, however, approximately 80% of patients have unresectable cancer at diagnosis. Although there has been some improvement in clinical outcome in the past 20 years (e.g., PRODIGE and MPACT trials), overall survival is still dismal. As such, there is an urgent unmet clinical need that necessitates further research and investigation toward the development of novel diagnostic and therapeutic measures.

The advent of genomic medicine has increased our appreciation of the genomic landscape in cancers, demonstrating a high degree of interpatient, intertumoral, and intratumoral heterogeneity, including for PDAC. This heterogeneity refers to a diverse collection of cells harboring distinct molecular signatures within the bulk tumor which not only play a role in oncogenesis but also bring about differential levels of sensitivity to treatment.\(^4\) For example, a genome-wide association study on large cohorts (>7000) of PDAC patients and control individuals has revealed numerous susceptibility loci containing a variety of genes, some of which have previously been implicated in oncogenesis.\(^5\) In addition, whole-exome sequencing of resected PDAC tumors has revealed associations between tumor mutational burden and spectrum and pathological features of the disease, patients’ survival, and clinically actionable cellular pathways, and identified potential therapeutic targets.\(^6\) The extensive genetic diversity seen in PDAC provides a rational explanation for the relatively slow progress in the development of effective systemic therapies.\(^7\) Meanwhile, it justifies the need for personalized therapeutic approaches based on the molecular profile of individual tumors to improve outcomes.

There are limited data on the efficacy of targeted therapies in locally advanced or metastatic pancreatic ductal adenocarcinoma (A-PDAC). Recently, the Know Your Tumour programme has reported on 1856 pancreatic patients who were referred for molecular testing.\(^8\) In their retrospective analysis, 58% (1082) patients received personalized reports based on their molecular testing results and 26% of these patients (282) had potentially actionable molecular alterations. Of the 677 patients who had follow-up data, 189 had an actionable molecular alteration. Importantly, of these, the 46 patients who received matched therapies had a significantly longer survival (2.58 years) compared to those who received unmatched therapies (1.32 years). However, those patients with actionable phenotypes receiving unmatched therapies did not have improved survival compared to those without an actionable molecular alteration. While this data supports the application of CGP in pancreatic cancer, the fact that only 2.5% of the original 1856 patients were able to have matched therapies suggests that widespread application of this approach may be challenging. Similarly, in a recent study of a molecular tumor board (MTB) in the United Kingdom, comprising 895 patients, although 20% had actionable mutations, only 7% received such therapies.\(^9\) However, there have been some recent initiatives focused on providing targeted treatments to patients with pancreatic cancer, with ongoing studies including the MoST (ACTRN12616000908437) and the TAPUR (NCT02693535) studies.

A major obstacle to personalized therapy for A-PDAC has been the difficulty in isolating high-quality tumor-derived genetic material in sufficient quantities for molecular profiling. Such challenges...
have been reported by authors of the Individualized Molecular Pancreatic Cancer Therapy Trial, which was designed to identify subsets of patients with advanced metastatic disease who could be targeted, based on mutations within their tumor genome, with three specific therapies.\textsuperscript{[10]} Due to reliance on formalin-fixed paraffin-embedded (FFPE) resection specimens and delays in accessing and analyzing archival material, no patients in the study were commenced on targeted therapy. However, it was possible to perform comprehensive genomic profiling (CGP) on the majority.

Similarly, more recently in the COMPASS trial, percutaneous biopsies were used in patients with advanced pancreatic cancer to provide tissue for whole-genome sequencing and transcriptomic profiling.\textsuperscript{[11]} Using laser capture microdissection, the investigators were able to obtain sufficient material for these in-depth analyses in 98% of patients at a median of 35 days. However, this technique was only available to patients who were amenable to percutaneous biopsy; it required an additional invasive diagnostic procedure (with a mean of 5 core biopsies per patient) and very specialized processing of samples including laser capture microdissection, which is not widely available. Although, they identified phenotypes that may be amenable to personalized therapy in 30% of patients, only 6.4% had directed therapy. Of those, only one patient halted their disease progression.\textsuperscript{[11]}

Accordingly, there is an urgent and unmet clinical need for new methodologies for the robust isolation of high-quality genetic material promptly from the vast majority of PDAC patients. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a relatively noninvasive technique that is routinely used to sample tumor tissue in a large proportion of PDAC patients for cytological diagnosis.\textsuperscript{[12,13]} Although EUS-FNA has been used to provide tissue for genetic analysis of PDAC, its wider clinical utility is still in its infancy. Furthermore, issues relating to insufficient tumor cellularity, poor quality DNA, and contamination by surrounding non-tumor tissue have, until now, collectively hampered its broader use in the clinic.\textsuperscript{[10,14,15]}

Our laboratory has recently optimized protocols for the simultaneous extraction of genomic DNA and RNA from PDAC EUS-FNA biopsies, and genome-wide transcriptome analysis of these biopsies was found to be consistent with data from the TCGA PAAD dataset, which was derived from genomic analysis of surgical resection specimens.\textsuperscript{[14]} Whole-exome sequencing using EUS-FNA material has also been performed in our laboratory and demonstrated a similar range of somatic mutations as reported by other groups. However, bioinformatic interpretation has proved difficult and time-consuming, partly due to the variability in tumor cellularity between specimens, which makes mutation calling challenging.

CGP is a more targeted sequencing approach which has been developed to genotype a wide range of hematological and solid tumors, and is recommended as routine clinical management in some settings.\textsuperscript{[17]} An example of this approach is the TruSight Oncology 500 assay (TSO500, Illumina), which is complemented by a commercially available, clinically focused bioinformatic support package (PierianDx Report). Using this assay, we have established an accurate and efficient technique to identify clinically relevant and targetable mutations in 40 PDAC EUS-FNA specimens from 32 PDAC patients, including 8 with matched pancreas and liver biopsies (unpublished data). Collectively, our novel data strongly suggest that high-quality genetic material can be obtained from PDAC tumors by EUS-FNA in sufficient quantities for subsequent clinically relevant CGP.

A number of actionable genotypes have been identified in PDAC. These include pancreatic cancers that harbor mutations in genes responsible for DNA damage repair, wildtype KRAS tumors, tumors with high mutational burden and tumors with rare but potentially important driver mutations such as BRAF, KRAS G12C mutations and fibroblast growth factor receptor and tyrosine-receptor kinase fusions.\textsuperscript{[18]} There are minimal data on the use of MTBs in pancreatic cancer. However, “the complexity and vast amounts of data generated through molecular profiling techniques, like next-generation sequencing, make expert review an absolute requirement to translate molecular profiles into clinical benefit for our patients.”\textsuperscript{[19]} The presence of a molecular pathologist in addition to the curated report from PierianDx or equivalent will greatly facilitate the interpretation of CGP.\textsuperscript{[9]} Therefore, we are establishing a pancreatic cancer MTB within the Monash Partners Comprehensive Cancer Consortium to assess the results of CGP.

**Rationale**

The aim of this study is to assess the feasibility and usefulness of CGP of EUS-FNA biopsies in patients...
with locally advanced and metastatic PDAC (advanced PDAC or A-PDAC). The standard of care for A-PDAC is palliative chemotherapy, which may improve median survival to 12 to 18 months.\textsuperscript{20,21}

Recently, the implementation of routine molecular screening in PDAC has been recommended for patients’ stratification towards novel therapeutics (The National Comprehensive Cancer Network Guidelines (NCCN) Version 1.2020 Pancreatic Adenocarcinoma).\textsuperscript{22} However, as yet, this has not been widely adopted. One of the barriers is that the EUS-FNA, the predominant method of obtaining tissue for diagnostic purposes, only provides a limited amount of tissue which makes molecular characterization difficult. In addition, formalin/paraffin preservation of tissue for subsequent histological analysis leads to the loss and/or degradation of genetic materials further hampering genetic analysis.

The best strategy for the molecular characterization of PDAC biopsy material is still unclear. Options include targeted sequencing, whole-exome or whole-genome sequencing, and transcriptomic analysis. Moreover, the interpretation of sequencing results is challenging, in particular, if a biopsy contains both malignant and nonmalignant cells in varying amounts. In addition, access to novel treatments may not be straightforward, which may limit the current usefulness of this approach. Finally, patients with A-PDAC tend to progress rapidly and may not meet physical and biochemical requirements for entry onto clinical trials, providing a limited window of opportunity for the application of targeted therapies. The aim of this study is to examine the feasibility and potential benefit of introducing baseline routine CGP of A-PDAC using EUS-FNA material, early in the patient’s journey.

We have recently developed a technique for the isolation of DNA and RNA from an additional fresh frozen EUS-FNA biopsy taken at the time of diagnostic EUS (Monash Health HREC Ref: 15450A). Since this additional biopsy has not been cytologically assessed, there is a possibility that it may not contain malignant tissue due to sampling error. We have also recently developed a diagnostic signature of pancreatic cancer based on targeted RNA sequencing on a custom-designed NanoString platform (NanoString Technologies, Seattle WA), which in combination with KRAS mutation analysis, has high sensitivity to differentiate pancreatic cancer from other causes of pancreatic masses including pancreatic neuroendocrine tumors and benign conditions such as autoimmune pancreatitis, even in non-diagnostic biopsy specimens. This study will enable us to investigate the utility of this diagnostic signature in confirming the presence of the pancreatic cancer cells in the biopsy specimen. To perform CGP, we then intend to assess the material using the TSO500 gene panel.

METHODS/DESIGN

AIMS

Primary objective
To determine the proportion of patients with A-PDAC that can have CGP, using either fresh frozen or archival EUS-FNA material.

Secondary objectives
To determine:
1. The proportion of participants that can have treatment recommendations based on CGP
2. The number of participants that have changes in their treatment based on CGP
3. The sensitivity and specificity of a previously established genetic signature of PDAC
4. The quantity and quality of DNA and RNA that can be obtained from the various types of fresh frozen and archival PDAC biopsies.

Tertiary objectives
To investigate:
1. The potential correlations between CGP and stage, prognosis, and response to treatment
2. The overall survival of patients who receive targeted therapy compared to those receiving only standard therapy.

Design and setting
Endoscopic ultrasound molecular evaluation of pancreatic cancer is a prospective cohort trial involving up to 6 moderate-to-high volume pancreatic cancer units in Victoria, Australia with a target accrual of 150 A-PDAC patients within 36 months and a 2-year follow-up. The study flow chart is presented in Figure 1. It is expected that the majority of participants will be those who have already consented for their tissue to be biobanked in the Victorian Pancreatic Cancer Biobank (VPCB at the time of diagnostic EUS.

Inclusion criteria
- Patients aged 18 years or older, with either cytologically proven pancreatic adenocarcinoma obtained by
EUS-FNA or a clinical diagnosis of pancreatic adenocarcinoma made based on “suspicious” cytology in conjunction with supporting biochemical and radiological data
- Metastatic, locally advanced (based on the NCCN guidelines version 2, 2017 criteria) or recurrent disease
- Available tumor tissue for DNA/RNA extraction obtained by EUS FNA
- Eastern Cooperative Oncology Group Performance Status 0-2
- Life expectancy of at least 3 months from the time of screening
- Clinically deemed suitable for systemic therapy.

Exclusion criteria
- Patients with operable or borderline resectable pancreatic cancer
- Neuroendocrine pancreatic cancers
- Evidence of comorbid disease that would preclude chemotherapy and
gastrointestinal obstruction
- Presence of any serious medical or psychiatric conditions that might compromise protocol-based management.

Interventions
Molecular analysis will generally be performed on the additional research biopsy taken at the time of standard diagnostic EUS-FNA as part of the VPCB (HREC15450A), and may be performed on archival or biobanked tissue if available. As part of this biobanking project, an additional 1-2 ‘passes’ of the needle will be used to obtain cells for banking. The additional pass (es) will be promptly snap-frozen and stored in liquid nitrogen long term. If fresh frozen material is not available or suitable, CGP may also be attempted on genetic material that is extracted from archival FFPE blocks or scraped from cytology slides after digital images have been obtained to provide a permanent record of the diagnosis. As a multicenter project, the number of passes used for routine diagnostic purposes, the choice of needle type (fine needle aspiration or fine needle biopsy) and gauge, and the use of rapid on-site evaluation and macroscopic onsite evaluation will be left up to the discretion of the endoscopists on each study site. However, the type and gauge of the needle will be recorded to assess the amount of genetic material recovered by each type. Patients may be offered a further EUS-FNA or other biopsy for the purpose of obtaining fresh frozen tissue if the extracted DNA/RNA is insufficient for detailed analysis.

The results of the comprehensive genomic profile will be reviewed by the MTB and reported back to the treating oncologist. Participants with actionable molecular phenotypes who have exhausted conventional options.
chemotherapy may be candidates for potential targeted therapy either by entry into a relevant clinical trial (e.g., MoST study) or by directly approaching the pharmaceutical industry for compassionate access as required. In case of a positive germline mutation, a referral for genetic counseling will be made. Patients’ clinical data will be deidentified and recorded in the Upper Gastrointestinal Cancer Registry (UGICR), to be assessed for uptake of targeted therapies and overall survival.

**Study plan**

**Molecular analyses**

In patients with adequate DNA and RNA, CGP of the tumor will be performed using the TSO 500 (or similar) gene panel. The tissue will also be assessed with a custom-designed NanoString panel, which has previously been developed to establish a “genetic” diagnosis of pancreatic cancer. A molecular diagnosis of pancreatic cancer is defined as the presence of at least one mutation in KRAS, TP53, SMAD4, CDKN2A or another typical gene along with a NanoString signature that is consistent with PDAC. If both the mutation profile and the NanoString signature are inconsistent with the diagnosis of PDAC, it is likely that sampling error has occurred, which will inform the interpretation of sequencing results.

Peripheral blood will also be stored for potential germline testing if a germline mutation is suspected and for future circulating tumor DNA analysis to determine whether targeted or CGP of advanced pancreatic cancer can be performed using liquid biopsy.

**DNA/RNA extraction**

Total RNA and gDNA may be extracted from one of three sources, comprising of the biobanked snap-frozen EUS-FNA samples, supernatant resulting from centrifugation of EUS-FNA biopsies before paraffin preservation—both stored in the Victorian Cancer Biobank, and FFPE specimens or cytology slides available in pathology departments. Fresh frozen tissue would be the prioritized material, wherever it is available. DNA and RNA will be simultaneously extracted from fresh/frozen tissues using the AllPrep DNA/RNA Universal Kit (Qiagen), and quantified using the Nanodrop spectrophotometer (ThermoScientific) and Qubit Fluorometer (Life Technologies). Quality will be assessed using the Bioanalyzer and TapeStation (Agilent Technologies).

**NanoString gene panel (diagnostic signature)**

The diagnostic signature will be assessed using a custom-designed 201 gene NanoString Custom CodeSet. RNA (50ng) from each sample is added to a Master Mix containing the Hybridization Buffer and Reporter CodeSet, then undergoes hybridization at 65°C for 16 h before a ramp down to 4°C. Samples are immediately made up to 35 µL using RNase free water, loaded into nCounter Sprint Cartridges and run using the SPRINT profiler in the Monash Biochemistry Imaging Facility.

**TSO500 gene panel**

The TruSight Oncology 500 (TSO-500) panel (Illumina) is a next-generation assay of 523 DNA genes and 55 RNA genes, enabling CGP of tumors and measurement of immunotherapy biomarkers (microsatellite instability and tumor mutation burden). This assay is complimented by a comprehensive bioinformatic support package (PierianDx). DNA and RNA samples will be interrogated following standard protocols through TruSight Oncology 500 libraries in the Monash Health Translation Precinct using NextSeq500 (Illumina) high output mode and v2.5 chemistry. In the event of high-quality DNA but poor quality RNA availability, the DNA portion of the assay may be run without matching RNA, although the preference will be to use both.

**Molecular tumor board review**

An MTB, comprised oncologists, surgeons, a molecular pathologist and a clinical geneticist, will be convened under the auspices of Monash Partners Comprehensive Cancer Consortium and/or one of the constituent health services, with meetings being held at least every 3 months. The outcome of the MTB will be formally documented in the participant’s medical record with a report distributed to the treating oncologist. The local medical officer will also be informed about the patient’s review at MTB.

**Follow up**

Patients will be followed up by the UGICR, an opt-out clinical quality registry which maintains comprehensive information on patient demographics, disease stage, treatment, and patient outcomes, including overall survival. The registry is linked to the Victorian Cancer Registry, which provides data on the date of death. As part of this trial, the registry will interrogated at 12, 24 and 36 months to establish treatment history, including targeted treatments.
Outcomes
The overarching aim of this study is to determine the proportion of patients with A-PDAC that can have CGP using EUS-FNA material at the conclusion of the trial (36 months). However, EUS-FNA material can be processed in three ways. First, and traditionally, FFPE processing of the biopsy material and cytology slides. In addition to this at our institution, we have developed a biobanking protocol to collect two more samples. One is collection of supernatant material usually discarded during the FFPE procedure and second, an additional biopsy which is freshly frozen and stored in liquid nitrogen.

We expect that the success of CGP will be dependent on the nature and quality of the EUS-FNA tissue. Therefore, this study will compare the relative efficacy of CGP using these three approaches.

The secondary aims of this trial are to assess the quantity and quality of genetic materials derived from each approach, the sensitivity and specificity of a previously established molecular diagnosis of PDAC (at 36 months) and the potential clinical benefits provided by comprehensive genomic analysis as a change in treatment recommendations at 12, 24 and 36 months when medical records are assessed.

The tertiary or exploratory outcomes are related to the potential impacts of CGP and targeted therapy on overall survival. This trial is not powered to address these questions but is an attempt to examine any potential impact to guide future studies. In addition, biobanked blood can later be used to determine the feasibility of liquid biopsy in targeted or CGP of A-PDAC.

Adverse events
Adverse events are, according to the definitions, any unfavorable or unintended event affecting study subjects. Since this project predominantly involves the use of archival or previously banked tissue, it is anticipated that it does not pose a direct risk to the physical health of the participants. However, some adverse events may arise. These include potential complications (<5%), such as pancreatitis or bleeding, as a result of an additional EUS if performed solely to obtain genetic material, as well as any psychological impact if the patient’s biopsy material is deemed inadequate for comprehensive molecular profiling, or if a germline mutation is identified. If a potentially targetable phenotype is revealed by the molecular characterization of a PDAC, it is possible that the introduction of targeted therapy may be associated with the risk of adverse events. However, this is outside the scope of this trial. As much as possible, it is hoped that novel targeted therapies will be administered within the context of a separate clinical trial (e.g., the MoST study) and in accordance with evidence-based medicine.

Data management
The parameters necessary to evaluate the study endpoints and the reason for the end of protocol treatment will be documented. Data collection will be performed by trained local research staff and stored securely at Monash University, as well as the UGICR which complies with all applicable data protection and privacy obligations.

Sample size and statistical analysis
This will be a multicenter study seeking to enroll 150 patients of which 100 will be estimated to have sufficient DNA/RNA to perform molecular phenotyping. It is expected that 50 patients with A-PDAC will be screened per year, of which 33 will have sufficient genetic material to allow CGP.

The co-primary endpoints of the study are to determine the proportion of patients with A-PDAC that can have the successful molecular analysis of either fresh frozen or archival EUS-FNA material. We postulate that the proportion of patients who can have successful molecular phenotyping will be substantially higher in the fresh frozen cohort than that in the archival cohort. We expect that most patients will have fresh frozen tissue available as part of the VPCB or similar biobank, although it may be hard to predict uptake from centers where biobanking is not routine.

We expect that 100 TSO-500 gene panels should be sufficient to establish the proportion of patients with targetable mutations with a reasonable level of confidence given the expected rate is 20%.

Monitoring of clinical studies
During site initiation for the clinical study, the Coordinating Principal Investigator/Study Delegates will review the clinical investigation plan with site staff. This is an investigator-initiated study and therefore a Source Data Verification plan will be proposed to verify key points of the clinical study. Site staff will be required to redact and send requested information as per the
Source Data Verification plan for remote monitoring. This will include, but not be limited to, deidentified pathology reports and imaging reports.

The clinical study will consist of a central review of radiologic imaging to confirm the resectability of pancreatic cancer on a case-by-case basis by review of multidisciplinary team outcomes. Resectability will be defined according to NCCN Guidelines Version 2 (2017).

**DISCUSSION**

CGP of PDAC enables us to improve precision therapy for the patient. There are a number of potentially treatable molecular phenotypes in PDAC. A recent study which performed targeted genome profile analysis on 3594 PDAC samples found that 17% of them contained genomic alterations that make the tumor cells susceptible to currently used anticancer agents. The most common molecular phenotype (14%) related to defects in DNA damage repair defects. A recent randomized trial of the poly-ADP ribose polymerase (PARP) inhibitor, Olaparib, in patients with germline BRCA1 and BRCA2 mutations and advanced pancreatic cancer demonstrated longer progression-free survival compared to placebo in patients with the stable disease following first-line chemotherapy. This has now become the standard of care. Patients with somatic mutations with defects in double-strand DNA repair mechanism may also respond to PARP inhibition although this is yet to be demonstrated in a clinical trial. Furthermore, patients with DDR deficiency have been shown to have a superior response to platinum-based chemotherapy. A retrospective study of 58 patients with germline mutations in BRCA1 and BRCA2 reported a 22-month versus 9-month median overall survival for patients treated with platinum versus nonplatinum-based chemotherapy, respectively.

A relatively common subtype of pancreatic cancer is wild-type KRAS PDAC. Wild-type KRAS colon and lung cancer are known to be responsive to epidermal growth factor receptor (EGFR) inhibition, suggesting that EGFR inhibition is a potential therapeutic option in wild-type KRAS PDAC. We are currently conducting a single center single-arm cohort trial in wild-type KRAS pancreatic cancer through which PDAC patients with wild-type KRAS were commenced on panitumumab (EGFR inhibitor) as second- or third-line therapy. This trial has demonstrated that it is possible to use molecular analysis of EUS-FNA material to select patients for a precision medicine trial. However, it is now recognized that a significant proportion of wild-type KRAS cancer harbor other driver mutations which may represent more attractive targets than EGFR inhibition. Microsatellite unstable high/tumor mutational burden high tumors are relatively infrequent findings in PDAC but are thought to account for approximately 1% of patients. This population may respond to immunotherapies such as checkpoint inhibitors. There are a number of other rare mutations that may be amenable to targeted therapies which may be available through clinical trials or based on compassionate access. Indeed, as part of the wild-type KRAS trial described above we recently identified a patient with a KRAS G12C mutation who has been referred for entry into a trial of the novel agent, AMG510. The TSO500 gene panel is a pancreatic cancer panel that encompasses over 500 driver mutations and has previously been validated in solid tumors. Taken together, we expect that at least one of these mutations will be present in ~20% of patients with PDAC.

A recent randomized trial of the novel agent, AMG510. The TSO500 gene panel is a pancreatic cancer panel that encompasses over 500 driver mutations and has previously been validated in solid tumors. Taken together, we expect that at least one of these mutations will be present in ~20% of patients with PDAC.
Last but not least, liquid biopsies may eventually provide the most efficient way of performing CGP. Although it is outside the scope of this project, blood will be stored in the VPCB to allow this to be tested in future. CGP of the matched primary tumor is likely to greatly facilitate the interpretation of CGP of peripheral blood and would be of additional benefit.

**Financial support and sponsorship**

This study is an extension of an already ongoing research, funded by the Victorian Cancer Agency grant number M17001 3167532, to further incorporate CGP of PDAC. Additional funding for this component of the project may be provided from a bequest to Monash Health towards pancreatic cancer research. An application for access to these funds will be submitted as required.

**Conflicts of interest**

Manoop S. Bhutani is a Senior Associate Editor of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this Editor and his research groups.

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