MOIRA CLAY CONSULTING

2023 PanKind Early Detection Workshop Report

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Prepared by Moira Clay Consulting Pty Ltd for PanKind, Australian Pancreatic Cancer Foundation

The 2023 PanKind Early Detection Workshop was an initiative of PanKind, the Australian Pancreatic Cancer Foundation to develop a strategic and systematic path to accelerate the early detection of pancreatic cancer. Prior to the workshop, a high-level analysis of research in early detection of pancreatic cancer within Australia and globally was performed, including an overview of national competitive funding and a snapshot of relevant translational activities. A comprehensive report summarising the state of play of early detection of pancreatic cancer research was provided to all participants in advance of the workshop.

Introduction

A hybrid in-person and online planning workshop was held on Tuesday 24th October. The workshop was facilitated by Professor Moira Clay and Dr Laura Genovesi from Moira Clay Consulting. Workshop participants included stakeholders from all aspects of the pancreatic cancer space including researchers, clinicians, people with lived experience of pancreatic cancer (as a patient or carer), industry, and government. A full list of attendees is provided in Appendix 1.

The aim of the workshop was to obtain stakeholder input into the gaps and challenges with the early detection of pancreatic cancer, opportunities and priorities to progress the early detection of pancreatic cancer, and the scope for future directions in early detection. Outcomes from the workshop will enable PanKind to prioritise investment in the early detection of pancreatic cancer to maximise impact, and build on existing knowledge, platforms, and activities.

The workshop covered:

- Lived Experience perspective on early detection.
- Health system perspective on early detection.
- Where are we up to now with the early diagnosis of pancreatic cancer?
- What can we learn from other cancers?

The meeting began with a brief round table on what participants aimed to get out of the workshop. General comments included:

- Collaboration between multidisciplinary experts is urgently required to drive improved patient outcomes for those diagnosed with pancreatic cancer.
- Ensure that the various siloes (disciplinary, institutional, funding, regulatory) are overcome to enable streamlined work across the academic and clinical research spectrum.
- Recognition of the role of general practitioners within the broader multidisciplinary team and optimal care pathway for individuals with pancreatic cancer.
- Continued advocacy for better treatment options for patients with pancreatic cancer to improve their quality and quantity of life.

Session 1: Lived experience perspective

Lived experience perspective is integral to shaping the priorities for the early detection of pancreatic cancer. Discussion with lived experience participants identified several important themes:

- Individuals who were diagnosed with or at high-risk (HR) of developing pancreatic cancer were of generally of very good health, exercising daily with minimal if any symptoms of disease.
- The diagnosis of pancreatic cancer is not straight forward and more accurate diagnostic tests, particularly for early stage disease, are urgently required. One participant described their incidental diagnosis during follow-up imaging for their previously identified intraductal papillary mucinous neoplasm (IPMN). Their pancreatic cancer went undetected by CT imaging and blood levels of CA19-9 remained normal despite having pancreatic cancer.
- Need to advocate for greater awareness and education of the signs, symptoms, and risk factors for developing pancreatic cancer with the general population. Another participant described how the diagnosis of a close family member with pancreatic cancer prompted their own investigation due to their recent understanding that this placed them at high risk for developing pancreatic cancer. Without this awareness, they would have never gone down this path.
- Scientists were encouraged to put the inherent competition that exists within the career path aside, to come together and identify a focus and work together for a common cause.
- It was noted that establishing a collaborative, multidisciplinary national network linked into the broader international community remains a priority for the field to advance outcomes for patients. It was emphasised that the early diagnosis of any cancer is incredibly challenging, particularly one with vague and non-specific symptoms. It was stated that a collaborative, multidisciplinary global network was the only way to tackle a challenge of this size and drive an early detection agenda that will improve outcomes for patients and their families.

- The field was encouraged to leverage the recent pancreatic cancer focus of Cancer Australia and engage with the National Pancreatic Cancer Roadmap, launched by Cancer Australia with public consultation in July 2020.

Session 2: Health systems perspective

The session commenced with setting the scene for how the early diagnosis of pancreatic cancer can be approached, either through the screening and surveillance of high risk individuals or by reducing delays in diagnosis within general practice.

Randomised controlled trials (RCT) were discussed as the only method for establishing the effectiveness of surveillance programs for individuals at HR of developing pancreatic cancer. However, it was noted that RCTs for HR individuals remains challenging given the low incidence of pancreatic cancer and therefore not entirely feasible. In the absence of this, evidence supporting the effectiveness of a surveillance program for HR individuals was presented from an observational study, indicating that cancers diagnosed in HR individuals were indeed at an earlier stage than those typically diagnosed without surveillance. It was also noted that the definition of HR patients differs across guidelines and that HR populations need to be better defined. A suggestion was made as to whether patients with new-onset diabetes could be included as a cohort in surveillance programs given their higher incidence of developing pancreatic cancer. It was concluded that this would be unlikely given that pancreatic cancer is responsible for less than 1% of new-onset diabetes cases. The testing of all new onset diabetic patients using current invasive diagnostic tests would be anticipated to overwhelm the health system and lead to unfavourable risk/benefit balance. It was also noted that surveillance data from HR individuals does not translate to the general population. It was concluded that new-onset diabetes patients and other potential HR groups were more likely to be added to surveillance programs once more reliable, non-invasive biomarkers were developed.

Diagnosing pancreatic cancer early in general practice is challenging, with several factors contributing to this presented to the group. These include:

- The broad scope of primary care, with general practitioners (GPs) needing to know more than 100 conditions to manage 75% of the problems that present in clinic.
- The low prevalence of pancreatic cancer, with less than one patient presenting to a general practitioner (GP) per year.
- The non-specific signs and symptoms of the disease. It was stated that approximately 61% of patients required more than three visits to their GP prior to their diagnosis.
- The low positive predictive value (PPV) of each sign and symptom of pancreatic cancer, identified from an analysis of primary care GP data including over one million people across 100 GP sites across Australia.

The critical role of GPs in the early diagnosis of pancreatic cancer was recognised by the group, with GPs representing the first point of contact for most patients. Participants discussed additional supports that could be provided to GPs to ensure a timelier diagnosis, with a decision support tool for unexpected weight loss proposed as one option. The role of providing increased education to GPs on the signs and symptoms of pancreatic cancer was discussed, and whether there were key symptoms that were more likely to be indicative of pancreatic cancer. Jaundice was stated as the most predictive symptom, however the low PPV of jaundice and all other symptoms again raised.

The work undertaken at the Jreissati Pancreatic Centre at Epworth was discussed with participants. The Jreissati Pancreatic Centre is a centre of excellence in research, clinical care and patient experience for individuals with pancreatic cancer and represents the only centre of its kind in Australia. The three distinct parts of the centre were presented to participants:

- Clinical care, with the goal of connecting patients to specialists as quickly as possible. The centre contains a team of nurses that triage patient referrals to specialists within 72hrs.
- Research, consisting of 26 studies across the research portfolio, 19 actively recruiting. The goal is to implement the findings of the Jreissati Pancreatic Centre research into clinical care to improve survival rates and quality of life for patients. It was noted that a large proportion of these studies are focused on the early detection of pancreatic cancer.
- Patient experience and advocacy, with support and education provided for patients and GPs.

The role that patient education plays in the early detection of pancreatic cancer was highlighted by an example presented to the group. Jreissati makes available various online educational videos, with the video with the highest number of views explaining the diagnosis of IPMN and other benign cysts and their potential to develop into pancreatic cancer. It was discussed that the high views of this particular video were representative of the relatively high incidence of IPMN and other benign cysts diagnosed from patient imaging and indicative of the high level of concern surrounding this within the community. It was discussed with the group that the diagnosis of cysts represents a possible opportunity to transform how these patients are managed with respect to monitoring and ongoing investigation into the factors that are defining who goes on to develop pancreatic cancer.

A comment was then made that one of the barriers to the effective, sensitive monitoring of cysts was the limitations of current imaging modalities used in the clinic. The role of artificial intelligence (AI) combined with magnetic resonance imaging (MRI) was proposed to the group to increase detection rates of pancreatic cancer from cysts. It was stated that AI-assisted diagnostic techniques may become an essential factor in the adequate and accurate diagnoses of pancreatic cancer in the foreseeable future and should be made available to patients 24 hours a day. It was noted that more time and focus needs to be spent on developing more accurate biomarker tests and technologies, rather than rushing to implement screening programs. The group discussed what an ideal study could look like, with blood samples taken from patients to run a multitude of tests to assess the predictive value of markers together with data linkage capacity to facilitate large scale studies within Australia. AI specialists were proposed as required partners for biomarker development and the group was encouraged to think of ways to work more closely with this discipline, in addition to looking at organisations linked in with coeliac patients (due to possible increased risk of developing pancreatic cancer) and similar work within other cancer types.

Session 3: Where are we at with early diagnosis of pancreatic cancer?

Participants were presented the high-level details of the National Pancreatic Cancer Roadmap developed by Cancer Australia and how that aligned with the steps of the Optimal Care Pathway (OCP) for people with pancreatic cancer. It was discussed how the Roadmap provides national focus on priorities for improving outcomes and survival for Australians affected by pancreatic cancer.

Comprised of 33 Key Priority Areas (KPAs) and 60 strategies for collective action over the next four years to 2027, the aim of the roadmap is to set a shared agenda to drive improvements in pancreatic care, experiences and outcomes across the continuum of care, including a focus on early detection. It was stated that KPAs were developed following extensive evidence gathering and stakeholder consultation activities, with additional opportunities for consultation with the sector in the future.

Five specific KPAs of the Roadmap were briefly discussed:

- Development of pancreatic cancer specific risk assessment tool and the framework for future targeted risk stratified surveillance program. This work is led by Rachel Neale from Queensland Institute of Medical Research (QIMR).
- Establish the guidelines for integrating a decision support tool for assessment of signs and symptoms of pancreatic cancer into primary care. This work is led by Rachel Neale from QIMR.
- Develop standardised pathway for timely referral to specialist pain management expertise. This work is led by researchers at The University of Melbourne.
- Establish standardised pathways for early referral to palliative care for people with advanced pancreatic cancer. This work is led by researchers at The University of Melbourne.
- Improve the provision of culturally appropriate models of care for Aboriginal and Torres Strait Islander people and people from culturally and linguistically diverse backgrounds affected by pancreatic cancer. This work is led by researchers at The University of Queensland.

These KPAs of the Roadmap align with the strategic objectives of the recently announced Australian Cancer Plan, with the recognition that the overall aim of the Australian Cancer Plan was to achieve equity for all Australians diagnosed with cancer. It was stated to the group that indigenous Australians are 1.5 times more likely to develop pancreatic cancer than non-Indigenous Australians. Addressing this and achieving better outcomes for indigenous Australians is a strategic objective within the Australian Cancer Plan (Strategic Objective 6)

Success in the early detection of pancreatic cancer was defined by Cancer Australia as the following:

- An increase in the numbers of patients diagnosed with resectable disease and go on to have resection, which should ultimately give rise to increased survival rates.
- Increased confidence of GPs and primary care professionals in feeling equipped to diagnose and refer patients to appropriate pathways for their ongoing investigation.

The commitment of Cancer Australia to the development of the new discoveries required for early detection of pancreatic cancer was questioned, with reference to the paucity of funding provided for fundamental pancreatic cancer research from Cancer Australia through the Priority-driven Collaborative Cancer Research Scheme (PdCCRS) (2019-present). The group was reassured that allocated research investment for areas of unmet and emerging need will be made available by Cancer Australia in partnership with the National Health and Medical Research Council and Medical Research Future Fund as part of the Australian Cancer Plan (Strategic Objective 4.2.2).

The critical importance of fundamental research in the exploration of more innovative, accurate biomarker tests and technologies to improve the early detection and management of pancreatic cancer became the focus on the discussion. The potential of extracellular vesicles (EVs) as diagnostic and prognostic biomarkers in a liquid biopsy test was presented to the group, with their ubiquitous presence throughout a variety of readily accessible body fluids including saliva, serum, urine and plasma. The use of EVs was compared to other traditional molecular biomarkers such as circulating tumour cells (CTCs) and cell-free DNA (cfDNA), with the possibility raised that EVs might overcome the observed detection issues with some technologies measuring other molecular biomarkers in early diagnosis. The recent launch of a clinical study, Exoluminate, by Biological Dynamics Inc was mentioned, where EVs are isolated and purified from patient's blood samples on the basis of alternating current electrokinetics. The trial is currently open to individuals with elevated risk of developing pancreatic cancer to evaluate the performance of the assay in the early detection of pancreatic cancer.

Participants were encouraged to look beyond investigating one type of molecular biomarker in isolation, with a more realistic view of a future liquid biopsy test used in the clinical setting thought to integrate a variety of molecular markers into a panel. A future view of screening of all risk groups for pancreatic cancer using all sample sources (blood, urine, stool, pancreatic juice, saliva) for a range of molecular marker types (EVs, CTCs, cfDNA) was proposed. To achieve this, the important role of AI in the integration all data types was again raised, with the potential to perform combinatorial analysis of imaging data and all types of molecular marker analysis to identify emerging biomarkers for early diagnosis. To achieve this, again the urgent need to break down the silos across disciplines and perform collaborative, multidisciplinary research was strongly reinforced, facilitating innovative scientific approaches their translation into the clinic for patients.

Session 4: What can we learn from other cancers?

The session commenced with a discussion on the some of the challenges associated with the development of a population cancer screening program, such as the high costs of these programs ($435M spent on cancer screening programs alone in 2017, AIHW estimate) and the long timeline from establishing evidence from RCTs to full implementation of the program.

The development of Australia's National Bowel Cancer Screening Program was used as an example, with three international RCTs providing the required evidence resulting in implementation of the program 26 years later. Participants were reminded of the ethical considerations of population cancer screening program, where the health service is approaching a potentially asymptomatic individual as distinct to health care where most people are sick or injured and initiate contact with the service. On this basis, population cancer screening program demand a higher standard of evidence to ensure there is more benefit than harm. Participants were strongly urged to temper their enthusiasm and be realistic with respect to the development of a pancreatic cancer population screening program and streamline translation from research to practise without taking dangerous shortcuts. Caution was expressed with the hype surrounding the various multi-cancer early detection (MCED) tests currently under clinical investigation, such as the GRAIL Galleri MCED test, with lots of anxiety and uncertainty surrounding their ethical application within the health system with accumulating evidence regarding harms outweighing benefits for the population.

High uptake rates of any population cancer screening program is vital for early detection, reducing mortality rates, optimising healthcare spending and enhancing the overall health of the population. The low uptake rates of Australia's National Bowel Cancer Screening Program were presented to participants, with only 41% of eligible Australians undertaking the test due to the unpopularity of providing a faecal sample. New research focused on identifying new blood biomarkers for bowel cancer was described, with the aim of transitioning this test to the more popular blood test. The challenge with identifying biomarkers that are representative of the extensive intertumoural heterogeneity across patients of the population was mentioned. Rather than focusing efforts on a single layer of "omics", a multi-omics approach integrating data from epigenomics, genomics, transcriptomics and proteomics was proposed and heralded as the key to identifying the appropriate blood-based biomarkers for the early detection of bowel cancer. While fundamental or discovery research is clearly required to identify these biomarkers and develop innovative technologies for their detection, the lack of translational research to bridge their validation and transition to the clinic was highlighted as a significant barrier to progress blood-based screening for bowel cancer.

The discussion on biomarkers and liquid biopsy technologies in the workshop so far was focused on their role in the early detection of cancer. Discussion next moved to their distinct role predicting treatment response in Melanoma, based on the finding that patients with no detectable circulating tumour DNA (ctDNA) had a vastly improved overall survival to those that had detectable levels following treatment. Various challenges with ctDNA and liquid biopsy approaches were presented,

including the false negative rate due to some cancers showing minimal shedding and the false positive rate due to the errors introduced during DNA extraction and downstream steps of the process. Based on the lessons from the Melanoma field, it was again proposed that ctDNA and liquid biopsy be incorporated as part of a more multi-modal approach for the early diagnosis of pancreatic cancer.

Session 5: Opportunities to progress early detection in pancreatic cancer.

Attendees at the workshop discussed five questions:

1. **What does the optimal future look like with no constraints?**

Six themes emerged from responses to this question:

- Establish a purpose-driven national pancreatic cancer consortium to create a formalised network for collaboration. This consortium should include individuals working in pancreatic cancer across all disciplines within Australia and contain the appropriate governance framework.
- Collaboration within and across disciplines (engineering, general practise, oncology, AI, biology/biomedical science) is critical for innovation in diagnostic technology. Drivers for collaboration need to be investigated to provide additional incentives and key performance indicators (KPIs) to accelerate collaborative activity.
- A multimodal approach to identify accurate, reliable biomarkers for multiple patient groups and incentives to validate them in a translational setting. Patients' groups include:
    - Those with early stage (Stage 0 -1) pancreatic cancer. The ideal clinical study to investigate these was detailed, with a suite of exploratory biomarker analyses performed from a range of body fluids (blood, urine, saliva, pancreatic cyst fluid, stool and biopsied tissue) from internationally recruited stage 1 patients, following marker validation by an RCT. The study could be run via / within the established national pancreatic cancer consortium together with international partners.
    - Patients with high risk of relapse. Biomarkers to predict which patients were at increased risk of relapse are required to influence patient management.
- Strategic partnerships with various industry partners. These partnerships could be developed as an arm within the consortium with the potential to be a revenue for the consortium.
- Increased training for Endoscopic ultrasound fine-needle aspiration (EUS-FNA). There is increasing global demand for the technically challenging EUS-FNA and the path to attaining proficiency is long and arduous.
- Co-designed lived experience framework embedded within the pancreatic cancer sector.
- Improved equity of access to pancreatic cancer treatment.

2. **What are the barriers for achieving this?**

Five themes emerged from responses to this question:

- Insufficient funding
- Low incidence of disease compared to other cancers
- Potential intellectual property disputes between industry partners (such as pharmaceutical companies) and academic research institutions, slowing down research progress and translation to clinic.
- Lack of strategy defining the priorities to translate discovery research into clinical practise

- Structural barriers (ethical standards, distinct governance structures) to collaboration between local health districts

3. What are the steps needed to advance pancreatic cancer research in Australia?

Establish a purpose-driven national pancreatic cancer consortium

- Develop the national pancreatic cancer consortium mission statement. One suggestion was to improve outcomes for all patients with pancreatic cancer.
- Strategically define and prioritise research focus areas within the preclinical and clinical setting based on the mission statement of the consortium.
- Perform background analysis on Australian research activity and establish a "research registry". This could include information on which researchers are active in the pancreatic cancer space, what technologies are being used and what samples are being collected.
- Establish a decentralised pancreatic cancer biobank with appropriate governance, ethics and steering committees. This could exist as a hybrid model and combine samples from the Australian Pancreatic Cancer Genome Initiative (APGI) BioResource.
- Build an online communication channel within the consortium for the interaction of scientists, clinicians, patient advocates, and other members as a networking and education platform. This would represent an avenue for early career researchers to share their novel ideas, obtain feedback and identify training opportunities for laboratory techniques and other components required to achieve research aims.
- Host online national scientific symposia for pancreatic cancer to foster increased collaboration and provide additional avenues to showcase Australian pancreatic cancer research to encourage those from other disciplines to join pancreatic cancer.
- Develop KPIs around the total number of early stage pancreatic cancer samples collected, number of national groups collaborating on projects, applying for grants and publishing research articles.

Increased funding for research to support the future next generation workforce

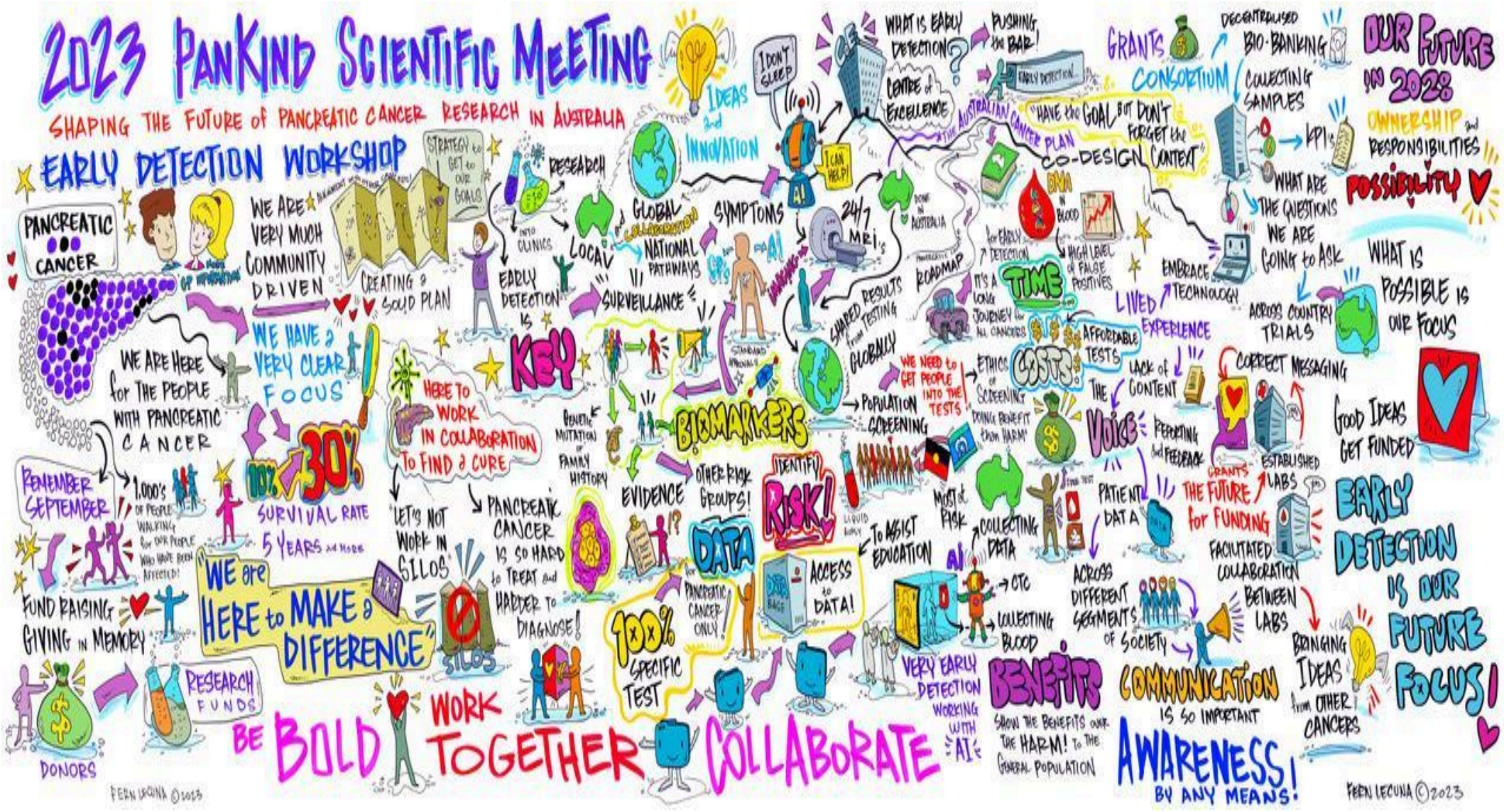
- Leverage partnership with Cancer Australia to increase government funding to pancreatic cancer through future PdCCRS and other schemes.
- Advocate to health service and the Royal Australian College of General Practitioners (RACGP) to provide more protected time for research.
- Require specified funding that enables longer-term projects focused on the application of skills and technologies from established laboratories from other disciplines to pancreatic cancer.
- Provision of structured PhD scholarships that facilitate cross-disciplinary placement of students across multiple national and international laboratories.
- Specified early and middle career fellowship funding for researchers to span multiple research disciplines and attract individuals to the pancreatic cancer field.
- Reserve some seed funding committed to co-funding and leveraging successful MRFF applications.

Develop a lived experience platform

- The poor prognosis of patients diagnosed with pancreatic cancer means that the field currently lacks the stories from those with lived experience, those who bring critical unique knowledge to health systems and research.
- Careful listening to those with lived experience is required to ensure effective bi-directional communication to inform and co-design pancreatic cancer research projects.
- Increase awareness and education at several levels with the entire community on the impact of a pancreatic cancer diagnosis, driving greater engagement with the sector.

- Ensure the equity of all groups of pancreatic cancer sufferers, including indigenous, regional and other minority groups within society.
- Increase the accountability for reporting research outcomes to those with lived experience.

Figure 1: Graphical representation capturing the main discussion points of the workshop (Credit: Fern Lecuna)



Conclusions

The workshop provided a comprehensive overview of the opportunities and challenges associated with the early diagnosis of pancreatic cancer, in the context of activity in other cancer types. Invited presentations and the wider engagement with a diverse range of stakeholders who attended the workshop identified several key themes for improving early detection rates and ultimately patient outcomes. These include:

- Lived experience perspective highlights the need for greater public awareness of pancreatic cancer and improved early detection methods, with individuals often in good health and vague symptoms before diagnosis.
- Surveillance or screening programs for high-risk individuals is challenged by the overall low incidence of the disease and the lack of reliable, sensitive biomarkers and/or non-invasive screening tests to track disease progression from an early stage.
- GPs play a crucial role in reducing delays in diagnosis, with increased support and education for GPs and patients proposed to facilitate earlier referral and diagnosis.
- The early detection of pancreatic cancer will likely involve a multimodal diagnostic approach including a panel of molecular markers integrated with imaging data using AI.
- The field needs to leverage government consultation and funding initiatives such as the National Pancreatic Cancer Roadmap and the Australian Cancer Plan.
- Increased multi-disciplinary collaboration and a national consortium is urgently needed to break down the siloes between stakeholders within the field; prioritise focus areas for discovery, preclinical and clinical research; maximise resources and drive the innovation required to advance outcomes for patients with pancreatic cancer.

The outcomes from this workshop will inform the future development of a research strategy and initiatives to maximise impact for the early detection of pancreatic cancer.

Appendix 1: Early Detection Workshop Participants

Name	Organisation	Name	Organisation
Minoti Apte	Curtin	Vasilios Liapis	UniSA
Chris Baggoley	PanKind	Frank Lin	Garvan
Claudine Bonder	Centre for Cancer Biology	Javiera Martinez Gutierrez	UniMelb
Ilaria Casari	Curtin	Alan McArthur	PanKind
Sofia Casbolt	PanKind	William McGahon	RBWH
Lorraine Chantrill	ISLHD Cancer Services	Ross McKinnon	Flinders
Daniel Croagh	Monash	Rachel Neale	QIMR
Marco Falasca	Curtin	Katia Nones	QIMR
Frederic Hollande	UniMelb	Chamini Perera	UNSW
John Hooper	UQ	Ashleigh Poh	Jreissati Pancreatic Centre
Rohan Jeffs	PanKind	Kristjan Porm	PanKind
Milton Kirkwood	AGITG	Helen Rizos	Melanoma Institute of Australia
Barry Kitchen	Monash	Sumit Sahni	USyd
Zaklina Kovacevic	UNSW	Michelle Stewart	PanKind
James Lawson	Cancer Australia	Alina Stoita	St Vincent's Hospital
Caroline Le	Jreissati Pancreatic Centre	Nigel Turner	Victor Chang
Fern Lecuna	Duel Designs	Tracy Walker	PanKind
Jason Lee	QIMR	Jean Winter	Flinders
Terry Slevin	Public Health Association of Australia	Dannel Yeo	Centenary Institute
Ying Zhu	UTS	Erin Symonds	Flinders