Chapter 4
Challenges and Opportunities for Early Pancreatic Cancer Detection: Role for Protein Biomarkers

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The Case for Earlier Detection

Currently, for three out of four PDAC patients, the diagnosis of PDAC comes at a time when the disease is advanced. Late diagnosis severely limits treatment options and contributes to the poor overall 5-year survival of 7%. Reliable diagnostic biomarkers that facilitate earlier diagnosis are much needed [1]. Generally speaking, it is recognised that early detection of cancer increases the opportunities for effective management and treatment (http://www.who.int/cancer/prevention/diagnosis-screening/en). Biomarker development projects aim to introduce diagnostic biomarkers that will permit PDAC detection at a time when therapeutic intervention that leads to improved prognosis is feasible. It is essential to ensure that earlier detection facilitates interventions that both improve outcome and well-being for patients, without simply increasing the time interval between diagnosis and death, known as lead time. Much research supports the benefit of earlier PDAC detection. Patients in whom PDAC is incidentally diagnosed have longer median survival compared with PDACs discovered when patients are symptomatic [2]. Furthermore, patients diagnosed with stage I disease survive markedly better compared to patients with all other stages [2]. Surgery followed by chemotherapy confers a significant survival advantage [3, 4]. In this setting, the 5-year survival is 70% for stage I disease and 22% for stage III disease. The ESPAC-4 trial which compared

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gemcitabine to combination gemcitabine/capecitabine therapy in R0/R1 resected PDAC patients demonstrated superior 5-year survival of 28·8% in the gemcitabine/capecitabine arm [5]. By contrast, for patients with locally advanced and metastatic pancreatic cancer randomised to either gemcitabine or gemcitabine/capecitabine, the 1-year survival in the superior arm of gemcitabine/capecitabine was 24% [6]. Thus, detecting PDAC at a time when patients are eligible for potentially curative surgery or for neoadjuvant therapy to downstage locally unresectable disease could significantly improve prognosis. The success of early detection schemes will require education of both the general public and healthcare professionals so that possible warning signs of pancreatic cancer are recognised. Alongside education, effective screening will be a major element in earlier detection of PDAC.

Challenges Associated with Diagnostic PDAC Marker Development

PDAC early detection faces a number of critical challenges (Table 4.1). PDAC is relatively uncommon, and it is therefore difficult for a single group or institution to amass the number and variety of samples required for successful biomarker development. PDAC tumours exhibit both intra-tumour and inter-individual variation [7,

Table 4.1 Challenges and potential solutions to early detection biomarker development for pancreatic cancer

Description	Challenge	Potential solutions
PDAC is a relatively uncommon disease	Large numbers of samples are required for novel biomarker development	National and international collaboration is required for adequate sample availability
PDAC tumours exhibit both intra-tumour and inter-individual variation	Large numbers of samples are required to enable diversity to be captured	National and international collaboration is required Capture as much clinico-pathological data relevant to samples as possible Sub-categorise samples to allow biomarker performance in individual categories to be manifested
PDAC is accompanied by comorbidities	Comorbidities such as obstructive jaundice, new-onset diabetes mellitus and chronic pancreatitis could influence biomarker behaviour or mislead biomarker analysis (e.g. the biomarker detects the comorbidity rather than the principal disease)	Carefully design studies Include groups that control for comorbidities, allowing the biomarkers' power to discriminate cancer from controls to be accurately assessed Be clear about the intended use population

Table 4.1 (continued)

Description	Challenge	Potential solutions
The majority of PDAC patients are diagnosed with late-stage disease	Use of late-stage samples in biomarker discovery and/or validation may lead to the detection of biomarkers capable of detecting late-stage disease, but not necessarily early-stage disease	Include patients with early-stage disease and studies Use pre-diagnostic samples where possible Collect custom-made bespoke cohorts in order to obtain pre-diagnostic samples with pancreatic cancer detection specifically in mind

8]. This heterogeneity is likely to be reflected in a variation in biomarkers from patient to patient, and robust biomarker panels may be required. PDAC is often accompanied by obstructive jaundice, which can lead to false-positive findings in blood-borne biomarker studies [9–11]. Moreover, PDAC-associated diabetes is present in a substantial proportion of individuals with pancreatic cancer [12]. Therefore, it is conceivable that biomarkers appearing to relate to PDAC could be the consequence of diabetes and as such may be present in cancer-free individuals who have diabetes. Finally, PDAC tissue exhibits areas of chronic pancreatitis. Understanding the impact of comorbidities on PDAC biomarkers is essential and requires carefully designed studies. Depending on the intended use population, samples from multiple disease controls may be required.

To date, most studies aimed at identifying early-stage biomarkers of PDAC have used samples from patients already diagnosed with PDAC and are thus compromised by both late changes during tumorigenesis that are not seen in early-stage disease and the general poor health of patients with advanced disease. It is recognised that new lines of early detection research should include relevant early-stage, pre-diagnostic samples in order to validate existing biomarkers and offer chances of discovering new biomarkers of early PDAC. Some of the protein markers discussed below have been discovered or validated in such samples.

How Would a Biomarker Panel Be Used?

The intended use of a biomarker will dictate the required sensitivity and specificity and the patient and control groups required during biomarker development. Individual and tumoural heterogeneity suggests that no single biomarker on its own will give adequate sensitivity and that a panel of two or more protein biomarkers will be required. Moreover, if the biomarker is being used to stratify risk within a population, then it is likely that follow-up screening will be carried out to achieve diagnosis (Fig. 4.1). Thus, while high sensitivities and specificities are desirable, currently it is envisaged that a positive biomarker test will not be used as a stand-alone diagnostic.

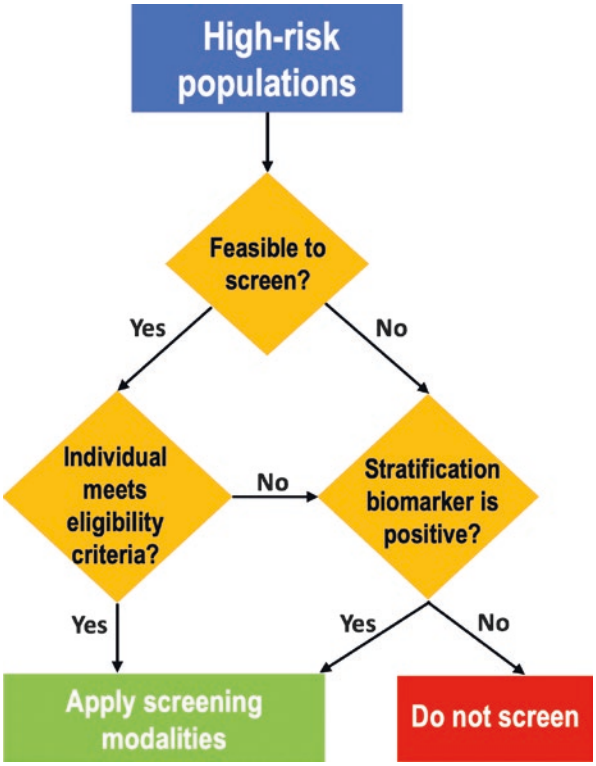

Fig. 4.1 Pathways to screening in high-risk groups; role of biomarkers. Currently there are no biomarkers suitable for screening the general population. Although PDAC is a leading cause of cancer deaths, it is relatively uncommon. A screening test would have to be extremely specific (approaching 100%) in order to avoid large numbers of false positives, and no such screening modality presently exists. For some high-risk populations, it is feasible to screen individuals who meet the eligibility criteria. However, even if individuals in this group do not meet the eligibility criteria, a positive biomarker result may suggest that screening via existing modalities (EUS, CT/MRI scan, biochemistry panels) is warranted. Within some high-risk groups, such as individuals with new-onset diabetes mellitus, subjecting all individuals to screening is not feasible due to the low incidence of PDAC within the population. Biomarkers for early detection of PDAC could select for those at a higher risk of a PDAC diagnosis, creating an enriched group of the highest-risk individuals to be screened. Those with a negative result from the biomarker test and therefore deemed to be at lower risk would be spared the worry and inconvenience of screening, while the healthcare system would avoid the associated burden and costs of unnecessary screening

Barriers to Screening for PDAC

Until relatively recently, cancers, such as breast and cervical cancer, seemed intractable. However, mortality from these cancers has decreased, in part attributed to the introduction of screening programmes which facilitate detection of early lesions or localised tumours that are easier to treat. There are practical barriers to screening the general public for PDAC. Although the mortality rate of PDAC is very high, the

disease is relatively uncommon, with an incidence in Europe of 8/100,000 (Age Standardised Rate) [13]. Given the diagnostic accuracy of current detection methods, this is too low to permit screening of the asymptomatic adult population. False positives for this disease are especially serious, as it is not easy to access pancreatic lesions. For some patients, a definitive diagnosis requires surgery, and this carries the risk of significant morbidity and mortality. There are at least two ways in which the accuracy of screening for PDAC could be improved. Firstly, the development of a high-performing screening test could make screening possible. Secondly, restricting screening to those at the highest risk of PDAC would increase the rate of disease detection and reduce the occurrence of false-positive findings. These two options are not mutually exclusive, and implementing a higher-performing screening test in a high-risk population would offer the best chances of increasing accuracy [2]. Effective screening requires many conditions to be met, including that its effectiveness is proven, that it is resourced sufficiently to cover the group being screened, that a pathway exists for confirming diagnoses and for offering treatment and follow-up where tests show abnormal results, and, finally, that the prevalence of the disease should be sufficiently high to justify the costs of screening. The cost-benefit analysis should take into account the cost of the initial screening test as well as the cost of subsequent tests required to confirm the diagnosis. Since, in all cases, abnormal results require confirmatory tests, keeping false positives to a minimum is essential to reduce costs. Thus, great attention needs to be paid to the specificity of the test. Ghatnekar et al. [14] describe a model which enabled them to determine cost and the quality-adjusted life years (QALY) of screening for PDAC using a biomarker panel. According to their model, screening high-risk individuals for PDAC using a serum biomarker panel is highly desirable.

High-Risk Groups

An estimated 10% of patients with PDAC have a family history of the disease. For a proportion of these families, the pattern of risk is consistent with autosomal dominant predisposition [15]. In Europe, the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) is the largest registry of families with an inherited risk of PDAC. The United States also has successful pancreas screening [16]. Currently, screening is restricted to families with an inherited risk [17]. By contrast, 90% of PDAC cases cannot be predicted by family history and are considered sporadic. No current screening modality exists for sporadic PDAC.

Epidemiological data indicate that PDAC can cause diabetes mellitus [18], with new-onset diabetes an early warning sign of the presence of PDAC [18]. Sharma et al. reported that pancreatic cancer patients are hyperglycaemic for an average duration of 36–30 months before PDAC diagnosis [19]. At the time of PDAC diagnosis, the majority of PDAC patients have diabetes [12, 20]. By contrast, the prevalence of diabetes in individuals with lung, breast, prostate, and colorectal cancers is no higher than non-cancer controls [21]. New-onset diabetes

occurs in ~50% of PDAC cases; it is the largest high-risk group for sporadic PDAC. With regard to early detection, distinguishing new-onset diabetes caused by PDAC (known as type 3c) from the more common type 2 form of the disease would allow for earlier diagnosis of PDAC [18]. However, hyperglycaemia and diabetes are common in the general population, and additional factors will need to be considered in order to enrich individuals within this group who are most likely at risk of being diagnosed with PDAC. Based on data from four independent cohorts of patients with new-onset diabetes, Sharma et al. identified three factors which were strongly correlated with PDAC [22], change in weight, change in blood glucose, and age at onset of diabetes. These form the basis of the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model. Biomarkers may allow for further enrichment of the new-onset diabetes group for PDAC.

The Need for Better Biomarkers

CA19–9 is the only biomarker in routine use for the management of PDAC [23, 24]. It has a number of limitations including lack of expression in ~5% of the population and elevation in related diseases including chronic pancreatitis and obstructive jaundice [23, 25]. CA19–9 has a sensitivity/specificity of ~85%/~85% for the detection of advanced PDAC [26]. Since PDAC is relatively uncommon, screening the general population with CA19–9 is not feasible because for every true positive identified, several thousand false positives would also be identified. All positives (both true and false) would require additional tests (imaging, biochemical panels) to verify the presence of PDAC. The ratio of true positives to false positives is far too low to justify the costs of additional tests and the potential harm caused to individuals without the disease who test positive for it. Consequently, biomarkers with superior sensitivities and particularly superior specificities are required.

Progress in Protein Biomarker Development

A number of recent studies which reported protein biomarkers are compiled here (Table 4.2). Given the large body of literature to select from, we have prioritised studies which have either used pre-diagnostic samples, included samples from early-stage disease cases, or contained large numbers of subjects. Additionally, we have made subjective decisions about the studies that are most relevant to our own research interests. Liquid biopsy denotes a sample of body fluid collected in a minimally invasive manner [27]. The liquid biopsy most frequently analysed for biomarkers of PDAC is blood (Table 4.2), although other body fluids such as urine and saliva have also been investigated.

Table 4.2 Selected blood-borne protein biomarkers

Protein biomarkers	Analysis included	Performance	Sample source	Reference
CA19–9 and TSP-1	Multiple reaction monitoring (MRM)	AUC of 0.86 to distinguish PDAC (in samples taken between 0 and 24 months prior to diagnosis) from control	Blood; pre-diagnostic PDAC cases (UKCTOCS), chronic pancreatitis, healthy controls, diagnosed PDAC, KPC mice	Jenkinson et al. [28]
ERBB2, ESR1 and TNC	Antibody microarray	AUC of 0.86 for diagnosed PDAC; AUC of 0.68 for the pre-diagnostic samples	Blood; KPC mice, pre-diagnostic plasma samples from women in the Women's health initiative (WHI)	Mirus et al. [29]
CA19–9	ELISA and/or CLIA	At 95% specificity, the sensitivity of CA19–9 (>37 U/mL) was 68% up to 1 year, and 53% up to 2 years prior to diagnosis	Blood; pre-diagnostic PDAC cases (UKCTOCS)	O'Brien et al. [30]
LYVE-1, REG1A, and TFF1	GeLC/MS/MS, ELISA	AUC of 0.92 to distinguish stage I and II PDAC cases from healthy controls	Urine; PDAC samples, including with early stage, healthy control, chronic pancreatitis	Radon et al. [31]
CA19–9 with THBS2	ELISA	AUC >0.84 to distinguish PDAC of all stages from controls	Blood; PDAC samples, including with early stage, healthy control, chronic pancreatitis	Kim et al. [32]
29-protein biomarker panel	Antibody microarray	AUC of 0.96 to distinguish stage I and II PDAC cases from healthy controls	Blood; PDAC samples, including with early stage, healthy control, chronic pancreatitis	Mellby et al. 2018 [33]

AUC area under the curve, *GeLC-MS/MS* SDS-PAGE-Liquid Chromatography-Tandem Mass Spectrometry, *UKCTOCS* United Kingdom Trial of Ovarian Cancer Screening

Future Perspectives

There is no doubt that improvements have been made in the way in which biomarkers are discovered and validated. A key issue for biomarker programs that use samples from individuals already diagnosed with PDAC is gauging whether biomarker alterations, evident at the time of diagnosis, are detectable earlier in the disease pathway. A number of cohort studies containing samples taken from individuals who went on to be diagnosed with PDAC show that certain candidate markers perform poorly in pre-diagnostic samples. Lokshin and co-workers [34] used pre-diagnostic sera from PDAC patients from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) to evaluate the performance of 67 proteins. They concluded that most biomarkers identified in previously conducted case/control studies are ineffective in pre-diagnostic samples, including examples such as MIC-1, TIMP-1, ICAM1, HE4, OPG, MUC1, and MMP9. Jenkinson et al. [35]

similarly reported that ICAM-1 and TIMP-1, promising candidate PDAC diagnostic markers, failed to show significant elevation in samples from the UKCTOCS study taken 0–12 months prior to PDAC diagnosis [35]. Both ICAM-1 and TIMP-1 proteins were significantly elevated in blood from PDAC patients with obstructive jaundice [35], and this finding possibly explains the observed upregulation of these proteins in diagnosed PDAC cases.

The use of existing cohorts for the discovery or validation of PDAC early detection biomarkers is not ideal. Existing cohorts lack important demographic data such as diabetes status, presence of obstructive jaundice, or history of chronic pancreatitis. For this reason bespoke pre-diagnostic cohorts are currently being assembled. In the United States, Chari and colleagues in the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) have begun to assemble a prospective high-risk cohort of 10,000 individuals with new-onset diabetes mellitus, called NOD [36]. In the United Kingdom, a similar cohort of 2500 individuals, called UK-NOD, is being led at University of Liverpool by the authors of this book chapter, and there are other similar initiatives underway in Europe. Together, these multi-centre collaborative projects have the scale to acquire the high numbers of individuals (with presymptomatic PDAC and new-onset type 2 diabetes mellitus) necessary for rigorous validation of existing biomarkers and the discovery of new early detection biomarkers for PDAC. High-risk registries of familial PDAC will also provide an invaluable resource for the development of early PDAC biomarkers. It is foreseeable that biomarkers for early detection of PDAC will initially be tested and used in high-risk groups. This progress in early detection, along with concurrent advances in treatment, will undoubtedly lead to improvements in outcomes for PDAC patients.

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