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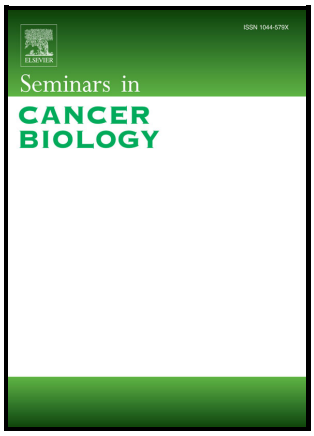

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Biomarkers, Omics and Artificial Intelligence for Early Detection of Pancreatic Cancer.

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is frequently diagnosed in its late stages when treatment options are limited. Unlike other common cancers, there are no population-wide screening programmes for PDAC. Thus, early disease detection, although urgently needed, remains elusive. Individuals in certain high-risk groups are, however, offered screening or surveillance. Here we explore advances in understanding high-risk groups for PDAC and efforts to implement biomarker-driven detection of PDAC in these groups. We review current approaches to early detection biomarker development and the use of artificial intelligence as applied to electronic health records (EHRs) and social media. Finally, we address the cost-effectiveness of applying biomarker strategies for early detection of PDAC.

Keywords: Pancreatic cancer, early detection, biomarkers, artificial intelligence, omics

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most aggressive form of pancreatic cancer and is the focus of this review. PDAC is the third leading cause of cancer death in men and women combined in the United States [1] and the fourth in Europe [2]. The incidence of the disease is increasing and is mirrored by an increase in mortality; the overall 5-year survival rate is 13% [1]. The symptoms of PDAC can be vague, making it difficult to diagnose early, when the chances of effective treatment and cure are highest. Consequently, at the time of presentation, some 50% of patients have metastatic disease and 30-35% of patients have locally advanced disease [3]. Only 15 to 20% of patients are eligible for potentially curative surgery [4].

Challenges of PDAC detection test development

Despite its high mortality-to-incidence ratio, the prevalence of PDAC within the general population is relatively low with lifetime risk estimated as 1.7% [5]. Consequently, a PDAC test developed for population-wide screening would need to achieve exceptionally high specificity to be at an acceptable level [6]. False positives can provoke worry, unnecessary clinical work-up and incur high costs. Therefore, the focus of current early detection strategies is on identifying people at high risk who are most likely to benefit from longitudinal surveillance, and developing biomarker and imaging-based modalities that will assist in PDAC surveillance [7]. Given the consequences of late diagnosis for the patient, high sensitivity is also desirable. A second notable challenge is the lack of bespoke pre-diagnostic cohorts in which to develop or test emerging biomarkers. Cohort development is costly and takes time. However, testing the performance of candidate biomarkers in samples taken prior to a diagnosis of pancreatic cancer is an important component of biomarker development. Individual differences and tumour heterogeneity mean that in all likelihood multiple biomarkers will be needed to detect all individuals with PDAC.

2. Surveillance for PDAC and high-risk groups

a. Surveillance for PDAC

i. Familial pancreatic cancer and hereditary cancer syndromes

Individuals with a lifetime risk of PDAC exceeding 5% are considered at high risk. This includes people in families with familial pancreatic cancer , or with hereditary cancer syndromes [8]. Germline mutations in *BRCA2*, *BRCA1*, and *PALB2* genes involved in the homologous recombination DNA damage repair pathway, are most frequent [9], with pathogenic mutations in *BRCA2* conferring a 3.5 to 5.8-fold increased lifetime risk of PDAC compared to non-*BRCA2* mutation carriers. Around 1% of families with a history of PDAC have mutations in the *PALB2* gene, which encodes a binding partner of *BRCA2* [10]. Individuals with germline mutations in *ATM*, also involved in homologous DNA repair, have a significantly higher cumulative risk of developing PDAC compared to those with a family history but no identified mutation [11]. Germline genetic variations of the *CDKN2A* gene, which encodes the tumour suppressor protein p16, have a 5-24% lifetime risk of PDAC and a tendency to develop cancer at a younger age [12]. Peutz-Jeghers syndrome is an autosomal dominant condition caused by a mutation in the STK11 gene, which leads to high penetrance hamartomatous polyposis and a lifetime risk of 11-36% with an average diagnosis age of 41 years [13-15]. Lynch syndrome, caused by mutations in DNA mismatch repair genes, such as *MSH2*, *MLH1*, *MSH6*, *PMS2*, and *EPCAM*, significantly increases the risk of PDAC to 9 times that of the general population [16]. Li-Fraumeni syndrome (LFS) is a genetic disorder caused by a mutation in the tumour suppressor gene *TP53*. Individuals with LFS have a significantly higher risk (relative risk of 7.3) of developing pancreatic cancer [17].

Individuals with hereditary pancreatitis (HP) also have a high risk of pancreatic cancer decades after the initial onset of pancreatitis. HP carries a 30-40% estimated cumulative risk of developing pancreatic cancer by age 70 [18]. This condition is often linked to mutations in the *PRSS1* gene causing autosomal dominant inheritance of the disease [19].

ii. Cystic lesions

Mucinous pancreatic cysts, including Intraductal Papillary Mucinous Neoplasms (IPMNs) and Mucinous Cystic Neoplasms (MCNs) are believed to give rise to up to 15% of PDACs [20]. IPMNs are categorised based on their location, into main duct (MD-IPMN), branch duct (BD-IPMN) and mixed type (MT-IPMN). The high incidence of PDAC associated with MD-IPMN and MT-IPMN argues for their surgical resection, while BD-IPMN are less likely to have high grade dysplasia or be associated with PDAC and are not recommended for surgery [21]. Mutational profiles (in somatic genes) can aid in the identification of cystic type. Serous cystadenomas, a common non-malignant cyst type, are associated with mutations in *VHL*, while mutations in *KRAS* or *GNAS* are common in the cyst fluid of IPMNs and MCNs [22]. Recently, it has emerged that patients with IPMN carrying a PDAC-predisposing germline mutation are at higher risk of malignant transformation and merit an intensive follow-up [23].

iii. Surveillance modalities

Surveillance of individuals at high risk of PDAC is recommended using endoscopic ultrasound (EUS) or magnetic resonance imaging/cholangiopancreatography (MRI/MRCP), with consensus statements on the standardisation of EUS imaging and reporting, and MRI screening and reporting respectively published by The Pancreatic Cancer Early Detection (PRECEDE) Consortium [24, 25]. Both modalities have advantages and limitations, and their choice should be based on a case-by-case basis, according to the patient's features and the centre's availability. The PRECEDE and International Cancer of the Pancreas Screening Consortia have provided detailed indications of the screening interval to adopt [26, 27]. Individuals with

hereditary pancreatitis and *PRSS1* mutation are offered surveillance with CT scanning due to a markedly elevated risk of PDAC [28].

b. New-onset diabetes as a facilitator of early detection

At the time of diagnosis of PDAC, approximately 85% of patients have glucose dysregulation, with 40 – 65% of patients having diabetes mellitus (DM) [7]. While approximately 15% of DM in PDAC patients is long-standing (present >3 years), the remainder is new-onset diabetes mellitus (NOD). In effect, NOD is an early warning sign of the presence of PDAC, and individuals with NOD over 50 years have a 6 to 8-fold higher risk of PDAC than the general population [29-31]. Pancreatic cancer-associated diabetes is a form of pancreatogenic diabetes (commonly referred to as type 3c diabetes), which results from exocrine pancreatic disease, including pancreatic cancer and chronic pancreatitis. Unlike type 1 and type 2 disease, type 3c is caused by structural and functional damage to the pancreas.

Developing strategies to enable screening of individuals with NOD for PDAC is a priority [6, 32]. A significant challenge is the low prevalence of PDAC (0.8-1%) in this high-risk group, requiring enrichment for those most at risk, i.e. most likely to have PDAC [7]. The Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) tool utilises three factors, age, change in weight and change in blood glucose to stratify individuals with NOD into low, intermediate or high risk for PDAC [33]. ENDPAC is currently undergoing evaluation in a randomised controlled trial [34]. The feasibility of integrating a cancer decision support tool into primary care has already been demonstrated [35]. Biomarkers to support risk stratification are much needed. The UK Early Detection Initiative (UK-EDI) study is recruiting individuals with NOD to investigate biomarkers capable of detecting type 3c diabetes in this group [32]. Type 3c diabetes is often misdiagnosed as type 2 disease meaning opportunities to detect PDAC earlier are being lost. Distinguishing type 3c from type 2 diabetes at the point of diabetes diagnosis, will select a sub-population for PDAC screening [36].

For a summary of ongoing trials and studies for early PDAC detection see Table 1.

Table 1: Trials and Studies addressing early detection of PDAC.

Trial Name	Target Population(s)	Biomarker of Interest	Refer-ence
UK-EDI United Kingdom Early Detection study *(United Kingdom)*	1. NOD 2. Aged 50 years and above	Plasma protein biomarker panel differentiating between type-3c and type 2 diabetes; germline alterations	[37]
Early Detection Initiative (ENDPAC evaluation) Enriching New-onset Diabetes for Pancreatic Cancer *(United States)*	1. NOD 2. Aged 50 years and above 3. Index weight and left-window weight values available	ENDPAC risk score based on age at diagnosis and left-window weight and blood glucose measurements	[34]
PANLIPSY	1. Confirmed PDAC	Circulating Tumour Cells,	[38]

Early detection of pancreatic cancer by liquid biopsy *(France)*	2. Benign pancreatic disease 3. Healthy controls	ctDNA, EVs, circulating immune system, circulating cell- free nucleosomes, proteins, and microbiota	
VAPOR Volatile organic compound Assessment in Pancreatic ductal adenOcaRcinoma *(United Kingdom)*	1. Confirmed PDAC 2. Benign pancreatic conditions (NOD and CP) 3. Healthy controls	Volatile organic compounds in exhaled breath	[39]
EUROPAC European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer *(United Kingdom)*	1. Family history of PDAC - two or more First Degree Relatives (FDRs) 2. Gene mutation- *BRCA 1/2* 3. Peutz-Jeghers, Lynch, Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome	Genomic map	[40]
PCDC (PANXEON) PANcreatic cancer Exosome Early detectiON *(United States, Japan, Republic of Korea)*	PDAC (stages I-IV) and healthy controls	Panel of 13 miRNAs	[41]
ASCEND-PANCREATIC AssesSment of Early-deteCtion basEd oN liquiD Biopsy in PANCREATIC Cancer *(China)*	1. Early stage PDAC 2. Benign pancreatic disease 3. Healthy controls	cfDNA methylation, circulating tumour DNA (ctDNA) mutation, serum protein markers and blood miRNA markers	[42]
DAYBREAK Study iDentification and vAlidation Model of Liquid biopsY Based cfDNA Methylation and pRotEin biomArKers for Pancreatic Cancer *(China)*	1. Confirmed PDAC diagnosis 2. Benign pancreatic diseases	Biomarkers of cfDNA methylation, serum protein markers, blood miRNA markers	[43]
The PREPAIRD Study Personalized Surveillance for Early Detection of Pancreatic Cancer in High Risk Individuals *(Norway)*	1. Germline mutation in a PC susceptibility gene (CDKN2A, STK11, TP53, PRSS1) 2. Strong family history of PC	Personalized surveillance program for early diagnosis of pancreatic cancer	[44]
PRO-TECT PRedictiOn Algorithms for the DeTECTion of Early-Stage	Individuals above the age 50 with minimum 6 month from study entry	Pancreatic risk prediction using a machine learning model - if increased 18-month risk of	[45]

Pancreatic Cancer *(United States)*		pancreatic cancer, participants undergo MRI	
ExoLuminate Study for Early Detection of Pancreatic Cancer *(United States)*	1. Without PDAC but with family history of 2 or more FDRs; BRCA1, BRCA2, PALB2, ATM, MLH1, MSH2, MSH6, PMS2, EPCAM pathogenic or likely pathogenic variant and 1 FDR or Second Degree Relative with PDAC; FAMMM, Peutz-Jeghers, Hereditary pancreatitis with PRSS1 2. Pancreatic cysts 3. Acute or chronic pancreatitis 4. Stage I or II PDAC	Extracellular vesicles isolated from blood plasma	[46]
U01-Biomarkers for Noninvasive and Early Detection of Pancreatic Cancer *(United States)*	1. Diagnosed PDAC, pancreatic neoplasms 2.Pancreatitis 3. Diabetes 4. Healthy controls	Cell-free and exosomal miRNA biomarkers using small RNA-Seq in matched tissues and plasma in different cohorts	[47]
NODMED New Onset Diabetes Management for Earlier Detection of Pancreatic Cancer (*United States)*	Individuals above the age of 50 years with newly diagnosed type-2 diabetes who will undergo noninvasive test and upon "detected" result, an MRI imaging will be performed	5-hydroxymethylcytosine signatures in circulating cell free DNA- Bluestar Genomics	[48]
PANDOME A Pancreatic Cancer Screening Study in Individuals With New-Onset or Deteriorating Diabetes Mellitus (*United States)*	Individuals above the age of 50 years with: 1. Confirmed DM within last 12 months with record of prior normal HBA1c 2. DM without confirmed duration without record of prior normal HbA1c 3. Transition from pre-diabetes to DM 4. Deteriorating DM with >2% spike in HbA1c within last 6 months	1. MRI/MRCP at baseline 2. Further imaging upon recommendation of study committee	[49]

PRECEDE Pancreatic Cancer Early Detection Consortium (*United States)*	Individuals: 1. Without PDAC but with two or more FDRs; RCA1, BRCA2, PALB2, ATM, MLH1, MSH2, MSH6, PMS2, EPCAM pathogenic or likely pathogenic variant AND 1 first or second degree relative; FAMMM; Peutz-Jegher syndrome with STK11; Hereditary pancreatitis with PRSS1 2. Pancreatic cysts	Pathogenic germline variants (PGVs) in Pancreatic Cancer predisposition genes	[50]
PANC-O-MICS Precision Imaging for Early Detection and Targeted Treatment Monitoring in Pancreatic Cancer *(France)*	Individuals with: 1.Confirmed PDAC	The diagnostic performance of the radiomic and multiomic algorithm in pancreatic cancer detection and therapeutic response monitoring.	[51]
The LINFU® A Noninvasive Method for Increasing Exfoliation of Pancreatic Ductal Cells Into Pancreatic Fluid) U.S. Registry for the Detection of Low and High-Grade Atypia and Early, Asymptomatic PDAC *(United States)*	High risk asymptomatic patients being screened for pancreatic cancer who are scheduled for EUS± FNA, MRI/MRCP, ERCP, CT or CEUS.	The total number of asymptomatic pancreatic ductal adenocarcinomas and their noninvasive precursor lesions identified with **LINFU®** by analysis of pancreatic fluid will be compared to the number of these lesions identified with current screening tests, including EUS-FNA, MRI/MRCP, ERCP, CT and CEUS.	[52]
UroPanc Study *(United Kingdom)*	1.Symptomatic group with suspected PDAC 2.Asymptomatic group from EUROPAC trial (high-risk of developing PDAC)	Urinary biomarker panel (LYVE1, REG1B, TFF1), and affiliated PancRISK score alone or in combination with plasma CA19-9	[53]
DETECT Evaluation of a Mixed Meal Test for Diagnosis and Characterization and Type 3c Diabetes Mellitus Secondary to Pancreatic Cancer and Chronic Pancreatitis *(United States)*	1. PDAC 2. Chronic pancreatitis 3. Healthy controls	Pancreatic Polypeptide, glucose, C-peptide, insulin, glucagon, GLP-1, and GIP levels.	[54]

ADEPTS Accelerated Diagnosis of neuroendocrine and Pancreatic TumourS *(United Kingdom)*	1. Suspected PDAC 2. High-risk PDAC 3. Healthy controls	Blood, urine and tissue specimens	[6]

3. Biomarkers for early PDAC detection: Current state-of-the-art

a. Challenges

The lack of control biospecimens, such as from individuals with diabetes and chronic pancreatitis can weaken biomarker studies and ultimately impede translation of biomarker candidates to clinical use. Furthermore, with the majority of published biomarker candidates discovered or evaluated in samples from individuals already diagnosed with PDAC, understanding the performance of biomarkers in the months prior to PDAC diagnosis is challenging. The best characterised biomarker in a pre-diagnostic setting is CA19-9, the only biomarker in routine use for managing PDAC. It increases from 2 years prior to diagnosis, becoming highest close to diagnosis [55-57]. Using samples from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, Fahrmann and colleagues [57] reported CA19-9 to have a sensitivity of 60% at 99% specificity within 0 to 6 months before diagnosis. O'Brien et al. [55] reported a sensitivity of 68% at 95% specificity up to 1 year prior to diagnosis in samples from the UK Collaborative Trial of Ovarian Cancer Screening . Pre-diagnostic PDAC samples, collected with the specific purpose of PDAC detection and where samples and data directly relevant to PDAC are collected are desperately needed. The efforts of the Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) Consortium and UK-EDI to collect clinical data and longitudinal biospecimens for individuals with NOD that allow selection and testing of biomarkers in pre-diagnostic PDAC samples are therefore vital [36, 58].

b. Types of Biomarkers

i. Protein-based biomarkers

Multiple studies have proposed protein biomarkers as tools for early detection, usually in panels of two or more proteins and often combined with CA19-9. Here we focus only on studies that incorporated evaluation of protein biomarkers in samples taken prior to PDAC diagnosis.
Oldfield *et al*. [32] identified IL1-Ra and adiponectin as promising candidate biomarkers to distinguish individuals with pancreatogenic diabetes (type 3c; T3cDM) from those with type 2 diabetes mellitus (T2DM), with the aim of earlier detection of PDAC in NOD. IL1-Ra and adiponectin yielded an area under the receiver operating characteristic curve (AUC) of 0.90 for T3cDM vs T2DM and 0.91 for T3cDM vs NOD. Notably, IL1-Ra was significantly upregulated in pre-diagnostic PDAC samples up to 12 months prior to diagnosis.

Blyuss *et al*. [59] developed a risk score, PancRISK based on measurement of three proteins in urine (LYVE1, REG1B and TFF1), patient age and urine creatinine. Inclusion of CA19-9 resulted in a sensitivity of 0.96 with a specificity of 0.96 for the distinction of healthy controls from individuals with PDAC. In prediagnostic samples, PancRISK, combined with CA19-9, achieved an AUC of 0.892 up to 1 year before PDAC diagnosis, and 0.77 up to 2 years [60]. In a more

recent study, Nene et al. used ensemble modelling with cross-validation resampling to demonstrate the performance of a 20-feature panel, including proteins and clinical features[61]. The stacked ensemble approach achieved an AUC of 0.91 up to 1 yr prior to PDAC diagnosis and an AUC of 0.85 up to 2 years prior. These studies highlight the beneficial complementarity of protein biomarkers and clinical features in identifying individuals at risk of PDAC.

ii. Metabolic markers

The changes in glucose regulation observed in PDAC are an indicator of broader metabolic alterations occurring during tumour development, and several studies have reported metabolic markers as potential biomarkers for early disease detection. Wolpin *et al.* found that elevated circulating levels of branched chain amino acids (BCAAs) were associated with a greater than 2-fold increased risk of future PDAC diagnosis [62]. Systemic elevation in BCAAs is likely linked to tumour-driven muscle breakdown, with increased levels among the earliest metabolic changes in cancer cachexia, occurring before significant weight loss is observed. Wolpin's study reported the strongest elevation in risk, associated with BCAAs, to be present in individuals whose blood was collected 2 to 5 years prior to PDAC diagnosis, when occult disease is likely present.

Future diagnostic tools will be enhanced by their ability to distinguish PDAC from chronic pancreatitis. Metabolic markers have been suggested to have a role here. In a case-control study (n=914 subjects) Mayerle *et al.* found a nine-metabolite panel, in combination with CA19-9, to exhibit good accuracy (AUC=0.94; 95% CI 0.91–0.97) in the differentiation of PDAC from chronic pancreatitis [63]. Further development of metabolic biomarkers of PDAC will benefit from validation in relevant cohorts, including individuals with NOD.

iii. Cell-free DNA (cfDNA)

Cell-free DNA (cfDNA), generated by apoptosis, necrosis and active secretion, is found in blood, urine, saliva, and other extracellular fluids. A subfraction of cfDNA corresponds to tumour cell-free DNA (ctDNA). One of the first reports of cfDNA in PDAC using next-generation sequencing of 54 genes showed diagnostic accuracy of 97.7%, highlighting 5 genes (*KRAS, TP53, APC, FBXW7, and SMAD4*) [64]. Of more recent interest is the use of methylation signals from targeted circulating free DNA and machine learning classifiers for multi-cancer early detection (MCED). In one of the largest studies to-date, which included individuals already diagnosed with cancer or under investigation for suspected cancer, an MCED test using methylation signals on cfDNA detected 61.9% (13/21) of stage I, 60% (12/20) of stage II, 85.7% (18/21) of stage III, and 95.9% (70/73) of stage IV pancreatic cancers [65]. Recent data from the PATHFINDER study further indicate the potential of MCEDs applied in the detection of early-stage cancer in asymptomatic populations, however, more evidence will be needed to understand the true power of MCEDs in this setting [66]. An alternative approach relies on the targeted detection of differential 5-hydroxymethylcytosine (5hmC) methylation patterns in cfDNA of PDAC patients compared to non-cancer control subjects, particularly in genes associated with pancreas development or function, and cancer [67]. Incorporating machine learning an algorithm, based on 5hmC differential profiling and additional genomic features, was developed and had a sensitivity of 68.3% for stage I/II PDAC with varying diabetes status, with an overall specificity of 96.9% [68].

iv. RNA-based biomarkers

RNA biomarkers from body fluids include messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), piwi interacting RNA (piRNA), and circular RNA (circRNA). Elevated *FKBP1A* mRNA levels in circulating white blood cells of PDAC patients suggest its potential as an early detection biomarker [69]. Studies have also linked lncRNAs like *HOTTIP*, *MALAT-1*, *HOTAIR*, *MEG3*, *CASC2*, *H19*, and *LINC01559* to tumour functions, though further research is needed [70].

Extracellular vesicles (EVs), small lipid-bilayer nanovesicles released by cells, facilitate intercellular communication and carry biomolecules, including RNA [71]. Exosomes from PDAC patients have been found to over-express coding RNAs, such as *WASF2*, *ARF6*, *SNORA74A*, and *SNORA25*[72].

More recently, miRNAs have emerged as critical modulators of tumour biology, impacting tumour initiation, progression, and metastasis, making them novel biomarkers [73, 74]. miRNAs are categorised as oncogenic or tumour-suppressive. Aberrant expressions of miRNAs have been found in PDAC [75, 76], with upregulation of miR-21, miR-221, miR-210 and miR-155 and reduced expression of miR-34a/b, let-7, miR-146a, and miR-126 reported [77-80]. miR-210, miR-21, and miR-155, associated with enhanced cellular proliferation, migration, invasiveness, hypoxia, and cancer stemness [79, 80]. The implementation of miRNA expression as a non-invasive diagnostic tool for early diagnosis for pancreatic cancer has been widely studied [73, 81].

The minimal-invasive nature of miRNA-based tests, and their stability as potential biomarkers, offers significant advantages over tissue biopsies for routine screening and early detection. However, challenges remain due to limited tissue/disease specificity and selectivity, especially in early-stage PDAC. Standardising miRNA profiling and validation in large-scale trials is essential, along with accessible biobanks for independent patient samples.

v. Tumour-educated platelets

Cancer cells release factors stimulating platelet production in bone marrow, leading to an elevation in platelet levels in many cancers, including PDAC [82]. Tumour cells further influence platelets by triggering activation, aggregation, and release of intracellular contents [83]. Activated platelets in-turn interact with circulating tumour cells [84], potentially shielding them from immune surveillance and attracting stromal cells to distant sites, creating favourable environments for metastasis. Cancer-reprogrammed platelets, termed Tumour-Educated Platelets (TEPs), have emerged as promising non-invasive liquid biopsy candidates due to their unique molecular signatures acquired when altered by cancer cells [85].

Research is establishing solid links between platelets and PDAC. Cooke *et al*. found that platelet aggregation was significantly higher in patients with metastatic PDAC compared to healthy individuals [86], suggesting that the presence of the tumour may trigger platelet activation. Mitrugno and colleagues reported that platelets co-cultured with the PDAC cell line, PANC-1 induced cell proliferation by activation of c-Myc [87]. Additionally, both the proteome content [88] and several miRNAs [89] are altered when comparing the platelets of PDAC patients and healthy subjects. Moreover, the mRNA profiles of PDAC TEPs were found to be different

between KRAS mutant PDAC and KRAS wild-type [90]. Finally, in a study of 18 different tumours, PDAC included, a TEP RNA-based test showed promise for the detection of cancer as well as determining the site or origin [91].

vi. Volatile organic compounds (VOCs) in PDAC

Volatile organic compounds (VOCs) are a group of carbon-containing compounds that are sufficiently volatile to be in the gaseous form at ambient temperature and pressure, and which are released as by-products of metabolism in humans [92, 93]. Endogenously-produced VOCs can be exhaled in breath or detected in the headspace of biofluids such as urine and are measured using analytical techniques including mass-spectrometry and sensors [94-96]. Changes in metabolic pathways occurring early in PDAC development [97] are thought to contribute to an altered VOC profile in the breath of patients with cancer compared to those without [98].

Using mass spectrometry techniques, characteristic VOC signatures with sensitivity ranging from 70-100% and specificity 74-92% have been identified in the breath of patients with PDAC compared to controls [99-101]. Meanwhile, an electronic nose sensor has demonstrated 80% sensitivity and 92% specificity for the identification of PDAC patients using exhaled breath VOCs [102]. These studies have all been undertaken in symptomatic patients. Thus, their findings offer the potential for breath testing to be used to triage PDAC patients with non-specific symptoms who may otherwise only be diagnosed at a much later stage. Breath testing is deemed highly acceptable to patients and healthcare professionals alike, given its non-invasive nature and ease of use [103], making breath VOCs an attractive choice of biomarker for improving the earlier detection of PDAC. The potential to detect PDAC using urinary VOC measurement has also been demonstrated [104, 105].

Though promising, the feasibility studies undertaken thus far have involved small samples sizes ($n < 200$ participants). VAPOR-1 (Volatile organic compound assessment in pancreatic ductal adenocarcinoma; Table 1) is a multi-centre breath test study currently recruiting 771 participants across 18 hospital sites in the United Kingdom [ClinicalTrials.gov: NCT05727020]. The study aims to validate previously identified breath VOC biomarkers and refine the cancer detection model. This will be followed by a double-blind validation study, VAPOR-2.

vii. Paper-based substrates for the detection of biomarkers

A colorimetric paper-based nano-immunosensor, using gold nanoparticles (AuNPs) as a catalyst for colorimetric signals, has been used to detect PEAK1, an oncogenic pseudokinase overexpressed in PDAC [106]. This method enhances detection sensitivity by 10 folds, compared to AuNPs-based colorimetric immunoassays without signal amplification [107]. A 3D paper-based electrochemiluminescence immuno-device has also been developed for multiplexed biomarker detection and was shown to detect CA19-9 and other tumour markers in serum [108]. Moccia *et al*. used a peptide nucleic acid as a recognition element for miRNA-492 on a screen-printed electrochemical biosensor, obtaining a detection limit of 6nM, and demonstrating applicability for detection in serum [109]. Furthermore, a sensor for the biomarker miRNA-141, which is downregulated in PDAC tissues, has been developed using graphene oxide-quantum dots and an ssDNA detection probe, with integration in mobile devices. [110].

viii. Tumour interstitial fluid

A novel biomarker discovery approach, named EXPEL, that allows sampling of soluble biomarkers from fresh tissue has been developed [111]. The procedure uses rapid, pressure-assisted, interstitial fluid extrusion from tissue while preserving the specimen for full routine clinical pathology investigation. The method, described for colorectal cancer [111], gives access to proteins, metabolites, RNA, DNA and exosomes, enabling holistic biomarker discovery through OMICS profiling. Owing to its non-destructive nature, the technique provides both clinicians and researchers with the opportunity to analyse identical material. An additional method, PANEXPEL, specific for pancreatic cancer has been developed [112]. During endoscopic ultrasound-guided needle biopsy, once the needle-biopsy is collected, the contents are rinsed in a preservation solution, filtered for cells/tissue fragments and the flow-through discarded. Investigation of the discarded liquid, has found it to be ideal for preserving proteins, metabolites, DNA & RNA s, which can be extracted using simple biochemical procedures. A prospective clinical collection (ClinicalTrials.gov: NCT03791073) of over 200 samples from all suspected PDAC patients examined in the CHU Montpellier has begun.

ix. Microbiome

The microbiome is altered during cancer development and progression, making microbial-derived molecules attractive as potential biomarkers [113, 114]. Seminal studies in PDAC have shown that faecal microbiota can affect the tumour microbiome which in turn moderates the immune response and patient survival [115]. Kartal *et al*. [116] employed shotgun metagenomic and 16S rRNA amplicon sequencing to over 200 patients in a multicentric study, identifying a classifier comprising 27 microbial species that enabled discrimination of PDAC across different disease stages from controls. Likewise, using faecal and saliva metagenomics data, Nagata *et al*. [117] derived signatures including 30 gut, and 18 oral species associated with PDAC. Recent studies have established that composite microbial communities can serve as early diagnostic and prognostic biomarkers for pancreatic tumours [118]. Interestingly, gut virome (viruses that infect gut bacteria) have been proposed more recently as an additional promising layer of information that can be used to diagnose PDAC in a non-invasive fashion [119].

4. OMICS for Biomarkers of Early Detection and Population Stratification

a. Germline variants and polygenic risk score

Single nucleotide polymorphisms (SNPs) remain unchanged from birth to death, making their measurement through genotyping unbiased by contingent factors, such as the exposome, and rendering them attractive risk stratification biomarkers. Following the sequencing of the human genome, the first genome wide association studies (GWAS) were successfully performed, initially on common diseases and traits, and subsequently on rarer ones, such as PDAC [120]. Findings from GWAS were different than predicted. Single or small number of risk alleles with great effect sizes explaining a large proportion of the variance of each disease, or SNPs in genes known to be involved with the disease, such as p53, BRCA1 or ATM for many cancer types, it emerged that SNPs were associated with, at best, modest increase in risk, and

were often in unknown genes or in intergenic regions, labelled as gene deserts. Greater insight from further GWASs showed that, while the individual effect of each SNP is small, the combined effect of SNPs, calculated using polygenic risk scores (PRS) is not. For PDAC around 30 significant SNPs, predisposing for risk have been identified through GWAS or more focused studies, carried out by large international consortia [120-128]. Several PRS, using SNPs identified by the GWAS, have been analysed, and validated in multiple studies and they all show large effect sizes comparable to high penetrance mutations, usually surpassing established risk factors such as smoking and diabetes [129-134]. Galeotti and colleagues in a study conducted in the context of the PANDoRA consortium found that individuals with a high count of risk alleles (>80th percentile) had more than three times the risk compared to individuals in the lowest count of risk alleles (<20th percentile): OR=3.24 (95% CI 2.86 to 3.67, p=1.20×10−63). The results were replicated using PanScanI-III and PanC4 data with very similar results [130]. In the same manuscript the authors combined the effect of the PRS with smoking and diabetes, obtaining very large effect sizes OR=14.37 (95% CI 5.57 to 37.09, p=3.64×10−8) for the highest versus lowest quintile. Interestingly, Ke and colleagues using a machine learning integrative PDAC risk prediction model found that PRS was, after age, the second most important feature of the model [131]. Although proven to be a good strategy for risk stratification, PRS cannot yet be used to predict PDAC occurrence in the general population. In the future when more risk loci are discovered, PRS could become an extremely useful tool especially for high-risk individuals, such as family members of PDAC patients and individuals with new-onset diabetes.

b. ScRNA-Seq Spatial transcriptomics and early PDAC detection

The ability to stratify cancer patients accurately is necessary for personalised precision diagnosis. Moreover, heightened understanding of the biology underpinning PDAC subtypes could help direct our choices of early detection biomarkers. The advent of spatial technology [135] and its combination with single cell RNA Sequencing (scRNA-Seq) technology [136] has enabled ScRNA-Seq Spatial transcriptomics studies (scRNA-Seq-ST) on PDAC patient tissue sections, revealing gene expression profiles of different cell subtypes, including tumour, acinar, ductal, stromal and immune cells. scRNA-Seq-ST studies on PDAC have focused on characterising tumour heterogeneity, analysing precursors to PDAC, including IPMN and PanIN lesions, and profiling tumour subtypes [137]. Using two spatial transcriptomic technologies, Agostini *et al*. identified markers of different grades of IPMN [138]. The capacity for spatial transcriptomic technology to map the trajectory of normal cells all the way through to malignant ones opens opportunities for detecting early changes that could lead to useful biomarkers.

5. Artificial Intelligence (AI) and Models to predict risk

a. Machine Learning for detection of PDAC

Machine learning (ML) methods and artificial intelligence (AI) algorithms facilitate extraction of substantial information and patterns from big data. Various types of data, including medical images, data produced by omics technologies and patient records can be used as input to train and test the models generated by ML and AI algorithms for early detection of PDAC [139-142]. Deep learning and ML methods, such as convolutional neural network (CNN) or support vector machine (SVM), have been applied for detection of PDAC [139, 141, 143, 144].

b. EHR-based machine learning (ML) and deep learning (DL) models to predict the risk of PDAC

The advent of electronic health records (EHRs) has substantially increased the type and volume of patient data available for development of ML and DL algorithms for predicting PDAC risk [131, 140, 142, 145-154]. For example, PrismNN and PrismLR models were developed from EHRs of U.S. PDAC cases (n= 35,387) and controls (n=1,500,081), which uses neural networks and logistic regression, respectively. These models predicted patients with high PDAC risk 6-18 months before diagnosis [142]. Another study used ML model with ~6.2 million patients (~24,000 cases) from the Danish National Patient Registry (DNPR) and 3 million patients (~3,900 cases) from the U.S. Using the DNPR, the optimal model predicted pancreatic cancer occurrence within 36 months of diagnosis with an AUC of 0.83 when disease events within three months of cancer diagnosis were excluded from training [140].

Since 2011, several studies using EHRs to predict PDAC cancer risk have been conducted [131, 140, 142, 145-155]. The most frequently included variables were known PDAC risk factors such as gender, age, smoking, alcohol consumption, pancreatitis, diabetes, and weight, as well as clinical or laboratory data. The number of variables employed in a model ranged from 9 [156] to 87 [152]. Of ML and DL algorithms used to build predictive models for PDAC risk, the Random Forest algorithm was the most frequently employed, and the most used metric was the Area Under the Curve (AUC) of a Receiver Operator Characteristic curve (ROC). Santos *et al.* have compared 38 PDAC risk prediction models, most of which showed high accuracy. Limitations included a high risk of bias caused by inadequate reporting practices and the inclusion of individuals with advanced-stage tumours, which may skew the results [157].

c. Challenges in bringing Artificial Intelligence into clinical use for PDAC

Despite their potential, AI- and ML-based models are not ready for implementation into clinical practice. Significant challenges include the heterogeneity in variables, algorithms, and evaluation metrics employed by the studies, which make comparisons difficult. In addition, progress is hampered by the small number of participants used to build risk prediction models for PDAC. Factors contributing to these small numbers include the relative rarity of the disease and sociodemographic disparities during the recruitment process, with Black patients and patients treated at non-academic medical centres in the US less likely to be enrolled in clinical trials. [158-160]. Model overfitting is also a problem and occurs when a model is too complex and perfectly learns from training data but fails to generalize correctly on testing data [161, 162]. This lack of generalization is harmful since the model may display a poor discrimination ability, may produce inaccurate risk estimations, and may fail validation with an external cohort [163]. Furthermore, the models commonly use AUC of a Receiver Operator Characteristic curve, which frequently fails to find a clinical applicability [164]. In particular, when the number of cases is greater than the number of controls, AUC/ROC may be misleading when interpreting the specificity of a model [164]. The precision-recall curve represents a less biased evaluation metric [164], although it may be difficult for clinicians to understand and interpret [165].

Another challenge with the applicability of these algorithms is their “black-box” nature, which hinders model interpretability [154]. To address this challenge, the use of eXplainable AI (XAI) has recently been implemented, enabling the decision-making process of the algorithm to be comprehensible. To date, only 5 studies have employed XAI in the context of PDAC risk prediction, highlighting the novelty of this approach [140, 145, 166-168]. Notably, all of these studies employed the same algorithm, SHapley Additive exPlanations [169], which is considered the gold standard. Finally, there are a number of other potential pitfalls that pose

a challenge to the implementation of AI- and ML-based models in clinical practice. These include challenges related to the construction and deployment of models, as well as the development of appropriate policies, the management of data shifts and variability, and the financial costs associated with the implementation of such models [165, 170, 171].

d. Social media for early detection of PDAC

Social media platforms leverage different forms of communication to enhance public engagement with health information, thereby representing a viable and powerful option for the dissemination of medical knowledge [172, 173]. These platforms can reach individuals who are excluded from experimental trials and protocols, promoting early screening [6] and could improve pancreatic cancer outcomes by increasing awareness of risk factors and encouraging aided early symptom research [174]. Furthermore, participation in social media groups where individuals can communicate with healthcare professionals may enhance individual awareness on the disease, as previously reported for other diseases [175, 176].

Netnographies represent an example of how ethnographies can be implemented in the digital context to study interactions and behaviours within online communities [6, 177]. The employment of pattern analysis and topic modelling of users' online posts, netnographies may allow the identification of behavioural trends and contents with the potential to predict early PDAC [6].

Sentiment analysis is a natural language processing method that employs machine and deep learning and rule-based approaches to analyse emotions expressed in digital texts [178]. Through the analysis of emotions in online posts, sentiment analysis may allow the identification of shared lexical features for early PDAC screening and detection [179].

Despite the considerable potential of social media for the early PDAC detection, there are significant challenges to overcome, mostly related to the quality of information and resources about the disease [180] and the dissemination of misinformation [181, 182]. To realize the potential of social media to aid early detection of PDAC, methodologies need to be implemented, and online information needs to be monitored to prevent harmful decisions.

Ethical concerns related to the reuse of an individual's data must also be considered, particularly in the absence of adequate regulatory frameworks. Of particular relevance is the issue of the explicit informed consent of the users in reusing their data and that of anonymization [183]. In this context, research conducted with social media data should always consider contextual factors and, when possible, use basic interaction data, providing also full transparency on the types of data and their use [184].

e. Cost-effectiveness of implementing biomarkers in early detection of PDAC

Cost-effectiveness analysis (CEA) aims to evaluate the costs and effects of alternative methods for detecting PDAC. Health benefits are typically measured in quality-adjusted life years. To inform key stakeholders of the potential economic value of a new method, CEA should preferably be done at an early stage; that is, even before its clinical effectiveness is fully established [185]. Ghatnekar *et al*. [186] presented an example of an early-stage cost-effectiveness model to assess the benefits of a biomarker-driven screening method for the early detection of PDAC. Based on assumptions about PDAC incidence, test sensitivity and specificity, and relevant costs, they concluded that specific risk groups, including individuals with new-onset diabetes (NOD), could be screened at an acceptable cost. More detailed clinical prediction models have recently been developed and validated to identify patients with NOD

at highest risk for PDAC. These include the QCancer® (Pancreas) model [187] and the widely cited Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model [188]. Schwartz *et al*. [185] contended that risk-based screening using the ENDPAC score is straightforward to implement and likely to be cost-effective in the USA if more than 25% of pancreatic cancer patients diagnosed by screening are resectable. Using a population-representative NOD cohort from The Health Improvement Network network of European databases, Wang *et al*. [189] found that an early detection strategy targeting individuals with NOD with a minimum predicted three-year PDAC risk of 1.0% to 2.0% may be cost-effective, depending on willingness-to-pay thresholds in different countries. Based on all current evidence, Stefanova *et al*. [190] concluded that screening the NOD high-risk group for PDAC becomes cost-effective when an optimal biomarker signature can be selected.

6. Conclusion

The scientific literature contains abundant proposals for biomarkers with capacity to detect PDAC early. Almost invariably these candidates have been identified and validated in samples taken from individuals already diagnosed with PDAC. The performance of biomarkers in Stage I and II disease is often hailed as evidence that the biomarkers detect early disease, and this may be so. However, PDAC advances rapidly and the ability of biomarkers to detect the disease in the months leading to diagnosis, unless tested, remains unknown. Pre-diagnostic cohorts, such as the NOD cohorts [32, 58], that deposit samples and data from individuals prior to a diagnosis of PDAC have a vital role to play. These cohorts, however, are difficult and costly to assemble and by definition take time to mature, as the participants progress to a diagnosis of cancer. Nonetheless the need for high quality samples, stored rapidly and to exacting standard operating protocols remains key to unlocking effective early biomarkers, and shortcuts in either cohort assembly or high-quality sample collection ultimately waste time and effort.
Due to individual differences, and tumour heterogeneity, it has long been understood that no single biomarker will detect all individuals with PDAC, but rather panels of biomarkers will be needed. Going further, future models that integrate fluid-based biomarkers with AI algorithms of EHRs, for example, present an important opportunity to improve the precision and efficiency of early PDAC detection. Imaging technologies have advanced, as have methods for analysing image data, including radiomics and AI algorithms. Advances in imaging and data analysis for PDAC detection are reviewed elsewhere [191]. Wearable health technology, particularly flexible electronics, have garnered attention for their potential to monitor patient health more affordably, with quick access to health data, non-invasive methods, and the ability to scale up production [192]. There are currently no wearables that can detect pancreatitis or pancreatic cancer, however, emerging data regarding early, subtle signs of cancer in general, may be amenable to detection by electronic sensors and monitoring of behaviour using smartphones or wearables [193].

In parallel with biomarker development, it is important to assess the cost-effectiveness of proposed tests, to assist policymakers with decisions regarding implementation. Equally, gauging whether the tests will be acceptable to the individuals for whom they are being

developed and whether those individuals can be reached is essential. Community outreach should therefore be integral to biomarker research.

Although our understanding of the biology underpinning PDAC has advanced significantly in recent years, there remains much to learn. Fundamental research on this disease will continue to contribute to early detection strategies. To ascertain the true performance of early detection approaches, ideally clinical validation in carefully designed trials and ultimately evaluation in real-world contexts is needed [194].

Declaration of Competing Interest

EC, LO and WG are named as an inventor on patent WO2020169511A1, submitted by the University of Liverpool, that covers the measurement of adiponectin and IL-1Ra as a biomarker for early detection of pancreatic cancer. LO is supported by Cancer Research UK and Pancreatic Cancer UK. SP received consultancy fee from AlphaTau and a speaker fee from Fresenius Kabi. GBH is the founder of a cancer diagnostic company and is named on patents related to volatile biomarkers. AT participates in the clinical trial "New Biomarkers in Pancreatic Cancer Using EXPEL Concept (PANEXPEL)"; NCT03791073. The other authors report no declarations of interest. AP and PA are funded by the European Union – Next Generation EU, Misison 4 Component 2 Inv. 1.5 CUP: B13D21011850006. BR is supported by the Czech Health Research Council grant no. NW24-03-00024 and the National Institute for Cancer Research – NICR (Programme EXCELES, ID Project No. LX22NPO5102) – Funded by the European Union – Next Generation EU. GH is a founder of a cancer diagnostic company and named on patents related to volatile biomarkers. RVDM is funded by Cancer Research UK (CRUK) funding for "Detecting pancreatic cancer in the largest high-risk group for this disease: A top-down approach (CRUK Early Detection Programme); £100,018.00; 01/04/2019 – 30/06/2025. The study sponsor had no involvement in any aspects of the study.

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Author contributions according to CRediT taxonomy

Conceptualization: EC; **Funding acquisition:** DC; **Methodology:** EC, KM, LO, IS; **Writing – Original Draft:** EC, KM, LO, IS, MG, PA, RO'S, WG, SP, MNA, AP, JB-F, BHR, PU-O, CMW, GBH, JN, PS, DC, CR, AT, EAS, AF, CS, GP, EÖ, OUS, RVDM, NT; **Writing – Review & Editing:** EC, KM, LO, IS, MG, PA, RO'S, WG, SP, MNA, AP, JB-F, BHR, PU-O, CMW, GBH, JN, PS, DC, CR, AT, EAS, AF, CS, GP, EÖ, OUS, RVDM, NT.

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Declaration of Competing Interest

EC, LO and WG are named as an inventor on patent WO2020169511A1, submitted by the University of Liverpool, that covers the measurement of adiponectin and IL-1Ra as a biomarker for early detection of pancreatic cancer. LO is supported by Cancer Research UK and Pancreatic Cancer UK. SP received consultancy fee from AlphaTau and a speaker fee from Fresenius Kabi. GBH is the founder of a cancer diagnostic company and is named on patents related to volatile biomarkers. AT participates in the clinical trial "New Biomarkers in Pancreatic Cancer Using EXPEL Concept (PANEXPEL)"; NCT03791073. The other authors report no declarations of interest. AP and PA are funded by the European Union – Next Generation EU, Misison 4 Component 2 Inv. 1.5 CUP: B13D21011850006. BR is supported by the Czech Health Research Council grant no. NW24-03-00024 and the National Institute for Cancer Research – NICR (Programme EXCELES, ID Project No. LX22NPO5102) – Funded by the European Union – Next Generation EU. GH is a founder of a cancer diagnostic company and named on patents related to volatile biomarkers. RVDM is funded by Cancer Research UK (CRUK) funding for "Detecting pancreatic cancer in the largest high-risk group for this disease: A top-down approach (CRUK Early Detection Programme); £100,018.00; 01/04/2019 – 30/06/2025. The study sponsor had no involvement in any aspects of the study.