REVIEW

Early diagnosis of pancreatic cancer: What strategies to avoid a foretold catastrophe

Valeria Tonini, Manuel Zanni

Valeria Tonini, Manuel Zanni, Department of Medical and Surgical Sciences, University of Bologna, Bologna 40138, Italy

Corresponding author: Valeria Tonini, MD, PhD, Adjunct Associate Professor, Professor, Surgeon, Surgical Oncologist, Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti 9, Bologna 40138, Italy. valeria.tonini@unibo.it

Abstract

While great strides in improving survival rates have been made for most cancers in recent years, pancreatic ductal adenocarcinoma (PDAC) remains one of the solid tumors with the worst prognosis. PDAC mortality often overlaps with incidence. Surgical resection is the only potentially curative treatment, but it can be performed in a very limited number of cases. In order to improve the prognosis of PDAC, there are ideally two possible ways: the discovery of new strategies or drugs that will make it possible to treat the tumor more successfully or an earlier diagnosis that will allow patients to be operated on at a less advanced stage. The aim of this review was to summarize all the possible strategies available today for the early diagnosis of PDAC and the paths that research needs to take to make this goal ever closer. All the most recent studies on risk factors and screening modalities, new laboratory tests including liquid biopsy, new imaging methods and possible applications of artificial intelligence and machine learning were reviewed and commented on. Unfortunately, in 2022 the results for this type of cancer still remain discouraging, while a catastrophic increase in cases is expected in the coming years. The article was also written with the aim of highlighting the urgency of devoting more attention and resources to this pathology in order to reach a solution that seems more and more unreachable every day.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Early diagnosis; Liquid biopsy; Pancreatic cancer biomarkers; Artificial intelligence; Pancreatic cancer screening

Core Tip: Pancreatic ductal adenocarcinoma is one of the solid neoplasms with the worst prognosis. Surgical resection is the only potentially curative treatment. In 80% of patients, pancreatic ductal adenocarcinoma is discovered at a stage too advanced for surgery. The aim of this review was to summarize all the possible strategies available today for the early diagnosis of pancreatic ductal adenocarcinoma and the paths that research must take to make this goal ever closer. The article highlights the urgency of devoting more attention and resources to this pathology in order to reach a solution that seems more and more unreachable every day.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is ranked as the seventh leading cause of cancer deaths worldwide, while it ranks fourth in the Western world, just behind lung, colorectal and breast cancers. Rahib *et al*[1] estimated that it will become the second leading cause of cancer death by 2030. The 2020 global cancer statistics reported a total of nearly 496000 new cases of PDAC and more than 466000 related deaths. PDAC mortality is almost overlapping with incidence[2].

The 5-year survival rate of PDAC is less than 10%[3]. A study that included 84275 patients showed that the 5-year survival rate increased from 0.9% in 1975 to 4.2% in 2011, considering all stages of PDAC. In patients undergoing surgical resection, it increased from 1.5% to 17.4%[4], while in unresected patients by 0.8% in 1975 and 0.9% in 2011. The high mortality and poor improvement in survival rates over the years are due to several factors. First, the retroperitoneal location of the pancreas results in the appearance of symptoms only when the neoplasm has reached considerable size, and diagnosis is often made at an advanced stage of the disease. Second, PDAC is inherently characterized by a fierce biology with early metastasis, and in fact about half of patients have metastatic disease at the time of presentation. Third, PDAC drastically weakens patients, limiting the possibility of aggressive treatments. Finally, through the desmoplastic reaction, it shows resistance to many antineoplastic therapies[5,6].

The 5-year survival rate for patients with stage 0 (in situ) according to the Union for International Cancer Control classification is 85.8%, while that of patients with stage IA is 68.7%. In the early stages of the disease, therefore, the prognosis is relatively good[7,8]. Early diagnosis of the disease is therefore essential.

Our efforts should focus on recognizing risk factors that contribute to the development of the disease in order to define the population at risk that could benefit from a screening protocol and on researching new techniques for early diagnosis[9-12].

RISK FACTORS AND STRATIFICATION

Several non-modifiable and modifiable risk factors are correlated with PDAC. Non-modifiable risk factors include the patient's age, ethnicity, gender, blood type, microbiota, diabetes mellitus, family history and genetic predisposition, while modifiable risk factors include tobacco use, alcohol consumption, diet, pancreatitis, obesity and socioeconomic status[12]. According to some studies, one-third of all cancers could be prevented through lifestyle improvement. The EPIC study, for example, evaluated the association between healthy lifestyle index score and pancreatic cancer[13,14]. A three-point increase in this score, achieved through adherence to healthy behaviors, is associated with a 16%-23% lower risk[15]. No smoking, making your home/workplace smoke-free, maintaining a normal body weight, having a diet rich in grains, legumes, and vegetables and limiting alcohol intake are key factors in the prevention of PDAC.

According to several studies, the new onset of diabetes in an elderly patient should suggest PDAC, especially if such a finding is associated with unintentional weight loss[16-18]. A study by Pelaez-Luna *et al*[19] evaluated the use of computed tomography (CT) scans in asymptomatic patients at the time of diabetes diagnosis and found a higher likelihood of detecting potentially resectable tumors compared with scans performed 6 mo later. However, CT-based screening of all elderly patients with new-onset diabetes (NOD) is not feasible[18]. Screening programs and guidelines will likely be updated when the features that differentiate pancreatic cancer-associated diabetes from other cases of NOD are identified.

The creation of a pancreatic cancer risk prediction model based on the integration of multiple risk factors could contribute to its early detection[20]. Sharma *et al*[21] developed a model called Enriching New-Onset Diabetes for Pancreatic Cancer that weights the scores of three factors including weight change, blood glucose change and age at diabetes onset in patients with NOD. A score of at least three points in the Enriching New-Onset Diabetes for Pancreatic Cancer model was able to identify individuals who developed PDAC within 3 years of the onset of diabetes with good sensitivity and specificity[21].

In addition to the strictly environmental risk factors, familial pancreatic cancer and genetic syndromes (hereditary breast and ovarian cancer syndrome, Lynch syndrome, familial atypical multiple melanoma, Peutz-Jegher syndrome, Li-Fraumeni syndrome and hereditary pancreatitis) are added. Familial pancreatic cancer is defined by the occurrence of PDAC in at least two first-degree relatives and accounts for up to 10% of all cases of PDAC[22].

Patients at high risk for developing PDAC include those with inherited risk factors (both genetic syndromes and familial pancreatic cancer), those with NOD and those with cystic lesions of the pancreas.

Pancreatic cysts are found in approximately 8% of individuals over the age of 70 years[23] and include intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms, both of which are precursors to PDAC. IPMN and mucinous cystic neoplasms are collectively referred to as mucinous cystic lesions. In contrast to the third precursor lesion, pancreatic intraepithelial neoplasia, which can be identified only at surgical histopathology, mucinous cystic lesions are easy to detect and are found incidentally in 3% of CT subjects[23]. Therefore, their identification offers the potential for early diagnosis of PDAC. However, there are two problems. First, not all pancreatic cystic lesions are IPMN or mucinous cystic neoplasms. Many are cystic lesions without risk of malignant transformation, and therefore do not require surveillance. Second, most IPMN and mucinous cystic neoplasms do not progress to PDAC. Over the years, evidence has been found to predict the possibility of progression to PDAC[23].

In mucinous cystic neoplasms the presence of eggshell calcification, larger tumor size or a mural nodule on cross-sectional imaging is suggestive of malignancy[24]. Regarding IPMN, worrisome (main duct 5-9 mm, enhancing mural nodule < 5 mm, thickened, enhancing cyst wall, branch duct IPMN > 3 cm, abrupt caliber change in main duct with upstream atrophy, lymphadenopathy, pancreatitis, increased serum 19-9, cyst growth > 5 mm over 2 years) and high-risk features (main duct > 1 cm, enhancing, mural nodule > 5 mm, jaundice) have been defined[25].

However, these clinical features are still imperfect in differentiating between benign cysts and mucinous cystic lesions that harbor high-grade dysplasia or PDAC and require surgical resection and mucinous cystic lesions that have low-grade dysplasia and are safe to look at.

For the time being, a screening program is offered to individuals with a strong family history and/or genetic predisposition to develop pancreatic cancer and subjects with mucinous cystic lesions of the pancreas. The primary goals of screening are the detection of high-grade dysplastic precancerous lesions (IPMN and pancreatic intraepithelial neoplasia) and T1N0M0 pancreatic cancer that are more amenable to potentially curative resection[26].

The current recommendation is to perform endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography. Screening is recommended at age 50 years or 10 years before the youngest relative with PDAC in familial pancreatic cancer cases. In other settings, screening is performed between the ages of 35 years and 45 years. In case the patient had a normal pancreas on imaging, it is recommended to repeat the procedure every year alternating EUS and magnetic resonance cholangiopancreatography. However, no consensus has been found on the preferred modality and optimal timing/frequency. This reflects the absence of robust data in the literature and underscores the lack of biological tools to detect precancerous lesions early.

IMAGING

There are several imaging methods that can identify pancreatic cancer at an early stage. Contrast-enhanced CT and MRI according to Japanese guidelines[27] are the first methods to be performed in patients with suspected PDAC based on clinical symptoms, serum pancreatic enzymes, tumor markers and transabdominal US. They are supplemented by EUS and endoscopic retrograde cholangiopancreatography (ERCP).

A study evaluated the diagnostic accuracy of US, CT, MRI, and EUS in 200 cases of PDAC stage 0/1. Only 20% of patients were symptomatic[28]. The diagnostic accuracy was 67.5%, 98.0%, 86.5%, and 86.5%, respectively. According to some authors, CT and US are procedures with limitations in the early detection of pancreatic cancer because only indirect signs, such as pancreatic duct dilatation, localized pancreatic atrophy or local fat changes in the pancreatic parenchyma, can be detected with these methods[20].

Two systematic reviews[29,30] evaluated the performance of EUS in the diagnosis of pancreatic cancer. In the first review, EUS was shown to have higher sensitivity than CT (91%-100% *vs* 53%-91%),

while in the second review, Kitano *et al*[30] reported that EUS was more sensitive than US and CT (94% *vs* 67% and 98% *vs* 74%, respectively).

However, conventional EUS does not distinguish carcinoma from other etiologies very well because most pancreatic tumors, including benign ones, have a hypoechogenic appearance. Contrast-enhanced EUS can improve imaging of parenchymal perfusion and microvessels in pancreatic pathology. This method has higher sensitivity (94.5% *vs* 83.1%) and specificity (84.1% *vs* 78.6%) than conventional EUS [31,32].

Endoscopic ultrasonography guided fine needle aspiration (EUS-FNA) represents the first-line method for pathological diagnosis. In relation to lesion size, the accuracy of EUS-FNA is 93.4% for lesions ≥ 20 mm, 83.5% for lesions of 10-20 mm and 82.5% for lesions of 10 mm or less[33]. Sometimes CT, MRI and EUS fail to detect early stage pancreatic tumors and it is difficult to collect specimens with EUS-FNA. In this situation, especially with regard to PDAC in situ, the only available imaging finding is localized stenosis of the main pancreatic duct. Detailed evaluation of the pancreatic duct by ERCP and subsequent cytology of pancreatic juice become extremely important for diagnosis. In this context, ERCP has a sensitivity and specificity of 57.9% and 90.6%[34]. The sensitivity of pancreatic juice cytology in the diagnosis of PDAC in situ is 72.2%-100%[28,35].

ERCP is particularly useful in distinguishing autoimmune pancreatitis from PDAC, especially in patients[36] with atypical pancreatic parenchymal findings, such as focal enlargement of the pancreas and mass formation.

Ikemoto *et al*[37] proposed a recent algorithm for early diagnosis of PDAC in stage 0 and IA, with a promising long-term prognosis. In addition to pancreatic laboratory tests, US should be performed earlier in patients with risk factors in order to identify asymptomatic patients. Patients with an obvious tumor are managed according to conventional algorithms. Patients who do not have an overt pancreatic tumor but have indirect findings, such as abnormalities of the main pancreatic duct, cystic lesions or pancreatic atrophy, should be evaluated by MRI with magnetic resonance cholangiopancreatography. If the MRI shows abnormalities suggestive for PDAC, EUS-FNA is performed[37].

ARTIFICIAL INTELLIGENCE APPLIED TO IMAGING

Great hopes are now pinned on artificial intelligence (AI) for solving the most difficult problems in medicine, and these include the early diagnosis of PDAC. AI is the ability of a computer to perform functions and reasoning typical of the human mind completely autonomously. In the deepest sense, it is the ability of a machine to learn and improve automatically based on experience, provided directly through data. In this way, AI becomes a powerful tool for discovering signals that are difficult for humans to infer or describe and for expanding the frontiers of our scientific capabilities.

Muhammad *et al*[38] used AI to predict the risk of developing PDAC. By analyzing variables such as demographic data, comorbidities and family history, they built a model capable of predicting the development of PDAC with good accuracy [area under the curve (AUC) of 0.85][38,39].

The application of AI in the field of radiology is also very promising, as AI is capable of analyzing thousands of images on a pixel-by-pixel level, does not make human errors and achieves data processing in a short time[40]. Several studies have reported the application of AI in EUS image analysis of pancreatic diseases. Das *et al*[41] evaluated the performance of AI in differentiating PDAC from normal pancreas and chronic pancreatitis. The algorithm they used identified neoplasia with an AUC of 0.93. A recent study by Zhu *et al*[42] reported an overall accuracy of 94% by AI in distinguishing pancreatic cancer from chronic inflammation. CT is the most explored medical imaging modality with AI. Liu *et al*[43] reported an AUC of 0.963 for the diagnosis of PDAC using CT with the AI platform. In addition, the time to diagnosis was 20 s/case, certainly less than the time needed by radiologists. The same authors, in more recent work, found 99% accuracy for analysis based on the use of AI. In this study, AI provided higher sensitivity than radiologists (0.983 *vs* 0.929, respectively)[44]. AI missed 3 (1.7%) of 176 PDACs (1.1-1.2 cm), while radiologists missed 12 (7%) of 168 PDACs (1.0-3.3 cm), of which 11 (92%) were correctly detected by AI.

Two important ongoing projects should be noted. Project Felix is a multidisciplinary study led by Johns Hopkins University, which compared 156 PDAC cases and 300 healthy controls using deep learning computer models with manually segmented images. In an initial report, they reported a sensitivity and specificity of 94% and 99%, respectively[45]. The analysis was subsequently expanded to 575 normal patients and 750 patients with PDAC. The second ongoing project is being conducted by the Alliance of Pancreatic Cancer Consortium Imaging Working Group[46]. The goal of the project is to create a shared repository by collecting pre- and post-diagnosis CT, MRI and US images of patients with PDAC to develop AI that can predict the onset of pancreatic cancer and/or diagnose it at an early stage [47].

LIQUID BIOPSY

Serum biomarkers

Carbohydrate antigens: The most validated serum tumor marker in terms of diagnostic, prognostic and surveillance capacity for pancreatic cancer is CA19-9. The sensitivity and specificity of elevated CA19-9 to detect PDAC are 79% and 82%, respectively[48,49].

However, the use of CA19-9 has several limitations. Approximately 10% of the Caucasian population has reduced CA19-9 production due to Lewis antigen dependence. In addition, there are several conditions that result in the increase of the biomarker, such as obstructive jaundice, liver cirrhosis, chronic pancreatitis and cholangitis. The low positive predictive value of CA19-9 limits its application as a screening tool for larger populations[48,50-52]. Other carbohydrate antigens have been evaluated for early diagnosis of pancreatic cancer, such as CA125, CA72-4[53], CA50, CA199 and CA242[48,54]. The solitary diagnostic potential of these biomarkers could not be verified; however, they could help in discriminating between benign and malignant pancreatic lesions in combination with CA19-9[48].

Circulating tumor DNA and circulating tumor cells: New and interesting diagnostic tools in the field of pancreatic cancer are circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). In patients with malignancies, cell-free circulating DNA (cfDNA) molecules are released from tumor cells by apoptosis, necrosis or active release and are called ctDNA. The ctDNA contains mutations specific to the cancer cells from which they are released[55,56]. Thanks to these DNA molecules, it is therefore possible to trace the presence or absence of cancer.

However, a recent meta-analysis evaluated the role of ctDNA in the diagnosis of PDAC and found a rather low sensitivity[57]. This happens because in the early stages the rate of necrosis and apoptosis is lower and not enough ctDNA is released into the circulation (in the early stages of PDAC, only one molecule of circulating tumor DNA can be detected for every 5 mL of plasma)[57]. This challenge could be solved with technological advances, and ctDNA could become an important tool for early diagnosis.

CtDNA has been studied together with other biomarkers to improve its sensitivity and specificity. The combination of KRAS mutations in ctDNA and CA19-9 proved to be particularly interesting. Indeed, it showed a sensitivity and specificity of 0.98 and 0.77, respectively, to differentiate PDAC from chronic pancreatitis and sensitivity and specificity of 0.82 and 0.81 to differentiate PDAC from benign pancreatic tumors[56,58]. Combining the KRAS mutation in ctDNA with four protein biomarkers (CEA, CA19-9, hepatocyte growth factor and osteopontin) identified 64% of patients with pancreatic cancer with a specificity of 0.99[59]. This strategy seems to be very promising; however, it needs validation through studies on large populations.

Analysis of epigenetic alterations in cfDNA also seems to play an important role. By assessing the methylation status of two genes (*ADAMTS1* and *BNC1*) in cfDNA, it seems possible to identify pancreatic cancer early with a sensitivity of 0.95 and specificity of 0.92[60]. In a pilot study, it was reported that a model combining changes in 5-methylcytosine and 5-hydroxymethylcytosine in cfDNA achieved a sensitivity of 0.94 and specificity of 0.95, with an AUC of 0.99 for the diagnosis of PDAC[61].

The ability of targeted cfDNA methylation analysis to detect and localize multiple cancer types at all stages was evaluated. Among patients included with PDAC at different stages, a sensitivity of 0.63 in stage I, 0.83 in stage II, 0.75 in stage III and 1.0 in stage IV was found[62]. These changes in cfDNA methylation could be very useful for monitoring risk groups[63].

CTCs can be isolated tumor cells or cells organized in a group to form a tumor microthrombus[64] and are detected in 21%-100% of patients with PDAC[65]. According to some studies, they can be detected in 75%-80% of patients with early-stage tumors[66] and up to 88% of patients with precursor lesions, predominantly IPMNs[67-69]. Notably, CTCs identify patients with high-grade dysplasia, indicating its potential to stratify high-grade IPMNs against low-grade IPMNs and other benign cysts [67]. In a meta-analysis, the sensitivity, specificity and AUC for PDAC diagnosis of ctDNA, exosomes and CTCs were evaluated. They were 0.64, 0.92 and 0.94 for ctDNA, 0.93, 0.92 and 0.98 for exosomes and 0.74, 0.83 and 0.81 for CTCs, respectively[57]. This lower AUC of CTCs is due to the possibility that CTCs become trapped in the liver when traveling through the portal vein[57]. The ability to detect CTCs by analyzing portal vein blood is greatly increased. They can be found in 100% of patients with metastatic PDAC[70] and in 58% of resectable patients[71]. As with ctDNA, the low amount of CTCs in the early stages is the main factor hindering their use as biomarkers[57].

RNA, metabolites and exosomes: The most significant microRNAs are *miR-21*, *miR-25* and *miR-233*. *miR-21* has a sensitivity for early diagnosis of 0.90 and a specificity of 0.72, while *miR-25* has a sensitivity of 0.75 and 0.93, respectively[72,73]. In contrast, *miR-233* has proven useful in the differential diagnosis between benign and malignant IPMNs[74]. The microRNAs offer a cumulative sensitivity for early-stage pancreatic cancer of 0.79 and a specificity of 0.74[75]. The combined use of CA19-9 and microRNAs can improve diagnostic accuracy, especially *miR-216*[76-77].

Potentially useful biomarkers also include long non-coding (lnc)RNAs. *SNHG15* lncRNA expression is found to be increased in patients with pancreatic cancer compared to healthy controls[78]. Permuth *et al*[79] demonstrated that the differential diagnosis between malignant and nonmalignant IPMNs can be made through the combination of eight lncRNAs. In addition, some lncRNAs (*HAND2-AS1*, *CTD-*

2033D15.2 and *lncRNA-TGF*) are early markers of IPMNs[80]. Other lncRNAs that might be useful in the early detection of pancreatic cancer and IPMN are *HOTAIR*, *MALAT1*, *MEG3*, *H19*, *PVT1*, *HOTTIP*[81], *HAND2-AS1*, *CTD-2033D15.2* and *lncRNA-TGF*[82].

The role of serum metabolites in pancreatic cancer has become of interest with the advent of metabolomic technologies involving nuclear magnetic resonance and mass spectrometry[83]. An important study was performed by Michálková *et al*[84], who developed a nuclear magnetic resonance-based model that included 12 metabolites (3-hydroxybutyrate, lactate, glutamine, alanine, valine, lysine, citrate, histidine, isoleucine, glutamate, acetone and dimethylamine). The model has 94% accuracy, 100% sensitivity and 90% specificity in distinguishing patients with PDAC from healthy individuals[84].

Another study compared the metabolomic profiles of serum samples from patients with NOD and those with PDAC and NOD[85]. This identified 62 different metabolites and found that a panel including N-succinyl-L-diaminopimelic and PE (18:2) had high sensitivity (93.3%) and specificity (93.1%). Currently, studies focusing on metabolomics are expensive and consequently rare; however, it is offering great results on the early diagnosis of PDAC. Further studies are desperately needed.

Recent studies are focusing on multimarker panels in combination with CA19-9. The combined use of eight proteins (S100A11, ITGB5, PPY, ERBB3, SCAMP3, RET, 5-NT, CEACAM1) discriminated with fair accuracy between patients with early stage I/II PDAC and healthy individuals[48,86].

A new and still much to be studied chapter in PDAC concerns the study of exosomes. Kitagawa *et al* [87] studied molecules of exosomal mRNA (*CCDC88A*, *ARF6*, *Vav3* and *WASF2*) and nucleolar RNA (*SNORA14B*, *SNORA18*, *SNORA25*, *SNORA74A* and *SNORD22*) and obtained excellent results for early-stage neoplasia. Tumor-specific expression of exosome surface proteins, the so-called tumor-specific surfaceome, can also be analyzed. Castillo *et al*[88] characterized six PDAC-specific surfaceome proteins, such as CLDN4, EPCAM, CD151, LGALS3BP, HIST2H2BE and HIST2H2BF. These proteins were suggested as promising biomarkers for PDAC diagnosis by the authors. Yu *et al*[89] developed a signature with long RNAs from plasma extracellular vesicles. This signature identified stage I/II pancreatic cancer with very high accuracy and performed better than CA19-9 in distinguishing PDAC from chronic pancreatitis (AUC 0.931 *vs* 0.873)[89]. Serum biomarkers are summarized in Table 1.

Pancreatic juice and pancreatic cyst fluid

In addition to blood, other body materials can be exploited to diagnose PDAC. For example, pancreatic juice collected during ERCP and cyst fluid obtained by EUS-FNA can be analyzed for specific markers. They include KRAS and GNAS mutants (the latter specific for IPMNs) as well as TP53, SMAD4, PIK3CA, PTEN and AKT1, which are generally related to IPMN-associated tumors[90-92].

Biomarkers still under study include mucins (MUCs). Normal pancreatic tissue expresses low levels of MUCs, whereas in branch duct IPMNs there is upregulation of the mucin gene and even more pronounced changes in PDAC[93-95]. MUC4 and MUC16 are 100% specific for pancreatic cancer but have sensitivities of 63% and 67%, respectively[95]. The combined biomarker panel consisting of MUC5AC and CA19-9 also showed excellent performance in distinguishing pancreatic cancer subjects from healthy controls[96].

It also seems possible to distinguish pancreatic cystic lesions with high-grade dysplasia or malignancy by assessing interleukins (IL-1b, IL-5 and IL-8) present in pancreatic juice or by using the monoclonal antibody Das-1. Das-1 can detect pancreatic cysts at risk of malignancy with a sensitivity of 88% and specificity of 98%[97-99].

In recent work by Majumder *et al*[100], a panel of three methylated DNA markers (C13orf18, FER1L4 and BMP3) in pancreatic juice discriminated cases from controls with good accuracy. Using a specificity cutoff value of 86%, the panel distinguished patients with any stage of pancreatic cancer from controls with a sensitivity of 83% and identified patients with stage I or II PDAC or IPMN with high-grade dysplasia with a sensitivity of 80%[100].

Saliva

Progress has also been made in saliva evaluation. A recent study[101] identified seven upregulated genes (*MBD3L2*, *KRAS*, *STIM2*, *DMXL2*, *ACRV1*, *DMD* and *CABLES1*) and five downregulated genes (*TK2*, *GLTSCR2*, *CDKL3*, *TPT1* and *DPM1*) in subjects with PDAC compared with healthy controls or those with chronic pancreatitis. It was possible to discriminate patients with pancreatic cancer with sensitivity and specificity greater than 90% by combining the mRNAs of *MBD3L2*, *KRAS*, *ACRV1* and *DPM1*[101]. Xie *et al*[102] evaluated the expression of lncRNAs and found an upregulation of *HOTAIR* and *PV1T* in the PDAC group compared with controls and benign pancreatic cancers. The combination of salivary *HOTAIR* and *PVT1* differentiated PDAC from healthy controls with a sensitivity of 78.2% and specificity of 90.9% and PDAC from benign tumors with a sensitivity of 81.8% and specificity of 95%[103].

Urine

Radon *et al*[104] used three protein biomarkers (REG1A, TFF1 and LYVE1) to form a powerful urinary panel that could detect patients with stage I-II PDAC with an accuracy of more than 90%. Brezgyte *et al* [105] found increased levels of *miR-143*, *miR-204* and *miR-223* and reduced levels of *miR-30e* in the urine

Table 1 Serum biomarkers

Carbohydrate antigens	CtDNA	miRNA	lncRNA	Metabolites
CA19-9	KRAS	*miR21*	*SNHG15*	3-hydroxybutyrate
CA125	ADAMTS1	*miR25*	*HOTAIR*	Lactate
CA72-4	BNC1	*miR233*	*MALAT1*	Glutamine
CA50	5-methylcytosine	*miR216*	*MEG3*	Alanine
CA242	5-hydroxymethylcytosine	*miR-92-a-5p*	*H19*	Valine
		miR-125b-3p	*PVT1*	Lysine
		miR-532e5p	*HOTTIP*	Citrate
		miR-663	*HAND2-AS1*	Histidine
		miR-1469	*CTD-2033D15.2*	Isoleucine
				Glutamate
				Acetone
				Dimethylamine
				N-succinyl-L-diaminopimelic
				PE (18:2)
Exosomal mRNA molecules	**Exosomal small nucleolar RNA molecules**	**Exosome surfaceome**	**Exosomal long RNAs**	**Others**
CCDC88A	*SNORA14B*	*CLDN4*	*FGA*	CTCs
ARF6	*SNORA18*	*EPCAM*	*KRT19*	ITGB5
Vav3	*SNORA25*	*CD151*	*HIST1H2BK*	PPY
WASF2	*SNORA74A*	*LGAL53BP*	*ITIH2*	ERBB3
	SNORD22	*HIST2H2BE*	*MARCH2*	SCAMP3
		HIST2H2BF	*CLDN1*	RET
			MAL2	5-NT
			TIMP1	CEACAM1
				S100A11

CtDNA: Circulation tumor DNA; miRNA: MicroRNA; lncRNA: Long non-coding RNA; CTC: Circulating tumor cells.

of patients with stage I PDAC compared with the healthy population. However, further studies are needed to validate their clinical utility.

A case-control study that included 914 PDAC patients found the superiority of a panel of metabolites (proline, sphingomyelin, phosphatidylcholine, isocitrate, sphinganine-1-phosphate, histidine, pyruvate, ceramide, sphingomyelin) over CA19-9 in discriminating early-stage PDAC from chronic pancreatitis [106]. According to the authors, the metabolic panel could result in changes in the diagnostic pathway and treatment stratification for one-third of the included patients[106]. Biomarkers of pancreatic juice and cystic fluid, saliva and urine are listed in Table 2.

ARTIFICIAL INTELLIGENCE AND BIOMARKERS

AI can be applied to the identification of biomarkers. Zhang *et al*[107] identified a nine gene pair signature that can distinguish PDAC patients from non-PDAC patients. Alizadeh Savareh *et al*[108] evaluated the best miRNAs using a machine learning method to aid in the early detection of PDAC. The final model included *miR-92a-2-5p, miR-125b-3p, miR-532e5p, miR-663a and miR-1469* with a high performance in differentiating PDAC from controls (accuracy, 0.93; sensitivity, 0.93 and specificity, 0.92).

Table 2 Pancreatic juice and cyst fluid biomarkers, saliva biomarkers, urine biomarkers

Pancreatic juice and cyst fluid biomarkers

Mutant genes	Mucins	Interleukins	Methylated DNA markers
GNAS	MUC4	IL-1b	C13orf18
KRAS	MUC16	IL-5	FER1L4
TP53	MUC5AC	IL-8	BMP3
SMAD4			
PIK3CA			
PTEN			
AKT1			

Saliva biomarkers

Upregulated genes	Downregulated genes	LncRNA
MBD3L2	TK2	HOTAIR
KRAS	GLTSCR2	PVT1
STIM2	CDKL3	
DMXL2	TPT1	
ACRV1	DPM1	
DMD		
CABLES1		

Urine biomarkers

Protein markers	MiRNA	Metabolites
REG1A	miR-143	CA19.9
TFF1	miR-204	Proline
LYVE1	miR-223	Sphingomyelin (d18:2, C17:0)
	miR-30e	Phosphatidylcholine
		Isocitrate
		Sphinganine-1-phosphate
		Histidine
		Pyruvate
		Sphingomyelin (d17:1, C18:0)

miRNA: MicroRNA; lncRNA: Long non-coding RNA.

WHAT STRATEGIES TO AVOID A FORETOLD CATASTROPHE

As we have already mentioned in the introduction, the current predictions for PDAC give us a glimpse of a catastrophe on the horizon. If the increase in annual PDAC cases continues at the current rate, we will soon have a staggering number of cases without the weapons to stem this foretold catastrophe. The only option is to arm ourselves and not arrive unprepared for this hard battle. What strategies should we adopt to prepare for this ordeal? Undoubtedly first, we need to make academia, industry and the politics/economic world understand the urgency of finding solutions quickly, trying to interact with each other according to specific competencies. On the one hand, academia and industry will have to move forward together, as quickly as possible, in those research paths that we have broadly summarized in this article. On the other hand, the political/economic world, made aware of the emergency to be faced, will have to commit itself both to allocating more funding for research in this field and to lavishing more funding on public health. If public health had sufficient funds to subject all patients of a certain age to a simple screening ultrasound of the abdomen, perhaps many patients could be saved. But at present, with current resources, this scenario remains a pipe dream.

CONCLUSION

In this article, we have summarized all the possible strategies we have available today for the early detection of PDAC and the paths that research must pursue to make this goal ever closer. Unfortunately, in 2022 the results for this type of cancer still remain discouraging, while a catastrophic increase in cases is expected in the coming years. The article has been written with the aim of highlighting the urgency of devoting more attention and resources to this pathology in order to reach a solution that seems more and more unreachable every day.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Valeria Tonini 0000-0003-3130-2928; Manuel Zanni 0000-0001-7732-7739.

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REFERENCES

1   **Rahib L**, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

2   **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

3   **Oldfield LE**, Connor AA, Gallinger S. Molecular Events in the Natural History of Pancreatic Cancer. *Trends Cancer* 2017; **3**: 336-346 [PMID: 28718411 DOI: 10.1016/j.trecan.2017.04.005]

4   **Bengtsson A**, Andersson R, Ansari D. The actual 5-year survivors of pancreatic ductal adenocarcinoma based on real-world data. *Sci Rep* 2020; **10**: 16425 [PMID: 33009477 DOI: 10.1038/s41598-020-73525-y]

5   **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

6   **Grasso C**, Jansen G, Giovannetti E. Drug resistance in pancreatic cancer: Impact of altered energy metabolism. *Crit Rev Oncol Hematol* 2017; **114**: 139-152 [PMID: 28477742 DOI: 10.1016/j.critrevonc.2017.03.026]

7   **Ishii Y**, Serikawa M, Tsuboi T, Kawamura R, Tsushima K, Nakamura S, Hirano T, Fukiage A, Mori T, Ikemoto J, Kiyoshita Y, Saeki S, Tamura Y, Miyamoto S, Chayama K. Role of Endoscopic Ultrasonography and Endoscopic Retrograde Cholangiopancreatography in the Diagnosis of Pancreatic Cancer. *Diagnostics (Basel)* 2021; **11** [PMID: 33557084 DOI: 10.3390/diagnostics11020238]

8   **Egawa S**, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, Maguchi H, Yanagisawa A, Tanaka M. Japan Pancreatic Cancer Registry; 30th year anniversary: Japan Pancreas Society. *Pancreas* 2012; **41**: 985-992 [PMID: 22750974 DOI: 10.1097/MPA.0b013e318258055c]

9   **Singhi AD**, Koay EJ, Chari ST, Maitra A. Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology* 2019; **156**: 2024-2040 [PMID: 30721664 DOI: 10.1053/j.gastro.2019.01.259]

10 **Carreras-Torres R**, Johansson M, Gaborieau V, Haycock PC, Wade KH, Relton CL, Martin RM, Davey Smith G, Brennan P. The Role of Obesity, Type 2 Diabetes, and Metabolic Factors in Pancreatic Cancer: A Mendelian Randomization Study. *J Natl Cancer Inst* 2017; **109** [PMID: 28954281 DOI: 10.1093/jnci/djx012]

11 **Michl P**, Löhr M, Neoptolemos JP, Capurso G, Rebours V, Malats N, Ollivier M, Ricciardiello L. UEG position paper on pancreatic cancer. Bringing pancreatic cancer to the 21st century: Prevent, detect, and treat the disease earlier and better. *United European Gastroenterol J* 2021; **9**: 860-871 [PMID: 34431604 DOI: 10.1002/ueg2.12123]

12 **Hu JX**, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F. Pancreatic cancer: A review of epidemiology, trend, and risk factors. *World J Gastroenterol* 2021; **27**: 4298-4321 [PMID: 34366606 DOI: 10.3748/wjg.v27.i27.4298]

13 **Klein AP**. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. *Nat Rev*

Gastroenterol Hepatol 2021; **18**: 493-502 [PMID: 34002083 DOI: 10.1038/s41575-021-00457-x]

14 **McKenzie F**, Biessy C, Ferrari P, Freisling H, Rinaldi S, Chajès V, Dahm CC, Overvad K, Dossus L, Lagiou P, Trichopoulos D, Trichopoulou A, Bueno-de-Mesquita HB, May A, Peeters PH, Weiderpass E, Sanchez MJ, Navarro C, Ardanaz E, Ericson U, Wirfält E, Travis RC, Romieu I. Healthy Lifestyle and Risk of Cancer in the European Prospective Investigation Into Cancer and Nutrition Cohort Study. *Medicine (Baltimore)* 2016; **95**: e2850 [PMID: 27100409 DOI: 10.1097/MD.0000000000002850]

15 **Ferrari P**, Licaj I, Muller DC, Kragh Andersen P, Johansson M, Boeing H, Weiderpass E, Dossus L, Dartois L, Fagherazzi G, Bradbury KE, Khaw KT, Wareham N, Duell EJ, Barricarte A, Molina-Montes E, Sanchez CN, Arriola L, Wallström P, Tjønneland A, Olsen A, Trichopoulou A, Benetou V, Trichopoulos D, Tumino R, Agnoli C, Sacerdote C, Palli D, Li K, Kaaks R, Peeters P, Beulens JW, Nunes L, Gunter M, Norat T, Overvad K, Brennan P, Riboli E, Romieu I. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. *BMJ Open* 2014; **4**: e005245 [PMID: 24993766 DOI: 10.1136/bmjopen-2014-005245]

16 **Yuan C**, Babic A, Khalaf N, Nowak JA, Brais LK, Rubinson DA, Ng K, Aguirre AJ, Pandharipande PV, Fuchs CS, Giovannucci EL, Stampfer MJ, Rosenthal MH, Sander C, Kraft P, Wolpin BM. Diabetes, Weight Change, and Pancreatic Cancer Risk. *JAMA Oncol* 2020; **6**: e202948 [PMID: 32789511 DOI: 10.1001/jamaoncol.2020.2948]

17 **Roy A**, Sahoo J, Kamalanathan S, Naik D, Mohan P, Kalayarasan R. Diabetes and pancreatic cancer: Exploring the two-way traffic. *World J Gastroenterol* 2021; **27**: 4939-4962 [PMID: 34497428 DOI: 10.3748/wjg.v27.i30.4939]

18 **US Preventive Services Task Force**, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Curry SJ, Doubeni CA, Epling JW Jr, Kubik M, Landefeld CS, Mangione CM, Pbert L, Silverstein M, Simon MA, Tseng CW, Wong JB. Screening for Pancreatic Cancer: US Preventive Services Task Force Reaffirmation Recommendation Statement. *JAMA* 2019; **322**: 438-444 [PMID: 31386141 DOI: 10.1001/jama.2019.10232]

19 **Pelaez-Luna M**, Takahashi N, Fletcher JG, Chari ST. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *Am J Gastroenterol* 2007; **102**: 2157-2163 [PMID: 17897335 DOI: 10.1111/j.1572-0241.2007.01480.x]

20 **Yang J**, Xu R, Wang C, Qiu J, Ren B, You L. Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. *Cancer Commun (Lond)* 2021; **41**: 1257-1274 [PMID: 34331845 DOI: 10.1002/cac2.12204]

21 **Sharma A**, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, Chari ST. Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes. *Gastroenterology* 2018; **155**: 730-739.e3 [PMID: 29775599 DOI: 10.1053/j.gastro.2018.05.023]

22 **Goggins M**, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, Bassi C, Carrato A, Farrell J, Fishman EK, Fockens P, Gress TM, van Hooft JE, Hruban RH, Kastrinos F, Klein A, Lennon AM, Lucas A, Park W, Rustgi A, Simeone D, Stoffel E, Vasen HFA, Cahen DL, Canto MI, Bruno M; International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut* 2020; **69**: 7-17 [PMID: 31672839 DOI: 10.1136/gutjnl-2019-319352]

23 **Pereira SP**, Oldfield L, Ney A, Hart PA, Keane MG, Pandol SJ, Li D, Greenhalf W, Jeon CY, Koay EJ, Almario CV, Halloran C, Lennon AM, Costello E. Early detection of pancreatic cancer. *Lancet Gastroenterol Hepatol* 2020; **5**: 698-710 [PMID: 32135127 DOI: 10.1016/S2468-1253(19)30416-9]

24 **European Study Group on Cystic Tumours of the Pancreas**. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 2018; **67**: 789-804 [PMID: 29574408 DOI: 10.1136/gutjnl-2018-316027]

25 **Tanaka M**, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology* 2017; **17**: 738-753 [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007]

26 **Aslanian HR**, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. *Gastroenterology* 2020; **159**: 358-362 [PMID: 32416142 DOI: 10.1053/j.gastro.2020.03.088]

27 **Okusaka T**, Nakamura M, Yoshida M, Kitano M, Uesaka K, Ito Y, Furuse J, Hanada K, Okazaki K; Committee for Revision of Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society. Clinical Practice Guidelines for Pancreatic Cancer 2019 From the Japan Pancreas Society: A Synopsis. *Pancreas* 2020; **49**: 326-335 [PMID: 32132516 DOI: 10.1097/MPA.0000000000001513]

28 **Kanno A**, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, Hasebe O, Ohtsuka T, Nakamura M, Takenaka M, Kitano M, Kikuyama M, Gabata T, Yoshida K, Sasaki T, Serikawa M, Furukawa T, Yanagisawa A, Shimosegawa T; Japan Study Group on the Early Detection of Pancreatic Cancer (JEDPAC). Multicenter study of early pancreatic cancer in Japan. *Pancreatology* 2018; **18**: 61-67 [PMID: 29170051 DOI: 10.1016/j.pan.2017.11.007]

29 **Dewitt J**, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. *Clin Gastroenterol Hepatol* 2006; **4**: 717-25; quiz 664 [PMID: 16675307 DOI: 10.1016/j.cgh.2006.02.020]

30 **Kitano M**, Yoshida T, Itonaga M, Tamura T, Hatamaru K, Yamashita Y. Impact of endoscopic ultrasonography on diagnosis of pancreatic cancer. *J Gastroenterol* 2019; **54**: 19-32 [PMID: 30406288 DOI: 10.1007/s00535-018-1519-2]

31 **Bunganič B**, Laclav M, Dvořáková T, Bradáč O, Traboulsi E, Suchánek Š, Frič P, Zavoral M. Accuracy of EUS and CEH EUS for the diagnosis of pancreatic tumours. *Scand J Gastroenterol* 2018; **53**: 1411-1417 [PMID: 30394143 DOI: 10.1080/00365521.2018.1524023]

32 **Yamashita Y**, Shimokawa T, Napoléon B, Fusaroli P, Gincul R, Kudo M, Kitano M. Value of contrast-enhanced harmonic endoscopic ultrasonography with enhancement pattern for diagnosis of pancreatic cancer: A meta-analysis. *Dig Endosc* 2019; **31**: 125-133 [PMID: 30338569 DOI: 10.1111/den.13290]

33 **Haba S**, Yamao K, Bhatia V, Mizuno N, Hara K, Hijioka S, Imaoka H, Niwa Y, Tajika M, Kondo S, Tanaka T, Shimizu Y, Yatabe Y, Hosoda W, Kawakami H, Sakamoto N. Diagnostic ability and factors affecting accuracy of endoscopic ultrasound-guided fine needle aspiration for pancreatic solid lesions: Japanese large single center experience. *J Gastroenterol* 2013; **48**: 973-981 [PMID: 23090002 DOI: 10.1007/s00535-012-0695-8]

34 **Li H**, Hu Z, Chen J, Guo X. Comparison of ERCP, EUS, and ERCP combined with EUS in diagnosing pancreatic

neoplasms: a systematic review and meta-analysis. *Tumour Biol* 2014; **35**: 8867-8874 [PMID: 24891188 DOI: 10.1007/s13277-014-2154-z]

35   **Kawamura R**, Ishii Y, Serikawa M, Tsuboi T, Tsushima K, Nakamura S, Hirano T, Ikemoto J, Kiyoshita Y, Saeki S, Tamura Y, Miyamoto S, Nakamura K, Furukawa M, Ishida K, Arihiro K, Uemura K, Aikata H. Optimal indication of endoscopic retrograde pancreatography-based cytology in the preoperative pathological diagnosis of pancreatic ductal adenocarcinoma. *Pancreatology* 2022; **22**: 414-420 [PMID: 35219581 DOI: 10.1016/j.pan.2022.02.001]

36   **Kawa S**, Kamisawa T, Notohara K, Fujinaga Y, Inoue D, Koyama T, Okazaki K. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011. *Pancreas* 2020; **49**: e13-e14 [PMID: 31856100 DOI: 10.1097/MPA.0000000000001443]

37   **Ikemoto J**, Serikawa M, Hanada K, Eguchi N, Sasaki T, Fujimoto Y, Sugiyama S, Yamaguchi A, Noma B, Kamigaki M, Minami T, Okazaki A, Yukutake M, Ishii Y, Mouri T, Shimizu A, Tsuboi T, Arihiro K, Chayama K. Clinical Analysis of Early-Stage Pancreatic Cancer and Proposal for a New Diagnostic Algorithm: A Multicenter Observational Study. *Diagnostics (Basel)* 2021; **11** [PMID: 33673151 DOI: 10.3390/diagnostics11020287]

38   **Muhammad W**, Hart GR, Nartowt B, Farrell JJ, Johung K, Liang Y, Deng J. Pancreatic Cancer Prediction Through an Artificial Neural Network. *Front Artif Intell* 2019; **2**: 2 [PMID: 33733091 DOI: 10.3389/frai.2019.00002]

39   **Hayashi H**, Uemura N, Matsumura K, Zhao L, Sato H, Shiraishi Y, Yamashita YI, Baba H. Recent advances in artificial intelligence for pancreatic ductal adenocarcinoma. *World J Gastroenterol* 2021; **27**: 7480-7496 [PMID: 34887644 DOI: 10.3748/wjg.v27.i43.7480]

40   **Mendoza Ladd A**, Diehl DL. Artificial intelligence for early detection of pancreatic adenocarcinoma: The future is promising. *World J Gastroenterol* 2021; **27**: 1283-1295 [PMID: 33833482 DOI: 10.3748/wjg.v27.i13.1283]

41   **Das A**, Nguyen CC, Li F, Li B. Digital image analysis of EUS images accurately differentiates pancreatic cancer from chronic pancreatitis and normal tissue. *Gastrointest Endosc* 2008; **67**: 861-867 [PMID: 18179797 DOI: 10.1016/j.gie.2007.08.036]

42   **Zhu M**, Xu C, Yu J, Wu Y, Li C, Zhang M, Jin Z, Li Z. Differentiation of pancreatic cancer and chronic pancreatitis using computer-aided diagnosis of endoscopic ultrasound (EUS) images: a diagnostic test. *PLoS One* 2013; **8**: e63820 [PMID: 23704940 DOI: 10.1371/journal.pone.0063820]

43   **Liu SL**, Li S, Guo YT, Zhou YP, Zhang ZD, Lu Y. Establishment and application of an artificial intelligence diagnosis system for pancreatic cancer with a faster region-based convolutional neural network. *Chin Med J (Engl)* 2019; **132**: 2795-2803 [PMID: 31856050 DOI: 10.1097/CM9.0000000000000544]

44   **Liu KL**, Wu T, Chen PT, Tsai YM, Roth H, Wu MS, Liao WC, Wang W. Deep learning to distinguish pancreatic cancer tissue from non-cancerous pancreatic tissue: a retrospective study with cross-racial external validation. *Lancet Digit Health* 2020; **2**: e303-e313 [PMID: 33328124 DOI: 10.1016/S2589-7500(20)30078-9]

45   **Chu LC**, Park S, Kawamoto S, Wang Y, Zhou Y, Shen W, Zhu Z, Xia Y, Xie L, Liu F, Yu Q, Fouladi DF, Shayesteh S, Zinreich E, Graves JS, Horton KM, Yuille AL, Hruban RH, Kinzler KW, Vogelstein B, Fishman EK. Application of Deep Learning to Pancreatic Cancer Detection: Lessons Learned From Our Initial Experience. *J Am Coll Radiol* 2019; **16**: 1338-1342 [PMID: 31492412 DOI: 10.1016/j.jacr.2019.05.034]

46   **Young MR**, Abrams N, Ghosh S, Rinaudo JAS, Marquez G, Srivastava S. Prediagnostic Image Data, Artificial Intelligence, and Pancreatic Cancer: A Tell-Tale Sign to Early Detection. *Pancreas* 2020; **49**: 882-886 [PMID: 32675784 DOI: 10.1097/MPA.0000000000001603]

47   **Kenner B**, Chari ST, Kelsen D, Klimstra DS, Pandol SJ, Rosenthal M, Rustgi AK, Taylor JA, Yala A, Abul-Husn N, Andersen DK, Bernstein D, Brunak S, Canto MI, Eldar YC, Fishman EK, Fleshman J, Go VLW, Holt JM, Field B, Goldberg A, Hoos W, Iacobuzio-Donahue C, Li D, Lidgard G, Maitra A, Matrisian LM, Poblete S, Rothschild L, Sander C, Schwartz LH, Shalit U, Srivastava S, Wolpin B. Artificial Intelligence and Early Detection of Pancreatic Cancer: 2020 Summative Review. *Pancreas* 2021; **50**: 251-279 [PMID: 33835956 DOI: 10.1097/MPA.0000000000001762]

48   **Sturm N**, Ettrich TJ, Perkhofer L. The Impact of Biomarkers in Pancreatic Ductal Adenocarcinoma on Diagnosis, Surveillance and Therapy. *Cancers (Basel)* 2022; **14** [PMID: 35008381 DOI: 10.3390/cancers14010217]

49   **Fahrmann JF**, Schmidt CM, Mao X, Irajizad E, Loftus M, Zhang J, Patel N, Vykoukal J, Dennison JB, Long JP, Do KA, Chabot JA, Kluger MD, Kastrinos F, Brais L, Babic A, Jajoo K, Lee LS, Clancy TE, Ng K, Bullock A, Genkinger J, Yip-Schneider MT, Maitra A, Wolpin BM, Hanash S. Lead-Time Trajectory of CA19-9 as an Anchor Marker for Pancreatic Cancer Early Detection. *Gastroenterology* 2021; **160**: 1373-1383.e6 [PMID: 33333055 DOI: 10.1053/j.gastro.2020.11.052]

50   **Luo G**, Fan Z, Cheng H, Jin K, Guo M, Lu Y, Yang C, Fan K, Huang Q, Long J, Liu L, Xu J, Lu R, Ni Q, Warshaw AL, Liu C, Yu X. New observations on the utility of CA19-9 as a biomarker in Lewis negative patients with pancreatic cancer. *Pancreatology* 2018; **18**: 971-976 [PMID: 30131287 DOI: 10.1016/j.pan.2018.08.003]

51   **Loosen SH**, Neumann UP, Trautwein C, Roderburg C, Luedde T. Current and future biomarkers for pancreatic adenocarcinoma. *Tumour Biol* 2017; **39**: 1010428317692231 [PMID: 28618958 DOI: 10.1177/1010428317692231]

52   **Lee T**, Teng TZJ, Shelat VG. Carbohydrate antigen 19-9 - tumor marker: Past, present, and future. *World J Gastrointest Surg* 2020; **12**: 468-490 [PMID: 33437400 DOI: 10.4240/wjgs.v12.i12.468]

53   **Wang Z**, Tian YP. Clinical value of serum tumor markers CA19-9, CA125 and CA72-4 in the diagnosis of pancreatic carcinoma. *Mol Clin Oncol* 2014; **2**: 265-268 [PMID: 24649344 DOI: 10.3892/mco.2013.226]

54   **Dou H**, Sun G, Zhang L. CA242 as a biomarker for pancreatic cancer and other diseases. *Prog Mol Biol Transl Sci* 2019; **162**: 229-239 [PMID: 30905452 DOI: 10.1016/bs.pmbts.2018.12.007]

55   **Buscail E**, Maulat C, Muscari F, Chiche L, Cordelier P, Dabernat S, Alix-Panabières C, Buscail L. Liquid Biopsy Approach for Pancreatic Ductal Adenocarcinoma. *Cancers (Basel)* 2019; **11** [PMID: 31248203 DOI: 10.3390/cancers11060852]

56   **Heredia-Soto V**, Rodríguez-Salas N, Feliu J. Liquid Biopsy in Pancreatic Cancer: Are We Ready to Apply It in the Clinical Practice? *Cancers (Basel)* 2021; **13** [PMID: 33924143 DOI: 10.3390/cancers13081986]

57   **Zhu Y**, Zhang H, Chen N, Hao J, Jin H, Ma X. Diagnostic value of various liquid biopsy methods for pancreatic cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e18581 [PMID: 32011436 DOI:

10.1097/MD.0000000000018581]

58   **Wang ZY**, Ding XQ, Zhu H, Wang RX, Pan XR, Tong JH. *KRAS* Mutant Allele Fraction in Circulating Cell-Free DNA Correlates With Clinical Stage in Pancreatic Cancer Patients. *Front Oncol* 2019; **9**: 1295 [PMID: 31850201 DOI: 10.3389/fonc.2019.01295]

59   **Cohen JD**, Javed AA, Thoburn C, Wong F, Tie J, Gibbs P, Schmidt CM, Yip-Schneider MT, Allen PJ, Schattner M, Brand RE, Singhi AD, Petersen GM, Hong SM, Kim SC, Falconi M, Doglioni C, Weiss MJ, Ahuja N, He J, Makary MA, Maitra A, Hanash SM, Dal Molin M, Wang Y, Li L, Ptak J, Dobbyn L, Schaefer J, Silliman N, Popoli M, Goggins MG, Hruban RH, Wolfgang CL, Klein AP, Tomasetti C, Papadopoulos N, Kinzler KW, Vogelstein B, Lennon AM. Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers. *Proc Natl Acad Sci U S A* 2017; **114**: 10202-10207 [PMID: 28874546 DOI: 10.1073/pnas.1704961114]

60   **Eissa MAL**, Lerner L, Abdelfatah E, Shankar N, Canner JK, Hasan NM, Yaghoobi V, Huang B, Kerner Z, Takaesu F, Wolfgang C, Kwak R, Ruiz M, Tam M, Pisanic TR 2nd, Iacobuzio-Donahue CA, Hruban RH, He J, Wang TH, Wood LD, Sharma A, Ahuja N. Promoter methylation of ADAMTS1 and BNC1 as potential biomarkers for early detection of pancreatic cancer in blood. *Clin Epigenetics* 2019; **11**: 59 [PMID: 30953539 DOI: 10.1186/s13148-019-0650-0]

61   **Cao F**, Wei A, Hu X, He Y, Zhang J, Xia L, Tu K, Yuan J, Guo Z, Liu H, Xie D, Li A. Integrated epigenetic biomarkers in circulating cell-free DNA as a robust classifier for pancreatic cancer. *Clin Epigenetics* 2020; **12**: 112 [PMID: 32703318 DOI: 10.1186/s13148-020-00898-2]

62   **Liu MC**, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol* 2020; **31**: 745-759 [PMID: 33506766 DOI: 10.1016/j.annonc.2020.02.011]

63   **Brancaccio M**, Natale F, Falco G, Angrisano T. Cell-Free DNA Methylation: The New Frontiers of Pancreatic Cancer Biomarkers' Discovery. *Genes (Basel)* 2019; **11** [PMID: 31877923 DOI: 10.3390/genes11010014]

64   **Yeo D**, Bastian A, Strauss H, Saxena P, Grimison P, Rasko JEJ. Exploring the Clinical Utility of Pancreatic Cancer Circulating Tumor Cells. *Int J Mol Sci* 2022; **23** [PMID: 35163592 DOI: 10.3390/ijms23031671]

65   **Kaczor-Urbanowicz KE**, Cheng J, King JC, Sedarat A, Pandol SJ, Farrell JJ, Wong DTW, Kim Y. Reviews on Current Liquid Biopsy for Detection and Management of Pancreatic Cancers. *Pancreas* 2020; **49**: 1141-1152 [PMID: 33003085 DOI: 10.1097/MPA.0000000000001662]

66   **Ankeny JS**, Court CM, Hou S, Li Q, Song M, Wu D, Chen JF, Lee T, Lin M, Sho S, Rochefort MM, Girgis MD, Yao J, Wainberg ZA, Muthusamy VR, Watson RR, Donahue TR, Hines OJ, Reber HA, Graeber TG, Tseng HR, Tomlinson JS. Circulating tumour cells as a biomarker for diagnosis and staging in pancreatic cancer. *Br J Cancer* 2016; **114**: 1367-1375 [PMID: 27300108 DOI: 10.1038/bjc.2016.121]

67   **Poruk KE**, Valero V 3rd, He J, Ahuja N, Cameron JL, Weiss MJ, Lennon AM, Goggins M, Wood LD, Wolfgang CL. Circulating Epithelial Cells in Intraductal Papillary Mucinous Neoplasms and Cystic Pancreatic Lesions. *Pancreas* 2017; **46**: 943-947 [PMID: 28697136 DOI: 10.1097/MPA.0000000000000869]

68   **Franses JW**, Basar O, Kadayifci A, Yuksel O, Choz M, Kulkarni AS, Tai E, Vo KD, Arora KS, Desai N, Licausi JA, Toner M, Maheswaran S, Haber DA, Ryan DP, Brugge WR, Ting DT. Improved Detection of Circulating Epithelial Cells in Patients with Intraductal Papillary Mucinous Neoplasms. *Oncologist* 2018; **23**: 121-127 [PMID: 28860411 DOI: 10.1634/theoncologist.2017-0234]

69   **Vasseur A**, Kiavue N, Bidard FC, Pierga JY, Cabel L. Clinical utility of circulating tumor cells: an update. *Mol Oncol* 2021; **15**: 1647-1666 [PMID: 33289351 DOI: 10.1002/1878-0261.12869]

70   **Catenacci DV**, Chapman CG, Xu P, Koons A, Konda VJ, Siddiqui UD, Waxman I. Acquisition of Portal Venous Circulating Tumor Cells From Patients With Pancreaticobiliary Cancers by Endoscopic Ultrasound. *Gastroenterology* 2015; **149**: 1794-1803.e4 [PMID: 26341722 DOI: 10.1053/j.gastro.2015.08.050]

71   **Tien YW**, Kuo HC, Ho BI, Chang MC, Chang YT, Cheng MF, Chen HL, Liang TY, Wang CF, Huang CY, Shew JY, Chang YC, Lee EY, Lee WH. A High Circulating Tumor Cell Count in Portal Vein Predicts Liver Metastasis From Periampullary or Pancreatic Cancer: A High Portal Venous CTC Count Predicts Liver Metastases. *Medicine (Baltimore)* 2016; **95**: e3407 [PMID: 27100430 DOI: 10.1097/MD.0000000000003407]

72   **Deng T**, Yuan Y, Zhang C, Yao W, Wang C, Liu R, Ba Y. Identification of Circulating MiR-25 as a Potential Biomarker for Pancreatic Cancer Diagnosis. *Cell Physiol Biochem* 2016; **39**: 1716-1722 [PMID: 27639768 DOI: 10.1159/000447872]

73   **Li X**, Gao P, Wang Y, Wang X. Blood-Derived microRNAs for Pancreatic Cancer Diagnosis: A Narrative Review and Meta-Analysis. *Front Physiol* 2018; **9**: 685 [PMID: 29922178 DOI: 10.3389/fphys.2018.00685]

74   **Komatsu S**, Ichikawa D, Miyamae M, Kawaguchi T, Morimura R, Hirajima S, Okajima W, Ohashi T, Imamura T, Konishi H, Shiozaki A, Ikoma H, Okamoto K, Taniguchi H, Otsuji E. Malignant potential in pancreatic neoplasm; new insights provided by circulating miR-223 in plasma. *Expert Opin Biol Ther* 2015; **15**: 773-785 [PMID: 25819175 DOI: 10.1517/14712598.2015.1029914]

75   **Peng C**, Wang J, Gao W, Huang L, Liu Y, Li X, Li Z, Yu X. Meta-analysis of the Diagnostic Performance of Circulating MicroRNAs for Pancreatic Cancer. *Int J Med Sci* 2021; **18**: 660-671 [PMID: 33437201 DOI: 10.7150/ijms.52706]

76   **Shen SY**, Singhania R, Fehringer G, Chakravarthy A, Roehrl MHA, Chadwick D, Zuzarte PC, Borgida A, Wang TT, Li T, Kis O, Zhao Z, Spreafico A, Medina TDS, Wang Y, Roulois D, Ettayebi I, Chen Z, Chow S, Murphy T, Arruda A, O'Kane GM, Liu J, Mansour M, McPherson JD, O'Brien C, Leighl N, Bedard PL, Fleshner N, Liu G, Minden MD, Gallinger S, Goldenberg A, Pugh TJ, Hoffman MM, Bratman SV, Hung RJ, De Carvalho DD. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. *Nature* 2018; **563**: 579-583 [PMID: 30429608 DOI: 10.1038/s41586-018-0703-0]

77   **Cirmena G**, Dameri M, Ravera F, Fregatti P, Ballestrero A, Zoppoli G. Assessment of Circulating Nucleic Acids in Cancer: From Current Status to Future Perspectives and Potential Clinical Applications. *Cancers (Basel)* 2021; **13** [PMID: 34298675 DOI: 10.3390/cancers13143460]

78   **Guo XB**, Yin HS, Wang JY. Evaluating the diagnostic and prognostic value of long non-coding RNA SNHG15 in pancreatic ductal adenocarcinoma. *Eur Rev Med Pharmacol Sci* 2018; **22**: 5892-5898 [PMID: 30280769 DOI:

10.26355/eurrev_201809_15917]

79 **Permuth JB**, Chen DT, Yoder SJ, Li J, Smith AT, Choi JW, Kim J, Balagurunathan Y, Jiang K, Coppola D, Centeno BA, Klapman J, Hodul P, Karreth FA, Trevino JG, Merchant N, Magliocco A, Malafa MP, Gillies R. Linc-ing Circulating Long Non-coding RNAs to the Diagnosis and Malignant Prediction of Intraductal Papillary Mucinous Neoplasms of the Pancreas. *Sci Rep* 2017; **7**: 10484 [PMID: 28874676 DOI: 10.1038/s41598-017-09754-5]

80 **Satoh K**. Molecular Approaches Using Body Fluid for the Early Detection of Pancreatic Cancer. *Diagnostics (Basel)* 2021; **11** [PMID: 33671729 DOI: 10.3390/diagnostics11020375]

81 **Li Y**, Al Hallak MN, Philip PA, Azmi AS, Mohammad RM. Non-Coding RNAs in Pancreatic Cancer Diagnostics and Therapy: Focus on lncRNAs, circRNAs, and piRNAs. *Cancers (Basel)* 2021; **13** [PMID: 34439315 DOI: 10.3390/cancers13164161]

82 **Ding J**, Li Y, Zhang Y, Fan B, Li Q, Zhang J. Identification of key lncRNAs in the tumorigenesis of intraductal pancreatic mucinous neoplasm by coexpression network analysis. *Cancer Med* 2020; **9**: 3840-3851 [PMID: 32239802 DOI: 10.1002/cam4.2927]

83 **Schmidt DR**, Patel R, Kirsch DG, Lewis CA, Vander Heiden MG, Locasale JW. Metabolomics in cancer research and emerging applications in clinical oncology. *CA Cancer J Clin* 2021; **71**: 333-358 [PMID: 33982817 DOI: 10.3322/caac.21670]

84 **Michálková L**, Horník Š, Sýkora J, Habartová L, Setnička V. Diagnosis of pancreatic cancer via¹H NMR metabolomics of human plasma. *Analyst* 2018; **143**: 5974-5978 [PMID: 30270368 DOI: 10.1039/c8an01310a]

85 **He X**, Zhong J, Wang S, Zhou Y, Wang L, Zhang Y, Yuan Y. Serum metabolomics differentiating pancreatic cancer from new-onset diabetes. *Oncotarget* 2017; **8**: 29116-29124 [PMID: 28418859 DOI: 10.18632/oncotarget.16249]

86 **Yu J**, Ploner A, Kordes M, Löhr M, Nilsson M, de Maturana MEL, Estudillo L, Renz H, Carrato A, Molero X, Real FX, Malats N, Ye W. Plasma protein biomarkers for early detection of pancreatic ductal adenocarcinoma. *Int J Cancer* 2021; **148**: 2048-2058 [PMID: 33411965 DOI: 10.1002/ijc.33464]

87 **Kitagawa T**, Taniuchi K, Tsuboi M, Sakaguchi M, Kohsaki T, Okabayashi T, Saibara T. Circulating pancreatic cancer exosomal RNAs for detection of pancreatic cancer. *Mol Oncol* 2019; **13**: 212-227 [PMID: 30358104 DOI: 10.1002/1878-0261.12398]

88 **Castillo J**, Bernard V, San Lucas FA, Allenson K, Capello M, Kim DU, Gascoyne P, Mulu FC, Stephens BM, Huang J, Wang H, Momin AA, Jacamo RO, Katz M, Wolff R, Javle M, Varadhachary G, Wistuba II, Hanash S, Maitra A, Alvarez H. Surfaceome profiling enables isolation of cancer-specific exosomal cargo in liquid biopsies from pancreatic cancer patients. *Ann Oncol* 2018; **29**: 223-229 [PMID: 29045505 DOI: 10.1093/annonc/mdx542]

89 **Yu S**, Li Y, Liao Z, Wang Z, Qian L, Zhao J, Zong H, Kang B, Zou WB, Chen K, He X, Meng Z, Chen Z, Huang S, Wang P. Plasma extracellular vesicle long RNA profiling identifies a diagnostic signature for the detection of pancreatic ductal adenocarcinoma. *Gut* 2020; **69**: 540-550 [PMID: 31562239 DOI: 10.1136/gutjnl-2019-318860]

90 **Kanda M**, Knight S, Topazian M, Syngal S, Farrell J, Lee J, Kamel I, Lennon AM, Borges M, Young A, Fujiwara S, Seike J, Eshleman J, Hruban RH, Canto MI, Goggins M. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. *Gut* 2013; **62**: 1024-1033 [PMID: 22859495 DOI: 10.1136/gutjnl-2012-302823]

91 **Kanda M**, Sadakari Y, Borges M, Topazian M, Farrell J, Syngal S, Lee J, Kamel I, Lennon AM, Knight S, Fujiwara S, Hruban RH, Canto MI, Goggins M. Mutant TP53 in duodenal samples of pancreatic juice from patients with pancreatic cancer or high-grade dysplasia. *Clin Gastroenterol Hepatol* 2013; **11**: 719-30.e5 [PMID: 23200980 DOI: 10.1016/j.cgh.2012.11.016]

92 **Singhi AD**, McGrath K, Brand RE, Khalid A, Zeh HJ, Chennat JS, Fasanella KE, Papachristou GI, Slivka A, Bartlett DL, Dasyam AK, Hogg M, Lee KK, Marsh JW, Monaco SE, Ohori NP, Pingpank JF, Tsung A, Zureikat AH, Wald AI, Nikiforova MN. Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. *Gut* 2018; **67**: 2131-2141 [PMID: 28970292 DOI: 10.1136/gutjnl-2016-313586]

93 **Garcia-Carracedo D**, Chen ZM, Qiu W, Huang AS, Tang SM, Hruban RH, Su GH. PIK3CA mutations in mucinous cystic neoplasms of the pancreas. *Pancreas* 2014; **43**: 245-249 [PMID: 24518503 DOI: 10.1097/MPA.0000000000000034]

94 **Kaur S**, Kumar S, Momi N, Sasson AR, Batra SK. Mucins in pancreatic cancer and its microenvironment. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 607-620 [PMID: 23856888 DOI: 10.1038/nrgastro.2013.120]

95 **Nagata K**, Horinouchi M, Saitou M, Higashi M, Nomoto M, Goto M, Yonezawa S. Mucin expression profile in pancreatic cancer and the precursor lesions. *J Hepatobiliary Pancreat Surg* 2007; **14**: 243-254 [PMID: 17520199 DOI: 10.1007/s00534-006-1169-2]

96 **Henry KE**, Shaffer TM, Mack KN, Ring J, Ogirala A, Klein-Scory S, Eilert-Micus C, Schmiegel W, Bracht T, Sitek B, Clyne M, Reid CJ, Sipos B, Lewis JS, Kalthoff H, Grimm J. Exploiting the MUC5AC Antigen for Noninvasive Identification of Pancreatic Cancer. *J Nucl Med* 2021; **62**: 1384-1390 [PMID: 33712530 DOI: 10.2967/jnumed.120.256776]

97 **Maker AV**, Katabi N, Qin LX, Klimstra DS, Schattner M, Brennan MF, Jarnagin WR, Allen PJ. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. *Clin Cancer Res* 2011; **17**: 1502-1508 [PMID: 21266527 DOI: 10.1158/1078-0432.CCR-10-1561]

98 **Hao S**, Takahashi C, Snyder RA, Parikh AA. Stratifying Intraductal Papillary Mucinous Neoplasms by Cyst Fluid Analysis: Present and Future. *Int J Mol Sci* 2020; **21** [PMID: 32050465 DOI: 10.3390/ijms21031147]

99 **Das KK**, Geng X, Brown JW, Morales-Oyarvide V, Huynh T, Pergolini I, Pitman MB, Ferrone C, Al Efishat M, Haviland D, Thompson E, Wolfgang C, Lennon AM, Allen P, Lillemoe KD, Fields RC, Hawkins WG, Liu J, Castillo CF, Das KM, Mino-Kenudson M. Cross Validation of the Monoclonal Antibody Das-1 in Identification of High-Risk Mucinous Pancreatic Cystic Lesions. *Gastroenterology* 2019; **157**: 720-730.e2 [PMID: 31175863 DOI: 10.1053/j.gastro.2019.05.014]

100 **Majumder S**, Raimondo M, Taylor WR, Yab TC, Berger CK, Dukek BA, Cao X, Foote PH, Wu CW, Devens ME, Mahoney DW, Smyrk TC, Pannala R, Chari ST, Vege SS, Topazian MD, Petersen BT, Levy MJ, Rajan E, Gleeson FC,

Abu Dayyeh B, Nguyen CC, Faigel DO, Woodward TA, Wallace MB, Petersen G, Allawi HT, Lidgard GP, Kisiel JB, Ahlquist DA. Methylated DNA in Pancreatic Juice Distinguishes Patients With Pancreatic Cancer From Controls. *Clin Gastroenterol Hepatol* 2020; **18**: 676-683.e3 [PMID: 31323382 DOI: 10.1016/j.cgh.2019.07.017]

101   **Zhang L**, Farrell JJ, Zhou H, Elashoff D, Akin D, Park NH, Chia D, Wong DT. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010; **138**: 949-57.e1 [PMID: 19931263 DOI: 10.1053/j.gastro.2009.11.010]

102   **Xie Z**, Yin X, Gong B, Nie W, Wu B, Zhang X, Huang J, Zhang P, Zhou Z, Li Z. Salivary microRNAs show potential as a noninvasive biomarker for detecting resectable pancreatic cancer. *Cancer Prev Res (Phila)* 2015; **8**: 165-173 [PMID: 25538087 DOI: 10.1158/1940-6207.CAPR-14-0192]

103   **Ghafouri-Fard S**, Fathi M, Zhai T, Taheri M, Dong P. LncRNAs: Novel Biomarkers for Pancreatic Cancer. *Biomolecules* 2021; **11** [PMID: 34827663 DOI: 10.3390/biom11111665]

104   **Radon TP**, Massat NJ, Jones R, Alrawashdeh W, Dumartin L, Ennis D, Duffy SW, Kocher HM, Pereira SP, Guarner posthumous L, Murta-Nascimento C, Real FX, Malats N, Neoptolemos J, Costello E, Greenhalf W, Lemoine NR, Crnogorac-Jurcevic T. Identification of a Three-Biomarker Panel in Urine for Early Detection of Pancreatic Adenocarcinoma. *Clin Cancer Res* 2015; **21**: 3512-3521 [PMID: 26240291 DOI: 10.1158/1078-0432.CCR-14-2467]

105   **Brezgyte G**, Shah V, Jach D, Crnogorac-Jurcevic T. Non-Invasive Biomarkers for Earlier Detection of Pancreatic Cancer-A Comprehensive Review. *Cancers (Basel)* 2021; **13** [PMID: 34072842 DOI: 10.3390/cancers13112722]

106   **Mayerle J**, Kalthoff H, Reszka R, Kamlage B, Peter E, Schniewind B, González Maldonado S, Pilarsky C, Heidecke CD, Schatz P, Distler M, Scheiber JA, Mahajan UM, Weiss FU, Grützmann R, Lerch MM. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. *Gut* 2018; **67**: 128-137 [PMID: 28108468 DOI: 10.1136/gutjnl-2016-312432]

107   **Zhang ZM**, Wang JS, Zulfiqar H, Lv H, Dao FY, Lin H. Early Diagnosis of Pancreatic Ductal Adenocarcinoma by Combining Relative Expression Orderings With Machine-Learning Method. *Front Cell Dev Biol* 2020; **8**: 582864 [PMID: 33178697 DOI: 10.3389/fcell.2020.582864]

108   **Alizadeh Savareh B**, Asadzadeh Aghdaie H, Behmanesh A, Bashiri A, Sadeghi A, Zali M, Shams R. A machine learning approach identified a diagnostic model for pancreatic cancer through using circulating microRNA signatures. *Pancreatology* 2020; **20**: 1195-1204 [PMID: 32800647 DOI: 10.1016/j.pan.2020.07.399]

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