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Early detection of pancreatic cancer: current state and future opportunities

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Abstract

Purpose of review: Pancreatic ductal adenocarcinoma (PDAC) is third leading cause of cancer death in the United States, a lethal disease with no screening strategy. Although diagnosis at an early stage is associated with improved survival, clinical detection of PDAC is typically at an advanced symptomatic stage when best in class therapies have limited impact on survival.

Recent findings: In recent years this status quo has been challenged by the identification of novel risk factors, molecular markers of early-stage disease and innovations in pancreatic imaging. There is now expert consensus that screening may be pursued in a cohort of individuals with increased likelihood of developing PDAC based on genetic and familial risk.

Summary: This review summarizes the known risk factors of PDAC, current knowledge and recent observations pertinent to early detection of PDAC in these risk groups and outlines future approaches that will potentially advance the field.

Keywords

Pancreatic adenocarcinoma; PDAC; Pancreatic cancer screening; early detection

Introduction:

The incidence and mortality of pancreatic ductal adenocarcinoma (PDAC) is increasing worldwide. (1) PDAC is currently the third leading cause of cancer related mortality in the United States with an overall five year survival estimated to be 10%.(2–4) This dismal prognosis can be attributed to late stage presentation with only 15–20% eligible for curative resection and high degree of chemoresistance. (5,6) Over the next decade, PDAC is predicted to emerge as the second leading cause of cancer related mortality behind lung cancer. This underscores the need to develop rational, evidence based strategies for early

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detection of PDAC when it is still resectable, and simultaneously advance chemotherapeutic options to prolong survival following resection.(7,8)

While early diagnosis of PDAC does confer a survival advantage, there is no evidence that screening populations at average or low risk reduces morality or is cost effective. (9,10) Accordingly, the US Prevention and Screening Task Force (USPTF) cautions against screening the general population for PDAC.(11) Despite being a lethal cancer, PDAC is relatively uncommon with a incidence of 12 per 100,000) and 1–1.5% lifetime risk.(3,4) Currently there are no reliable biomarkers with performance criteria required for adoption in an asymptomatic prospective population.(12) Existing diagnostic modalities will result in prohibitively high false positive rates with detrimental consequences. Most importantly patients may be subjected to pancreatic resections of unclear benefit, which may include surgical resection of commonly identified low risk or benign lesions. (12,13) Besides risk of over diagnosis and its associated anxiety, patients may incur needless financial burdens related to the expense of screening population. (13) In this review, we will focus our discussion on the recent and emerging data in early detection of PDAC in various high-risk groups and summarize recent advances in early detection biomarkers and research initiatives.

Genetic and familial risk

In an enriched subset of individuals with a higher-than-average lifetime risk of the disease there is expert consensus that surveillance should be considered.(13,14) These high-risk individuals (HRIs) eligible for pancreatic cancer surveillance are currently defined by familial and genetic risk. Familial pancreatic cancer kindreds are defined as families with at least two first-degree relatives with PC or three or more first and second-degree relatives, and the lifetime cancer risk increases with the total number of family members affected. (15) Germline mutations in cancer predisposition genes: ATM, BRCA1 and 2, CDKN2A, and PALB2, hereditary syndromes associated with PDAC (Lynch, Li-Fraumeni and Peutz-Jeghers syndromes) and hereditary pancreatitis an autosomal dominant disease associated with gain of function PRSS1 variants have all been associated with an increased lifetime risk of PDAC.(16–22) (Table 1) Despite this established risk association, current evidence indicates that a germline mutation in a PDAC predisposition gene is identified in less than 10% PDAC cases. Both the National Comprehensive Cancer Network (NCCN) and American Society of Clinic Oncology (ASCO) have recommended that PDAC patients be offered germline genetic testing at index diagnosis, with the goal of improving risk assessment for family members. It is anticipated that as these recommendations gain more widespread practice implementation, the pool of HRIs eligible for PDAC surveillance will expand. Although HRIs defined either by genetic risk or family history or both provide an enriched population for implementation of early detection strategies, observations related the outcomes of surveillance remain limited. A 16-year follow up study of 354 HRIs described a shift towards earlier stage diagnosis for screen detected PDAC. Nine out of the 10 PDAC cases detected during surveillance in this cohort were diagnosed at a resectable stage and 3-year survival in this group was 85%.(23) In view of the low event rate of cancers in HRIs under surveillance understanding the impact of these findings in the larger population of

HRIs will require study in larger cohorts coupled with long-term follow-up of outcomes in HRIs with screen detected PDAC.

Magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are the currently recommended modalities of surveillance in HRIs. In a recent metanalysis of 24 studies including 2112 HRIs, EUS was significantly better at identifying focal pancreatic abnormalities but there no significant differences between EUS and MRI for detecting lesions with high-grade lesions or early stage PDAC. (24). Surveillance imaging is usually annual in asymptomatic individual in the absence of significant pancreatic abnormalities on the index examination. (13)If a pancreatic lesion concerning for neoplasm is identified, downstream testing and interventions need to be individualized. Pancreatic cysts are common and present in nearly 50% of HRIs at index evaluation and current risk stratification guidelines although reasonably specific, have suboptimal sensitivity for detecting advanced neoplasia in this high-risk population.(25) PDAC in HRIs appear to develop about a decade earlier than sporadic PDAC and hence the proposed age of initiating surveillance is 50, or 10 years earlier than the youngest relative with PDAC and at an earlier age in individuals with Peutz-Jeghers syndrome, hereditary pancreatitis and familial atypical multiple mole melanoma syndrome. It is critical that prior to surveillance initiation, HRIs are educated about limitations, risks, benefits, and cost implications. This includes the likelihood of identifying lesions with uncertain neoplastic potential requiring invasive interventions with potential for harm.

New-onset diabetes mellitus

New-onset diabetes mellitus (NOD) can be a harbinger of PDAC. Population-based studies have demonstrated that nearly 40% of patients with PDAC meet American Diabetes Association criteria for diabetes mellitus (DM) at diagnosis and in nearly half of them DM is new-onset i.e. diagnosed within the preceding 2–3 years.(26)

The metabolic alterations that predate the clinical diagnosis of PDAC also include changes in body composition. In a population-based case control study, loss of subcutaneous adipose tissue was noted to be significantly higher in PDAC cases starting about 18 months prior to the diagnosis and may be secondary to overexpression of uncoupling protein 1 (UCP1) in adipose tissue.(27)

Despite this high prevalence of DM at the time of PDAC diagnosis, only about 1% of individuals with NOD will be diagnosed with PDAC in the 3 years following DM diagnosis. The metabolic profile of individuals with DM frequently includes central obesity and weight gain. However, PDAC patients with NOD will frequently present with concomitant paradoxical weight loss. The recently reported Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) score leverages this phenomenon to further stratify NOD into different risk categories(28) The reported 3-year incidence of PDAC in NOD patients with ENDPAC score>3 was 3.6% and identifies a population that can be potentially targeted for screening. (28) Although, fasting blood glucose has been incorporated into clinical surveillance guidelines for other at-risk groups such as HRIs and individuals with pancreatic cysts, the additional risk conferred by NOD and hence the need to alter surveillance interval in these groups remain somewhat poorly defined.

Chronic pancreatitis

A recent meta-analysis evaluating 13 studies concluded that there was a 16-fold elevated risk of PDAC following a diagnosis of CP. CP patients with diabetes and high BMI or exocrine pancreatic insufficiency and a low BMI and those with a dilated main pancreatic duct may constitute specific risk groups among CP patients who would benefit from closer surveillance for PDAC.(29)

In CP, acoustic shadowing from calcification often obscures reliable visualization of neoplasm by endoscopic ultrasound (EUS). Emerging areas for EUS include incorporation of elastography and use of microbubble for contrast [contrast enhanced harmonic EUS (CH-EUS)] which uses the altered vascular characteristics of malignancy compared with surrounding tissues to enhance visualization.(8,30) A single center randomized trial (n=148) showed no significant difference in diagnostic performance between core samples obtained using 22 G FNA with standard EUS or when guided by CH-EUS.(31) Even in a subgroup involving focal chronic pancreatitis masses (n-34), the sensitivity of CH-EUS-FNA was not significantly better (82.8% vs. 75.8%, p=0.47) (31) In contrast, another prospective study involving 93 patients showed that CE-EUS improved FNA outcomes compared with conventional EUS-FNA.(32) But, the first pass rates of adequate sampling and sensitivity in the standard arm was also low (CE-EUS vs. EUS: 84.9% vs. 68.8%, P = 0.003 and 76.5% vs. 58.8%, P = 0.01, respectively) which questions the actual superiority of CE-EUS. (33) Recently EUS- based convolutional neural network model was shown to accurately differentiate autoimmune pancreatitis from PDAC with 90% sensitivity, 93% specificity for distinguishing AIP from PDAC.(34) Future studies assessing artificial intelligence based imaging in distinguishing CP from PDAC are needed.

Development of serum biomarker that can predict asymptomatic PDAC in the setting of CP with high degree of sensitivity and which will further prompt early diagnostic imaging will be the key in making early detection of PDAC a reality.(12)

Pancreatic cysts

Nearly 15% of PDAC are thought to arise from mucin producing cysts [intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasm (MCN)], although population-based prevalence estimates are scant.(12) IPMNs with main duct involvement are associated with highest risk for malignancy (36–100%) and surgical resection is indicated at the time of diagnosis. (35–39) In contrast, malignant transformation of branched duct IPMN (BD-IPMN) is seen in 1–36% of surgical resections.(40) Currently, algorithms to identify advanced dysplasia and early invasive cancer in pancreatic cysts are suboptimal, and novel imaging techniques and biomarkers for detection of advanced neoplasia in pancreatic cysts are areas of active research.

EUS-guided needle-based confocal laser endomicroscopy (nCLE) offers real-time microscopic imaging of cyst epithelium providing optical biopsies with high resolution (1–3.5 μm). A single-center prospective study demonstrated superior diagnostic accuracy of EUS-nCLE when compared with current standard of care using cyst fluid CEA and/or cytology (71% vs. 97%) in differentiating mucinous from non-mucinous cysts and

incorporation of artificial intelligence may further augment diagnostic performance.(41,42) Future multicenter studies should compare this technology with EUS-guided microforceps biopsies, novel markers and also assess the learning curve required to reduce risk of pancreatitis and standardize interpretation of these images before it can be widely employed in clinical practice.

In recent years, pancreatic cyst fluid (PCF) molecular assays have emerged as an adjunct to conventional cytology and carcinoembryonic antigen (CEA) for the evaluation of pancreatic cysts. Next generation sequencing (NGS) is more sensitive for detection of *KRAS/GNAS* mutations when compared to Sanger sequencing (89% vs. 65%). (43) Further the combination of *KRAS/GNAS* mutations and alterations in *TP53/PIK3CA/PTEN* detected by NGS had an 89% sensitivity and 100% specificity for advanced neoplasia. (43) In addition to NGS- based PCF testing, there are several other genetic, epigenetic, proteomic and carbohydrate-based PCF biomarkers that are being currently tested for clinical application.(12) Aberrant DNA methylation is an epigenetic phenomenon which is thought to be a key driver in the neoplastic progression of PCLs.(44–46). A panel of two methylated DNA markers (TBX 15, BMP3) assayed in cyst fluid distinguished high grade dysplasia and cancer from low grade dysplasia and non-dysplastic cysts with sensitivity and specificity above 90% (47). Further the detection accuracy was significantly better for this panel than CEA, with AUC of 0.93 (95% CI:0.86–0.99) and 0.72 (0.60–0.84), respectively.(47) A novel murine monoclonal antibody, mAb Das-1 assayed in PCF when cross-validated in a large, pathologically verified multicenter cohort of patients identified high-risk PCLs with 88% sensitivity and 98% specificity. (48) Promising biomarkers based on variable carbohydrate alterations to mucins detected in PCF, telomerase activity and protease expression are all being studied. (12) Currently the National Cancer Institute Early Detection Research Network has embarked on a double-blinded pancreatic cyst biomarker study for rigorous validation.

CompCyst, a supervised machine learning algorithm incorporating selected clinical features, imaging characteristics, and cyst fluid genetic and biochemical markers was more accurate than conventional clinical and imaging criteria alone.(49) CompCyst decreased the number of unnecessary surgeries by 60–74%.(49) There is an urgent need for population-level data on prevalence of pancreatic cysts and prospective, multicenter studies that validate the diagnostic performance of cyst fluid biomarkers in pancreatic cysts with worrisome or high risk clinical and imaging features.(12)

Biomarkers for early detection of PDAC

There is rapidly growing justification in the literature to support liquid biopsy approaches for early detection of PDAC.(50,51) For PDAC, although several promising candidate biomarkers are in different phases of validation, no one blood-based biomarker has been clinically translated for early detection (Table 2). Carbohydrate antigen 19–9 (CA 19–9) is the most widely used blood-based tumor marker for PDAC. There are concerns regarding the limited sensitivity of CA 19–9 in early stage PDAC as a standalone test, false-negative results in PDAC patients with Lewis-negative genotype and suboptimal specificity in patients with benign inflammatory pancreatic diseases and biliary obstruction. Recent

studies indicate that the combination of CA 19–9 and novel protein and molecular markers may improve diagnostic accuracy compared to CA 19–9.(52–54) However, prospective validation in the intended use enriched high risk population is essential prior to clinical translation. Moreover, biomarkers that detect cancer often rely on tumor burden and diagnostic sensitivity fades rapidly in the pre-diagnostic phase.(55) The paucity of pre-diagnostic biospecimens collected serially over time in individuals eventually diagnosed with PDAC and linked to high quality clinical and imaging data is a major limitation in the field of biomarker development for early detection. Moreover, the specificity thresholds of any diagnostic test should be matched to the population in which the test is intended for use. Although a near perfect specificity is necessary for an early detection test applied to an asymptomatic, average-risk population, for clinical application in a defined at-risk population in whom the lifetime prevalence of disease is anticipated to be >5%, a slightly lower specificity may be considered.

PDAC precursors arise in the ductal epithelium; DNA exfoliated into pancreatic juice may be targeted for early detection especially in early stages. Digital next generation sequencing of pancreatic juice has demonstrated that elevated mutant *TP53/SMAD4* concentrations can distinguish PDAC from controls (AUC 0.82, 95% CI: 0.72–0.93) demonstrating potential diagnostic utility.(56) In a recent multicenter prospective study, a panel of methylated DNA markers (*C13orf18, FER1L4*, and *BMP3*) assayed in secretin-stimulated pancreatic juice achieved reasonable accuracy for distinguishing PDAC cases from controls (AUC 0.90, 95% CI: 0.83–0.97).(57) These early results support the need for future studies exploring pancreatic juice biomarkers for early detection of PDAC. Protein signatures of PDAC can also be detected in urine. In a recent study with a limited number of Stage 1 and 2A PDAC (n=27), a panel of urine protein biomarkers in combination with clinical risk scores and serum CA 19–9 detected early stage PDAC with reasonable accuracy.(58) Although these urinary biomarkers have not yet been tested in high-risk individuals specifically, early validation results in case-control studies appear promising and noninvasive collection makes urinary biomarkers an attractive option for early detection of PDAC.

The CPDPC Consortium: Advancing the field of Early Detection of Pancreatic Cancer

The formation and funding of the Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) consortium was a landmark event in the field of early detection of PDAC. The consortium has started to assemble a large prospective cohort of individuals at greater than average risk for PDAC with clinically annotated biospecimens and imaging data that can then be made available for validation of promising early detection biomarkers, with the aim to identify the best-in-class approach to early detection. One of the signature protocols for CPDPC aims to recruit 10,000 individuals with NOD defined using stringent glycemic criteria. In this cohort, the study team aims to estimate the probability of PDAC over a 3-year follow up period and establish a reference set of biospecimens that can be used for future nested case-control studies.

Conclusion

Early detection of pancreatic cancer has been established as a priority not only by the CPDPC but also several other international consortia with the eventual goal transforming pancreatic cancer care. As the paradigm of defining and enriching risk continues to be refined and is expected to identify the screening target population, parallel efforts for identifying novel risk factors to augment the at-risk cohort is essential. The eventual clinical translation of tools and strategies for reliable early detection of PDAC will continue to require multimodality team science to purposefully address the multiple areas of unmet need.

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Key Points

- PDAC likely to emerge as the second leading cause of cancer related mortality
- USPTF recommends against screening of PDAC in the general population
- Screening may be pursued in high-risk individuals defined by genetic and familial risk
- EUS and MRI are currently recommended modalities for surveillance
- There is an urgent need to develop serum or urine biomarkers for early detection of PDAC

Table 1:

Risk factors for pancreatic cancer

Genetic mutations	*BRCA1, BRCA 2, CDKN2A/p16, ATM, PALB2, MLH1, MSH2, MSH6, PMS2, APC, STK11*
Family history	Individuals with at least two affected blood relatives on the same side of the family, of whom at least one is an FDR to the individual
Hereditary cancer syndromes	Familial atypical multiple mole melanoma syndrome Peutz Jeghers syndrome Li Fraumeni syndrome Lynch syndrome Familial adenomatous polyposis
Other risk factors	Chronic pancreatitis Hereditary pancreatitis New-onset diabetes mellitus Obesity Smoking Alcohol

Table 2:

Biomarkers and approaches in development for the early detection of pancreatic cancer

Biological fluid-based biomarker approaches	Cyst fluid	Monoclonal antibody Das-1 [48] KRAS/GNAS/TP53/PIK3CA/PTEN gene mutation [43] Methylated *TBX15* and *BMP3* [47]
	Pancreatic juice	Methylated *C13orf18*, *FER1L4*, and *BMP3* [57]
	Blood	-CA 19–9 (in a multi-marker panel) [54] -Thrombospondin 2 (THBS2) [53] -CancerSEEK: A panel of proteins and mutations in cfDNA[59] -Plasma methylated DNA markers [52]
	Urine	Protein panel including LYVE-1, REG1A, and TFF1[60]
	Stool	Proteobacterial and Firmicutes microbial dominance in early stages of PDAC [61]
Other novel approaches	END-PAC model	Score derived in individuals with new-onset diabetes mellitus using change in body weight, change in blood glucose, and age at onset of diabetes [28]
	CompCyst	Supervised machine-learning model incorporating clinical and imaging features, cyst fluid genetic and biochemical markers [49]
	EUS-based artificial intelligence models	-Detecting advanced neoplasia in pancreatic cysts [42] -Differentiating PDAC from pancreatitis [34]