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Early Detection of Pancreatic Cancer: Opportunities and Challenges

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Abstract

The vast majority of patients with pancreatic ductal adenocarcinoma (PDAC) presents with symptomatic, surgically unresectable disease. While the goal of early detection of PDAC is laudable, and likely to result in significant improvement in overall survival, the relatively low prevalence of PDAC renders general population screening infeasible. The challenges of early detection include identification of at-risk individuals in the general population who would benefit from longitudinal surveillance programs, and appropriate biomarker and imaging-based modalities utilized for PDAC surveillance in such cohorts. In recent years, various subgroups at higher than average risk for PDAC have been identified, including those with familial risk due to germline mutations, a history of pancreatitis, patients with mucinous pancreatic cysts, and elderly patients with new onset diabetes (NOD). The last two categories will be discussed at length in terms of the opportunities and challenges they present for PDAC early detection. We also discuss current and emerging imaging modalities that are critical to identifying early, potentially curable, PDAC in high-risk cohorts on surveillance.

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Early detection of pancreatic cancer: Overview

The overwhelming majority of patients with pancreatic ductal adenocarcinoma (PDAC) present with locally advanced or distant metastatic disease (80–85%), and only a minority of patients are surgically resectable (15–20%) [1, 2]. In prior limited clinical series from the Far East, patients with incidentally discovered PDAC, especially those with sub-centimeter lesions, were documented to have prolonged survival rates [3–5]. More recent data from a national registry of patients on longitudinal surveillance for PDAC incidence due to familial risk also underscores the notion that earlier diagnosis correlates with improved survival, albeit not always "cure". As treatment options for patients with resectable cancers continue to improve, including availability of multimodality neoadjuvant therapy [6, 7], and more potent adjuvant regimens [8], a "stage shift" from the current 15% resectable proportion to 50% or greater will unequivocally lead to improved survival in this otherwise dismal disease [9]. How, then, do we enable successful early detection of PDAC beyond anecdotal case reports?

While the goal of early detection in PDAC remains laudable, it is worth noting that the United States Prevention and Screening Task Force (USPSTF) has rendered a grade of "D" for screening for PDAC in the general population, suggesting that not only is it not helpful, but there is potential for significant harm. This is due, in large part, to the relatively low incidence of PDAC in the average risk population (~12 per 100,000), which substantially reduces the pre-test possibility of a laboratory test being truly positive. Thus, even biomarker assays with exceptionally high specificity of 99% will result in ~990 individuals undergoing imaging studies, and the associated anxiety that comes with the likelihood of a highly lethal cancer, without actually harboring the disease. The potential for over-diagnosis and over-treatment remains significant enough that a "PSA" (prostate specific antigen – a commonly ordered screening test for prostate cancer) assay for PDAC is impractical. Another challenge in PDAC early detection, which we will not be covering in this review due to brevity, pertains to the current lack of availability of credentialed biomarkers with performance criteria required for adoption in an *asymptomatic* prospective population. Nearly all classes of biomarker assays published to date in PDAC (proteins, autoantibodies, circulating DNA, microRNAs, methylated DNA, exosomes; a limited number of citations is referenced here [10–14]) have been used in the context of *symptomatic* disease, i.e., in a "diagnostic biomarker" context, with scant data in the setting of longitudinal surveillance in asymptomatic individuals ("surveillance biomarkers").

To avoid the perils of over-diagnosis and focus early detection efforts on individuals deemed to be at higher than average risk, we need to first define who those subsets of individuals are and quantify the degree of elevated risk. Once that has been determined, the next step is to determine when and how often to conduct surveillance in the at-risk individuals, and the modalities (biomarkers and imaging) that will be used in the surveillance *versus* diagnostic settings, respectively. In the context of PDAC, we are still early in deciphering this multistep paradigm, but unequivocal progress has been made, at least in the context of defining high-risk cohorts primed for surveillance. In a separate review of this special issue, Wood et al discuss one of the aforementioned high-risk groups, individuals with a familial (inherited) PDAC risk. In this article, we will focus our discussion on three remaining at-risk cohorts, patients with a history of pancreatitis, patients with mucinous cysts of the pancreas and

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elderly patients with new-onset diabetes (NOD) and highlight both the opportunities for leveraging these subsets as a means to achieve early detection and the pitfalls that exist today to actualize that vision. We will also discuss the current and emerging imaging modalities that are at the disposal of clinicians for localizing early primaries in individuals that are on surveillance in both cystic and non-cystic settings. Finally, we culminate this review with our vision for the future of early detection for PDAC, with an eye towards altering the trajectory of the usually lethal natural history of this cancer.

Pancreatitis associated risk factor for pancreatic cancer

There is emerging evidence that supports long-standing chronic pancreatitis as a strong risk factor for PDAC. The lag period between diagnosis of chronic pancreatitis and PDAC is usually one or two decades[15]. A recent meta-analysis of 13 studies showed that excluding cancer occurring in the first 2 years following a diagnosis of chronic pancreatitis, the lifetime risk of PDAC was elevated 16-fold[16]. Although there is a strong link between chronic pancreatitis and PDAC, < 5% of patients with chronic pancreatitis develop PDAC and it is a rare cause of PDAC[17]. Pancreatitis appearing a year or two before the diagnosis of PDAC is often the result of tumor-related ductal obstruction. Therefore, acute pancreatitis is considered to be a clinical manifestation of PDAC. However, the yield of PDAC after an episode of acute pancreatitis is ~1%, highest being in the first 2 years[16, 18]. Conversely, only a small fraction of PDAC patients (~5%) present with acute pancreatitis at the time of cancer diagnosis[18]. Since only a small proportion of pancreatitis, both acute and chronic, have or develop sporadic PDAC, using them as a potential high–risk screening groups for early detection of PDAC will require enrichment strategies to identify the subset with very high-risk.

Cystic precursor lesions of pancreatic cancer and the route to early detection: Overview

While a distinct minority, up to 15% of PDAC are thought to arise from mucinous pancreatic cysts that include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Most mucinous pancreatic cysts are IPMNs and can be broadly categorized based on location and extent of involvement within the pancreas as main-duct (MD-IPMN), branch-duct (BD-IPMN) and mixed type (MT-IPMN) [19]. MD-IPMNs account for 15–21% of IPMNs, often located within the pancreatic head and characterized by a segmental or diffuse dilatation of the main pancreatic duct (MPD) of >5 mm in diameter for which other causes of ductal obstruction have been excluded [20]. In comparison, BD-IPMNs comprise 41–64% of IPMNs, occur throughout the pancreas with a preference for the uncinate process and are frequently multifocal. BD-IPMNs are typically described as a unilocular or grape-like/multilobulated arrangement that communicates with the MPD. MT-IPMNs meet both criteria for MD-IPMN and BD-IPMN and consist of 22–38% of IPMNs.

Not surprisingly, the incidence of PDAC with an IPMN can vary based on subtype. PDAC is reported in 11–80% of MD-IPMNs and 20–65% of MT-IPMNs [21, 22]. Considering the high incidence of malignancy, patients with a MD-IPMN or MT-IPMN are often recommended to undergo surgical resection. However, malignant transformation of BD-IPMN is documented

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in 1–36% of surgical resections [20]. Moreover, as these statistics are based on surgical series, the malignant potential of a BD-IPMN may be overestimated. Further, on the basis of preoperative clinical, radiographic and pathologic findings, the distinction between a BD-IPMN and other pancreatic cysts is not trivial. Benign neoplastic and non-neoplastic cysts, such as serous cystadenomas and lymphoepithelial cysts, can preoperatively mimic BD-IPMNs.[23, 24] Consequently, key areas for early detection efforts have been the accurate diagnosis of BD-IPMNs and the identification of high-grade dysplasia and/or microscopic PDAC arising from BD-IPMNs. It is also important to note that patients with an IPMN are at an increased risk for not only developing IPMN-associated PDAC, but also PDAC independent from the IPMN ("concomitant carcinomas"). The reported incidence of concomitant carcinomas in IPMN patients ranges between 2%−11.2% [20]. Hence, the detection of a concomitant carcinoma is also an important focus for early detection strategies.

Epidemiologic risk factors for cystic precursor lesions

There are several risk factors for developing an IPMN and an IPMN-associated PDAC. With increasing use and advancements in radiographic imaging (*see later*), the presence of a pancreatic cyst is reported in 3% of computed tomography (CT) scans and 20% of magnetic resonance imaging (MRI) scans [25, 26]. This prevalence increases with age and up to 40% of patients over the age of 80 years are found to have a pancreatic cyst [27]. As approximately half of all pancreatic cysts are BD-IPMNs, advanced age is a well-recognized risk factor for both BD-IPMNs and BD-IPMN-associated PDAC [28]. In addition to non-IPMN associated PDAC, a causative link between diabetes and IPMNs has been described. Among BD-IPMN patients, 10–45% have a history of diabetes and, in the setting of diabetes, the incidence of detecting a BD-IPMN is higher [29–37]. Capurso et al identified a strong association between insulin use and the risk of an IPMN [38]. Moreover, diabetes is associated with a higher incidence of PDAC in resected IPMNs [39]. New-onset or worsening diabetes is also a significant predictor of the presence of a concomitant carcinoma [40]. However, NOD was not associated with an increased incidence of an IPMN in the absence of cancer and suggests that BD-IPMNs do not produce the same diabetogenic substances as PDAC (*see later*). Further, patients with chronic pancreatitis are at an increased risk of developing a BD-IPMN and BD-IPMN-associated PDAC [35, 38]. Interestingly, BD-IPMNs can often mimic retention cysts as seen in the background of chronic pancreatitis.[41] Conversely, chronic pancreatitis may be the consequence of longstanding occlusion of the pancreatic duct due to the mucin produced within an BD-IPMN itself.

Certain genetic syndromes and a family history of PDAC may also pose a risk (*see review by Wood et al in this issue*). IPMNs have been reported in patients with Peutz-Jeghers syndrome, McCune-Albright syndrome and in patients with familial adenomatous polyposis [42–45]. Some studies have suggested that BD-IPMNs and BD-IPMN-associated cancers may be particularly common among patients with a history of a first-degree family member with PDAC [38]. It is however unknown whether patients with a positive family history have a more rapid progression of developing an IPMN or associated PDAC.

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Diagnostic methods of evaluating BD-IPMN patients

In most cases, BD-IPMNs are discovered incidentally on routine imaging and patients are often asymptomatic at clinical presentation. Some patients may present with abdominal discomfort, abdominal pain, malaise and nausea; however, these symptoms are typically not attributable to the IPMN even if they were the initial indication for abdominal imaging [28]. Other symptoms that include back pain, weight loss, NOD, and obstructive jaundice are more often associated with malignant transformation of an IPMN, but once again are not entirely specific [29–32, 34, 35, 37, 46–52].

Considering the lack of symptoms in the majority of patients, conventional imaging modalities play a crucial role in the identification of IPMNs and IPMN-associated PDAC, as well as the detection of a concomitant carcinoma. Here we will discuss the performance of imaging modalities used in the context of cystic lesions; please see later for choice of imaging in the context of solid lesions (non-cystic PDAC).

Owing to the wide availability and rapidity of acquisition, CT is an ideal imaging method for the initial evaluation of a BD-IPMN with an accuracy of 56–85% [53]. The detection of calcifications within a pancreatic cyst and surrounding pancreatic parenchyma can aid in differentiating a BD-IPMN from its mimics [54–56]. MRI/magnetic resonance cholangiopancreatography (MRCP) is however considered by many as the standard modality for diagnosing a BD-IPMN with a sensitivity of up to 88% [53, 57–60]. MRI/MRCP is superior to CT in its ability to identify MPD connectivity and features of malignancy. Further, complementing MRCP with secretin stimulation can elucidate pancreatic ductal anatomy [53]. The lack of ionizing radiation makes MRI an ideal tool for frequent follow-up exams, especially in younger patients. But, the drawbacks of MRI include poor spatial resolution, low sensitivity for calcifications and susceptibility to motion-related artifacts [61].

Despite the quality of contemporary cross-sectional imaging, the accuracy of CT and MRI remain imperfect. Endoscopic ultrasound (EUS) has a higher resolution than cross-sectional imaging methods and can be useful for cases where a diagnosis of a BD-IPMN is uncertain, a BD-IPMN has worrisome features by CT/MRI, verification of malignancy in high-risk individuals and the identification of concomitant carcinomas [62, 63]. EUS excels in evaluating for imaging features often associated with malignancy, such as thick internal septations, mural nodularity, solid masses, MPD dilatation, filling defects in the MPD and vascular invasion [64, 65]. These features alone are however poor predictors of malignant transformation with an accuracy that ranges between 40–90% [66–68]. The true utility of EUS is enhanced when coupled with fine-needle aspiration (FNA) of *pancreatic cyst fluid* that can be used for biochemical, cytological and DNA analyses.

Pancreatic cyst fluid diagnostics for early detection of progression

Pancreatic cyst fluid (PCF) from BD-IPMNs is generally thick and highly viscous. The “string sign” method is a rapid assay to evaluate fluid viscosity and is performed by placing a drop of fluid between two fingers and separating them [69]. A positive “string sign” has up to 95% specificity for a mucinous pancreatic cyst [70]. Similarly, high concentrations of CEA (>192 ng/mL) within PCF are reflective of a mucinous pancreatic cyst and associated with a

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57–79% sensitivity [64, 71–74]. However, in certain circumstances, sufficient PCF may not be available for CEA testing. Regardless, both methods do not reliably differentiate BD-IPMNs from MCNs or the presence versus absence of PDAC. Cytological examination is a highly accurate test for the detection of malignancy with a specificity that approaches 100%, but this technique is hampered by the low cellularity of PCF and, therefore, the sensitivity of cytopathology varies widely from 25–88% [67, 75, 76]. The

Recently, next-generation sequencing (NGS) has emerged as an adjunct to the evaluation of PCF [71, 77–80]. Although cellular content and fluid volume of PCF can be suboptimal for routine ancillary studies, such as CEA and cytological examination, DNA from lysed or exfoliated cyst epithelium shed into the PCF can be analyzed for genomic alterations. NGS studies have identified distinct mutational profiles for the major pancreatic cysts and those that have progressed to PDAC [81–84]. The detection of *KRAS* mutations in PCF by NGS is associated with 76–89% sensitivity and 96–100% specificity for BD-IPMNs and MCNs [71, 78–80]. *GNAS* mutations are also found in 30–45% of BD-IPMNs, but highly specific for IPMNs, and have not been reported in MCNs [71, 78, 79]. Additionally, IPMN-associated cancers are reported to harbor mutations in *TP53*, *SMAD4*, *PIK3CA*, *PTEN* and/or *AKT1* with sensitivities and specificities of 32–79% and 96–100%, respectively [71, 85–90]. Of note, the high costs associated with NGS have impeded its widespread clinical application to PCF. However, with increasing availability of NGS, decreasing prices in reagents and the ability to batch specimens, the current cost of NGS-based PCF testing is one-third of the cost for an MRI/MRCP scan [91].

In addition to NGS-based PCF testing, there are several other genetic, epigenetic, proteomic and carbohydrate-based PCF biomarkers that are currently being validated for clinical use. For example, mucins or MUCs are a 21-member family of heavily glycosylated, high-molecular-weight glycoproteins and play a variety of roles in oncogenesis. Normal pancreatic ductal epithelium expresses low levels of mucins, such as MUC1; however, correlative histopathologic studies show that there is neo-expression and upregulation of mucins in BD-IPMNs, such as MUC2, MUC4 and MUC5AC, and more pronounced changes in expression in PDAC, such as MUC3, MUC4, MUC5AC, MUC5B, MUC6, MUC7, MUC13, MUC16 and MUC17.[92–95] Moreover, carbohydrate alterations to mucins detected in PCF have demonstrated high sensitivity and high specificity in differentiating mucinous from non-mucinous pancreatic cysts, and early detection of IPMN-associated PDACs.[96, 97] In fact, MUC4 and MUC16 are reported to be 100% specific for PDAC, while associated with sensitivities of 63% and 67%, respectively.[98] Promising biomarker results using PCF have also been reported for differentially methylated DNA, telomerase activity, protease expression and the overexpression of Das-1.[99–102] However, the majority of these biomarkers have not been rigorous validated within a diverse cohort of pancreatic cysts. Hence, the goal of the Pancreatic Cyst Biomarker Validation Study, an ongoing double blinded PCF biomarker study that is sponsored by the National Cancer Institute (NCI) Early Detection Research Network.[103]

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Current guidelines for surveillance and management of patients with pancreatic cysts: a murky road

In the absence of a perfect assay to detect BD-IPMNs and BD-IPMN-associated PDAC, the evaluation of pancreatic cysts necessitates a multidisciplinary approach that includes clinical presentation, radiographic/endoscopic ultrasound imaging and PCF analysis. The inability to predict the malignant transformation of a BD-IPMN within the patient's lifetime requires appropriate surveillance that accounts for epidemiologic risk factors, as well as other clinical, imaging and PCF findings. Moreover, as surgical intervention remains the preferred treatment option for mucinous pancreatic cysts, the operative mortality (2–4%) and morbidity (40–50%) of these procedures must be considered.[104–107] Consequently, consensus and evidence-based guidelines for pancreatic cysts and, specifically, BD-IPMNs have been developed by several medical societies, namely the International Association of Pancreatology (Fukuoka), American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), American College of Radiology (ACR) and European Study Group on Cystic Tumours of the Pancreas (ESGCTP) [22, 108–111].

While the surveillance strategy for BD-IPMNs will differ between these guidelines, they all agree that the risk of malignancy should be weighed against life expectancy and comorbidities. In addition, according to all guidelines, the presence of a mural nodule is the most predictive of malignant disease. Mural nodes are present in 36–70% of IPMN-associated cancers [31, 35, 49, 112]. Further, a thickened cyst wall is present in 65% of cases with malignancy [31, 113]. Studies have demonstrated a direct relationship between BD-IPMN size and the risk of malignancy; but BD-IPMN-associated cancers can occur in small cysts and larger cysts do not always harbor pancreatic cancer [34, 48, 114–116]. In the absence of a more practical approach, the Fukuoka and ACG guidelines advocate for varying time intervals for surveillance based on BD-IPMN size. The growth of the BD-IPMN should also be considered as growth of >2mm/year is associated with a 45% 5-year risk of developing malignancy as compared to 1.8% in slower growing BD-IPMNs [117–119]. However, it is important to note that BD-IPMN size can be discordant based on different imaging modalities and, therefore, the same imaging modality should be used for size comparison between follow-up intervals. The mean diameter of the MPD is also an important factor associated with malignancy [109, 111, 113, 120]. The Fukuoka and ESGCTP guidelines use a MPD diameter of 10 mm as an absolute indication for surgery. The AGA and ACG guidelines recommend an EUS-FNA for BD-IPMNs associated with MPD dilatation.

According to the Fukuoka, ACG and ESGCTP guidelines, surveillance for a BD-IPMN should be lifelong, but the AGA recommends ending surveillance after 5 years if there is no change in cyst size or other findings. Interestingly, the ACR advocates a 9- to 10-year follow-up, terminating at the age of 80 years. Kromrey et al found no incidence of pancreatic cancer during a 5-year follow-up study of 676 patients with pancreatic cysts [121]. Similarly, Moris et al identified no cases of malignancy among 112 BD-IPMNs with more than 5 years of follow-up [37]. In contrast, Del Chiaro et al reported an IPMN-related mortality of 5.8% after a 10-year follow-up period in patients without high-risk features at baseline [122].

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Upon resection of an BD-IPMN, the Fukuoka, ACG and ESGCTP guidelines recommend lifelong surveillance as long as the patient is a surgical candidate. However, surveillance according to the AGA guidelines is only recommended for patients with IPMNs harboring at least high-grade dysplasia. After resection of a benign BD-IPMN, He et al estimated the chances of developing a new IPMN at 1, 5 and 10 years after initial surgery were 4%, 25% and 62%, respectively, and requiring surgery due to high risk features were 1.6%, 14% and 18%, respectively [123]. The authors further found the chances of developing a new IPMN-associated PDAC or a concomitant carcinoma were 0%, 7% and 38% at 1, 5 and 10 years, respectively. Interestingly, the risk of a concomitant carcinoma continues after surgical resection of a BD-IPMN. Miyasaka et al found concomitant carcinomas among 4% of patients, who underwent pancreatectomy for a BD-IPMN [124]. There is however little consensus or evidence as to how to reliably survey and detect concomitant carcinomas.

Despite the development of guidelines for the management of BD-IPMNs, it is still challenging to determine which BD-IPMNs harbor PDAC, and, even more difficult, to determine which BD-IPMNs will undergo malignant transformation within the patient's lifetime.[91, 125] In addition, the quality of evidence on which these recommendations are based is admittingly poor. The aforementioned management algorithms do not address every possible clinical scenario, and, consequently, it is imperative to tailor surveillance and treatment to the individual patient. Thus, there is an urgent need for prospective, multicenter clinical trials that integrate epidemiologic risk factors, clinical presentation, radiographic findings and PCF analysis to provide evidence to guide future management decisions.

New onset diabetes (NOD) as an early detection "sieve" for PDAC surveillance: Overview

Though the association between diabetes mellitus (DM) and pancreatic ductal adenocarcinoma (PDAC) has been known since the 1800s [126], the intricate and multidirectional relationship between the two diseases is yet to be fully understood [127]. While long-standing type 2 DM is a modest risk factor (1.5 to 2-fold increased risk) for PDAC, new-onset DM (NOD) is a manifestation and harbinger of PDAC [127]. Increasing epidemiological, clinical and experimental evidence that NOD is a clinical manifestation of asymptomatic PDAC provides the promise for early detection of PDAC using DM.

Epidemiology of DM in PDAC

Prevalence of DM in PDAC ranges from 4% to 65%, depending on the ascertainment method of DM status [128–130]. Studies relying on medical records report a prevalence of 4–20% [128], while studies screening patients using oral glucose tolerance test have a prevalence of 45–65% [129, 130]. In prior studies using fasting blood glucose (FBG) levels, DM was present in nearly half the patients with PDAC at diagnosis [131]. These findings were confirmed in a population-based cohort of PDAC from Olmsted County, MN in whom FBG were used levels to define the glycemic status of all PDAC patients (Figure 2). In this study it was noted that 42% met the American Diabetes Association criteria for DM (of which 52% were NOD), 13% have advanced pre-DM (defined as FBG≥120mg/dl), 21% have impaired FBG and only 9% had a normal FBG level at PDAC diagnosis. The fact that ~85%

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of subjects have elevated FBG and ~50% have DM at PDAC diagnosis highlights that glucose hemostasis disturbance is a near universal phenomenon in PDAC [131].

Burden of diabesity on increasing incidence of PDAC

Modifiable risk factors associated with PDAC include DM and obesity, disorders that are secondary to chronic caloric excess. There is strong evidence that obesity is associated with increased risk for PDAC and the anticipated increase in incidence of PDAC could partly be attributed to the obesity endemic[132]. Meta-analysis of prospective cohorts concludes that there is a positive association between body mass index (BMI) and PDAC risk, such that an overall a 5 kg/m^2 increase in BMI is associated with a 12% increased risk for PDAC[133]. Recently, a study confirmed this association in a large cohort of obese adolescents followed for a median of 23-years, reporting a 4-fold increase risk of PDAC in adulthood[134]. While some epidemiologic studies have been confounded by DM contributing to the causal pathway between obesity and PDAC, larger studies indicate that obesity confers a significant cancer risk independent of the presence of diabetes[135]. The risk of PDAC in obesity is modestly elevated (1.12-fold increased risk/5 kg/m^2 compared to normal BMI) and the cohort of obese subject's needs enrichment to be a valid target for early detection[133].

Time course of hyperglycemia in pre-diagnostic PDAC

In a recent study FBG levels were plotted in PDAC and matched controls up to 60 months prior to PDAC diagnosis and corresponding index date in controls [136]. FBG levels were similar in cases and controls from −60 to −36 months. Starting 30–36 months before diagnosis glucose levels in PDAC progressively rose until diagnosis, crossing the DM threshold of 126 mg/dl around 6–12 months before diagnosis. Using clinic-based resected PDAC subjects, the same study also showed FBG levels correlates with PDAC tumor volume and FBG levels start rising when tumors are 1–2 cc in volume, crossing the DM threshold around 12cc [136]. All these findings strongly suggest hyperglycemia is as biomarker of early invasive PDAC, with mostly being new-onset starting 36 months prior to cancer diagnosis.

Pancreatic cancer impairs glucose homeostasis:

PDAC is diabetogenic.—In fact, it is one of the strongest and most consistent diabetogenic forces known to humans. It destabilizes glucose homeostasis in nearly all subjects in whom it occurs, making it one of the most prevalent phenotypic traits of PDAC.

A) Clinical Evidence: New-onset DM or worsening of long-standing DM occurs in majority of PDAC patients and proceeds by several months to few years [136–139]. Further, the rise in blood glucose in PDAC occurs well before visible appearance of tumor in the pancreas, suggesting that DM in PDAC cannot be attributed merely to destruction of the gland by the tumor [3, 140]. In addition, PDAC has been shown to cause insulin resistance and beta cell dysfunction, which resolve with tumor resection and glycemic status paradoxically improves despite removal of a third of the pancreas [131, 136, 141].

B) Laboratory evidence: PDAC cell line supernatants have long been known to be metabolically active. They cause beta cell dysfunction in human islets, rat islets and isolated

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beta cells by producing soluble factors that impair glucose metabolism in vitro and cause hyperglycemia in vivo [127, 142, 143]. They also induce insulin resistance in cultured hepatocytes and myoblasts [144, 145]. PDAC-derived exosomes cause paraneoplastic dysfunction of human beta-cells and inhibit insulin secretion thereby causing hyperglycemia[146]. In an accompanying editorial, Dr. Murray Korc called PDAC-induced DM an *exosomopathy* (a disease of exosomes) [147].

C) Animal models: There are to date no animal models of PDAC-induced DM. From published observation on KPC mice, it does not appear that they develop insulin resistance or hyperglycemia. Though a common phenomenon in humans, its lack of occurrence in animal models has hindered progress, with the entity being largely ignored. However, understanding why animal models do not develop DM and how that impacts the biology of the tumor needs further study.

Strategies for early detection of PDAC in the context of NOD

Since PDAC patients seldom exhibit disease-specific symptoms until late in the course of the disease [148], it is important to identify and develop strategies for early detection of asymptomatic PDAC. As previously stated, screening for sporadic PDAC in the "average risk" general population has been considered unrealistic because of its low incidence. In view of this, a **DEF** (*Define, Enrich, Find*) paradigm has been proposed that allows PDAC *surveillance* (*versus* screening) in a subset of higher risk asymptomatic patients where it might be most beneficial, of which NOD is currently the most promising in the elderly (≥50 years) population [149].

(i) Define: The first step towards surveillance for asymptomatic, early PDAC is to define a patient population with a higher than average risk of PDAC. In a population-based study from Olmsted County, MN of 2,152 new-onset DM subjects (glycemically defined) over age 50 years, 18 (0.85%) developed PDAC within 3 years of DM onset, having a 6–8-fold higher risk for PDAC compared to general population [150]. In a subsequent confirmatory study from another time period 0.90% of 1096 NOD subjects developed PDAC within 3 years of onset of NOD [151]. These observations have not yet been confirmed outside Olmsted County using glycemic criteria for NOD. Based on these estimates, a national consortium has been set up with support of NIH/NIDDK to validate and establish NOD as a high-risk group for PDAC (*see later*) [152]. It may be justifiably debated, however, that even with a 6–8-fold higher risk for PDAC, NOD *per se* does not have a high enough incidence to justify direct surveillance with imaging techniques, and therefore the need for enrichment strategies within the NOD subset.

(ii) Enrich: The second step is to enrich the NOD population further, and one could use clinical risk prediction models or biomarkers. So far, 2 clinical models have been published that enrich the NOD population. The Health Improvement Network (THIN) database UK model included 109,385 NOD subjects identified by physician diagnosis of DM and the final prediction model was based on demographic, behavioral, and clinical variables with predicted risk threshold of 44.7% sensitivity, 94% specificity, and a positive predictive value of 2.6% [153]. The other clinical model called Enriching New-onset Diabetes for Pancreatic

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Cancer (ENDPAC) score uses glycemic definition of NOD and includes 3 parameters; age, change in blood glucose and delta weight loss [151]. The ENDPDAC model risk stratifies the NOD subjects into 3 groups based on 3-year PDAC risk: low (<0.1%), intermediate (~0.5%) and very high (~4%) with the very-high risk score cutoff having a sensitivity and specificity of 80%. While, development of these clinical models shows encouraging preliminary results in differentiating type 2-NOD from PDAC-NOD, further validation is needed before being applied in clinical practice. At present, there are no reliable biomarkers that identify early PDAC or that differentiate between "usual" Type 2 NOD and PDAC-associated NOD in asymptomatic patients.

(iii) Find: The third step is to find a lesion in asymptomatic PDAC-NOD patient either using non-invasive imaging modalities (e.g. pancreas protocol CT) or invasive imaging (e.g. EUS). Prior pre-diagnostic imaging studies based on low quality scans suggest that PDAC is resectable as little as 6 months before clinical diagnosis when it is still asymptomatic, and that DM occurs at a resectable stage of disease [140]. We further discuss the role of imaging modalities in diagnosis of early PDAC in the next section.

Current studies

The NCI and the NIDDK initiated the Consortium for the study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) in 2015 with one of the key objectives being to establish an early detection approach for sporadic PDAC using NOD [152]. The aim is to assemble a cohort of 10,000 subjects with NOD ≥50 years to estimate the 3-year probability of PDAC in NOD, establish a bio-bank of specimens from pre-symptomatic PDAC subjects, conduct Phase 3 validation studies of promising biomarkers for identification of incident PDAC in NOD patients and develop future interventional screening protocols for early detection of PDAC. It is expected that 85–100 incidences of PDAC will be diagnosed during the study period in this cohort of 10,000 patients, based on the prevalence first described by Chari and colleagues [150].

Imaging strategies relevant to PDAC early detection: Overview

Traditionally, the clinical indications for diagnostic imaging for PDAC include detection of the primary tumor, determination of resectability, evaluation for distant metastasis, and measurement of treatment response [154]. In the context of early detection, imaging-based approaches can be grouped into traditional and non-traditional applications. Each imaging methodology has advantages and disadvantages that will be reviewed here; further, the practical implementation of imaging technologies will be discussed, with particular emphasis on areas of unmet need.

Traditional imaging techniques for pancreatic cancer detection

Over the past two decades, multiple studies have evaluated the accuracy of EUS, CT and MRI to detect a primary tumor in the pancreas, including in the context of early detection in high-risk cohorts. As noted, the following discussion is principally focused on non-cystic PDAC, with the role of imaging in cystic lesions having been discussed previously.

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(i) Endoscopic ultrasound (EUS)—EUS is considered the most sensitive method to detect early neoplasia in the pancreas. Indeed, a direct comparison of imaging modalities in the modern era showed that EUS identified pancreatic abnormalities in individuals considered to be high risk for developing PDAC 43% of the time, compared to 33% and 11% for MRI and CT, respectively [155]. A meta-analysis of 20 studies showed that the performance of EUS for PDAC varied by disease T stage. EUS had sensitivity and specificity of 72% and 90% for T1–2 cancers, respectively. For T3–4 tumors, EUS had 90% sensitivity and 72% specificity [156]. This modality can detect lesions as small as 2–3 mm in the pancreas [157], which is generally the resolution of CT and MRI. Even though EUS has excellent performance with visualizing and diagnosing PDAC, it is mainly used as part of the workup to obtain fine needle aspiration or biopsy material in patients suspected of having a primary tumor. The reason is that EUS is not a readily accessible imaging modality and is highly dependent on the skill of the operator. For these reasons, EUS is considered a complementary modality to the pancreatic protocol CT in current clinical practice, and the CT is considered the gold standard.

Emerging areas for EUS include the incorporation of elastography in the characterization of lesions, as well as the use of microbubbles for contrast. Elastography has been reported to show significantly lower values of elasticity for PDAC compared to normal pancreas (0.02% [95% CI, 0.01–0.02] vs 0.53% [95% CI, 0.45–0.61]) [158]. The incorporation of elastography in the evaluation of solid pancreatic lesions has resulted in sensitivities ranging from 75.9 to 100%, and specificities of 16.7 to 96.3% [159]. Microbubbles are another tool that can be used in conjunction with EUS to characterize pancreatic cancer. One readout of the test is the degree of vascularity of the tumor, which has been associated with the differentiation of the tumors on histology [160]. A pooled analysis of transabdominal ultrasound and EUS approaches with contrast enhancement showed a sensitivity of 89% and specificity of 84% [161]. Further incorporation of advanced imaging techniques with EUS in ongoing early detection protocols may be expected to improve yield of this diagnostic test, but operator dependencies remain a challenge for this modality.

(ii) Multi-detector CT—Multi-detector CT with contrast using thin axial sections with dual-phase pancreatic protocol acquisition represents the most ubiquitous and robust method to visualize the pancreas, as its operating characteristics allow for rapid imaging with good spatial and temporal resolution [154]. In general, CT has a sensitivity of 76–92% for diagnosing PDAC [162–164] and a specificity of 67% [162].

The performance of CT largely depends on the ability to administer intravenous contrast (usually at a rate of 3–5 ml/sec) and on the acquisition of the imaging at specific times relative to contrast injection. The consensus opinion [165] is that a pancreatic protocol CT scan should be done for evaluation of a suspected PDAC or when a routine CT scan was not of sufficient quality for accurate initial staging. During a pancreatic protocol CT, the arterial phase (~30 s post contrast injection) and portal-venous phase (~60–70 s post contrast injection) highlight different anatomical features of the pancreas and liver to enable visualization of primary and secondary tumors [166]. The difference in physical attributes between pancreatic tumors and the pancreatic parenchyma often results in seeing the classic hypodense mass in the pancreas, which is due to the dense desmoplasia and relative

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hypovascularity of PDAC [167]; however, there are iso-attenuating PDAC that may make detection and diagnosis more difficult. These iso-attenuating tumors with indistinct borders appear to have higher degree of stromal infiltrate and less aggressive biology compared to hypodense tumors with well-defined borders [168–170].

Recent advancements in CT technology have led to the implementation of the use of dual energy scans [171], which can simultaneously image the patient with two energies of x-rays (for example, 80 and 140 kVp). These different energies provide radiologists a wider range of images to view, and post-processing packages from vendors enable generation of images that show relative amounts of two or more materials that would be needed to obtain the imaging signal for each given voxel [172]. For example, iodine/water maps have been demonstrated to result in an improvement in the conspicuity of pancreatic tumors [173]. This raises the possibility that this imaging method [171, 173–177] may help increase the detection of small pancreatic tumors. Further prospective evaluation of dual energy CT in appropriate populations may be warranted.

(iii) MRI—Pancreas protocol MRI with contrast is another cross-sectional imaging modality that can be helpful in staging patients at initial presentation. Its advantages include that it does not rely on ionizing radiation for image acquisition and has better soft tissue resolution than CT. Disadvantages include the lack of standardization in the algorithms and parameters used to acquire advanced functional imaging sequences (e.g., diffusion weighted imaging [DWI], dynamic contrast enhancement [DCE]), susceptibility of the image quality to internal and external patient motion, cost relative to CT, and claustrophobia that some patients experience inside the machine. Further, a pancreatic protocol MRI with contrast is the preferred imaging alternative to a pancreatic protocol CT if a patient has an iodine contrast allergy. As mentioned above, MRI was reported to have better ability to detect pancreatic lesions than CT in a recent comparison study [155]. Further, a screening protocol in Sweden for patients with a genetic risk of developing pancreatic cancer showed that MRI was able to detect pancreatic lesions in 16 of 40 patients enrolled in the prospective study [178].

Non-traditional uses and techniques for imaging of pancreatic cancer

(i) Secondary signs of pancreatic cancer—Recent work indicates that cross sectional imaging may identify secondary changes in the body that indicate an incipient PDAC due to its systemic effects. It has been well recognized that anorexia, sarcopenia, and weight loss are hallmarks of PDAC [179–181]. In patients with localized PDAC, sarcopenia has been associated with survival outcomes and complications following surgery [182–184]. During neoadjuvant therapy, the ability of the patient to gain lean tissue has been associated with a higher likelihood of resection [185]. For example, these associations have recently been translated to patients with NOD (*see above*). Specifically, a change in weight was one of three factors that was developed and validated as a risk model in this population [186]. Moreover, peripheral tissue wasting was found to be a common finding on pretreatment CT scans of patients with PDAC, and exocrine insufficiency was evaluated as a contributing factor [187]. Although sarcopenia was not associated with patient survival in this study, the authors proposed that assessing peripheral tissue loss before overt disease presents may help

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identify PDAC at earlier stages. In particular, routine cross-sectional imaging may be used to measure adipose and muscle mass using validated methods [188, 189] in high-risk populations to identify early disease. These secondary signs of PDAC represent another method by which imaging may play an important role in early detection. Ongoing prospective studies in high-risk cohorts can easily integrate this assessment to potentially establish a role for anthropometric changes in the body as a method of cancer risk stratification.

(ii) Molecular imaging—The role of positron emission tomography (PET) imaging has been limited for PDAC, owing to the susceptibility of F^{18} fluorodeoxyglucose (FDG)-PET to both false positives (e.g., benign causes of inflammation like pancreatitis) and false negatives (e.g., non-FDG avid tumors). Several groups have investigated novel imaging agents that are coupled to ^{18}F. These remain in early stages of development, including investigations of lactose analogues and the hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP) [190]. Other strategies to detect pancreatic cancer with molecular imaging agents include targeting proteins that are overexpressed by the cancer (e.g., mesothelin), signaling pathways (e.g., epidermal growth factor receptor), tumor stroma (e.g., hedgehog signaling, vascular endothelial growth factor), and other targets that are associated with the disease (e.g., Plectin-1, MUC1) [191]. Another molecular imaging method that is of interest for early detection is hyperpolarized MRI, which can identify metabolic aberrations in the pancreas that indicate preneoplasia [192]. Further evaluation of these agents and techniques in preclinical models is warranted. Upon proper validation, translation in high-risk cohorts with pathological correlation will help bring these techniques to the forefront of early detection efforts.

Early detection of pancreatic cancer: The road ahead

In summary, we have discussed many of the opportunities in PDAC early detection that have emerged in the last decade, such as the identification of well-defined high-risk cohorts (e.g., familial kindred [*discussed separately*], patients with precursor cystic lesions, and those with NOD), and the improvements in imaging modalities available to clinicians. Nonetheless, vast challenges remain in terms of generalization of the lessons learned in early detection of PDAC, including (a) appropriately validated blood-based biomarkers that are poised for large-scale implementation in high-risk cohorts for diagnosing asymptomatic disease, (b) the choice of the best imaging modality for surveillance within the multitude of options discussed above, as well as (c) when and how often these imaging platforms should be used in the aforementioned cohorts for surveillance. For example, in the case of detecting circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), while both assays are reported to be highly specific as compared to an elevated serum CA19–9, they currently cannot be used for PDAC screening or early diagnosis because of their limited sensitivity. [11, 193]

Further, individuals with a germline mutation or those with precursor cystic lesions represent only a subset of patients that develop PDAC, and challenges remain in identifying the so-called “sporadic” high-risk individuals that might need to be on surveillance programs for PDAC. As discussed, NOD represents a manifestation of occult PDAC in such “sporadic” high-risk individuals, and a rather promising one at that, but the eventual goal of early

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detection for a lethal disease like PDAC might transcend to an even earlier point in the natural history, where we are deciphering "risk", and not early detection of an existing, albeit asymptomatic, cancer. This will require amalgamation of multiple genetic and environmental inputs, such as polygenic risk scores [194], BMI [195], smoking history etc. (Figure 4). Individuals that meet a defined "*risk threshold*" can then be placed on longitudinal surveillance programs, likely with the conduct of highly *sensitive* "surveillance biomarker" assays capable of identifying asymptomatic disease (the occurrence of NOD or worsening of hyperglycemia in such a surveillance population would certainly warrant additional investigation). At some point, the "surveillance biomarkers" would have to supplanted with "diagnostic biomarkers" that can predict the presence of an asymptomatic cancer with exceptionally high *specificity* (in order to avoid unnecessary imaging studies), culminating in diagnostic imaging of an early tumor being the final step in this multistep surveillance paradigm. There are substantial challenges to be overcome, but unequivocally, the roadmap now exists for making PDAC early detection a reality.

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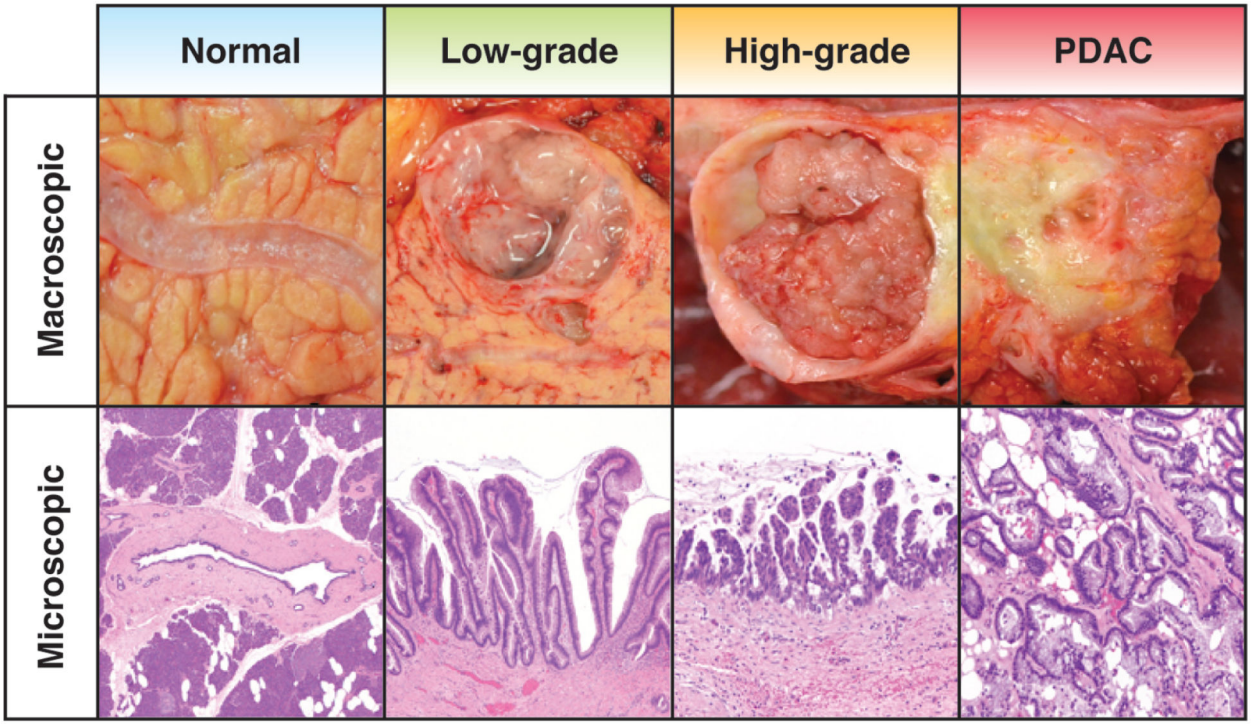

Figure 1:

The pathology of Intraductal Papillary Mucinous Neoplasms (IPMNs). The macroscopic and microscopic features of IPMNs are typically characterized by involvement of the main pancreatic duct, branch duct (shown here) or both. IPMNs are composed of mucinous epithelium that may be either flat or papillary in appearance. Based on the degree of cytoarchitectural atypia, IPMNs can be classified with low-grade or high-grade dysplasia. The most important prognosticator, however, is the absence or presence of an associated invasive pancreatic ductal adenocarcinoma (PDAC).

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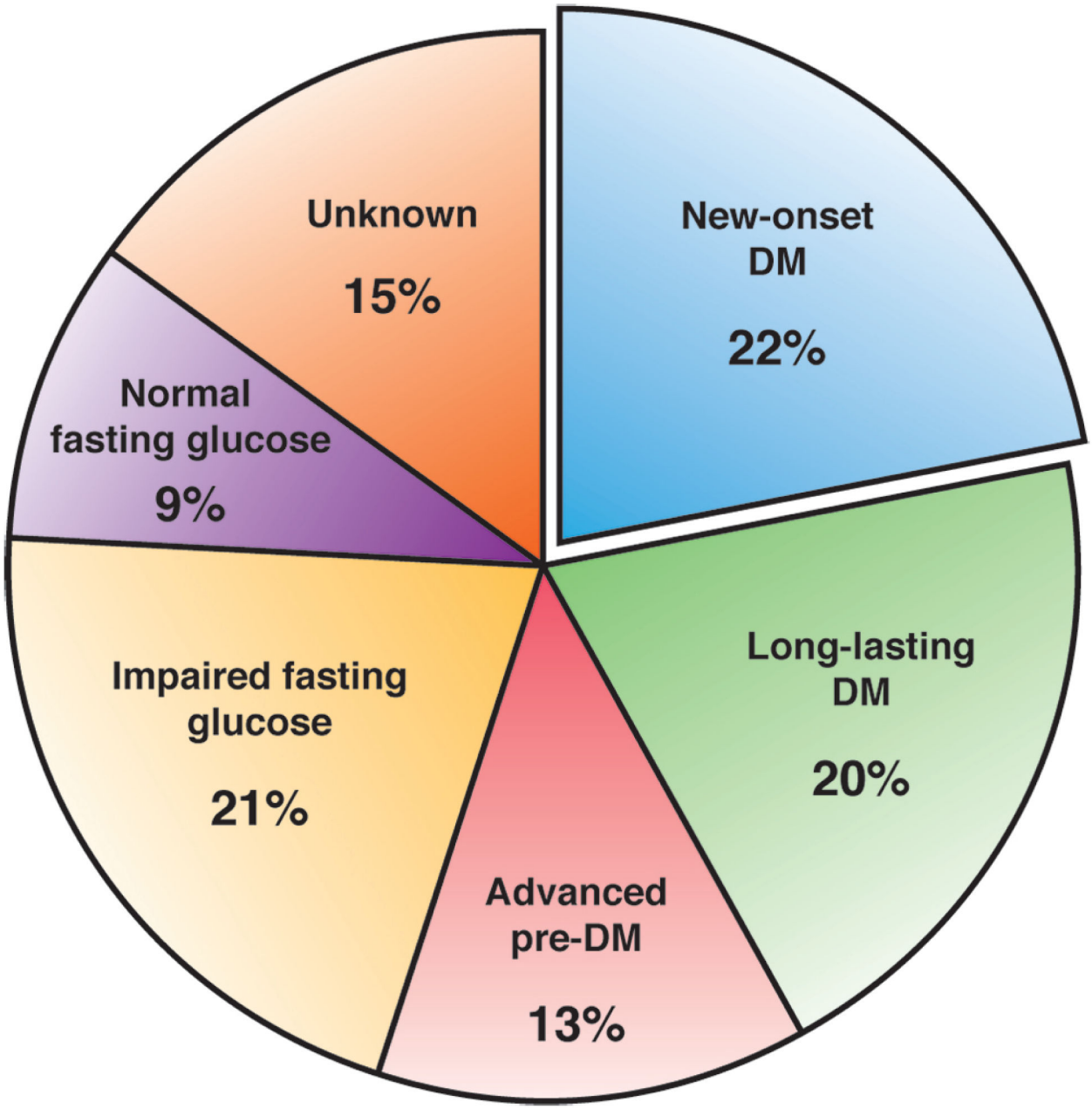

Figure 2:
Distribution of glycemic status based on fasting blood glucose levels in a population-based PDAC cohort (N = 219)

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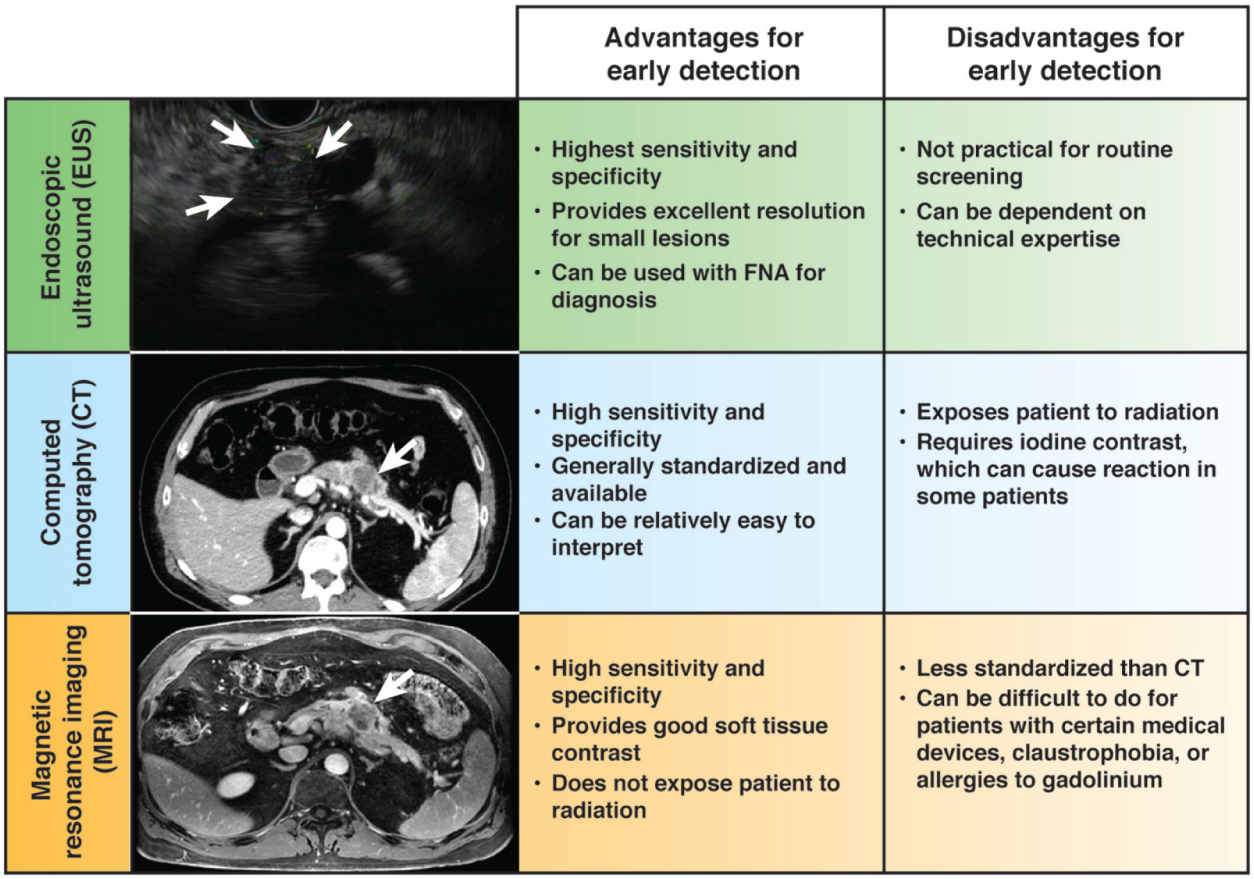

Figure 3:

Common imaging modalities for PDAC including endoscopic ultrasound (EUS, top), computed tomography (CT, middle), and magnetic resonance imaging (MRI, bottom). Each image shows a patient with a ~2 cm lesion in the body of the pancreas. Each modality has advantages and disadvantages for the purposes of early detection of PDAC. A few practical considerations are enumerated.

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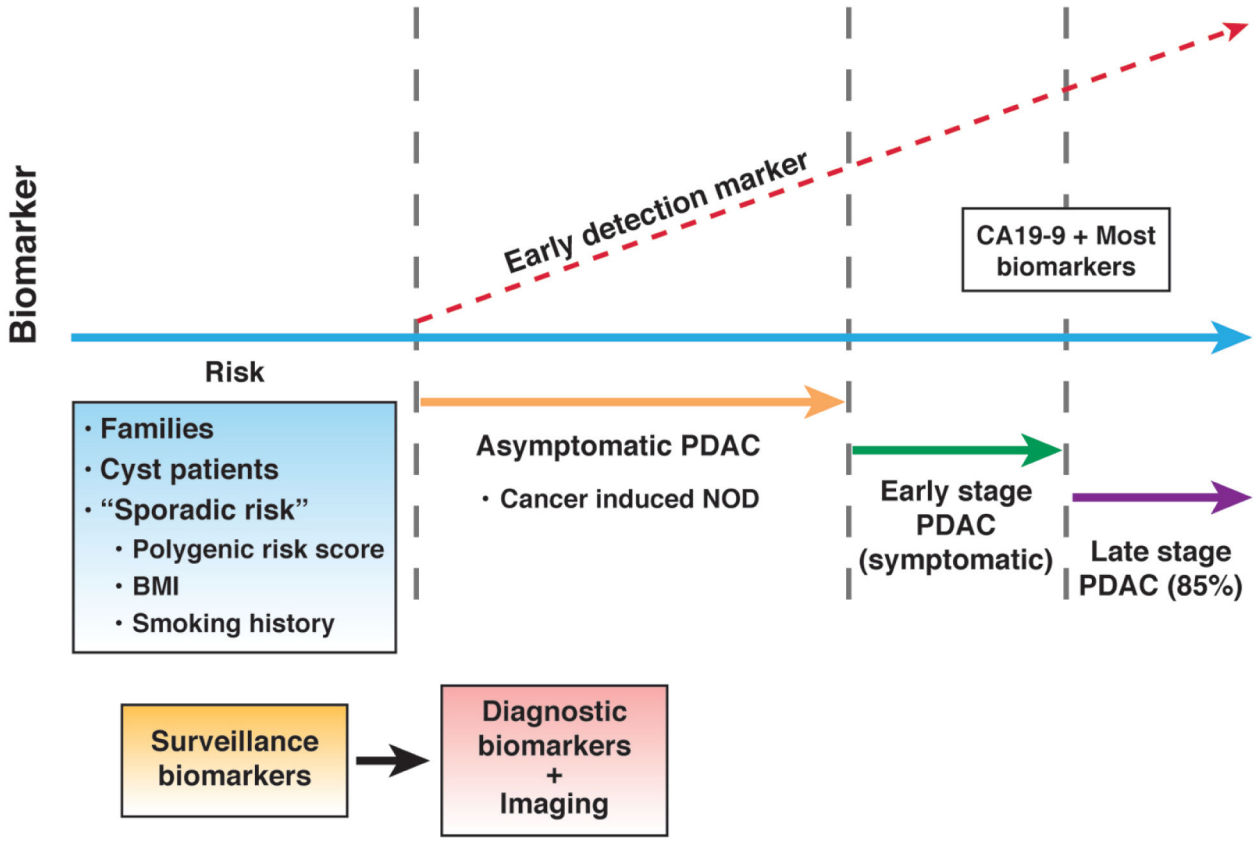

Figure 4:

The "future" of PDAC early detection. Currently, the majority of PDAC are diagnosed at a late stage of their natural history, when they are symptomatic, if not surgically unresectable. Individuals with a family history or with cystic lesions represent high-risk cohorts that can be entered into surveillance programs, but only comprise a subset of patients who develop PDAC. Determination of "sporadic risk" will require multiple input parameters (polygenic risk score, BMI, smoking history, other variables), but has the potential to impact the largest subset of individuals in the general population. Surveillance and diagnosis of asymptomatic PDAC in longitudinally monitored high risk cohorts will require biomarkers with exquisite sensitivity and specificity, to avoid the perils of false negatives and overdiagnosis, respectively. Imaging studies, using a bevy of localization modalities discussed in the text, represents the penultimate step before an intervention such as surgery for removing a potentially "curable" early PDAC.