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Is Screening for Pancreatic Cancer in High-Risk Individuals One Step Closer or a Fool's Errand?

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Pancreatic cancer (i.e., pancreatic ductal adenocarcinoma (PDAC)) is projected to become the second most common cause of cancer-related deaths in the United States by 2030[1]. Despite advancements in understanding the tumor biology and oncologic therapies, there have only been minor improvements in the 5 year survival rate, which remains <10%[2]. One of the key limitations to progress is the majority of patients are diagnosed at an advanced cancer stage (e.g., only 10–15% are candidates for potentially curative treatments, including surgery). Early diagnosis requires detection of PDAC prior to symptom onset, which develops late in the disease course, and currently there is not a validated method to screen for PDAC in the general population.

Screening for PDAC in average risk persons is destined to failure due to the low cancer prevalence. To illustrate this futility, consider the potential results of a hypothetical screening test with excellent sensitivity and specificity for PDAC:

> For example, the age-adjusted incidence of PDAC in subjects ≥50 years of age is approximately 37/100,000[3]. If a test with 99% sensitivity and 99% specificity for PDAC is used to screen 100,000 subjects ≥50 years of age, the test would identify nearly all PDAC in the population screened (n=36), but the test would also falsely identify another 1000 subjects as having PDAC.

Considering the potential medical, financial, and emotional harms associated with each false positive, this scenario is unacceptable. Thus, screening for PDAC using a single test to screen the general population (akin to colon and breast cancer) is certain to fail.

To overcome this challenge, one can develop and apply a series of filters (or sieves), to define and enrich a high risk population, then seek to find the early cancer (recently referred to as the "DEF approach"; define, enrich, and find)[4]. By enriching the screening pool with patients at higher risk for PDAC, the false positive rate of subsequent testing is reduced substantially and overall balance of potential benefits and harms becomes more favorable. One useful filter to enrich the population for PDAC screening is family history and genetic

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profile. Patients satisfying different combinations of family history (including number and proximity of affected relatives) and germline mutations that result a lifetime cumulative risk exceeding 5% are categorized as “high risk individuals (HRI)” by the International Cancer of the Pancreas Screening (CAPS) Consortium[5]. The CAPS Consortium has also thoughtfully discussed various aspects of screening for PDAC in HRI, including age to initiate screening and preferred diagnostic modalities, and have updated guidelines pending final review.

Despite increasing global interest in screening patients fulfilling HRI criteria for PDAC, the reported diagnostic yield is widely variable. The current study from Corral et. al involves a systematic review and meta-analysis to evaluate the detection rate of high-risk pancreatic lesions (defined as high grade PanIN, high grade dysplasia, or invasive adenocarcinoma) in subjects categorized as HRI for PDAC based on family history and genetic profile[6]. Their meta-analysis included studies published through 2017, and most subjects were from a familial pancreatic cancer kindred that lacked an identifiable genetic mutation. In the pooled analysis the detection rate of high risk lesions in this study was 0.74 per 100 patient years.

Heterogeneity is one of the greatest challenges in this clinical context and is important to accurately interpret the results from the current study. First, varying definitions of HRI were used in the studies evaluated in the meta-analysis. This is not surprising as definitions used in the large CAPS Consortium have evolved as more data accumulate. However, several of the studies included subjects that are not currently categorized as HRI (e.g., family history of PDAC not fulfilling criteria for familial pancreatic cancer syndrome or BRCA2 mutation without a positive family history). Inclusion of these subjects in the pooled analysis may lead to underestimation of the true detection rate. Additionally, researchers used different testing modalities that may influence detection rates; namely, prior studies have demonstrated improved detection rates with endoscopic ultrasound compared to cross-sectional imaging. This variability in testing modalities is the result of a variety of factors, including patient preference, clinician preference, and payer acceptance. The authors have taken several measures to minimize heterogeneity, but the final detection rate estimate remains imprecise, and requires future refinement based on studies with more consistent inclusion criteria and screening methods. Along those lines, Canto et al. recently published an update of their single center experience following >350 HRI subjects. In this study they report a cumulative detection of 7% for high risk pancreas lesions (during a median follow-up of >5 years) and an annual rate of progression to high risk lesion of 1.6%[7].

Future studies are needed to identify additional filters that can be applied to the HRI to improve the effectiveness of PDAC screening. Furthermore, broader efforts will be needed to convincingly improve the survival of PDAC through early detection since the vast majority (90–95%) of patients who develop PDAC do not have a family history or associated genetic mutation. Evidence has accumulated over the last two decades demonstrating increased risk of PDAC in those with new onset diabetes (NOD). Specifically, there are converging lines of research suggesting that NOD is a paraneoplastic syndrome in many PDAC patients caused by the tumor[8, 9]. In two population-based studies from Olmsted County, Minnesota, subjects >50 years of age with NOD defined by glycemic criteria had a 3 year incidence rate of PDAC of ~1%, a risk comparable to that of HRI subjects. These data need validation in

other cohorts[3, 10]. Although prevalent diabetes is common in subjects >50 years of age, truly new onset diabetes is uncommon (estimates in Olmsted County range from 0.45% to 1% per year). Recently clinical risk-prediction models for PDAC in NOD have been reported but require external validation[3, 11]. There are also biomarker panels that appear promising,[12].

The National Institutes of Health launched the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) to further examine the complex relationships between diabetes and pancreatic diseases in 2015[13]. The Consortium has developed two studies that will help refine the use of NOD for early detection of PDAC. First, the New-Onset Diabetes (NOD) study seeks to further refine the incidence rate of PDAC amongst patients with NOD[14]. This study will enroll 10,000 adult subjects (ages 50–80) with NOD at >15 centers across the United States. This study will definitively determine the risk of incident PDAC in NOD and will also provide a platform for validation of clinical models and existing or future biomarkers for detection of early stage PDAC. Second, the DETECT (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis) study will enroll approximately 450 subjects with various subtypes of diabetes, including NOD secondary to PDAC, chronic pancreatitis, and type 2 DM[15]. Subjects will undergo a two hour mixed meal test to examine the primary hypothesis that a blunted pancreatic polypeptide response can distinguish these subtypes of pancreatogenic DM from type 2 DM. This study will simultaneously compare differences in insulin, glucagon, and incretin hormone responses between these groups and provide the opportunity for validation of novel biomarkers for pancreatogenic DM. Collectively, these two studies will help us better understand the relationship between diabetes and PDAC, and guide future studies seeking to further develop and validate filters for early detection of PDAC. Findings from these, and other, studies can be applied to further refine the screening approach for PDAC in HRI's.

It may be tempting to take the position that screening for this highly lethal cancer is a 'fool's errand' because it is not feasible in the general population; however, there are key opportunities on the horizon that will refine our understanding of the ideal patient population for screening, which will improve the profile of potential benefits and harms from screening. Early detection of PDAC is no small task, but, as the Chinese proverb reminds us, 'the journey of a thousand miles starts with one step'. Studies evaluating those at increased risk for PDAC due to family history, genetic profile, and NOD, represent multiple steps in the right direction.

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Abbreviations:

CAPS	International Cancer of the Pancreas Screening
HRI	high risk individual

NOD	new onset diabetes
PDAC	pancreatic ductal adenocarcinoma

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Table.

Level of agreement to recommend pancreatic cancer screening for various combinations of family history and genetic profile. The percentages represent the proportion of international experts (among 49 voting participants) in the CAPS Consortium who agreed with screening for the respective combination[5]. Blank boxes indicate no vote was reported for the combination. Color coding reflects the strength of support for screening (green ≥75%; yellow- 50–74%; red - <50%). FDR, first degree relative. Adapted with permission[16].

	Number of affected relatives						
	None	1		2		≥3	
		1 FDR	No FDR	≥1 FDR	No FDR	≥1 FDR	No FDR
No germline mutation	No	No	No	Yes (92% if 2 FDRs and 78% if 1 FDR)	No 25%	Yes 92%	---
BRCA1	---	Indeterminate 69%	---	Yes 78%	Indeterminate 69%	Yes 78%	---
BRCA2	Indeterminate 51%	Yes 86%	---	Yes 90%	Yes 90%	Yes 90%	---
PALB2	No	Yes 78%	---	Yes 78%	---	Yes 78%	---
STK11	Yes 96%	Yes 96%	Yes 96%	Yes 96%	Yes 96%	Yes 96%	Yes 96%
CDKN2A	Indeterminate 57%	Yes 88%	Indeterminate 57%	Yes 88%	Indeterminate 57%	Yes 88%	Indeterminate 57%
Lynch syndrome *	No	Yes 88%	No 44%	Yes 88%	Indeterminate 53%	Yes 88%	Indeterminate 53%

*Associated with *MLH1, MSH2, MSH6,* or *PMS2* gene mutations.