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# Select Population-Based and Translational Research for Improving Pancreatic Cancer Early Detection

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<http://dx.doi.org/10.5772/57531>

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## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) comprises majority of pancreatic neoplasm and remains to pose an enormous challenge to patients and clinicians with the worst survival rate among all major malignancies. PDAC is the fourth leading cause overall and second leading cause of gastrointestinal cancer death in the United States. [1] It is estimated that 45,220 new cases and 38,460 deaths would result from pancreatic cancer in the United States in 2013. [2] Worldwide, there were more than 277,668 new cases and 266,029 deaths from this cancer in 2008. [3] In comparison to other major malignancies such as breast, colon, lung and prostate cancers with their respective 89, 64, 16, 99% 5-yr survival rate, PDAC at 6% is conspicuously low[2]. For PDAC, the only curative option is surgical resection, which is applicable in only 10–15% of patients due to the common discovery of late stage at diagnosis. [4] In fact, PDAC is notorious for late stage discovery as evidenced by the low percentage of localized disease at diagnosis, compared to other major malignancies: breast (61%), colon (40%), lung (16%), ovarian (19%), prostate (91%), and pancreatic cancer (7%) [5].

With the high contribution of late-stage discovery and general lack of effective medical therapy, one critical approach in reversing the poor outcome of pancreatic cancer is to develop an early detection scheme for the tumor. Despite the poor prognosis of the disease, for those who have undergone curative resection with negative margins, the 5-year survival rate is 22% in contrast to 2% for the advanced-stage with distant metastasis. [6, 7] An earlier diagnosis with tumor less than 2 cm (T1) is associated with a better 5-yr survival of 58% compared to 17% for stage IIB PDAC. [8] Ariyama, et al showed 100% survival in 79 patients with tumors less than 1 cm undergoing curative resection. [9] Also as the recent report indicates, the estimated time from the transformation to pre-metastatic growths of pancreatic cancer is

approximately 15 years [10], there is a wide potential window of opportunity to apply developing technologies in early detection of this cancer.

In this article, we will discuss the current status of the PDAC cancer detection/diagnostic modalities and ongoing research endeavors in developing early detection schemes for this devastating disease.

## 2. Current status of PDAC cancer detection and diagnosis – Imaging-based tests

As clinical symptoms of early stages of PDAC is commonly nonspecific and as currently available clinical markers such as CA19-9, CEA, have low sensitivity and specificity at early stage disease [11], clinicians who are suspecting the occurrence of PDAC in a patient rely heavily on diagnostic imaging tests for assessment of a potential tumor.

Over the past few decades, endoscopic ultrasound (EUS) has proven itself to be a superior imaging modality for detection of a small or early-stage pancreatic neoplasm as compared to others such as transabdominal ultrasound (US), computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), positron emission tomography (PET) and angiography. [12, 13, 14, 15, 16, 17] Yasuda and Rosch had initially demonstrated the superiority of EUS in detection of pancreatic lesions <2 cm in diameter. [12, 18] More recently, De Witt, et al had verified the superiority of EUS as compared to multi-detector CT scan. In their study, the sensitivity of endoscopic ultrasonography (98% [95% CI=91% to 100%]) for detecting a pancreatic mass (of any size) was significantly greater than that of CT images (86% [CI=77% to 93%];  $p=0.012$ ) [13]. In another study, Khashab, et al demonstrated that the sensitivity of EUS in detecting pancreatic tumor was greater than CT (91.7% vs. 63.3%;  $P=.0002$ ) and particularly for pancreatic neuroendocrine tumors (84.2% vs. 31.6%;  $P=.001$ ), which commonly consist of smaller pancreatic lesions. Furthermore, EUS detected 20 of 22 CT-negative tumors (91%) in this study. [14] In a retrospective study published by Klapman, et al, EUS diagnosis of pancreatic cancer was found to be highly specific with a negative predictive value (NPV) of 100%. Following the EUS examination, no work-up was required in 119/135 (88%) of patients. [15]

A challenge in imaging-based studies remains to be distinguishing pancreatic malignant lesions from chronic inflammatory changes. Bhutani, et al reviewed 20 cases of missed pancreatic cancer on EUS evaluation in a multicenter retrospective study. They found missed neoplasms in patients with chronic pancreatitis, recent episodes of acute pancreatitis, diffusely infiltrating carcinoma, or a prominent ventral/dorsal split. [16] Conventional power Doppler EUS has some utility in this regard; Saftoiu, et al in a study of 42 patients showed that absence of power Doppler signals inside a suspicious pancreatic mass had a sensitivity of 93% and a specificity of 77%, with an accuracy of 88% in the diagnosis of pancreatic cancer. In the presence of peripancreatic collaterals, the sensitivity and specificity for the diagnosis of pancreatic cancer rose to 97% and 92%, respectively, with an accuracy of 95%. [17]

Elastography is a newer EUS imaging modality used for the real-time visualization of tissue elasticity, and it demonstrates the difference in tissue stiffness between diseased and normal regions. [19, 20] Tumor is commonly stiffer than the normal surrounding tissue, and this characteristic is utilized in the determination of presence of neoplastic lesion, including pancreatic cancer. [21] Giovannini, et al tested this method for the differential diagnosis of benign and malignant lymph nodes and focal pancreatic masses in a small study of 49 patients and showed a sensitivity and specificity of 100% and 67% for the diagnosis of malignant pancreatic lesions. They concluded that this technique could be used to guide biopsy sampling for PDAC diagnosis. [22]

Contrast enhancing agents such as galactose microparticles (Levovist) and sulfur hexafluoride microparticles (SonoVue, a second-generation agent) have been applied in the diagnosis of pancreatic malignancy by assessing the differential vascular perfusion in the pancreatic mass. [23, 24] Hocke, et al reported the differentiation of inflammation versus pancreatic carcinoma based on perfusion characteristics of the microvessels. [25] By using the contrast-enhanced EUS, the sensitivity of the diagnosis of malignant pancreatic lesion with chronic inflammatory pancreatic disease increased to 91. 1% (in 51 of 56 patients) and the specificity to 93. 3% (in 28 of 30 patients) in comparison to conventional EUS sensitivity and specificity of 73. 2% and 83. 3%, respectively. Applicability of an additional modality such as the low mechanical index contrast-enhanced imaging (wide band harmonic imaging) technique has been reported in 6 patients by Dietrich, et al with good arterial, portal venous and parenchymal contrast enhancement. [26] Further study for accuracy of this particular diagnostic testing is anticipated.

### **2.1. EUS-guided Fine Needle Aspiration (FNA) in pancreatic cancer**

Studies have shown that the accuracy of EUS-FNA is better compared to both ERCP brushings and CT-or transabdominal ultrasound-guided FNA for the PDAC diagnosis. [27, 28] EUS-FNA has reported success rates of 90–95%, with an overall sensitivity and specificity of 90% and near-100%, respectively. [29, 30, 31, 32] The main advantage of EUS-guidance is the ability to visualize and target small pancreatic masses. Lesions of 5 mm or less could be visualized and sampled, which might not have been accessible or identifiable by other imaging modalities. [33] Krishna, et al, in a review of 213 patients, found EUS-guided FNA to be highly accurate for diagnosing malignancy in patients with a focal pancreatic lesion noted on CT scan/MRI without obstructive jaundice. EUS-FNA had 97. 6% accuracy for diagnosing a malignant neoplasm, with 96. 6% sensitivity, 99. 0% specificity, 96. 2% negative predictive value, and 99. 1% positive predictive value. [34] Agarwal, et al compared 81 consecutive patients who underwent EUS, EUS-FNA and spiral CT with a multiphase pancreatic protocol for clinical suspicion of PDAC. They showed that the accuracy of spiral CT, EUS, and EUS-FNA was 74% (n=60/81, CI 63-83%), 94% (n=76/81, CI 87-98%), and 88% (n=73/81, CI 81-96%), respectively, for detecting pancreatic cancer. In their study, absence of a focal lesion on EUS reliably excluded pancreatic cancer irrespective of clinical presentation (NPV 100% n=5/5, CI 48-100%). [35]

From a practical standpoint, tumor cell seeding of the FNA tract is rare and only a few EUS cases have been reported. Micames, et al in their study demonstrated that EUS-FNA has a

lower risk of peritoneal contamination with malignancy than CT-guided FNA (2.2% versus 16.3%), respectively. [36] This is a potential complication of EUS-FNA that would need to be kept in mind by clinicians when FNA sampling of a lesion is being considered. [37, 38]

### 3. Molecular markers & pancreatic cancer

In order to enhance the diagnostic accuracy of PDAC, molecular markers on EUS-FNA samples have been evaluated in recent years. Utilities of DNA mutations such as *k-ras* and loss of heterozygosity are being reported as potential surrogate markers of the malignancy. [39, 40] In a recent study, Takahashi, et al assessed *k-ras* point mutations in PDAC and chronic focal pancreatitis samples obtained by EUS-FNA. [41, 42, 43] The study revealed the presence of point mutations of *k-ras* in 74% of patients with PDAC compared to no mutations in chronic focal pancreatitis. In another study, Tada, et al reported a high (more than 2% of total *k-ras* gene) mutation rate in 20 of 26 cases of EUS-FNA specimens (77%) and in 12 of 19 cases of pancreatic juice (63%) in PDAC. [44] However, the presence of *k-ras* mutations in chronic pancreatitis and premalignant conditions such as intraductal papillary mucinous neoplasm as well as lack of such mutations in 20% of pancreatic cancer has limitations for using this test solely as a diagnostic tool. Other studies analyzing p53 by immunohistochemistry, [45] telomerase activity with a ribonucleoprotein enzyme, [46] and a broad panel of microsatellite allele loss markers demonstrated similar results. [47] In the presence of inconclusive EUS-FNA cytology, molecular markers could complement EUS-FNA cytology results to help establish the diagnosis of malignancy.

## 4. Select population-based research for early detection scheme development

### 4.1. Screening for pancreatic cancer in high-risk individuals

Currently, a general population-screening program for PDAC is not cost-effective because of low relative disease incidence and non-availability of simple, cheap, highly accurate non-invasive tests. The main aim of the screening is to detect clinically significant precursor lesions or early stage PDAC. However, since the overwhelming majority of premalignant lesions and small pancreatic cancers are asymptomatic, we do not yet have a routinely utilized surrogate marker to identify a subset population for screening. Consequently, as one of the approaches in investigating the genetic risks, research has focused on investigating a subset of individuals with a higher-risk for PDAC development in order to elucidate the genetic predilection. Up to 10% of pancreatic cancer patients have a familial basis and they have increased risk of developing both pancreatic and extra-pancreatic malignancies. [48, 49, 50, 51, 52] Classic categorization of high-risk patients are based on the highly associated genetic risks defined as those who are either members of a family with at least two first-degree relatives affected by

the disease or are part of an inherited pancreatic cancer syndrome with a known genetic mutation. (Table 1)

Syndrome	Inheritance	Gene Mutation	Risk of PDAC
<b>Peutz-Jeghers syndrome [53]</b>	Autosomal dominant (AD)	STK11/LKB1	Standardized Incidence Ratio (SIR) = 132
<b>Hereditary Pancreatitis [54, 55, 56]</b>	AD	PRSS1 SPINK1	Odds ratio (OR) = 69.9
<b>Familial atypical multiple mole melanoma syndrome [57, 58, 59]</b>	AD	CDKN2A	SIR=13-38
<b>Hereditary breast-ovarian cancer syndrome [60, 61, 62, 63, 64, 65, 66]</b>	AD	BRCA2 BRCA1	BRCA2: OR=3.5-10-fold increased risk BRCA1: OR=2.26 times average population
<b>Lynch syndrome [59, 67]</b>	AD	MLH1, MSH2, MSH6 or PMS2	SIR = up to 8.6
Cystic fibrosis [68]	Autosomal recessive	CFTR	OR = 5.3-6.6

**Table 1.** PDAC related genetic syndromes

#### 4.1.1. Familial pancreatic cancer

Familial pancreatic cancer (FPC) cohort is distinguished by individuals with a strong family history of PDAC-i. e. with the cancer in at least two first-degree relatives and individuals with three or more affected family members (one of whom must be a first-degree relative) – and is considered to be high-risk and a candidate for screening programs. [69, 70, 71] Currently, the genetic basis for most cases of FPC is not fully understood. However, various studies have demonstrated the presence of a germline mutation in the BRCA2 gene [61, 62, 63, 64], association of BRCA1 [72], paladin gene mutation [73] and involvement of other genes: apolipoprotein A4, CEA, keratin 19, stratifin (14-3-3σ), trefoil factor, and calcium binding protein S100 A6 [74, 75] in FPC, and more recently identification of PALB2, [76] as a pancreatic cancer susceptibility gene. These facts suggest that multiple and heterogeneous factors are likely at play for the genesis of PDAC in this subset.

Analysis of the PDAC kindred data from Johns Hopkins' National Familial Pancreas Tumor Registry (NFPTR) has demonstrated that the relative risk of PDAC in persons with two affected first-degree relatives is 6.4% and the cumulative life-time risk is 8%-12%; in individuals with three affected first-degree relatives, the relative risk for PDAC increases to 32% and the cumulative life-time risk to 16%-32%. [77] Tersmette, et al in their analysis of the NFPTR found

an 18-fold increase in risk of PDAC, and an estimated lifetime risk of 9%-18% in the group. [78] Brune, et al in their recent article reported a higher risk of PDAC among members of FPC kindred with a younger age of onset (age < 50 years). [79] Rulyak, et al in another study found smoking as a strong risk factor in FPC kindred, particularly among males and those under age 50. This risk increases by 2.0-3.7 times over the inherited predisposition and lowers the age of onset by 10 years. [80] A computer-based risk assessment tool, PancPRO, has been developed and is available for calculating the risk assessment for individuals with familial pancreatic cancer (<http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp>). [81]

#### 4.1.2. Screening modalities & the current screening programs

Most of the screening programs have tried to use biomarkers complemented by imaging tests to identify the early lesions. As stated earlier, a commonly used marker, CA19-9, is neither specific nor sensitive independently for reliable detection of early pancreatic cancer or pancreatic precursor lesions. Kim, et al in their studies found only 0.9% positive predictive value using a cut-off value of 37 U/mL. [82] Recently, many biomarkers have been investigated including MIC-1, CEACAM-1, SPan1, DUPAN, Alpha4GNT, and PAM4, but none is validated for routine clinical use. [83] In another approach, elevated fasting-glucose level has been shown to be a marker for early cancer in sporadic cases [84] and is currently used by the EUROPAC study in high-risk individuals with molecular analysis of pancreatic juice for the *k-ras* and *p53* mutations in addition to *p16* promoter methylation status.

Multiple international programs exist that screen for pancreatic cancer in high-risk individuals in a research setting. "Cancer of the Pancreas Screening Study" (CAPS study), led by John Hopkins University, is the largest screening program that involves 24 American Centers of Excellence. To date, three studies, CAPS 1, CAPS 2 and CAPS 3, have been completed. (Table 2)

In the CAPS 1 study, thirty-eight patients were studied; 31 (mean age, 58-yr; 42% men) from a kindred with > 3 affected with pancreatic cancer; 6 from a kindred with 2 affected relatives, and 1 was a patient with Peutz-Jeghers syndrome (PJS). Six pancreatic masses were found by EUS: 1 invasive ductal adenocarcinoma, 1 benign intraductal papillary mucinous neoplasm, 2 serous cystadenomas, and 2 nonneoplastic masses. In this study, the diagnostic yield of screening was 5.3%. [85] In the CAPS 2 study a 10% diagnostic yield of screening for pre-invasive malignant lesions was found. [86] In this study, screening was performed using annual EUS and CT. If an abnormality was detected, ERCP was offered. Seventy-eight high-risk patients (72 from a FPC kindred, 6 PJS) and 149 control patients were studied. Of these, eight patients had confirmed pancreatic neoplasia by surgery or FNA (10% yield of screening); 6 patients had benign intraductal papillary mucinous neoplasms (IPMNs), 1 had an IPMN that progressed to invasive ductal adenocarcinoma, and 1 had high-grade pancreatic intraepithelial neoplasia (PanIN-3). The CAPS 3 study was a multicenter prospective, controlled cohort study that involved annual screening using EUS and MRCP, MRI with secretin and a panel of candidate DNA and protein markers in serum and pancreatic juice (CA19-9, macrophage inhibitory cytokine-1 (MIC-1), DNA hypermethylation, and *k-ras* gene mutations) as indicators of pancreatic neoplasm. Over 200 patients were enrolled over a three-year period. The study

has recently been completed and the results on the detection modality comparison demonstrate that the EUS has the highest rate of detection of early neoplastic changes in up to 42.6% of the asymptomatic high-risk group. [87]

In another study from the University of Washington, high-risk familial cohorts were screened using EUS and beginning 10 years prior to the earliest PDAC death in the family. If EUS was normal, then they were followed-up with a repeat EUS at 2-3 year intervals. In case of abnormal EUS findings, they were referred for ERCP and if abnormalities were noted, patients were offered surgical intervention. [88] Patients with abnormal EUS, but normal ERCP were offered annual EUS. Out of 75 subjects screened, 15 had abnormalities on EUS and ERCP and went to surgery. The histology revealed premalignant lesions in all: PanIN-3 in 10 cases and PanIN-2 in five. [89] This study gave a diagnostic yield of 13% (10 out of 75) for detecting PanIN-3 premalignant lesions. One patient developed unresectable pancreatic cancer while under annual surveillance.

In Europe, the European Registry for Familial Pancreatic Cancer and Hereditary Pancreatitis (EUROPAC) incorporated EUS, ERCP and molecular analysis of the pancreatic juice looking for early mutations (*p53*, *k-ras*, and *p16*), and the results are pending. A German Study (FaPaCa) enrolled 76 patients in a screening program using yearly EUS, MRCP and laboratory tests (genetic analysis of *CDKN2a* and *BRCA2* genes, CA19-9 and CEA). Any suspicious lesion was evaluated with EUS ± FNA after 6 weeks and a close follow-up at 12 weeks. If an abnormality was detected, the patient underwent operative exploration with intraoperative ultrasound, limited pancreatic resection with frozen section, and if cancer was detected, total pancreatectomy was performed. Ten solid lesions were seen on EUS as compared to only seven detected by MRCP. Out of the seven MRCP-detected lesions, six had limited resections and the histology showed one patient with PanIN-3, one with PanIN-2, one with PanIN-1, and three were benign lesions. These results gave a diagnostic yield of 1.3% in detecting PanIN-3. [90] A recent study from the Netherlands that used only EUS as the first screening modality in 44 high risk asymptomatic subjects showed a 7% diagnostic yield for asymptomatic cancers and a 16% diagnostic yield for premalignant lesions (IPMN-like lesions). [91]

Study	CAPS1	CAPS2	CAPS3	U of Washington	FaPaCa	Dutch Study
Diagnostic Yield*	5.3 (2/38)	10 (8/78)	42 (92/216)	13% (10/75)	1.3 (1/76)	23 (10/44)

\*Represents finding of abnormal imaging such as mass (solid, cyst) or abnormal duct

CAPS: Cancer of the Pancreas Screening Study; FaPaCa: Familial Pancreatic Cancer Study

**Table 2.** Results of screening programs for pancreatic cancer in high-risk groups

Questions remain regarding the cost-effectiveness of these screening modalities. Rulyak, et al reported that screening was cost-effective with an incremental cost-effectiveness ratio of \$16,885/life-year saved (assuming a 20% incidence of dysplasia and a 90% sensitivity of EUS and ERCP). [92] Rubenstein, et al performed a systematic review, and created a Markov model



for 45-year-old male first-degree relatives, with findings of chronic pancreatitis on screening by EUS. They compared 4 strategies: do-nothing, prophylactic total pancreatectomy (PTP), annual surveillance by EUS, and annual surveillance with EUS and fine needle aspiration. In the do-nothing strategy, the lifetime risk of cancer was 20% and it provided the greatest remaining years of life, the lowest cost, and the greatest remaining quality-adjusted life years (QALYs). PTP provided the fewest remaining years of life and QALYs. Screening with EUS provided nearly identical results to PTP, and screening with EUS/FNA provided intermediate results between PTP and the do-nothing approach. Total pancreatectomy provided the longest life expectancy if the lifetime risk of PDAC was at least 46% and provided the most QALYs if the risk was at least 68%. [93] Further assessment of the models in other clinical scenarios with developing technology would be in order.

## 5. Future of pancreatic cancer screening

Current EUS screening programs have demonstrated that the endoscopic evaluation can detect premalignant lesions and early cancers in certain subsets of high-risk groups, although cost-effectiveness still remains an issue. However, as the majority of PDAC diagnosis is given to patients who develop the disease sporadically without a recognized genetic abnormality, the application of this modality for PDAC detection screening is very limited for the general adult population. In order to further delineate and expand the at-risk subset, there is a strong need for novel surrogate markers which allow identification of the group with increased PDAC risk for whom the endoscopic/imaging-based screening strategy could be applied.

### 5.1. Select population based research — Identification of a higher-PDAC-risk group

A practical approach for further selection of the potential screening population is to focus on selective clinical parameters that would be used to characterize the subset of the general population at increased PDAC risk. For instance, based on the epidemiological evidence, such clinical parameters include incidence of hyperglycemia or diabetes, which are being noted in 50-80% of pancreatic cancer patients [94, 95, 96, 97, 98]. Though this subset does not encompass all PDAC patients, this group includes a much larger proportion of PDAC patients whom we may select further to screen for PDAC. Similarly, patients with a history of chronic pancreatitis or obesity are reported to have increased PDAC risk during their lifetime [99, 100, 101, 102, 103, 104]. Animal studies investigating effects of diet-induced obesity in a PDAC mouse model demonstrated increased occurrence of pancreatic inflammation and accelerated pancreatic neoplastic changes, supporting the association of obesity and pancreatic inflammation and PDAC risks. [105, 106] Considering the millions of patients who are being diagnosed with diabetes, chronic pancreatitis, or obesity annually as opposed to PDAC, further refinement of screening of these patient groups is critically needed to justify developing a larger scale screening protocol in the future.

## 5.2. Translational research – Application of systems biology approach

As we continue to translate the advancement of biological understanding of PDAC, we strongly anticipate that better biomarkers will become available in the near future that would identify higher-risk individuals within the general population for developing early-stage PDAC. Aside from the previously referenced reports, many genetic, epigenetic, proteomics, metabolomics, glycomics findings-utilizing systems biology approaches-are being considered for biomarker identifications for PDAC detection. In transcriptomics analysis of blood biomarkers in PDAC-associated diabetes mellitus, for example, gene expression analysis in blood from PDAC patients with new-onset diabetes versus long-term or no history of diabetes revealed a set of differentially expressed genes such as vanin-1 and matrix metalloproteinase 9, which are able to discriminate the PDAC group with sensitivity of 92% and specificity of 84%. [107] From proteomics analyses, shotgun approaches with highly accurate mass spectrometric assays demonstrated such proteins as apolipoprotein CIII [108], mannose-binding lectin 2, myosin light chain kinase 2 [109], CXC chemokine ligand 7 [110], TIMP1-ICAM1 [111], and alpha-1 antitrypsin [112] as candidate biomarkers of PDAC. These and other candidate biomarkers need to be validated with larger populations with appropriate control groups.

With the technological advancement in the mass spectrometric techniques over the recent decades and resumed interest in the cancer-associated metabolic abnormality, [113, 114] application of metabolomics in the cancer field has attracted more attention. Metabolomics allows for elucidating the complete set of metabolites or low-molecular-weight intermediates in the physiological, developmental or pathological state of the cell, tissue, organ, or organism. [115] And metabolomics study of PDAC detection biomarkers will seek identification of a set of small molecules or metabolites (or chemical intermediates) that are potential discriminators of developing PDAC and the controls. Recent reports from our group as well as others have demonstrated specific small molecules such as amino acids, bile acids, and various lipids and fatty acids as potential candidates for PDAC biomarkers. [116, 117, 118, 119] Since a metabolome represents a current physiological readout of the biochemical state in an individual's biofluid or tissue space and as the functional end-product of the varying signals from the genome and proteome, it reflects the up-to-date phenotypic state of an individual in the presence of environmental stimuli. Thus, metabolomics data potentially provides additional temporal information to cancer risks derived from gene-based PDAC risk data alone. Since many enzymes in a metabolic network determine metabolites' concentrations and nonlinear quantitative relationship from the genes to the proteome and metabolome levels exist, a metabolome cannot be easily decomposed to a specific single marker, which will designate the disease state. [120] So, in order to delineate a physiological or pathological state, multiple metabolomic features might be required for accurate depiction of such a state as a developing cancer. In addition, future studies are anticipated to incorporate further cancer systems' biological knowledge, including multi-omics-based analyses for optimal designation of PDAC biomarkers, which would be utilized in conjunction with a clinical-parameter-derived population subset for establishing the PDAC screening population. Subsequently, further validation studies for the PDAC biomarkers need to be performed.

## 6. Conclusion

Current imaging-based detection and diagnostic methods for PDAC is effectively providing answers to clinical questions raised for patients with signs or symptoms of suspected pancreatic lesions. However, the endoscopic/imaging-based schemes are currently limited in applications to early PDAC detection in asymptomatic patients, aside from a relatively small group of known genetically high-risk groups. There is a high demand for developing a method of selecting distinct subsets among the general population for implementing the endoscopic/imaging screening test effectively. Application of combinations of clinical risk parameters/factors with the developing molecular biomarkers from translational science brings high hopes of providing us with early PDAC detection markers, and developing effective early detection screening scheme for the patients in the near future.

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