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Identifying Complex High-Risk Individuals (HRI-C) for Early Detection of Occult Pancreatic Cancers Using Risk Models and Biomarkers.

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Abstract: Early detection and diagnosis of pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) offers the best option for effective treatment and prolonged survival. Image-based screening programs are useful in early detection of pancreatic cancers in high-risk individuals (HRI) defined by strong family history and/or pathogenic variants (PV) in hereditary cancer syndrome (HCS) genes associated with an increased risk for PDAC development. However, this only applies in about 10% of people who eventually develop pancreatic cancer. An additional 15% of PDACs are associated with a pancreatic cystic neoplasms. Thus, the majority (~75%) of patients diagnosed with PDAC are not candidates for surveillance under an existing framework. Based on growing evidence we believe that early detection is also possible in what we call *Complex High-Risk Individuals* (HRI-C) through frequent, time-limited image-based screening. These HRI-C are identified by combining multiple clinical and genetic risk factors alongside early markers of pancreatic cancer (e.g. family history, past medical history, social history, and multiple genetic factors in individuals with worrisome individual or combinations of biomarkers of occult pancreatic cancer in older individuals (>50 years) such as new onset diabetes (NOD), new idiopathic acute or chronic pancreatitis, maldigestion with exocrine pancreatic insufficiency (EPI), abnormal liver injury test (especially biliary), unexplained weight loss and typical cancer-associated pain patterns). Here we propose a potentially cost-effective clinical decision pathway aimed at improving early detection, diagnosis and outcomes of this large group of individuals at risk for developing PDAC.

Keywords: SEER Program; Early Detection of Cancer; Early Detection; Genetic Testing; Computer-Assisted Numerical Analysis, Multifactorial Inheritance; Pancreatic Neoplasms

Outline:

Abbreviations: AP, acute pancreatitis; BC, breast cancer; CA 19-9; carbohydrate antigen 19-9; CDC, Center for Disease Control; CECT, contrast-enhanced CT scan; CP, chronic pancreatitis; CRC, colorectal cancer; DM, diabetes mellitus; ENDPAC, Enriching New-onset Diabetes for Pancreatic Cancer score; EPI, exocrine pancreatic insufficiency; FDR, first-degree relative; GWAS, genome-wide association studies; Hb, hemoglobin; HbA1c, hemoglobin A1c; HCS, hereditary cancer syndrome; HRI, high-risk individuals; HRI-C, complex high-risk individuals; IPMN, intraductal papillary mucinous neoplasm; LFT, liver function/injury test; NCI, National Cancer Institute; NOD, new onset diabetes; PDAC, pancreatic ductal adenocarcinoma; PPV, positive predictive value; PV, pathogenic variants; QALY, quality-adjusted life year; RAP, recurrent acute pancreatitis; SEER, Surveillance, Epidemiology, and End Results Program; SNV, single nucleotide variant.

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1. Introduction

Pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) remains a recalcitrant cancer with 5-year survival at ~13%. Typically, pancreatic cancers are detected after they have metastasized (stage IV), and traditional chemotherapy appears to extend life by weeks to months rather than years. Indeed, the poor outcome with standard treatment (< 50% five-year survival) resulted in congress calling on the National Cancer Institute (NCI) to develop scientific framework to assist in making progress against the deadliest cancers (i.e. PDAC). PDAC screening is not recommended in the general population due to its low incidence; however, it is reasonable to consider surveillance of the pancreas in those individuals at increased risk for developing this malignancy. The following current key points regarding a high-risk individual (HRI) should be considered:

- Detection of PDAC at an early stage is possible though image-based screening of HRI.[2, 3]
- About 10% of patients with PDAC meet HRI criteria based on family history or hereditary cancer syndrome (HCS) pathogenic variant (PV) gene mutations associated with increased risk for developing a PDAC.[4]
- It is estimated that ~15% of PDACs arise from a cystic lesion, typically an Intraductal Papillary Mucinous Neoplasm (IPMN).[5]
- Early clinical biomarkers of PDAC are non-specific. These include new-onset diabetes mellitus (NOD)[6], acute pancreatitis (AP), chronic pancreatitis (CP), unexplained weight loss, jaundice or unexplained liver function/injury test (LFT, especially biliary), new abdominal pain and/or maldigestion (e.g. exocrine pancreatic insufficiency, EPI) and others. But the positive predictive value (PPV) for PDAC is very low, especially in low-risk groups such as those under the age of 50 years.[7, 8]
- The only FDA-approved biomarker for PDAC is CA 19-9, which was approved for monitoring treatment response and not early detection. CA 19-9's use for early detection is limited in part because of suboptimal performance characteristics related to population-based cutoff values that are useless in some individuals because of underlying genetic variants that change normal expression levels.[9, 10]

This article is for providers caring for adult patients with risks and/or symptoms of possible pancreatic cancer. It has two major sections. **First**, a detailed review of the evidence for classifying patients as high-risk individuals (HRI). **Second**, a proposed clinical workflow for triaging an individual into screening tests (HRI-C) or standard care based on combined clinical biomarkers of PDAC set within the context of epidemiological risk factors and genetic risk factors. **The goal** is to facilitate the rapid detection of PDAC by screening patients who are HRI-C (i.e. do not fit Familial or HCS criteria).

2. Risk factors versus Biomarkers

The terms *risk factors* and *biomarkers* have specific meanings that are important for patient evaluation. A risk factor is something that *increases the chance* of developing a disease. In contrast, a biomarker is an objective, quantifiable *characteristics of biological processes* that has clinical, imaging or laboratory-defined statistical ranges of normal and abnormal that may indicate disease. This is important since, in the context of pancreatic cancer oncogenesis AP, CP and DM can be risk factors OR biomarkers, depending on the *time of disorder onset* relative to PDAC evaluation.

The pancreas has three cell types with different functions. The islet cells make insulin, the acinar cells make pancreatic digestive enzymes (zymogens) and the duct cells secrete bicarbonate-rich fluid to deliver the zymogens to the intestines for nutrient digestion. Injury, inflammation and/or stress causes dysfunction resulting in diabetes mellitus, acute and chronic pancreatitis, atrophy and exocrine pancreatic insufficiency (EPI). The etiology is critical. Pancreatic neoplasms, including IPMN and PDAC cause injury, inflammation and duct obstruction with EPI, and in some cases a paraneoplastic syndrome with diabetes (see below). In the case of PDAC, AP, CP, EPI and DM are considered non-specific "biomarkers" of cancer. On the other hand, since inflammation is a major driver of oncogenesis, a history of AP, CP, EPI and DM are considered "risk factors" for PDAC.

As discussed below, the rapid growth and metastasis of PDAC suggest that the more time that elapses after the sudden onset of AP, CP, EPI and/or DM (e.g. > 2-3 years), the less likely it is that these clinical disorders are caused by pancreatic cancer, and more likely that they are caused by something else. However, because it is critical to make an *early diagnosis* of PDAC, it becomes imperative to determine the etiology of AP, CP, EPI and/or DM as soon as possible after their sudden development in at-risk patients (e.g. age >50 years). The discussion below and final clinical decision pathway is used to illustrate our approach.

3. Screening adults for PDAC

Population-based improvement in survival of colorectal cancer (CRC) and breast cancer (BC) have been achieved using age- and sex-based screening programs such as colonoscopy for early CRC detection and mammography for BC.[11, 12] This is not possible for PDAC because early preneoplastic lesions are difficult to detect, highly sensitive and specific biomarkers are not yet available, the incidence of PDAC is low compared to CRC and BC in women, and the time frame between a detectable lesion and metastatic disease is short. Furthermore, obtaining tissue samples for pathologic diagnosis is more challenging because of the location of the pancreas and risk of triggering acute pancreatitis (AP). Thus, widespread screening for average risk individuals is neither feasible or effective, since the invasive follow-up procedures, cost, and anxiety for false positive signals is substantial.[13]

4. Surveillance for PDAC based on Family History and known highly pathogenic variants

Unlike population-based screening, targeted surveillance of subpopulations at increased risk for pancreatic cancer can be efficacious. This approach is based on a medical genetics approach to pathogenic mutations with late, variable penetrance that run in families. Studies from the United States and Europe have shown that systematic, periodic image-based surveillance of HRI is feasible and that the outcome of incident PDAC (or pre-PDAC lesions) is markedly improved compared to PDAC survival in the general population.[2, 3, 14, 15] Furthermore, several consensus recommendation have been published that support this approach, although the exact level of risk that specific PV confer and the details of an individual's HCS pedigree are not always certain.[4, 16-18] HRIs can also be defined by having one or more first-degree relatives (FDR) with PDAC (especially with onset less than 50 years of age[19, 20]) (See Porter[19] Figure 1 *hyperlink*) for increased PDAC based on number of FDR and age <50y). Family members of hereditary cancer kindreds where the pathogenic variant is known and where there is a high lifetime probability of PDAC (e.g. >5%) are also defined as HRI and should be considered for a surveillance program. Note that additional genetic risk factors are also inherited, indicating that overall risk is not defined by one pathogenic variant, and that family history is also important.

5. Image-based Screening

The purpose of using image-based screening for the early detection of PDAC is that a tissue diagnosis is required before treatment begins and high-quality imaging informs the endoscopist or radiologist on *where* to biopsy. Two modalities of image-based screening are typically used: magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS).[21, 22] The frequency is typically annual beginning at age 40-50 years for HRI, or 10 years before the youngest PDAC case among FDRs. The modality depends on the expertise of the center and may utilize alternating techniques for annual screening. Due to radiation exposure, most centers avoid CT scans. Further, it is recommended that pancreatic surveillance for selected high-risk individuals to detect early pancreatic cancer and its high-grade precursors should be performed in a research setting by multidisciplinary teams in centers with appropriate expertise.[16]

6. Monitoring of pancreatic cystic lesions

Guidelines currently exist for the management of IPMNs and cystic lesion. [23-26] These criteria will not be reviewed here. They include high-risk features that are typically biomarkers of developing PDAC or other pancreatic cancers. Thus they markedly increase the likelihood of cancer when found in the context of multiple underlying risk factors.

7. Experimental Screening Methods

Long standing CP is a significant *risk factor* for PDAC, and especially for patients with hereditary pancreatitis (*PRSS1* gain-of-function mutations[27]). Refraining from smoking is the best recommendation for reducing the risk of PDAC[28, 29], but there are currently no proven ways to screen for early PDAC in these patients because of the fibrosis and altered morphology of the diseased pancreas.[30]

There are many new technologies that use serum or urine biomarkers to aid in the early detection of occult pancreatic cancers.[31, 32] Most of these are not FDA approved and many include CA19-9 (see Brezgyte[32] Table 2 *hyperlink*) and below (Section 11). Examples include: CA19-9 with an additional panels of serum proteins[33], urine protein biomarkers LYVE1 and REG1B[31], circulating microRNA[34], microRNA in exomes[35], and other liquid biopsy techniques (including circulating tumor cells, small extracellular vesicles, and tumor DNA[36]) such as multiplexed glycan immunofluorescence to detect circulating PDAC cells in serum.[37] Many of these show promise. Inclusion of these patients in clinical studies is encouraged.

8. Surveillance for PDAC in individuals with complex high-risk scores (HRI-C)

Systematic surveillance protocols for PDAC must be limited to high-risk individuals. Major determinates include the current risk, likelihood that they will develop PDAC within a specific time frame and the cost-effectiveness of the testing protocol (e.g. cost of testing per quality-adjusted life year, QALY). Although cost-effectiveness models may be subject to bias, it is generally agreed that image-based surveillance of HRI for PDAC is cost-effective.[38-40] However, as demonstrated in a recent study of HRI with CDKN2A-p16-Leiden mutations, the lifetime risk of PDAC for example needed to be >10% in a lifetime.[41] In contrast, overall risk of PDAC based on polygenic risk scores (PRS) and/or lifestyle risk and/or medical condition risk does not reach these levels of risk alone, and additional risk factors such as biomarkers of an occult PDAC must be considered.

9. Biomarkers of an occult PDAC.

New onset biomarkers of pancreatic injury, inflammation or duct obstruction are non-specific biomarkers of pancreatic cancer *and* other etiologies. Indeed, clinicians have known for decades that a variety of clinical signs and symptoms often precede the diagnosis of PDAC. These clinical signs are typically associated with a tumor blocking the main pancreatic duct and/or common bile duct (e.g. double-duct sign) as well as down-stream effects of blocked duct systems. A summary of biomarkers of occult PDAC is given in **List 1.** Of note, a large deep machine learning study of the Netherlands and US Veterans confirmed clinical features traditionally linked to an occult PDAC developing 1, 2, and 3 years before PDAC is diagnosed (Table 5 *hyperlink*), supporting their use as biomarkers.[42]

The problem with this list is that most of the signs and symptoms are **non-specific**; they are often abnormal due to medical disorders *other than* PDAC. Each factor has a differential diagnosis. However, these clinical features *are* occasionally biomarkers of PDAC and confer moderate to high likelihood of PDAC within individuals with overall high risk for PDAC. We will use NOD to demonstrate the challenges and use of these nonspecific biomarkers.

New onset diabetes (NOD)

Diabetes is the most common metabolic disorder among Americans, affecting 11.6% of the U.S. population (CDC Statistics link). Recently there has been great interest in the relationship between NOD in older individuals as an early indicator of an occult PDAC. The initial observation was that 40% of patients with PDAC have diabetes[43] with about half of the diabetes cases having progressive fasting hyperglycemia and/or diabetes 30 to 36 months prior to the PDAC diagnosis.[6, 43] The observation was incorporated into the Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC) score to stratify patients into high-risk and low-risk of having cancer. The model included new onset hyperglycemia and diabetes (NOD), plus age and unexplained weight loss.[7] Other studies confirm the observation, but among patients in other populations with NOD, less than 2% had PDAC.[44, 45]

Cost effectiveness research has been done using NOD plus ENDPAC score with a 1-time CT scan (no surveillance). This approach was cost-effective in patients ≥50 years of age with 3-year risk of PDAC of >0.5% ($65,076 / QALY)[46], or at 66 years of age with risk of 0.5% ($290,123 / QALY) or a risk of 5% ($5,407 / QALY)[47] – summarized in Wang.[40] Note that it was not NOD alone, but NOD in patients stratified into high-risk subgroups.

List 1. *New Onset* Clinical signs and symptoms of and occult PDAC.

A. Pancreatic mass effects.
- Acute pancreatitis; AP (if within 1-2 years*)
- Duct dilatation*
- Cystic lesions (>3 cm*)
- Chronic pancreatitis; CP (if within 1-2 years*)
- Pancreatic atrophy
- Exocrine pancreatic insufficiency (EPI) +/- steatorrhea (e.g. from duct obstruction*)

B. Biliary obstruction
- Enlarged gallbladder (Courvoisier's sign*)
- Elevated liver function (injury) test (LFTs)
- Obstructive jaundice* – (may have dark colored urine and clay-colored stools)

C. Other common signs
- Diabetes mellitus; NOD (without strong family history or obesity and with weigh loss*)
- Unexplained weight loss (>10% of body weight*)
- New onset, unexplained pain (may radiate to the back)
- Loss of appetite
- Nausea and vomiting
- Gastric outlet obstruction
- Depression
- Deep venous thrombosis
- Others

* Represents high-risk biomarkers (OR > 2)

10. Time dependence of biomarker-associated PDAC Risk

The level of risk of new onset signs and symptoms is not persistent and increases (e.g. initial severity of diabetes) then diminishes over time with the duration of NOD diabetes (chart)[48] reaching a population-risk level after 2-3 years. For AP, risk of PDAC after first AP attack approaches that of age-matched controls with time (chart).[49] Quantitatively, the relative risk of PDAC after AP (in older age groups[50]) is ~19x for years 0-2, ~2.5x to 3.5X in years 2-5, and then ~1x at >5 years in two large studies[49, 51], while slightly higher for each category in another study of US veterans.[52] In the latter study, after an AP episode, about 1.5% of patients were diagnosed to have PDAC.[52] One reason is that if the sign or symptom is due to PDAC, then the cancer will likely declare itself within the 1-, 2-, or 3-year timeline. If not, the signal is more likely a false positive and unlikely due to PDAC. For chronic pancreatitis, the hazard ratio (HR) of PDAC was the highest within the first 2 years of the diagnosis of chronic pancreatitis (HR 103.59; 95% CI: 69.25–154.98) and declined substantially thereafter (HR 4.29; 95% CI: 1.97–9.33).[50] Thus, CP remains among the highest non-genetic risk factor for PDAC.

11. CA19-9 as a more specific biomarker of PDAC

CA19-9 is a specific domain of a normal human glycoprotein expressed on the surface of some epithelial cells. However, it is shed in large amounts from PDAC cells and can be measured in the blood as a biomarker of pancreatic cancer.[9, 10] It has been the only FDA approved biomarker for monitoring PDAC progression for years. However, the use for early detection of PDAC is challenging since many people have genetic variants in genes associated with CA19-9 synthesis (*FUT2, FUT3*) that leads to very little CA19-9 production resulting in a false negative test, while others release it in abnormally high amounts leading to false positive interpretation. For a detailed expert review see Whitcomb et al (SMART-MD Journal of Precision Medicine - *hyperlink*).[10]

Table 1. Epidemiology risk of PDAC.

Risk factor	Relative Risk (95% CI)	References
Age	Peak ~ 69Y	SEER data
Sex	Similar (M>W)	SEER data
Ancestry	Similar (B>W)	SEER data
Family history	1.7-1.8	1
Smoking	1.5-2.2	1
"Gastritis"*	1.2-1.7	1, 53
Alcohol consumption (heavy)	1.1-1.5	1
Acute pancreatitis (>2 y prior)*	1.57-2.61	49, 51, 54
Chronic pancreatitis (>2 y prior)	2.7-5.1	1, 53
Diabetes Mellitus (>3 y prior)	1.4-2.2	1
Obesity**	1.2-1.5	53, 55
High red meat / fat diet	1.1-1.5	1
High fruits and vegetables	0.5-1.0	1

Representative relative risk values are from Maisonneuve and Lowenfels.[1] *Gastritis is used here to represent both H. pylori infection[1] and PPI use[53]. The risk of AP is from Kirkegard[51], and similar to Munigala[54] and Jeong[49] **The risk of PDAC in patients with high body mass index may be associated with increased chronic inflammation (measured by c reactive protein, CRP) rather than adipose mass. [53, 55]

12. Defining HRI-C within Patients with New Onset, Non-Specific Biomarkers of PDAC

The likelihood of PDAC within 1 to 3 years of evaluation of non-specific biomarkers (List 1) is highly dependent on their *overall (absolute) risk* for PDAC (high pretest probability). This includes both epidemiology-assessed risks and genetic risks.

Epidemiology-defined risk of PDAC

Epidemiology studies have clearly identified and quantified multiple risk factors summarized on **Table 1**.[1, 48, 53] The relationship between age, sex, and ancestry likelihood for an individual to develop PDAC can be estimated from a U.S.A. population using SEER data from the NCI. Multiple cohort studies, populations-based studies and meta-analysis provide relative risk for the other factors in Table 1. Note that AP, CP and DM can be risk factors (Table 1) and biomarkers (List 1) depending on the timing and underlying etiology. Pancreatic injury any time in a lifetime (e.g. AP) causes permeant immunological and epigenetic changes to the pancreas. Tissue injury and inflammation contributes to DNA damage, damage to acinar cells, ducts and pancreatic islet cells (increasing the likelihood of post-AP diabetes) and drives progression to CP.[56] Post-AP diabetes has a much higher risk of PDAC then DM alone or DM prior to AP or CP.[57] The risk of recurrent AP (RAP) is greater than AP, but for PDAC risk, the highest risk is CP that develops without AP[58] suggesting that there may be alternative pathways driving the CP to PDAC progression in these cases (such as the desmoplastic response to PDAC being misinterpreted as fibrosis from CP).

Genetically defined risk of PDAC

Genetic risk falls into four general categories summarized in **List 2**. The clinical pathway of individuals with high-risk germline PV(s) has been defined by consensus guidelines.[4, 17]. Acquired (somatic) mutations are not considered here. They are critically important for the progressive oncogenesis of PDAC, but currently require tissue collection to detect. Tissue-based molecular diagnostic evaluation can be invaluable, when indicated.[26, 59]

List 2. Types of Genetic Risk of PDAC

1) High-risk PV that causes HCS and have a >5% lifetime risk of PDAC (Mendelian disease model).
2) Lower risk PV variants that may increase the risk of PDAC but do not independently confer a lifetime risk of PDAC of >5%.
3) Patients with a family history of PDAC but without PDAC in FDRs. This type of familial history confers moderately increased risk (OR 1.7-1.8).[1]
4) Polygenic risk scores (PRS) with dozens of genetic factors that are associated with PDAC In genome wide association studies (GWAS) are weighted and combined to provide a PRS to classify risk compared to others within a population.

The second, third and fourth type of genetic variant risk are less well defined, but they are still very important as significant complex risk factors for PDAC (discussed below).

13. Combining risk factors and biomarkers

A risk factor is something that increases the chance of developing a disease (above). When multiple risk factors occur together the overall risk reflects the sum or a multiple of the independent factors (typically calculated as the sum of the natural log of the relative risk or odds ratio of the factors; i.e. nl(OR)).

New onset diabetes becomes more accurate in subsets with additional risk factors for PDAC

NOD is a nonspecific potential biomarker of PDAC (discussed above). However, this biomarker becomes more specific within the context of other risk factors such as age and unintentional weight loss (ENDPAC Score[7]), or multiple factors including age, body mass index, weight change, smoking, diabetes (insulin use, oral hypoglycemics, metformin), proton pump inhibitors (PPI), laboratory results (HbA1c), Hb, total cholesterol, creatinine and alkaline phosphatase[45, 60]). In another study using the UK Biobank, Sharma et al demonstrated that the probably of PDAC in patients with NOD was significantly higher if they had a high PRS for PDAC. These studies demonstrate the importance of evaluating NOD in HRI (defined here by other biomarkers and/or genetic PRS).[61]

Polygenic risk scores (PRS)

PRS are becoming more widely used as an understanding of their development and utility are recognized. The origin of the PRS comes from genome-wide association studies (GWAS), where single nucleotide variants (SNVs) are statistically associated with either cases or controls (see NHGRI blog). For each case and control the sum of all the risk alleles (with protection being inverse of risk) are added together with the number of SNVs displayed on a linear scale, forming a bell curve distribution. However, not all SNVs have the same damaging effects, so the patient's score is usually adjusted by an additional weighting factor for each SNV diplotype. The mean or median values of the control and case curves are compared, allowing a relative risk of the sum of SNV-associated values for each person to be calculated. Since the median number of risks SNVs differs depending on the number of SNVs included (and other factors), the results are often translated into quintiles (5 groups of low risk to high risk) or deciles (10 groups).

Based on the methods to build PRS, most of the SNVs are common (i.e. found in GWAS framing haplotypes). Some PRS may add additional, well established risk variants or PVs. The number of SNVs used is also variable, and can include over a thousand SNVs, although adding multiple exceedingly rare SNVs adds minimal classification value.

For PDAC PRS we currently use the version developed by Sharma[61] (see Sharma discussion on PRS development). However, better PRS are continually being developed since there is variability in SNVs across different ancestries.[62] and more extensive calibration with additional populations is needed. When evaluated in the UK Biobank, patients with high PDAC PRS scores (top 20th percentile) comprised over 29% of PDAC cases, demonstrating the enrichment of PDAC subjects in this versus 12.7% of PDAC patients in the lowest 20th percentile) (Phil Greer MS, personal communications). Thus, PDAC PRS are useful as a risk classifier, but does not predict PDAC since only about 1% of individuals will develop PDAC in their lifetime.

14. Clinical Decision Support Pathway

Figure 1 A clinical decision pathway including the current consensus approach to identifying family history-based HRI for pancreatic cancer screening (top left) and a new complex risk and biomarker-based approach recommended by the authors (bottom, gray).

Box 1. Routine care includes a careful family history and assessment of risk factors or cancers such as PDAC. If the patient has a family history cancer (see text; with or without pathogenic germline genetic variants) then see Box 1 to determine if they are a HRI. If the patient is not a family-based HRI then routine care includes an annual general evaluation (Box 6).

Box 2. The initial step to identify HRI is to take a detailed family history (see text). If the patient has a high-risk family history, then they should be referred to a genetic counselor for germline sequencing of high-risk variants (Box 3). If not, then go to Box 6.

Box 3. Genetic counselors are professionals who are trained in Medical Genetics (not Precision Medicine). They are skilled at evaluating an individual's family tree to determine if the patient meets genetic testing guidelines and to counsel the patient and family. This may include advising the patient on social and ethical issues associated with genetic testing (informed consent) and ordering germline DNA testing if indicated.

Box 4. Genetic counselors and medial geneticist help interpret family histories and DNA sequence to determine if there are pathogenic variants (i.e. disease causing). Genetic counselors also help patients cope with a diagnosis of a life-changing genetic disease. If the patient does not meet HRI criteria, then go to Box 6. If an individual meets criteria for HRI then they should be counseled on the option to enter an annual, image-based surveillance program (Box 5). We recommend that they be referred to a center that specializes in early detection of PDAC for annual image-based testing (see text).

Box 5. Interpretation of pancreatic images requires a specific skillset, and non-expert radiologist may miss PDACs that are detectable on some cross-sectional images.[63] Expert centers are experienced at evaluating images and interpreting other subtle factors, and may have ongoing research projects with the ability to offer additional biomarkers or liquid biopsies for early detection of PDAC. They typically have multidisciplinary teams to rapidly confirm a PDAC diagnosis and initiate treatment rapidly (yellow ellipse). If no neoplasm detected, repeat in 1 year.

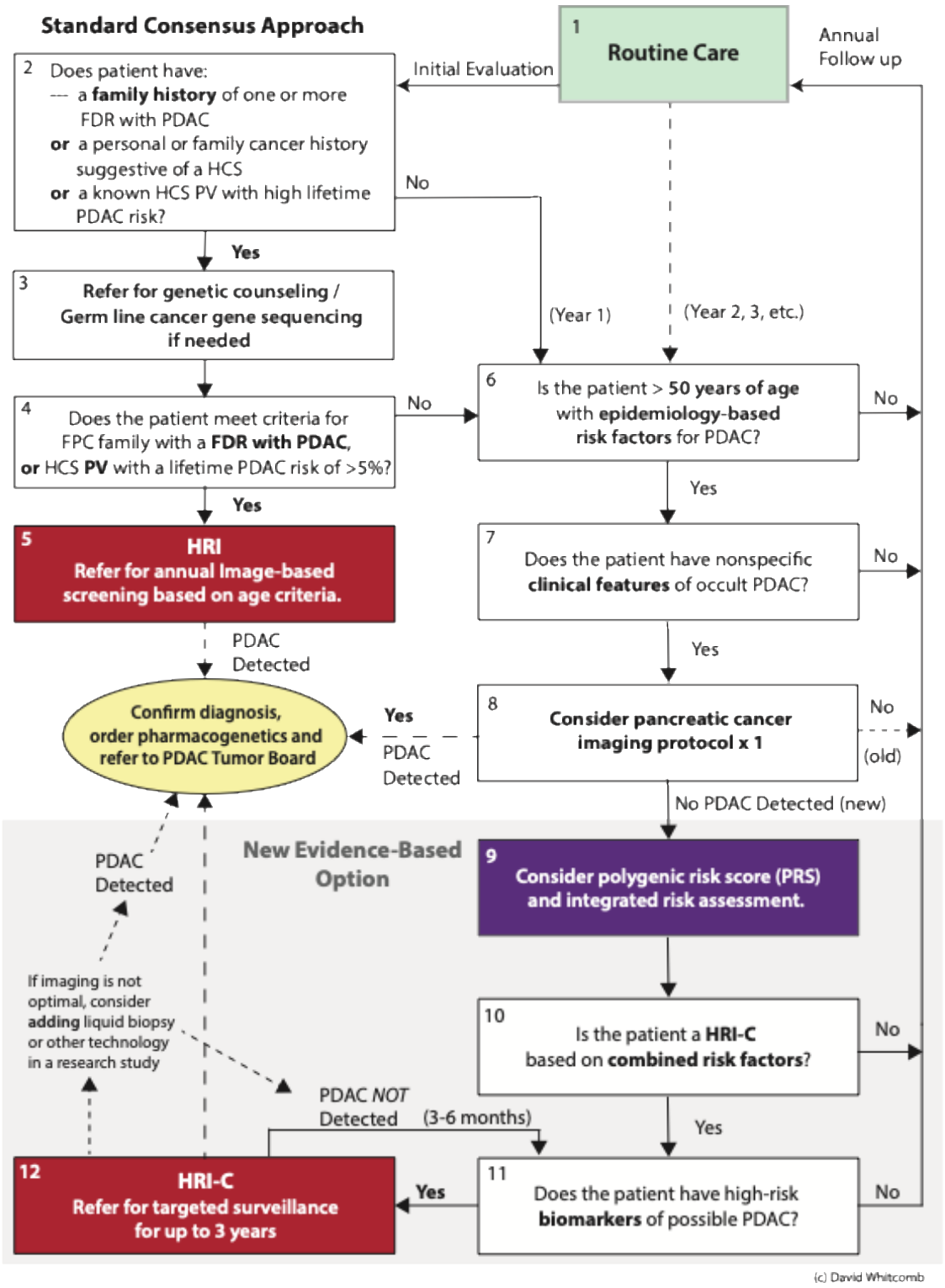

Figure 1. Clinical decision support pathway for PDAC screening. Pathway to Standard Consensus Approach to identify HRI is at the top (triggered by patient family history), and the evidence-based HRI-C is at the bottom (grey, based on age and clinical risk factors). HRI-C pathway begins with patients $\geq$ 50 years of age with history-based risk of PDAC (box 6) and emerging, non-specific clinical features that includes an occult PDAC in the differential diagnosis (Box 7). Red boxes, referral for special testing; purple box; Special diagnostic testing ordered by the managing physician that include genetic risk factors. Dashed lines represent conditional pathways.

Box 6. Routine care includes cancer screening for eligible patients. For PDAC, an age ≥50 years is a population-based risk factor where risk begins increasing significantly. Risk factor associated with PDAC include family history (not meeting HRI criteria), smoking, heavy alcohol drinking, remote (>2 year) history of pancreatitis and diabetes mellitus, hepatitis B (in China)[53] and others (Table 1). If the individual has significant risk factors, then go to Box 7. If not, then return to Routine Care (Box 1).

Box 7. If the patient has multiple risk factors for PDAC (Box 6), then they should be assessed for non-specific biomarkers of PDAC (List 1). If no clinical signs of PDAC are present (e.g. NOD) then the risk of PDAC within the next year is <0.5% (go to Box 1). It there are new onset, non-specific biomarkers of an occult PDAC, go to Box 8.

Box 8. If the patient has multiple epidemiologic risk plus *new onset* non-specific biomarkers of PDAC, and the projected 1-year likelihood of PDAC is >1%, then consider a one-time pancreas-protocol CT scan as a screening test (see text). If the risk unknown or if the screening CT is negative, then we recommend proceeding to Box 9.

Box 9. This step represents a structured analysis of all available data with and integrated risk assessment. *It is critical that all relevant information is included in the assessment in order to calculate an accurate absolute risk assessment.* Here, additional generic analysis is included through a polygenic risk score (PRS). In addition, genetic analysis of the FUT2/FUT3 genotypes should be done to determine predicted cut-off levels for CA19-9 and CEA. As a clinically useful example, The SNaP-Shot: Pancreatic Cancer Biomarker and Risk report (Ariel Precision Medicine, Pittsburgh, PA) automatically calculates these risks factors and biomarkers to give the likelihood of PDAC within the next year and calculates normal limits of CA19-9 and CEA.

Box 10. The decision on whether a patient is designated a complex high-risk individual (**HRI-C**) and sent for image-based screening depends on the likelihood of pancreatic cancer within the next 1 year and a cost-effectiveness analysis. For example, a practice or institution may set the threshold for screening at 1%, 2% or 3% likelihood of PDAC in the next 1, 2 or 3 years. The cost of screening individuals within populations with higher or lower predicted incidents of PDAC is weighed against the QALY in the decision making process.[40] If the overall risk is below threshold, then return to Box 1 (anticipating annual evaluation or sooner if new symptoms develop). If the risk level reaches threshold, then go to Box 11.

Box 11. This decision state is *dynamic* with likelihood of PDAC changing over time based on PDAC biomarker trajectory from the time of onset. The likelihood that AP is caused by an occult PDAC, for example, drops exponentially with time until the overall risk reaches population levels at about 2 years past date of onset (see Ref 50, Fig 1; Ref 51 Fig 1; Ref 52, Fig 2b). In contrast, likelihood increases when biomarkers of disease are progressing such as unexplained NOD, progressive weight loss, or increases of more specific biomarkers of occult PDAC such as CA19-9 levels (see SMART-MD.org *SMART-MD Journal of Precision Medicine* 1(1):14-27). Highest risk biomarkers include those linked directly with pancreatic dysfunction in List 1A and 1B (See also Placido, Tables 5B, 5D[42]). If the specified threshold is met then continue with image-based screening (Box 12). If threshold is not reached then return to usual care (Box 1).

Box 12. HRI-C should be cared for at expert pancreas centers for image-based surveillance (see Box 5). However, the interval follow-up should be shorter (e.g. 3-6 months) and for 2 to 3 years, as the probability of an occult cancer as the cause of worsening high-risk, non-specific biomarkers without progression over 3 years is small (e.g. new AP, NOD - see text). If imaging is sub-optimal (e.g. patients with longstanding CP) consider liquid biopsy, multi-analyte panels or other technology within a research context. If no PDAC is detected return to Box 11 in 3-6 months to repeat the high-risk biomarker tests and reevaluate PDAC likelihood. If the likelihood of pancreatic cancer drops below HRI-C threshold, then return to usual care (Box 1).

15. Discussion

Here we describe a clinically actionable decision support pathway for the early detection and diagnosis of PDAC with anticipated downgrade in the stage at diagnosis and better outcome. Each of the steps has strong supporting evidence components, although prospective analysis of the overall impact of integrating these steps that were designed to maximize efficiency is still needed.

The key principles are that new onset potential biomarkers of pancreatic cancer are non-specific in general, but they are *more* specific in high-risk individuals (i.e. a higher pretest probability). The relative risk of most clinical features is low (e.g. OR <2, Table 1), but the effects are generally additive. Inclusion of genetic risk factors into this equation may increases the absolute risk significantly.

A key component of this approach is including genetic risk factors to include innate risk into the pretest probability equation. The traditional Medical Genetics approach of searching for very high-risk PV in hereditary cancer families is important because the innate risk is high enough to justify image-based screening for pancreatic cancer. But this approach only affects a small fraction of people who develop PDAC. In a similar way, multiple genetic *risk factors* (rather than one *pathogenic variant*) also increase the risk of pancreatic cancer. While pathogenic variants are identified by studies of hereditary cancer families, the genetic risk variants are more common and are identified in pancreatic cancer in genetic association studies. Although the effect of any one variant is low, the more risk variants that an individual harbors, the higher the overall risk of pancreatic cancer. A polygenic risk score (PRS) is the effect-adjusted sum of risk variants. This score is then compared to the distribution of scores in control populations and pancreatic cancer populations to place the individual into a relative risk scale.

The complex-risk HRI-C individuals differ from family history-based HRI by three important features. First, the screening is *triggered* by the new onset of nonspecific *biomarkers* of pancreatic cancer in older individuals, especially new idiopathic AP, new CP without AP, new onset DM, new onset maldigestion/exocrine pancreatic insufficiency, unexplained weight loss and combinations of these biomarkers. Second, the *frequency* of image-based screening is increased to every 3-6 months, rather than yearly. Third, *the screening process ends* with either detection of pancreatic cancer or a change in the biomarker trajectory over time the diminishes the likelihood that the marker is abnormal due to pancreatic cancer.

In summary, effective management of PDAC will require advances in multiple areas including: 1) expanding the pool of high-risk individuals, 2) improvement in early detection technologies including blood-based biomarker test and advanced imaging, 3) diagnosing the cancer at an early stage, and 4) improved therapies for all stages of PDAC. Here, we provide evidence-based arguments for a practical step-by-step clinical decision pathway to identify and manage a much larger fraction of individuals who will develop pancreatic cancer by detecting these cancers at a much earlier stage through image-based screening where therapy is more effective. We believe that this approach will become the standard of care for expanded PDAC screening with an anticipated outcome of saving lives in a cost-effective way.

16. Conclusion

The poor life-expectancy of individuals diagnosed with PDAC is driven by detection and diagnosis at late stages where current therapies are ineffective in achieving complete remission. Non-specific signs and symptoms of occult PDAC often occur months to years before PDAC is diagnosed, typically at advanced stages. The use of genetic testing as a tool to enrich for PDAC risk in individuals with early non-specific signs of PDAC, combined with well-established clinical risk factors, can be used to identify high-risk individuals that we identify as HRI-C. We developed a simple clinical algorithm to help practicing physicians recognize occult PDACs early using image-based screening protocols at expert centers with the possible addition of liquid biopsies and multi-analyte biomarkers within a research setting. Prospective use and evaluation of this approach in real-world clinical settings is needed to determine the impact of this approach in saving lives.

References

1. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol*. 2015;44(1):186-98 D.O.I: 10.1093/ije/dyu240. PMID: 25502106

2. Dbouk M, Katona BW, Brand RE, Chak A, Syngal S, Farrell JJ, et al. The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival. *J Clin Oncol*. 2022;40(28):3257-66 D.O.I: 10.1200/JCO.22.00298. PMID: 35704792

3. Archibugi L, Casciani F, Carrara S, Secchettin E, Falconi M, Capurso G, et al. The Italian registry of families at risk for pancreatic cancer (IRFARPC): implementation and evolution of a national program for pancreatic cancer surveillance in high-risk individuals. *Fam Cancer*. 2024;23(3):373-82 D.O.I: 10.1007/s10689-024-00366-3. PMID: 38493228

4. Daly MB, Pilarski R, Yurgelun MB, Berry MP, Buys SS, Dickson P, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020. *J Natl Compr Canc Netw*. 2020;18(4):380-91 D.O.I: 10.6004/jnccn.2020.0017. PMID: 32259785

5. Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology*. 2015;148(4):824-48 e22 D.O.I: 10.1053/j.gastro.2015.01.014. PMID: 25805376

6. Sharma A, Smyrk TC, Levy MJ, Topazian MA, Chari ST. Fasting Blood Glucose Levels Provide Estimate of Duration and Progression of Pancreatic Cancer Before Diagnosis. *Gastroenterology*. 2018;155(2):490-500 e2 D.O.I: 10.1053/j.gastro.2018.04.025. PMID: 29723506

7. Sharma A, Kandlakunta H, Nagpal SJS, Feng Z, Hoos W, Petersen GM, et al. Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes. *Gastroenterology*. 2018;155(3):730-9 e3 D.O.I: 10.1053/j.gastro.2018.05.023. PMID: 29775599

8. Khan S, Safarudin RF, Kupec JT. Validation of the ENDPAC model: Identifying new-onset diabetics at risk of pancreatic cancer. *Pancreatology*. 2021;21(3):550-5 D.O.I: 10.1016/j.pan.2021.02.001. PMID: 33583686

9. Dbouk M, Abe T, Koi C, Ando Y, Saba H, Abou Diwan E, et al. Diagnostic Performance of a Tumor Marker Gene Test to Personalize Serum CA19-9 Reference Ranges. *Clin Cancer Res*. 2023;29(20):4178-85 D.O.I: 10.1158/1078-0432.CCR-23-0655. PMID: 37566230

10. Whitcomb DC, Oranburg TD, Vallente R, Brand RE. SMART Medical Review: CA 19-9 and pancreatic ductal adenocarcinoma (PDAC).: CA 19-9 and Pancreatic Cancer. *SMART-MD JPM*. 2024;1(1):14-27 D.O.I: https://doi.org/10.69734/psc3br75.

11. Ladabaum U, Dominitz JA, Kahi C, Schoen RE. Strategies for Colorectal Cancer Screening. *Gastroenterology*. 2020;158(2):418-32 D.O.I: 10.1053/j.gastro.2019.06.043. PMID: 31394083

12. Monticciolo DL, Newell MS, Moy L, Lee CS, Destounis SV. Breast Cancer Screening for Women at Higher-Than-Average Risk: Updated Recommendations From the ACR. *J Am Coll Radiol*. 2023;20(9):902-14 D.O.I: 10.1016/j.jacr.2023.04.002. PMID: 37150275

13. Kim JE, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *J Gastroenterol Hepatol*. 2004;19(2):182-6 D.O.I: 10.1111/j.1440-1746.2004.03219.x. PMID: 14731128

14. Konings I, Canto MI, Almario JA, Harinck F, Saxena P, Lucas AL, et al. Surveillance for pancreatic cancer in high-risk individuals. *BJS Open*. 2019;3(5):656-65 D.O.I: 10.1002/bjs5.50180. PMID: 31592073

15. Baydogan S, Mohindroo C, Hasanov M, Montiel MF, Quesada P, Cazacu IM, et al. New-onset diabetes is a predictive risk factor for pancreatic lesions in high-risk individuals: An observational cohort study. *Endosc Ultrasound*. 2024;13(2):83-8 D.O.I: 10.1097/eus.0000000000000057. PMID: 38947744

16. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020;69(1):7-17 D.O.I: 10.1136/gutjnl-2019-319352. PMID: 31672839

17. Sawhney MS, Calderwood AH, Thosani NC, Rebbeck TR, Wani S, Canto MI, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. *Gastrointest Endosc*. 2022;95(5):817-26 D.O.I: 10.1016/j.gie.2021.12.001. PMID: 35183358

18. Tempero MA. NCCN Guidelines Updates: Pancreatic Cancer. *J Natl Compr Canc Netw*. 2019;17(5.5):603-5 D.O.I: 10.6004/jnccn.2019.5007. PMID: 31117041

19. Porter N, Laheru D, Lau B, He J, Zheng L, Narang A, et al. Risk of Pancreatic Cancer in the Long-Term Prospective Follow-Up of Familial Pancreatic Cancer Kindreds. *J Natl Cancer Inst*. 2022;114(12):1681-8 D.O.I: 10.1093/jnci/djac167. PMID: 36029239

20. Molina-Montes E, Gomez-Rubio P, Marquez M, Rava M, Lohr M, Michalski CW, et al. Risk of pancreatic cancer associated with family history of cancer and other medical conditions by accounting for smoking among relatives. *Int J Epidemiol*. 2018;47(2):473-83 D.O.I: 10.1093/ije/dyx269. PMID: 29329392

21. Gonda TA, Farrell J, Wallace M, Khanna L, Janec E, Kwon R, et al. Standardization of EUS imaging and reporting in high-risk individuals of pancreatic adenocarcinoma: consensus statement of the Pancreatic Cancer Early Detection Consortium. *Gastrointest Endosc*. 2022;95(4):723-32 e7 D.O.I: 10.1016/j.gie.2021.10.025. PMID: 34736932

22. Solea SF, Brisc MC, Oraseanu A, Venter FC, Brisc CM, Solea RM, et al. Revolutionizing the Pancreatic Tumor Diagnosis: Emerging Trends in Imaging Technologies: A Systematic Review. *Medicina (Kaunas)*. 2024;60(5) D.O.I: 10.3390/medicina60050695. PMID: 38792878

23. Ohtsuka T, Fernandez-Del Castillo C, Furukawa T, Hijioka S, Jang JY, Lennon AM, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology*. 2024;24(2):255-70 D.O.I: 10.1016/j.pan.2023.12.009. PMID: 38182527

24. Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology*. 2017;17(5):738-53 D.O.I: 10.1016/j.pan.2017.07.007. PMID: 28735806

25. Hamada T, Oyama H, Tange S, Hakuta R, Ishigaki K, Kanai S, et al. The Revised Kyoto Criteria and Risk of Malignancy Among Patients With Intraductal Papillary Mucinous Neoplasms. *Clin Gastroenterol Hepatol*. 2024;22(12):2413-23 e18 D.O.I: 10.1016/j.cgh.2024.05.043. PMID: 38880125

26. Nikiforova MN, Wald AI, Spagnolo DM, Melan MA, Grupillo M, Lai YT, et al. A Combined DNA/RNA-based Next-Generation Sequencing Platform to Improve the Classification of Pancreatic Cysts and Early Detection of Pancreatic Cancer Arising from Pancreatic Cysts. *Ann Surg*. 2023 D.O.I: 10.1097/SLA.0000000000005904. PMID: 37212422

27. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nature Genetics*. 1996;14(2):141-5 D.O.I. PMID: 8841182

28. Shelton CA, Grubs RE, Umapathy C, Yadav D, Whitcomb DC. Impact of hereditary pancreatitis on patients and their families. *J Genet Couns*. 2020 D.O.I: 10.1002/jgc4.1221. PMID: 32026589

29. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary

pancreatitis. *Journal of the American Medical Association*. 2001;286(2):169-70 D.O.I. PMID: 11448279

30. Greenhalf W, Levy P, Gress T, Rebours V, Brand RE, Pandol S, et al. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatology*. 2020;20(5):910-8 D.O.I: 10.1016/j.pan.2020.05.011. PMID: 32624419

31. Tajbakhsh J, Debernardi S, Blyuss O, Bai J, Weng R, Lo S, et al. A CLIA/CAP Compliant Noninvasive Laboratory Developed Test for Early Detection of Pancreatic Ductal Adenocarcinoma. *J Mol Diagn*. 2024 D.O.I: 10.1016/j.jmoldx.2024.10.001. PMID: 39521243

32. Brezgyte G, Shah V, Jach D, Crnogorac-Jurcevic T. Non-Invasive Biomarkers for Earlier Detection of Pancreatic Cancer-A Comprehensive Review. *Cancers (Basel)*. 2021;13(11) D.O.I: 10.3390/cancers13112722. PMID: 34072842

33. Haab B, Qian L, Staal B, Jain M, Fahrmann J, Worthington C, et al. A rigorous multi-laboratory study of known PDAC biomarkers identifies increased sensitivity and specificity over CA19-9 alone. *Cancer Lett*. 2024;604:217245 D.O.I: 10.1016/j.canlet.2024.217245. PMID: 39276915

34. Reyaz I, Khan B, James N, Azhar H, Rehman A, Younas MW, et al. Emerging Horizons in the Diagnosis of Pancreatic Cancer: The Role of Circulating microRNAs as Early Detection Biomarkers for Pancreatic Ductal Adenocarcinoma. *Cureus*. 2024;16(1):e53023 D.O.I: 10.7759/cureus.53023. PMID: 38410292

35. Lai X, Wang M, McElyea SD, Sherman S, House M, Korc M. A microRNA signature in circulating exosomes is superior to exosomal glypican-1 levels for diagnosing pancreatic cancer. *Cancer Lett*. 2017;393:86-93 D.O.I: 10.1016/j.canlet.2017.02.019. PMID: 28232049

36. Zhao Y, Tang J, Jiang K, Liu SY, Aicher A, Heeschen C. Liquid biopsy in pancreatic cancer - Current perspective and future outlook. *Biochim Biophys Acta Rev Cancer*. 2023;1878(3):188868 D.O.I: 10.1016/j.bbcan.2023.188868. PMID: 36842769

37. Binkowski B, Klamer Z, Gao C, Staal B, Repesh A, Tran HL, et al. Multiplexed Glycan Immunofluorescence Identification of Pancreatic Cancer Cell Subpopulations in Both Tumor and Blood Samples. *bioRxiv*. 2024 D.O.I: 10.1101/2024.08.22.609143. PMID: 39229066

38. Perry LM, Bateni SB, Bold RJ, Hoch JS. Is Improved Survival in Early-Stage Pancreatic Cancer Worth the Extra Cost at High-Volume Centers? *Journal of the American College of Surgeons*. 2021;233(1):90-8 D.O.I: 10.1016/j.jamcollsurg.2021.02.014. PMID: 33766724

39. Peters MLB, Eckel A, Seguin CL, Davidi B, Howard DH, Knudsen AB, et al. Cost-Effectiveness Analysis of Screening for Pancreatic Cancer Among High-Risk Populations. *JCO Oncol Pract*. 2024;20(2):278-90 D.O.I: 10.1200/OP.23.00495. PMID: 38086003

40. Wang L, Levinson R, Mezzacappa C, Katona BW. Review of the cost-effectiveness of surveillance for hereditary pancreatic cancer. *Fam Cancer*. 2024;23(3):351-60 D.O.I: 10.1007/s10689-024-00392-1. PMID: 38795221

41. Ibrahim IS, Vasen HFA, Wasser M, Feshtali S, Bonsing BA, Morreau H, et al. Cost-effectiveness of pancreas surveillance: The CDKN2A-p16-Leiden cohort. *United European gastroenterology journal*. 2023;11(2):163-70 D.O.I: 10.1002/ueg2.12360. PMID: 36785917

42. Placido D, Yuan B, Hjaltelin JX, Zheng C, Haue AD, Chmura PJ, et al. A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories. *Nat Med*. 2023;29(5):1113-22 D.O.I: 10.1038/s41591-023-02332-5. PMID: 37156936

43. Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology*. 2008;134(1):95-101 D.O.I: 10.1053/j.gastro.2007.10.040. PMID: 18061176

44. Shah I, Wadhwa V, Bilal M, Germansky KA, Sawhney MS, Pancreas Cancer Screening Study G. Prospective Assessment for Prediabetes and New-Onset Diabetes in High-Risk Individuals Undergoing Pancreatic Cancer Screening. *Gastroenterology*. 2021;161(5):1689-91 e1 D.O.I: 10.1053/j.gastro.2021.06.055. PMID: 34175285

45. Boursi B, Finkelman B, Giantonio BJ, Haynes K, Rustgi AK, Rhim AD, et al. A Clinical Prediction Model to Assess Risk for Pancreatic Cancer Among Patients With New-Onset Diabetes. *Gastroenterology*. 2017;152(4):840-50 e3 D.O.I: 10.1053/j.gastro.2016.11.046. PMID: 27923728

46. Kowada A. Cost-effectiveness of Abdominal Ultrasound Versus Magnetic Resonance Imaging for Pancreatic Cancer Screening in Familial High-Risk Individuals in Japan. *Pancreas*. 2020;49(8):1052-6 D.O.I: 10.1097/MPA.0000000000001614. PMID: 32769852

47. Schwartz NRM, Matrisian LM, Shrader EE, Feng Z, Chari S, Roth JA. Potential Cost-Effectiveness of Risk-Based Pancreatic Cancer Screening in Patients With New-Onset

Diabetes. *J Natl Compr Canc Netw*. 2021;20(5):451-9 D.O.I: 10.6004/jnccn.2020.7798. PMID: 34153945

48. Grigorescu RR, Husar-Sburlan IA, Gheorghe C. Pancreatic Cancer: A Review of Risk Factors. *Life (Basel)*. 2024;14(8) D.O.I: 10.3390/life14080980. PMID: 39202722

49. Jeong SH, Hurh K, Park EC, Leigh JH, Kim SH, Jang SI. Risk of Pancreatic Cancer After Acute Pancreatitis: A Retrospective Analysis of the Korean National Sample Cohort. *J Korean Med Sci*. 2024;39(4):e21 D.O.I: 10.3346/jkms.2024.39.e21. PMID: 38288535

50. Sadr-Azodi O, Oskarsson V, Discacciati A, Videhult P, Askling J, Ekbom A. Pancreatic Cancer Following Acute Pancreatitis: A Population-based Matched Cohort Study. *Am J Gastroenterol*. 2018;113(11):1711-9 D.O.I: 10.1038/s41395-018-0255-9. PMID: 30315287

51. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, Mortensen FV. Acute Pancreatitis and Pancreatic Cancer Risk: A Nationwide Matched-Cohort Study in Denmark. *Gastroenterology*. 2018;154(6):1729-36 D.O.I: 10.1053/j.gastro.2018.02.011. PMID: 29432727

52. Munigala S, Kanwal F, Xian H, Scherrer JF, Agarwal B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014;12(7):1143-50 e1 D.O.I: 10.1016/j.cgh.2013.12.033. PMID: 24440214

53. Chandana SR, Woods LM, Maxwell F, Gandolfo R, Bekaii-Saab T. Risk factors for early-onset pancreatic ductal adenocarcinoma: A systematic literature review. *Eur J Cancer*. 2024;198:113471 D.O.I: 10.1016/j.ejca.2023.113471. PMID: 38154392

54. Munigala S, Almaskeen S, Subramaniam DS, Bandi S, Bowe B, Xian H, et al. Acute Pancreatitis Recurrences Augment Long-Term Pancreatic Cancer Risk. *Am J Gastroenterol*. 2023;118(4):727-37 D.O.I: 10.14309/ajg.0000000000002081. PMID: 36473072

55. Li Z, Jin L, Xia L, Li X, Guan Y, He H. Body mass index, C-reactive protein, and pancreatic cancer: A Mendelian randomization analysis to investigate causal pathways. *Front Oncol*. 2023;13:1042567 D.O.I: 10.3389/fonc.2023.1042567. PMID: 36816931

56. Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. *Pancreatology*. 2016;16:218-24 D.O.I: 10.1016/j.pan.2016.02.001. PMID: 26924663

57. Cho J, Scragg R, Petrov MS. Postpancreatitis Diabetes Confers Higher Risk for Pancreatic Cancer Than Type 2 Diabetes: Results From a Nationwide Cancer Registry. *Diabetes Care*. 2020 D.O.I: 10.2337/dc20-0207. PMID: 32616613

58. Cook ME, Bruun NH, Davidsen L, Drewes AM, Olesen SS. Multistate Model of the Natural History of Inflammatory Pancreatic Diseases: A Nationwide Population-based Cohort Study. *Gastroenterology*. 2023;165(6):1547-57 e4 D.O.I: 10.1053/j.gastro.2023.08.042. PMID: 37659669

59. Singhi AD, Nikiforova MN, Chennat J, Papachristou GI, Khalid A, Rabinovitz M, et al. Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures. *Gut*. 2020;69(1):52-61 D.O.I: 10.1136/gutjnl-2018-317817. PMID: 30971436

60. Boursi B, Finkelman B, Giantonio BJ, Haynes K, Rustgi AK, Rhim AD, et al. A clinical prediction model to assess risk for pancreatic cancer among patients with prediabetes. *Eur J Gastroenterol Hepatol*. 2022;34(1):33-8 D.O.I: 10.1097/MEG.0000000000002052. PMID: 33470698

61. Sharma S, Tapper WJ, Collins A, Hamady ZZR. Predicting Pancreatic Cancer in the UK Biobank Cohort Using Polygenic Risk Scores and Diabetes Mellitus. *Gastroenterology*. 2022;162(6):1665-74 e2 D.O.I: 10.1053/j.gastro.2022.01.016. PMID: 35065983

62. Bogumil D, Conti DV, Sheng X, Xia L, Shu XO, Pandol SJ, et al. Replication and Genetic Risk Score Analysis for Pancreatic Cancer in a Diverse Multiethnic Population. *Cancer Epidemiol Biomarkers Prev*. 2020;29(12):2686-92 D.O.I: 10.1158/1055-9965.EPI-20-0963. PMID: 32958499

63. Cao K, Xia Y, Yao J, Han X, Lambert L, Zhang T, et al. Large-scale pancreatic cancer detection via non-contrast CT and deep learning. *Nat Med*. 2023;29(12):3033-43 D.O.I: 10.1038/s41591-023-02640-w. PMID: 37985692

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