REVIEW

Early prediction of pancreatic cancer from new-onset diabetes: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Società Italiana Endocrinologia (SIE)/Società Italiana Farmacologia (SIF) multidisciplinary consensus position paper

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Pancreatic cancer (PC) is a common cause of cancer-related death, due to difficulties in detecting early-stage disease, to its aggressive behaviour, and to poor response to systemic therapy. Therefore, developing strategies for early diagnosis of resectable PC is critical for improving survival. Diabetes mellitus is another major public health problem worldwide. Furthermore, diabetes can represent both a risk factor and a consequence of PC: nowadays, the relationship between these two diseases is considered a high priority for research. New-onset diabetes can be an early manifestation of PC, especially in a thin adult without a family history of diabetes. However, even if targeted screening for patients at higher risk of PC could be a promising approach, this is not recommended in asymptomatic adults with new-onset diabetes, due to the much higher incidence of hyperglycaemia than PC and to the lack of a safe and affordable PC screening test. Prompted by a well-established and productive multidisciplinary cooperation, the Italian Association of Medical Oncology (AIOM), the Italian Medical Diabetologists Association (AMD), the Italian Society of Endocrinology (SIE), and the Italian Society of Pharmacology (SIF) here review available evidence on the mechanisms linking diabetes and PC, addressing the feasibility of screening for early PC in patients with diabetes, and sharing a set of update statements with the aim of providing a state-of-the-art overview and a decision aid tool for daily clinical practice.
Key words: diabetes, pancreatic carcinoma, early diagnosis, consensus, hyperglycaemia

INTRODUCTION

According to the World Health Organization (WHO), pancreatic cancer (PC) is the seventh leading cause of cancer-related death in both sexes worldwide, in spite of its relatively low incidence (12.9 per 100 000 person-years).[1] Up to 95% of these tumours arise from exocrine pancreas, the vast majority (85%) from the ductal epithelium. PC incidence and death rates vary with age, sex, and race/ethnicity: the disease is rare in young adults (<45 years of age) peaking in the 7th and 8th decades,[2,3] with a slightly higher incidence in males (M/F: 1.3/1) and in black people. PC prognosis is extremely poor (overall survival <10% at 5 years): this is largely due to the difficulties in identifying PC at an early stage as well as its aggressive behaviour (local invasion, distant metastases, and poor

response to therapy).[4,5] The development of strategies for early diagnosis of resectable PC is therefore critical for improved survival rates.

A family history of PC, chronic pancreatitis, intraductal papillary mucinous neoplasm (IPMN), gallstone disease, and pancreatic cyst are the main non-modifiable risk factors. The vast majority of PCs arise sporadically with limited family history. Lifestyle plays an important role since tobacco, alcohol consumption, physical inactivity, obesity, and unhealthy diet are all well recognized risk factors for the pathogenesis of PC.[6] Hyperglycaemia is also associated with an increased risk: it is now clear that diabetes mellitus (DM) can represent both a risk factor and a consequence of PC. Indeed, patients with DM show a twofold risk of developing PC compared with the general population,[7,8] and people with new-onset DM (NOD) show a sixfold to eightfold higher risk of being diagnosed with PC within 36 months, with a 3-year incidence of PC being ∼1%.[9,10] As a consequence, NOD in a thin, older adult, as well as a sudden worsening of a pre-existent DM, should prompt consideration of screening for early detection of a potentially resectable PC.

DM is a major public health problem worldwide. The absolute number of people with DM is steadily increasing all over the world. According to the International Diabetes Federation (IDF), 463 million people have DM (1 in 11 adults), and by 2030 the number of people aged >65 years with DM is expected to reach 195 million (276 million by 2045).[11]

Arguably, both the prevalence of DM and the incidence (and mortality) of PC will continue to rise as the population ages, in Westernized countries.[12] The National Cancer Institute (NCI) has acknowledged that studying the relationship between DM and PC is a high priority for research in this field.[9,13] Population-based screening for PC is not recommended in older, otherwise asymptomatic adults with NOD, due to the high incidence of DM, to the lack of a safe and affordable PC screening test, and to the fact that it would discover only a small number of PCs.[14] However, a targeted screening for patients at increased risk of PC could represent a promising approach for early detection, thereby improving survival.[15] Identification of features differentiating PC-associated DM from other cases of NOD would help direct screening efforts to the subgroup of people who would most benefit from this strategy.

To better analyze this topic, a multidisciplinary panel of experts from four Italian scientific societies [the Italian Medical Diabetologists Association (AMD), the Italian Association of Medical Oncology (AIOM), the Italian Society of Endocrinology (SIE), and the Italian Society of Pharmacology (SIF)], met with the following aims: to review published data on the mechanisms linking PC and DM; to describe the difficulties in the early detection of PC among people with NOD; and to address the feasibility of screening for early PC in patients with DM. To the purposes of this consensus, the research of the multidisciplinary panel focused on pancreatic ductal adenocarcinoma, the most common PC. An in-depth review of available literature was collegially conducted, and the analysis carried out led the multidisciplinary group to share a set of update statements, providing a state-of-the-art overview and a decision aid tool for clinical practice.

MATERIALS AND METHODS

A web-based search of MEDLINE/PubMed library data published for all relevant studies up to December 2020 was carried out using the following keywords: 'Pancreatic Neoplasms/diagnosis*' OR 'Pancreatic Neoplasms/epidemiology' OR 'Carcinoma, Pancreatic Ductal/diagnosis' AND 'Diabetes Mellitus, Type 2' AND 'Early Detection of Cancer*' OR 'Early Diagnosis' OR 'Patient-Specific Modeling*' OR 'Risk Assessment' OR 'Biomarkers, Tumor/blood' OR 'CA-19-9 Antigen/blood*'. Only papers written in English were included. Forty-six papers were selected by the authors. Each paper was retrieved and its references were reviewed to identify additional studies. Furthermore, the authors searched scientific societies' recommendations on this topic. A panel of experts appointed by AMD and AIOM provided additional biological and clinical information, which helped greatly in clarifying some issues in the absence of clear-cut information from the literature. The final draft was then submitted to the evaluation of experts from each scientific society, and modified according to their suggestions and comments.

Epidemiology and pathophysiology

A bidirectional and complex association between PC and DM has been documented in many epidemiological studies.[16] DM is a metabolic disorder of two major subtypes (type 1 and type 2) with multiple aetiology, characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism due to defects in insulin secretion, action, or both. Type 2 DM (T2DM) comprises >90% of all cases of diabetes, is the most common type in older populations, and steps up with aging. In the last few decades, the prevalence of DM has been increasing annually by 0.3%-0.5% and raised from 5.8% in 2006 to 9.3% in 2019, as reported by the IDF, and it has been estimated that the figure will increase to 10.2% by 2030. T2DM spread and the huge health care burden further distinguish it from pancreatogenic or type 3c diabetes (T3cDM), which has been classified as diabetes secondary to pancreatic exocrine disease (e.g. pancreatitis, haemochromatosis, and cystic fibrosis), even if the mechanisms and pathogenesis of DM in these latter diseases seem to be different from those in PC. Indeed, T2DM has been associated with an increased risk for several human cancers, such as liver, colorectal, endometrial, bladder, breast, and PC.[8,17]

Medications used in the treatment of T2DM may independently modify the risk of PC, even if evidence is poor. Indeed, it has been suggested that metformin reduces PC risk, whereas insulin may increase it. Preliminary evidence suggesting an association between incretin-based medications, including glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl-peptidase-4 (DPP-4) inhibitors, and

chronic pancreatitis, leading with time to PC, has not been definitively confirmed by large-scale epidemiological studies or by recently published cardiovascular outcome trials.

The most frequent pancreatic malignant tumor is ductal adenocarcinoma.[18] In 2018 the Global Cancer Observatory, an interactive web-based platform, referred that PC is the 14th neoplasm worldwide, sorting by new cases per year, and the recent Cancer Statistics Review reported that the trend of incidence of PC, through years, is stepping up.[19] Due to its poor prognosis, PC is the seventh leading cause of cancer death worldwide.[1] The association between DM and PC seems quite clear and their relationship intertwined, with NOD as a clue as well as an attractive screening tool for early detection of PC. Both diseases currently show a globally progressive increased incidence. DM and PC also share several modifiable common risk factors, such as cigarette smoking, obesity, alcohol intake, fatty diet, insulin resistance, and high levels of circulating insulin.[20] The strong association between obesity and PC, for instance, has been mainly attributed to insulin resistance (with resulting hyperinsulinemia) and chronic inflammation.

DM has been implicated as a predisposing factor for PC.[21-23] Impaired glucose tolerance or overt DM is present in 80% of patients with PC, and longstanding DM shows a twofold relative risk for PC compared with the general population.[24] Hyperglycaemia could promote cancer progression by enhancing metabolic capacities of cancer cells,[25] protecting cancer cells from cytochrome c-mediated apoptosis,[26] and facilitating PC metastasis, resulting in a more aggressive cancer phenotype.[27] Moreover, hyperglycaemia, insulin resistance, hyperinsulinism, low-grade inflammation and alteration in the insulin-like growth factor axis, which are cornerstones of DM, have been associated with PC.[28,29] However, considering overall data, DM seems to be a modest risk factor for the development of PC. By contrast, strong epidemiological and clinical evidence supports that PC may be a risk factor for DM. Duration of DM inversely correlates with the relative risk of PC, and the diagnosis of PC peaks shortly after (or before) diagnosis of DM, supporting the hypothesis that DM may be a consequence of the neoplasia.[30]

PC may cause pancreatic duct obstruction and atrophy of the pancreas worsening insulin secretion even if, at DM onset, there is frequently no radiographically detectable mass or pancreatic atrophy.[31] Moreover, beta-cell loss should result in low insulin levels, while PC is usually associated with high insulin levels and marked insulin resistance.[32] Furthermore, available data support the hypothesis that cancer cells might induce paraneoplastic beta-cell dysfunction, inhibit insulin secretion, and induce DM, thus representing an early disease manifestation rather than a predisposing risk factor.[33] The markedly increased risk of PC in patients with NOD compared with longstanding DM, and resolution or amelioration of DM with cancer-related therapies support this hypothesis.[34] Notwithstanding the foregoing, reverse causality, lifestyle changes after diabetes diagnosis, or use of certain antidiabetic medications may be misleading factors in addressing the relationship between DM and PC. The interaction between DM and PC remains a matter of debate and further investigation is needed to address this issue.

Pancreatogenic diabetes (T3cDM)

T3cDM is often misdiagnosed as T2DM, due also to insufficient knowledge differentiating typical features between the two types of diabetes. The true worldwide prevalence of T3cDM is unknown. Some older studies estimated a low prevalence around 0.5%-1.15% among all cases of DM in North America.[35] Other studies from South East Asia, where tropical or fibrocalcific pancreatitis is endemic, showed a greater prevalence of nearly 15%-20% of all patients with DM. Recent reviews estimated a prevalence of 5%-10% among all patients with DM in Western populations, indicating that the condition is more common than generally thought.[36] Chronic pancreatitis seems to be the main underlying cause of T3cDM. Until additional studies are carried out, it is reasonable to assume that the true prevalence of T3cDM probably ranges from 1% to 9% of all cases of DM, with 4%—5% as a reasonable estimate.[37]

The pathophysiology of T3cDM is mostly linked to that of pancreatic inflammation and irreversible fibrosis of islet cell that progresses to islet cell loss. In the early phase of T3cDM, the damage involves β-cell mass but also pancreatic polypeptide-secreting cells. In the late phase of the disease, the damage involves α-cells resulting in decreased glucagon levels.[38] Differently from T2DM, β-cell function is not the only one to be impaired in T3cDM. The pathophysiology of the disease is explained by considering five major functional changes: insulin deficiency, insulin resistance, pancreatic immunopathogenesis, reduced incretin effect, and genetic association with the disease[36] (Tables 1 and 2).

Biological tests and predictive models to detect PC in people with diabetes

Early PC detection is challenging, and many efforts have been made in recent years to select high-risk subjects for targeted screenings. Since most patients with early-stage PC are asymptomatic, a specific and sensitive screening system seems the only way to get to an early detection.

Carbohydrate antigen 19-9. Carbohydrate antigen 19-9 (CA19-9) is one of the most important and widely used blood biomarkers for PC. Some studies tested CA19-9 as a population screening test for PC. The largest one found abnormal levels of CA19-9 in ∼1000 out of >70 000 asymptomatic subjects, but only 4 were actually affected by PC.[40] CA19-9 levels can be raised not only in PC, but also in benign diseases of pancreas, biliary tract, and other organs (Table 3), but there is some evidence that its levels are significantly greater for malignant than for benign diseases.[42] A cut-off of 75 U/ml showed a sensitivity and specificity of 69.5% and 98.2% for the detection of PC, respectively, but mostly in advanced stages.[5] It has moreover been reported that ∼5% of the population are Lewis blood group-negative [Le (a-b-)] and cannot synthesize

Table 1. Differential characteristics of T2DM and T3cDM

	T2DM	T3cDM
Age at onset	Adult	Childhood/adult
Risk factors	- Obesity - Sedentary lifestyle - Inheritance - History of gestational diabetes	- Acute/chronic pancreatitis - Cystic fibrosis - Hemochromatosis - Pancreatic cancer - Pancreatectomy
Pathogenesis	- Progressive insulin secretory defect on the background of insulin resistance - Impairment in insulin signalling pathways and reduced expression of glucose transporters in insulin sensitive tissues - Increased blood glucose level due to insulin resistance - Hyperinsulinemia in the early phase - Reduced insulin secretion in the late phase due to beta-cell damage causing insulin deficiency	- Inflammation, fibrosis in pancreatic tissue and subsequent damage - Reduction in insulin receptor and glucose transporter (GLUT2) in hepatocytes causing hepatic insulin resistance - In the early phase, β-cell and exocrine pancreatic cell damage cause hypoinsulinemia, PP, and pancreatic enzyme insufficiency - In the late phase, α-cell damage causes reduced glucagon levels contributing to hypoglycaemic episodes - Reduced incretin (GIP) and PP levels due to islets damage - Reduced pancreatic enzyme level due to exocrine tissue damage
Diagnostic criteria	- Absence of type 1 diabetes mellitus autoimmune markers - Hyperinsulinemia/insulin resistance in the early phase of the disease - Hypoinsulinemia in the late phase of the disease - Reduced peripheral and hepatic insulin sensitivity	- Presence of exocrine pancreatic insufficiency (monoclonal faecal elastase-1 test or direct function tests) - Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT) - Absence of type 1 diabetes mellitus autoimmune markers - Impaired incretin secretion - Low serum levels of lipid soluble vitamins (A, D, E and K)

CT, computed tomography; GIP, gastric inhibitory peptide; MRI, magnetic resonance imaging; PP, pancreatic polypeptide; T2DM, type 2 diabetes mellitus; T3cDM, type 3c diabetes mellitus.

CA19-9: these individuals may show false negative levels of CA19-9.[43]

Circulating tumor DNA. Cell-free DNA (cfDNA) is composed of non-encapsulated DNA fragments circulating in the bloodstream derived from dying cells and has an average length of 170 bases.[44] Cancer-cell derived cfDNA (circulating tumor DNA, ctDNA) detection represents a promising strategy for the early detection of different types of cancer: high levels of ctDNA have been shown in >85% of patients with advanced forms of several cancers, but a smaller significant fraction of patients with earlier stages of cancer showed detectable levels of ctDNA.[45]

Pancreatic metabolites. Other pancreatic metabolites, such as docosahexaenoic acid, LysoPC (14:0) and histidyl-lysine[46]

Table 2. Clinical and laboratory findings in T2DM and T3cDM

	T2DM	T3cDM
Ketoacidosis	Rare	Rare
Hypoglycemia	Rare	Common
Peripheral insulin sensitivity	Decreased	Increased
Hepatic insulin sensitivity	Normal or decreased	Decreased
Insulin levels	High or normal (inappropriate for elevated glucose)	Normal (inappropriate for elevated glucose) or low
PP levels	Normal or high	Low or absent
Glucagon levels	Normal or high	Normal or low
GIP levels	Variable	Low
GLP1 levels	Variable	Variable

GIP, gastric inhibitory peptide; GLP1, glucagon-like peptide 1; PP, pancreatic polypeptide; T2DM, type 2 diabetes mellitus; T3cDM, type 3c diabetes mellitus.

Adapted from Andersen et al.[38] and Cui and Andersen.[39]

and microRNA blood levels alterations (such as miR-20b-5p, miR-29a, and miR-18a-5p) have recently been proposed as promising biomarkers for detecting PC in NOD patients.[47]

Combination tests. Cohen et al.[48] found KRAS mutations in the ctDNA in 30% of stage I and II (American Joint Committee on Cancer, AJCC) PC patients, respectively: this rate was higher in stage II versus stage I, and in larger versus smaller neoplasms. Interestingly, they also tested for this mutation plus a 'combination assay' of protein biomarkers: carcinoembryonic antigen (CEA), hepatocyte growth factor (HGF), and osteopontin (OPN). This assessment succeeded in detecting 64% of resectable PCs. Mellby et al.[49] carried out a large proteomic study on >1700 case-control samples to find out a biomarker signature enabling early PC detection: the group selected a panel of 29 biomarkers (CA19-9 was not included) (Table 4) that has been validated in an independent case-control study. This panel showed a robust sensitivity/specificity of 93%/95% for stage I and II PC versus controls; diabetes, including NOD, was not a confounding factor in the classification of noncancer versus PC patients. In the validation cohort, the results showed a specificity of 99% and a positive/negative predictive value of 0.46/1.0 in patients with higher risk of PC, such as patients with NOD older than 55 years.

New perspectives may come from initiatives such as the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC), which was activated in 2015 by the NCI and the National Institute of Diabetes and Digestive and Kidney Disease (NIDDKD). Among its main objectives, the project includes the identification of effective approaches to early detection of pancreatic ductal

Table 3. Pathological conditions associated with increased levels of carbohydrate antigen 19-9 (CA19-9) besides pancreatic cancer

Organ/system	Pathologic condition
Pancreatic diseases[a]	Acute pancreatitis
	Chronic pancreatitis
	Pancreatic abscess
	Pseudo-pancreatic cyst
Hepatobiliary diseases[b]	Cholangiocarcinoma
	Cholangitis
	Choledocholithiasis
	Cholelithiasis
	Cirrhosis of liver
	Hepatitis
	Hepatocellular carcinoma
	Liver cyst
	Liver abscess
	Polycystic liver disease
Gastrointestinal malignancies[c]	Colorectal cancer
	Esophageal cancer
	Gastric cancer
Miscellaneous[d]	Bronchitis
	Congestive heart failure
	Cystic fibrosis
	Diverticulitis
	Hashimoto's thyroiditis
	Lung cancer
	Ovarian cyst
	Pleural effusion
	Renal cyst
	Rheumatoid arthritis

CA 19-9 ranges: [a]3-22 U/ml; [b]50-99,000 U/ml; [c]37-100 U/ml; [d]112-1338 U/mL.

Modified from Ballehaninna and Chamberlain.[41]

Table 4. Consensus signature of biomarkers for pancreatic cancer

Apolipoprotein A1
Aprataxin and PNK-like factor
Calcineurin B homologous protein 1
Calcium/calmodulin-dependent protein kinase type IV
Complement C3, C4, and C5
Cyclin-dependent kinase 2
Disks large homolog 1
GTP-binding protein GEM
HADH2 protein
Intercellular adhesion molecule 1
IFN-γ
IL-4, IL-6, IL-13
Lewis x
Lymphotoxin-alpha
Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 1
Myomesin-2
Plasma protease C1 inhibitor
PR domain zinc finger protein 8
Properdin
Protein kinase C zeta type
Protein-tyrosine kinase 6
Serine/threonine-protein kinase MARK1
Sialyl Lewis x
VEGF
Visual system homeobox 2

GTP, guanosine triphosphate; IFN, interferon; IL, interleukin; MARK1, microtubule affinity regulating kinase 1; PNK, polynucleotide kinase; VEGF, vascular endothelial growth factor.

Modified from Mellby et al.[49]

adenocarcinoma among people with NOD. This project plans to establish a large prospective cohort involving 10 000 participants with NOD at >50 years of age. Many clinical and biological data shall be collected and evaluated from this high-risk group, according to the concept of biorepository and data registry (from health records, biological fluids, tissues, radiological images, etc.), therefore validating effective biomarkers and predictive risk models for an early detection of PC.[9]

Predicting models. In recent years, efforts have been made to create a score to assess the risk of PC in patients with NOD. An example is the UK model The Health Improvement Network (THIN): based on electronic health records, Boursi et al.[50] developed a model able to identify the population with a 5% 3-year predicted risk of ductal PC among people with NOD, with 11% sensitivity and 99.7% specificity (AUC 0.82). This model incorporates age, body mass index (BMI) change, smoking, diabetes medications, proton pump inhibitors, changes in haemoglobin A1c, total cholesterol, creatinine and alkaline phosphatase.[50] The same model evidenced lower accuracy (AUC 0.71) if applied to individuals with pre-diabetes, with good discrimination and calibration.[51]

Sharma et al.[10] proposed another model named Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC). They conducted a retrospective cohort study of 1561 patients with NOD and developed a model that included three factors: change in body weight and change in blood glucose from 1 year before diabetes diagnosis, and age at onset. An END-PAC score of ≥3 found out PC with a sensitivity of 78%, specificity of 82%, and increased the PC prevalence of 0.82% in the population-based cohort to 3.6% (4.4-fold).[10] Patients with NOD should be considered at high risk with a score of ≥3, low risk if ≤0, and intermediate risk with a score of 1-2. High-risk patients should undergo imaging to exclude PC [computed tomography (CT) and endoscopic ultrasound (EUS)], low-risk patients can definitely be considered as affected by T2DM, whereas intermediate-risk patients are the most troublesome: these patients are the best candidates for the tests mentioned in the previous section.[52] Unfortunately, these tests are not widely available and do not seem to be cost-effective.

Munigala et al.[53] made a further attempt toward a predictive model. In a large cohort of patients with NOD (>73 000 people) they evaluated the incidence of PC and assessed its risk based on five factors: being non-obese [relative risk (RR) = 1.51], ≥65 years of age (RR = 2.01), heavy smoker (RR = 1.55), with a history of chronic pancreatitis (RR = 4.72), or gallstone disease (RR = 2.02). The combination of these risk factors in NOD resulted in up to 0.72% 3-year risk of PC. In any case, this likelihood was considered as not being high enough to recommend further evaluation of all these patients for underlying PC.

The ongoing DETECT study (on behalf of the CPDPC) will examine differences in hormone and glucose excursions following a mixed meal test in order to distinguish T2DM from pancreatogenic diabetes, based on the different pathophysiological mechanisms underlying the two conditions. The aim of this study will also be to create a repository of specific biomarkers.[54]

How to screen patients with DM for PC

Early detection of PC is generally regarded as the only way to improve overall long-term patient survival.[55] In the early stages of the disease [pancreatic intraepithelial neoplasia (PanIN), stage I] most patients are either asymptomatic or present non-specific symptoms, such as pyrosis, abdominal discomfort, and weight loss. When symptoms attributable to PC occur, the disease is at an already advanced stage and surgical resection is usually unfeasible.[56] Since PC is rather uncommon, a generalized screening of asymptomatic adults is strongly discouraged,[14] and none of the main PC identification imaging technologies are cheap or simple enough to be used in more widespread screening. The pre-test probability should be ≥16% for PC screening to be cost-effective.[57] Nonetheless, an interesting publication suggests that PC screening should be carried out only in a population with a risk of 5% or higher.[58]

Chari[59] propose the use of two 'sieves' for the selection of the population to be screened: the first sieve is for high-risk patients (hereditary PC, NOD), whereas the second one is for specific characteristics of these high-risk groups (known risk factors, suggestive symptoms, serum biomarkers, non-invasive imaging).

Elderly patients with NOD show a sixfold to eightfold higher risk of sporadic PC compared with the general population.[60] This risk is not high enough to call for a direct surveillance with diagnostic imaging, and this group should be 'enriched' with biomarkers or image-based modalities of clinical risk assessment.[61] Discerning between T2DM and T3cDM would be of the utmost importance, but there are no specific biomarkers to date. As previously mentioned, CA 19-9, the most widely employed marker, is insufficiently sensitive and unable to detect PC in asymptomatic patients.[62]

Additional risk factors potentially 'enriching' the NOD patient population are advanced age,[59] sudden weight loss and/or low BMI at the time of the DM diagnosis,[63] fast worsening of glucose control, or rapid development of hyperglycemia.[64,65] As already mentioned, a promising risk stratification model has been identified and is awaiting validation (END-PAC),[10] along with some other predictive models for clinical risk prediction.[9,50]

Based on the aforesaid, people >50 years of age at the time of DM diagnosis with low BMI and with a somewhat unexplained sudden weight loss, with high fasting blood glucose levels at the time of the diagnosis, or with rapid worsening of glucose control, ought to be closely monitored because of their higher risk of PC.

Transabdominal ultrasound still represents a widely used, low cost, and non-invasive imaging modality. Unfortunately, its sensitivity and specificity are limited, especially for early detection of PC, relying upon patient condition (obesity, bowel gas) and the operator's skill. The gold standard diagnostic test for early-stage PC detection still remains contrast-enhanced multidetector CT, being 76%-97% sensitive and 67% specific, with an accuracy of 89%.[66,67] EUS is the most accurate method for high-risk patients, with 72% sensitivity and 90% specificity in the earliest phases of the disease.[68,69] Moreover, EUS can also be employed for fine needle aspiration (FNA) biopsy. However, since this procedure is highly dependent on the skill of the operator, it cannot be carried out routinely. Magnetic resonance imaging (MRI) is particularly helpful in staging PC patients and has better soft tissue resolution than CT.[68] Its reported sensitivity is 93% with a specificity of 89% and accuracy of 90%. Disadvantages include procedural costs and the lack of standardization in the algorithms and parameters used to acquire advanced functional imaging sequences.[61] For inherited/familial PC patients, guidelines recommend CT, EUS, or MRI at least once a year.[70,71] A 6-24 month surveillance is recommended for patients with precancerous lesions (mucin-producing cysts).[72] No recommendations however exist for ruling out PC among high-risk NOD patients, to date.

Summary of available evidence and panel conclusions

The relationship between DM and PC is a widely investigated and equally debated issue. Although the correlation between the two conditions is well established in clinical practice, clear indications for early detection of PC in NOD patients are still lacking.

What about PC

- Albeit uncommon, the incidence of PC is steadily increasing and its prognosis remains very poor.
- The need for an early detection is universally recognized as a key point for life saving.[73,74]
- No guidelines currently recommend the screening of the general population of asymptomatic adults at intermediate risk of PC, mainly due to its low incidence.[75]
- Screening is indicated for some people clusters at increased risk of PC[75,76] (see Table 5).

What about DM and PC

- DM has a high prevalence and strong incidence, representing both a risk factor and a consequence of PC (reverse causality).
- People with longstanding DM have twice the risk of developing PC than the general population.
- NOD is frequently associated with PC, often disappearing after its resection.
- People with NOD have a sixfold to eightfold increased chance of being diagnosed with PC within 3 years. About 0.8%-1% of individuals >50 years old with NOD have PC.
- People with NOD constitute a population at significantly higher risk of PC, therefore deserving particular attention and surveillance. Moreover, NOD may occur when PC is still resectable.

Table 5. Factors significantly increasing the risk of PC		

Inherited risk	• People with two or more cases of PC among first degree relatives
	• Specific syndromes
	  o Hereditary breast ovarian cancer syndrome (HBOC)
	  o Lynch syndrome 2
	  o Peutz-Jeghers syndrome
	  o Familial atypical multiple mole melanoma (FAMMM)
	  o Li-Fraumeni syndrome
	• Germline mutations CDKN2A, BRCA2, PALB2	

Pancreatic cystic lesions	• Intraductal papillary mucinous neoplasm (IPMN) • Mucinous cystic neoplasm • Pancreatic intraepithelial neoplasia (post-surgery histopathology)	Notes: although most pancreatic cysts are benign, some can develop into PC. Evaluation of molecular markers (KRAS −GNAS mutations in cystic fluid) and/or advances in endoscopic techniques may be the future.
New onset diabetes mellitus	Within 24-36 months from the diagnosis of diabetes: sixfold to eightfold increased risk of pancreatic ductal adenocarcinoma compared with general population	Notes: no screening programme is still recommended (predicting models may be the future)
Presence of risk factors and suggestive symptoms	Modifiable (smoking, obesity) Non-modifiable (age) Comorbidities (chronic pancreatitis, cystic lesions) Early symptoms (weight loss, dyspepsia, bloating, dorsal pain, change in bowel habits)	Notes: decision support tools combining these factors are desirable for screening and/or a quick referral to multidisciplinary diagnostic centres

PC, pancreatic cancer.

Type 3c DM and PC

- T3cDM is estimated to account for 5%-10% of all cases of DM in Western populations.
- Among people with NOD, discriminating between cancer-related T3cDM (lower incidence) and T2DM (much higher incidence) plays a crucial role in the effective identification of subjects at risk of PC.[75]
- T2DM and T3cDM show different risk factors and pathophysiological clinical aspects (see Tables 1 and 2).

Who should be screened for early detection of PC among people with NOD?

- Screening for PC is not currently recommended among people with NOD, due to its high incidence.
- People >50 years old at the time of DM diagnosis with low BMI and/or unexplained sudden weight loss, high fasting blood glucose levels, or with rapid worsening of glucose control, ought to be closely monitored because of their higher risk of PC.
- Individual risk stratification tools and clinical prediction models or biomarkers are essential for active surveillance on this cluster.[75,77]
- Currently, some clinical models are promising for stratifying cancer risk in people with NOD. Some examples are the UK model THIN and the END-PAC score, or the predictive model proposed by Munigala et al.[10,50,51,53]
- Despite encouraging preliminary results, further validation is needed before these models can be routinely applied in clinical practice.

How to perform screening?

- Despite several attempts, no single biomarker currently appears suitable for clinical use for early detection of

pancreatic ductal cancer. The biologic (highly heterogeneous) and epidemiologic (low incidence) features of PC make it difficult to acquire the quantity of samples necessary for identifying a reliable and validated single biomarker.[78]

- CA19-9, currently the only biomarker routinely used in clinical practice for pancreatic ductal cancer, is not recommended as a screening tool. For this purpose, its combination with additional markers may be useful.
- Large national and international collaborations are undoubtedly required for the gathering of databases and sample repositories to identify prediagnostic cohorts or registries of people at high risk of PC. Analyses from biological fluids and tissues may be gathered, and their information should be shared to be integrated with other medical health records such as radiomics and quantitative imaging, artificial intelligence-assisted CT, and novel MRI methods. Based on all these data, the development of specific endogenous and synthetic biomarkers, as well as validated risk models, is eagerly awaited.[75]
- The ongoing DETECT study (Evaluation of a Mixed Meal Test for Diagnosis and Characterization of Pancreatogenic Diabetes Secondary to Pancreatic Cancer and Chronic Pancreatitis), supported by the CPDPC, aims to shed light on the different glucose homoeostasis profile between these two subtypes of DM. The study focuses on the evaluation of beta-cell function, insulin secretion, and glucagon response to characterize the two forms and facilitate early detection of PC in adults with NOD.[54,79]
- CT is a potential candidate for mass screening due to favourable features (affordable cost, low-middle invasiveness, and time saving). Nevertheless, the use of contrast-enhancing agents for maximizing its diagnostic accuracy and frequent X-ray exposure may have side-effects.

- MRI has long been used for the diagnosis and staging of PC. Claustrophobia and metallic implants, as well as the considerable time to obtain images, are the main drawbacks making it unsuitable for screening.
- Although relatively invasive and time consuming, EUS is the most accurate method for early detection of PC (stages T1-T3). It is considered a complementary imaging modality for completing the diagnostic workup and obtaining tissue samples (FNA), but it is not suitable for mass screening. The incorporation of elastography may enhance its accuracy.[80]
- The profitable integration of blood-based biomarkers and radiological images on tailor-made high-risk cohorts is currently the most promising strategy towards an early detection of PC.[61]

Future perspectives. The key step towards early detection of PC is to identify well-tailored cohorts of people at high risk, to whom a suitable combination of non-invasive biomarkers can be applied, in order to identify people who should undergo imaging procedures. NOD, due to its close relationship with PC, constitutes a key model for the study and validation of new effective markers for an early detection of PC.

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