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From classical approaches to artificial intelligence, old and new tools for PDAC risk stratification and prediction

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is recognized as one of the most lethal malignancies, characterized by late-stage diagnosis and limited therapeutic options. Risk stratification has traditionally been performed using epidemiological studies and genetic analyses, through which key risk factors, including smoking, diabetes, chronic pancreatitis, and inherited predispositions, have been identified. However, the multifactorial nature of PDAC has often been insufficiently addressed by these methods, leading to limited precision in individualized risk assessments. Advances in artificial intelligence (AI) have been proposed as a transformative approach, allowing the integration of diverse datasets—spanning genetic, clinical, lifestyle, and imaging data into dynamic models capable of uncovering novel interactions and risk profiles. In this review, the evolution of PDAC risk stratification is explored, with classical epidemiological frameworks compared to AI-driven methodologies. Genetic insights, including genome-wide association studies and polygenic risk scores, are discussed, alongside AI models such as machine learning, radiomics, and deep learning. Strengths and limitations of these approaches are evaluated, with challenges in clinical translation, such as data scarcity, model interpretability, and external validation, addressed. Finally, future directions are proposed for combining classical and AI-driven methodologies to develop scalable, personalized predictive tools for PDAC, with the goal of improving early detection and patient outcomes.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest malignancies, with high mortality rates primarily due to its aggressive nature and frequent late-stage diagnosis. Despite accounting for only 3 % of all cancer cases, PDAC is responsible for 7 % of all cancer-related deaths, with 194,688 deaths in Europe and North America registered in 2022 [1], underscoring the urgent need for effective risk stratification and early detection strategies. In 2022, the International Agency for Research on Cancer (IARC) reported 510,992 new cases of pancreatic cancer globally and 467,409 deaths, illustrating the alarming incidence-to-mortality ratio of this disease. The development of PDAC involves a range of environmental, genetic, and lifestyle factors, often interacting in ways that remain poorly understood [2,3]. This multifactorial nature poses a significant challenge in identifying high-risk individuals, especially given the low incidence of PDAC, which limits the statistical power of conventional study designs and complicates the identification of actionable risk factors. Accurate assessment of these

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risk factors is essential for stratifying individuals by susceptibility, enabling targeted prevention, early detection efforts, and personalized management strategies.

Historically, epidemiological studies, including prospective cohort and case-control designs, have been central in identifying PDAC risk factors such as smoking, diabetes, and family history [2,3]. While these traditional approaches have provided foundational insights, they face limitations in achieving precision for individualized risk assessment.

As understanding of PDAC aetiology improves, there is an urgent need for advanced predictive models capable of integrating large and heterogeneous datasets. Technological advancements, particularly in artificial intelligence (AI), offer the potential to develop improved risk stratification tools that account for complex interactions among demographic, genetic, and lifestyle factors. Such AI-driven models could enable more precise PDAC risk prediction and potentially facilitate earlier intervention.

This review will explore both classical epidemiological approaches and emerging AI-driven models for PDAC risk stratification. By examining the strengths and limitations of each method, we aim to provide a comprehensive overview of how integrated, advanced models could reshape PDAC risk assessment, offering valuable insights for future research and clinical practice.

2. Conventional approaches in PDAC risk stratification

Conventional statistical approaches used to model and quantify the associations between risk factors (or exposure variables, *e.g.*, smoking, BMI, diabetes, genotypes) and PDAC risk mostly encompassed regression-based methods, including logistic regression and Cox proportional hazard models. Typically, logistic regression models have been employed on data collected in case-control studies, allowing for direct estimation of the risk of developing the disease as a binary outcome through the Odds ratio (OR). The OR has high interpretability, also in the context of regression models adjusted for multiple exposure variables. It indicates the change in odds of developing the disease at the increase in the exposure (*e.g.*, increase in BMI, increase in alcohol intake). The logistic regression model can easily handle continuous and categorical variables without requiring normal distribution and also allows for the investigation of first-order interactions (*e.g.*, gene-environment, gene-gene interactions), thus representing a robust and useful model. For instance, smoking has consistently shown an OR between 1.13 and 1.81 [4], while high alcohol consumption (4–6 drinks/day) is associated with 20–50 % risk increase compared to individuals consuming less than 1 drink/day [5]. Genetic factors, such as the ABO blood group, have also emerged as important considerations, with non-O blood types showing a modestly elevated risk. Recent interaction studies employing logistic regression suggested that environmental and lifestyle variables and host genetics affect PDAC risk independently [6,7]. These findings underscore the role of case-control studies, in elucidating both genetic and lifestyle factors that contribute to PDAC, which are critical for stratifying risk within the population [8–12]. However, logistic regression is not perfectly suited for modelling complex non-linear relationships, because it assumes linearity between the exposures and the log-odds of the outcome, sometimes requiring variable transformation or the introduction of spline functions that complicate the interpretability of the estimate. Additionally, logistic regression cannot easily model multifaceted or high-order interactions (*i.e.*, interactions between three or more variables). Finally, despite the power of the model increases with sample size, logistic regression cannot handle many exposure variables relative to the number of subjects under analysis, thus requiring very large sample sizes to avoid decreasing performances in such cases [13].

Conversely, the Cox proportional hazards regression has been typically employed with data collected using large-scale prospective cohort studies, such as the Nurses' Health Study, the Health Professionals Follow-up Study and the European Prospective Investigation into Cancer and Nutrition (EPIC) [14–22]. These studies, tracking over 280,000 participants across decades, provide robust, longitudinal data by assessing risk factors prior to disease onset, thus minimizing recall bias [23]. Cox proportional hazard models quantify the association between possible risk factors and PDAC incidence over time, estimating a hazard ratio (HR). The HR represents the change in the hazard of developing PDAC associated with an increase in the exposure variable, with the hazard being the risk at a given time point. One of the advantages of this method is the easy handling of time-dependent variables that may change over time (*e.g.*, starting of quitting smoking). However, this method assumes a constant HR over time, which does not always hold true and similarly to logistic regression, it is not suited for dealing with complex non-linear relationships between variables. Furthermore, the relatively low incidence of PDAC poses significant challenges in assembling cohorts large enough to achieve the statistical power required for precise stratification. To enhance statistical power and overcome the limitations inherent in individual studies, **meta-analyses** and **pooled analyses** have combined data from multiple sources, providing a more refined understanding of PDAC risk factors across diverse populations. The advantage of meta-analysis is that, in addition to providing estimates of the effect size, it also quantifies the related heterogeneity based on the between-study variance and allows for different approaches based on the estimated heterogeneity. For instance, meta-analyses have confirmed a substantially elevated PDAC risk in patients with new-onset diabetes (3.81- to 5.2-fold increase) [3,24,25] and a 16-fold increased risk in individuals with chronic pancreatitis [26], highlighting the role of pre-existing pancreatic inflammation in cancer susceptibility. These analyses demonstrate the value of data synthesis in clarifying PDAC risk associations, particularly when single studies lack the power to detect significant effects.

2.1. The importance of multiple risk factors in PDAC stratification

As discussed in the previous paragraph, case-control studies are widely used in PDAC research. However, these studies typically investigate only a few factors at a time and often report individual effects without exploring potential synergies between those. Since PDAC is a multifactorial disease, it is essential to identify the relevant risk factors and understand how they interact. Among the risk factors for PDAC that have been consistently identified across multiple studies, there are unmodifiable factors such as age, sex, and ethnicity. While these provide valuable population-level insights, they lack precision for individual risk assessment. PDAC incidence rises significantly after age 65, with males slightly more affected, possibly due to hormonal or lifestyle differences [27,28]. Ethnicity is also a well-established risk factor, with African Americans having higher PDAC risk compared with Europeans, likely due to genetic predispositions and socioeconomic factors affecting healthcare access and lifestyle [29,30].

Smoking increases PDAC risk by a two-fold factor compared to never smokers (pooled OR 2.2, 95 % CI 1.7–2.8) [4], because of tobacco-related carcinogens such as nitrosamines, with residual risk lasting up to a decade after cessation [2,3]. Obesity and diabetes increase the risk by 20–50 % through chronic inflammation and insulin resistance [2,3]. The ABO blood group is an established genetic factor, with non-O blood types (A, B, AB) showing modestly increased risks (ORs: 1.38, 1.47, 1.53, respectively) [31–33]. Table 1 shows the list of known PDAC risk factors and the methodologies used to determine them.

While these factors enhance understanding, their individual predictive power remains limited, as evidenced by their modest OR values. The World Health Organization estimated that in 2020, 22.3 % of the global population, approximately 1.5–2 billion people, used tobacco. This example highlights that, although cigarette smoking is a risk factor for pancreatic cancer, it cannot be used as a standalone criterion in screening programs. Implementing a prevention program for 2 billion individuals for cancer with an incidence of approximately 19 per

Table 1
Summary of Key Risk Factors for PDAC and Methods of Identification: Odds Ratios, Study Types, and Utility for Risk Stratification.

Method	Study design	Statistical Method	Factor	Reference group	Estimate	Effect [95 % CI]	PDAC cases	Population	Reference study
Retrospective studies	**Nested case-control**	**Unconditional logistic regression**	**ABO: Blood group A**	ABO: Blood group 0	OR	1.38 [1.18–1.62]	700	Pooled	Wolpin et al., 2010 [31]
			ABO: Blood group AB	ABO: Blood group 0	OR	1.47 [1.07–2.02]	97		
			ABO: Blood group B	ABO: Blood group 0	OR	1.53 [1.21–1.92]	226		
	Case-control study	**Unconditional logistic regression**	**Smoke: current smokers**	Smoke: never smokers	OR	1.17 [1.02–1.34]	1.635	Pooled	Bosetti et al., 2012 [4]
			Smoke: former smokers	Smoke: never smokers	OR	2.20 [1.71–2.83]	2.327		
	Cohort study	**Cox proportional hazards models**	**Metabolic health**	Metabolically healthy, normal weight	HR	1.52 [1.27–1.81]	190	Metabolically unhealthy, normal weight	Chung et al., 2021[34]
			Metabolic health	Metabolically healthy, normal weight	HR	1.34 [1.12–1.61]	172	Metabolically unhealthy, obese	
			Metabolic health	Metabolically healthy, normal weight	HR	1.07 [0.88–1.31]	133	Metabolically healthy, obese	
	Cohort study	**Cox proportional hazards models**	**Diabetes mellitus**	No diabetes mellitus	HR	3.81 [2.97–4.88]	346	New-onset diabetes mellitus	Lee et al., 2023 [25]
			Diabetes mellitus	No diabetes mellitus	HR	1.53 [1.11–2.11]	112	Long-term diabetes	
	Cohort study	**Fine and Gray regression**	**Worrisome feature: Main duct dilation (>5 mm)**	-	HR	3.17 [2.44–4.11]	111	Grouped	Armstrong et al., 2024 [35]
			Worrisome feature: Calcifications	-	HR	1.05 [0.68–1.64]	111		
			Worrisome feature: Solid component	-	HR	1.89 [1.34–2.66]	111		
			Worrisome feature: Cyst size	-	HR	1.26 [1.20–1.33]	111		
	Case - control study	**Unconditional logistic regression**	**Sex**	Males, age< 60	OR	1.24 [1.08–1.42]	1.954	Females, age< 60	McWilliams et al., 2016 [27]
				Males, age< 45	OR	1.08 [0.73–1.59]	226	Females, age< 45	
	Retrospective cohort study	**Joinpoint regression models**	**Age**	-	AAPC	0.62 [0.51–0.74]	128.194	Females, age> 55	Gaddam et al., 2021 [36]
				-	AAPC	0.92 [0.82–1.01]	123.166	Males, age> 55	
				-	AAPC	1.93 [1.57–2.28]	13.919	Females, age< 55	
				-	AAPC	0.77 [0.50–1.05]	18.45	Males, age< 55	
	Retrospective cohort study	**Tiwari method**	**Ethnicity**	White ethnicity	IRR	1.28 [1.26–1.29]	472.069	Black ethnicity	Tavakkoli et al., 2020 [37]
Prospective studies	**Cohort study**	**Cox proportional hazards models**	**BMI: Overweight**	BMI: Normal weight	HR	1.68 [1.27–2.23]	56	Grouped	Zohar et al., 2018 [38]
			BMI: Obesity	BMI: Normal weight	HR	3.75 [2.66–5.28]	36		
	Matched cohort study	**Cox proportional hazards models**	**Acute pancreatitis**	No acute pancreatitis	HR	19.28 [14.62–25.41]	435	General, < 2 years	Kirkegård et al., 2018 [39]
			Acute pancreatitis	No acute pancreatitis	HR	2.43 [1.73–3.41]	435	General, 2–5 years	
			Acute pancreatitis	No acute pancreatitis	HR	2.02 [1.57–2.61]	435	General, > 5 years	
Meta-analysis	**Meta-analysis**	**Random-effects model, Logistic regression**	**ABO: Blood group A**	ABO: Blood group 0	HR	1.36 [1.24–1.50]	1.664	CagA-endemic subpopulation	Risch et al., 2013 [12]
			ABO: Blood group A	ABO: Blood group 0	HR	1.42 [1.24–1.64]	2.118	CagA-non endemic subpopulation	
			ABO: Blood group AB	ABO: Blood group 0	HR	1.52 [1.24–1.85]	264	CagA-non endemic subpopulation	
			ABO: Blood group B	ABO: Blood group 0	HR	1.38 [1.16–1.64]	611	CagA-non endemic subpopulation	

(*continued on next page*)

Table 1 (*continued*)

Method	Study design	Statistical Method	Factor	Reference group	Estimate	Effect [95 % CI]	PDAC cases	Population	Reference study
	Meta-analysis	**Random-effects models**	**Chronic pancreatitis**	No chronic pancreatitis	EE	16.16 [12.59–20.73]	70	Pooled	Kirkegård et al., 2017 [26]

100,000 would be neither practical nor efficient.

Integrated models combining demographic, genetic, and lifestyle data are essential for precise stratification, enabling targeted prevention and early detection strategies.

Clinical conditions such as new-onset diabetes [24], pancreatitis [39], and the presence of pancreatic lesions like intraductal papillary mucinous neoplasm (IPMN) [40] define high-risk subgroups compared to the general population. Unlike other risk factors, these conditions are highly specific to pancreatic cancer, whereas many well-known risk factors are associated with a wide range of diseases, making them less useful for targeted screening. These specific subgroups may, therefore, serve as valuable targets for tailored screening programs. Additionally, while risk factors such as tobacco smoking have a cumulative effect over time, new-onset diabetes and pancreatitis show a stronger association with PDAC within the first 2–3 years of diagnosis, providing a crucial window for early detection.

2.2. Diabetes

Diabetes is a well-established risk factor for PDAC, with both long-standing and newly diagnosed cases linked to increased risk. Long-term diabetes is associated with a 1.5–2.4-fold increase in PDAC risk, while newly diagnosed diabetes carries an even higher risk, with estimates ranging from 3.81- to 5.2-fold [3,24,25]. This association is thought to result from mechanisms involving chronic hyperglycaemia and insulin resistance, which may foster a pro-inflammatory environment that leads to cancer development.

While the previously discussed risk factors provide valuable information, they often lack the precision needed for individualized PDAC risk prediction. In contrast, **new-onset diabetes** in individuals over 50, emerges as a more specific criterion for identifying a well-defined, high-risk group within the general population. Focusing risk assessment on new-onset diabetes could enable more effective stratification, affording a unique opportunity to detect PDAC earlier, potentially at a more treatable stage. The probability of being diagnosed with pancreatic cancer within three years of meeting the criteria for new-onset diabetes is reported to be approximately 0.8–1 % [41,42], roughly corresponding to a PDAC incidence of up to 1 000 per 100,000 diabetic individuals, which is fifty times more frequent than in the general European population, where the crude incidence rate is 19 per 100,000 [43]. Glucose dysregulation is a common feature among individuals diagnosed with pancreatic cancer. Around 80 % of pancreatic cancer patients have impaired fasting blood glucose, advanced pre-diabetes or diabetes [44,45]. Diabetes in this context is predominantly new-onset. Hyperglycaemia begins 36–30 months before pancreatic cancer diagnosis and increases over time, with patients developing diabetes 12–6 months prior to cancer diagnosis [46]. Thus, new-onset diabetes may be considered a symptom of pancreatic cancer and because of the high frequency of pancreatic cancer in patients who experience diabetes, individuals with new-onset diabetes are the largest high-risk group for PDAC.

Developing strategies to detect PDAC in this high-risk group is now a priority [47–49]. In the United States an algorithm, named Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC), which considers age, changes in weight and changes in diabetes parameters is undergoing evaluation to determine its effectiveness in selecting those individuals with new-onset diabetes who would derive most benefit from being evaluated for pancreatic cancer [48]. In Great Britain, the UK Early Detection Initiative (UK-EDI) is establishing a cohort of individuals over 50 years, diagnosed with diabetes in the previous six months.

2.3. Pancreatitis

Pancreatitis is a significant risk factor for PDAC. It is characterised by pancreatic tissue injuries that lead to inflammation, fibrosis and DNA damage, thus promoting neoplastic progression [50]. A large nested case-control study including 250,009 individuals, among which 41,669 acute pancreatitis (AP) patients suggested an HR of 19.28 (95 % CI 14.62–25.41) within two years since diagnosis. However, the risk decreased over time, reaching an HR of 2.02 (95 % CI 1.57–2.61) after five years from diagnosis [39]. AP may evolve into chronic pancreatitis (CP), whose pooled estimate for PDAC risk has been reported as HR of 16.16 (95 % CI 12.59–20.73) within two years after CP diagnosis [26]. The risk, initially increased 16-fold, reduced to eight-fold and then three-fold after five and nine years post-CP diagnosis, respectively. [26]. Up to 7 % of CP patients may develop pancreatic cancer [50–52] and a linear relationship has been reported in the proportion of CP patients who develop pancreatic cancer over time (1.8 % and 4.0 % after 10 and 20 years since CP diagnosis, respectively) [53,54]. Given the high risk of patients in this subgroup, a close follow-up in the first years following CP diagnosis may be critical for early PDAC identification. Surveillance has been suggested for individuals with hereditary pancreatitis carrying mutations in serine protease 1 (*PRSS1)* or cyclin dependent kinase inhibitor 2 A (*CDKN2A)* genes, but not for CP patients with mutations in serine peptidase inhibitor Kazal type 1 (*SPINK1)* gene [55,56]. However, no agreement has been reached on the optimal screening method for CP patients without mutations. Furthermore, the differential diagnosis between CP and PDAC can be difficult, and finer discriminating approaches are needed. Rückert et al. retrospectively assessed the potential value of an index combining age, obstructive jaundice, weight loss, transaminase levels, and serum concentration of amylase and CA 19–9 as key parameters to distinguish individuals developing PDAC among CP patients [57]. Their model, consisting of an index calculated through the sum of the individual scores (ranging from 1 to 3) assigned to each variable, was characterised by a moderate sensitivity of 0.75 and specificity of 0.80 with large confidence intervals in receiver operating characteristics (ROC) curve analysis. Zhang et al. proposed a different score based on age, CA 19–9 levels, splenic vein invasion, irregular dilatation of the pancreatic duct, and non-truncated pancreatic duct stenosis [58]. The score was calculated by summing the log-odds from univariate logistic regression analyses, each divided by the smallest estimated log-odds. The Area Under the Curve (AUC) from this model was 0.78, suggesting a possible approach for improving the distinction between CP and pancreatic cancer patients. Cai et al. attempted to develop a risk-stratification approach in CP patients with focal pancreatic mass lesions, which often are characterised by endoscopic ultrasound-fine needle aspiration false-negative results [59]. The authors proposed a score including sex, presence of one or more focal pancreatic mass lesions, mass location, and direct bilirubin and CA 19–9 levels and reported an AUC of 0.72, indicating a moderate discrimination ability. A risk prediction model for pancreatic cancer was proposed in another study including two cohorts of 2 545 and 415 CP patients from the United States and China, respectively, using cyst diagnosis of the pancreas (coded as detected/non detected), weight loss, and high platelet levels as independent predictive variables [60]. The authors reported moderate predictive values, with an AUC of 0.83 and 0.73 in

the two cohorts. A smaller study on 581 CP patients suggested higher PDAC risk in individuals with diabetes mellitus and high BMI, and in individuals with pancreatic exocrine insufficiency and low BMI [61]. However, these two subgroups were characterised by a limited number of individuals. A retrospective study on 1 766 CP patients suggested the dramatic effect of duct dilatation on the risk of pancreatic cancer, with a ten-fold risk increase [54].

These studies are valuable initiatives for risk stratification in high-risk groups, highlighting the need for developing longitudinal studies and prospective cohorts of CP patients.

2.4. Pre malignant pancreatic lesions

Pancreatic cystic neoplasms contribute to the development of PDAC [62]. Intraductal papillary mucinous neoplasms (IPMN) are the most investigated cystic lesion and are characterised by malignant progression rates ranging between 3 % and 15 % for branch-duct IPMN and 40–90 % for main-duct IPMN [63]. IPMNs offer a unique opportunity for early detection strategies and surveillance [64–66]. A retrospective analysis of 2 197 IPMN patients with imaging data indicated that worrisome features at presentation, smoking status, and symptomatic presentation were predictive of IPMN progression [35]. Smoking status was also reported in a recent study on 354 IPMN patients as a predictor for progression (HR = 3.81, 95 % 1.43–10.09, $p = 0.007$)[67]. The authors suggested discontinued surveillance for these IPMN patients, in line with a recent report that estimated 106,211 dollar savings in case of surveillance discontinuation after five years [68] and the new International Kyoto guidelines [69]. A prospective multicentre surveillance study by the Japan Pancreas Society conducted over five years on 2 104 branch-duct IPMN suggested cyst size, pancreatic duct size, and mural nodules as predictors of progression [70]. However, cyst-related characteristics were not indicators of concomitant PDAC development. In addition to IPMN, other pancreatic lesions should be assessed for patient stratification concerning PDAC risk. A retrospective multicentre study comparing 700 IPMN-derived PDAC with 2 350 pancreatic intraepithelial neoplasia (PanIN)-derived PDAC reported reduced overall survival for the latter group (43.1 vs 23.0 months, respectively), with HR of 1.66 (95 % CI 1.44–1.90), $p < 0.001$ [40]. Therefore, the development of *ad hoc* cohorts, including individuals with pancreatic lesions, should be the first step for stratifying the patients into low, medium, and high risk of developing PDAC to improve intervention and surveillance systems. Several blood-based biomarkers have been proposed for IPMN progression towards malignancy. Among these, the most studied are micro RNAs and genetic polymorphisms [71–74]. For a detailed description please see another review of this special issue [74].

3. Genetic Factors

3.1. Familial genetic variations

The identification of high-risk groups within the general population represents the most efficient risk stratification strategy. Moreover, data integration, analysing multiple factors simultaneously, has shown promising results that could be translated into clinical practice. A better understanding of the genetic architecture of PDAC susceptibility, identifying individuals who are genetically predisposed to develop PDAC, will be instrumental in developing new risk stratification instruments. Genetic testing for known PDAC-associated genes such as BRCA1/2 DNA repair associated (*BRCA1/2)*, ATM serine/threonine kinase (*ATM)*, partner and localizer of BRCA2 (*PALB2)*, and *CDKN2A* may provide clinicians with actionable insights for classifying individuals according to their familial or hereditary risk profiles [75]. However, the use of rare high penetrance mutations for PDAC screening is the focus of debate, and several recent reviews have questioned the use of high penetrance mutations for screening.

Familial genetic mutations are present in roughly 10 % of all PDAC cases; however, this does not imply that PDAC developed as a result of these mutations. Genetic predisposition plays a key role, particularly in familial pancreatic cancer cases (FPC), defined as individuals with at least two affected first-degree relatives (FDRs) without a known hereditary syndrome. Studies, including Klein et al., show a proportional risk increase: 4.6-, 6.4-, and 32-fold for individuals with one, two, and three affected FDRs, respectively [76]. This highlights the importance of family history in identifying high-risk groups. Approximately 50 hereditary cancer syndromes have been identified to be linked to an increased PDAC risk, with PDAC susceptibility genes including *BRCA2, ATM, PALB2, CDKN2A, PRSS1,* mutL homolog 1 *(MLH1),* mutS homolog 2 *(MSH2),* serine/threonine kinase 11 *(STK11)*, and tumor protein p53 (*TP53)*. Except for *PRSS1*, which leads to pancreatic cancer through hereditary pancreatitis, these genes primarily predispose individuals to various cancers (pleiotropic effect) rather than being directly linked to pancreatic cancer aetiology. In contrast, genes more closely related to pancreatic biology, such as carboxypeptidase A1 (*CPA1)* and carboxypeptidase B1 (*CPB1)*, which encode pancreatic enzymes, have been identified as PDAC susceptibility genes, with rare deleterious variants found in approximately 1 % of pancreatic cancer patients [77,78]. Recent gene panel studies have identified rare germline mutations in other cancer predisposition genes, such as RAD51 paralog C (*RAD51C)*. However, their contribution to pancreatic cancer susceptibility remains uncertain due to their low frequency [79].

Another example of the challenges in identifying genetic mutations associated with PDAC is checkpoint kinase 2 (*CHEK2)*, a gene linked to an increased risk of breast cancer. While some evidence suggests an association with pancreatic cancer, the rarity of these mutations and their sporadic occurrence in PDAC cases make it difficult to establish a clear causal relationship. As a result, their role in pancreatic cancer risk remains inconclusive [80].

Understanding the genetic syndromes and mutations associated with PDAC is crucial for identifying high-risk individuals and guiding targeted surveillance and prevention strategies. Table 2 reports a list of genes frequently mutated in PDAC.

3.2. Common germline genetic variants

In the last 15 years, genome-wide association studies (GWAS) have been very successful in finding risk loci for many human diseases, especially in populations of European, American and western Asian descent. For PDAC, around 30 single nucleotide polymorphisms (SNPs) have been identified, however, the mechanistic link with the disease remains elusive for most of them [33,90–97]. A detailed description of germline genetic variability in relation to the risk of developing PDAC has been reported by Gentiluomo et al. [98].

Another drawback of GWASs is that multiple testing imposes a strict threshold to declare significance ($p < 5x10^{-8}$) that may result in potential false negatives. A possible strategy to understand why a genomic region may influence PDAC risk and to exploit GWAS data to find more associations is the use of secondary analyses. They consist in the reanalysis of GWAS summary statistics (i.e., odds ratios or betas) alongside the use of data on the possible function of the SNPs. For a SNP to be considered functional, the two alleles need to exert a different effect on a particular quantitative trait, for example, if allele A of SNP rs123456 is associated with increased expression of gene 1 compared to allele B, that SNP is an expression quantitative trait locus (eQTL). An additional viable approach is to select SNPs that have proven or predicted characteristics that increase the possible association with a particular trait, for example being pleiotropic. The general strategy is to select a limited set of SNPs (in the order of the thousands), test them in a discovery case-control set and then replicate the best findings in independent large populations. This is possible largely thanks to the easiness of using available datasets such as the database of Genotypes and Phenotypes (dbGaP) where hundreds of thousands of genotypes are archived, the FinnGen study [99] and the UK Biobank [100] and JAPAN cohorts [90].

Table 2
Summary of the main genetic factors and relative syndromes/diseases associated with pancreatic cancer risk.

Method	Study design	Gene	Associated disease	Estimate	Effect [95 % CI]	PDAC cases	Population	Reference study
Retrospective studies	**Cohort study**	**APC**	FAP	RR	4.5 [1.2–11.4]	4	1391 patients with FAP	Giardiello et al., 1993 [81]
	Cohort study	**ATM**	ATM syndrome	OR	4.21 [3.24–5.47]	2149	Multi-gene hereditary cancer-screened individuals	Hall et al., 2021 [82]
	Case-control study			OR	5.71 [4.38–7.33]	343	Mayo Clinic patient registry	Hu et al., 2018 [83]
	Cohort study	**BRCA1**	-	RR	2.26 [1.26–4.06]	26	General (BCLC families)	Thompson and Easton, 2002 [84]
	Cohort study	**BRCA2**	-	RR	3.51 [1.87–6.58]	14	General (BCLC families)	BCLC consortium, 1999 [85]
	Cohort study	**STK11**	Peutz-Jeghers syndrome	RR	139.7 [61.1–276.4]	7	Peutz-Jeghers syndrome individuals	Resta et al., 2013 [86]
	Cohort study	**MSH2, MLH1, MSH6**	Lynch syndrome	HR	30.5 [14.2–65.7]	47	147 families with MMR gene mutations, individuals with age 20–49 years	Kastrinos et al., 2014 [87]
				HR	5.1 [2.2–11.8]	47	147 families with MMR gene mutations, individuals with age 50–70 years	
				HR	8.6 [4.7–15.7]	47	147 families with MMR gene mutations, individuals with age 20–70 years	
		MLH1		HR	7.5 [2.4–23.0]	13	147 families with MMR gene mutations	
		MSH2		HR	10.9 [5.5–21.9]	31	147 families with MMR gene mutations	
	Cohort study	**PALB2**	-	RR	2.37 [1.24–4.50]	99	764 families with at least one member with a *PALB2 pathogenic variant*	Yang et al., 2020 [88]
	Cohort study	**TP53**	Li-Fraumeni syndrome	RR	7.3 [2.0–19.0]	4	180 families referred for TP53 mutation analysis	Ruijs et al., 2010 [89]
	Cohort study	**PRSS1**	Hereditary pancreatitis	SIR	53 [23–33,39, 40–66,35,67–80,90, 91–118]	8	246 HP patients	Lowenfels et al., 1997 [119]
	Case-control study	**SPNK1**		HR	12.0 [3.0–47.8]	7	Carriers with pancreatic symptoms	Muller et al., 2019 [120]
	Case-control study	**CPB1**		P-values from Fisher's exact test	$P < 0.01$	9	Affected individuals with familial pancreatic cancer	Tamura et al., 2018 [77]
		CPA1		OR	9.36 [1.15–76.02]	7		
Prospective studies	**Cohort study**	**CDKN2A**	FAMM	RR	43.8 [13.8–139.0]	7	Melanoma-prone families	Helgadottir et al., 2014 [121]

Secondary analyses approaches have been proven particularly successful in PDAC, especially those that employed one or more replication sets. For example, SNPs in long noncoding RNA [101], miRNA and related binding sites [102], pancreatic cancer familial genes [103,104], and SNPs acting as eQTL [105] or as methylation QTL [106,107] have been linked to PDAC risk through secondary analyses. An additional strategy employed using secondary analysis was testing variants that belong to specific pathways, such as inflammation response, atopic condition and immunogenic response, autophagy, DNA repair and DNA damage, mitochondrial metabolism, taste perception, estrogen metabolism and telomere maintenance [108–118,122,123].

3.2.1. *Caveat associated with secondary analysis*

Secondary analysis approaches have been instrumental in leveraging GWAS data and in increasing our knowledge on the genetic susceptibility of PDAC; however, they are prone to a potential bias caused by linkage disequilibrium (LD). SNPs are inherited in LD blocks and therefore many alleles show the same ORs and p-values, complicating the identification of the real culprit from those in LD with it. This problem is also shared by secondary analysis since the SNPs selection process is substantially made through databases that associate a genotype with a quantitative trait, through a statistical test. Therefore, alleles that are in LD will all share the same estimate and the same p-value and the only way to clarify which allele is responsible for the change in the quantitative trait is going to be *ad hoc* functional studies. In summary, secondary analyses must be considered as tools to identify LD blocks, inside which there is at least one functional SNP associated with a disease, more than a tool to identify single variants.

3.2.2. *Fine-mapping*

Fine-mapping is a strategy for identifying causal variants. It combines deep sequencing approaches, such as targeted and whole exome sequencing (TES and WES), and targeted sequencing of specific non-coding regions, with bioinformatic tools accounting for LD, functional annotation based on molecular data, and *in silico* predictions [124,125]. Therefore, fine-mapping results can integrate findings from GWAS studies with functional information and provide relevance to statistical associations identified with other approaches. The first fine-mapping study on pancreatic cancer led to the discovery of several previously unidentified genetic variants in three genomic regions (1q32.1, 5p15.33 and 13q22.1) associated with pancreatic cancer risk [126], most of which were low (MAF<5 %) or rare (MAF<2 %) frequency variants. Following studies identified potentially functional genetic variants in genomic regions associated with pancreatic cancer risk, such as 13q22.1 [127], 5p15.33 [128,129], and regions that have been previously suggested to be involved in pancreatic cancer prognosis, such as the *CAV1-CAV2* locus [130,131], and *ABO* [132]. Given the promising results of fine-mapping, further development of bioinformatic and

statistical approaches and lower error-prone sequencing technologies may allow in the future for improved genetic screening.

3.2.3. Applications in Clinical Surveillance

Targeted screening protocols are being developed for high-risk individuals identified through genetic testing, such as *BRCA2* or *CDKN2A* mutation carriers. These persons may benefit from routine imaging techniques, such as endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI), which are effective for detecting early pancreatic lesions [133]. Initiatives like the Cancer of the Pancreas Screening (CAPS) consortium and the UK Early Detection Initiative (UK-EDI) are refining screening protocols based on genetic risk profiles, helping to reach an overall consensus for optimizing surveillance strategies for hereditary high-risk populations [134,135].

3.3. Gene panel testing

Current genetic risk stratification approaches often incorporate gene panel testing, which allows for simultaneous screening of multiple cancer susceptibility genes [136,137]. Gene panels offer a comprehensive view of genetic risk by identifying not only high-penetrance mutations but also combinations of moderate-risk variants. While such variants may be individually low-frequency and limited in terms of effect, they may collectively contribute significantly to PDAC susceptibility in families with a history of cancer. For instance, genes like *RAD51C* and *CHEK2*, though infrequently linked to PDAC on their own, may add to cumulative risk within a familial cancer context. Germline genetic testing has revealed that 4–19 % of PDAC patients carry pathogenic variants, with high-penetrance mutations in genes such as *STK11*, *CDKN2A*, *BRCA1*, *BRCA2*, and *ATM* contributing significantly to familial cancer predisposition [138]. Microsimulation models, which consist in simulating population health trajectories over time based on health data, have demonstrated that genetic testing can inform targeted screening strategies, such as MRI-based surveillance, significantly improving life expectancy (LE) in high-risk individuals [139]. For instance, annual screening from age 40 in carriers of *STK11* mutations can yield LE gains of up to 620 days for men and 510 days for women. These findings may suggest possible beneficial effects of integrating gene panel testing into routine clinical practice to optimize early detection and prevention strategies for PDAC, especially in first-degree relatives of PDAC patients. Despite these benefits, the implementation of genetic testing in clinical settings remains underutilized, suggesting a critical gap in personalized cancer care.

4. Integrating genetic data into comprehensive risk models

4.1. Genetic and multifactorial scores

Polygenic risk score (PRS) offers a promising approach to assess individual PDAC risk by aggregating the effects of multiple common genetic variants with modest effect sizes, providing a comprehensive overview of the genetic risk even in the absence of high-penetrance mutations [98]. PRS can be calculated by summing the number of risk alleles (unweighted PRS) or by weighting each allele by its effect size as estimated from GWAS findings (weighted PRS) [140]. Since the first study in 2012, when a PRS was applied on 2 857 cases and 2 967 controls from PanScan I-II GWAS data [141], several others used PRS to predict pancreatic cancer risk [142–149]. The specific effect sizes varied based on the quantiles compared (e.g., highest vs lowest, middle vs highest) the number of SNPs and the sample size of the population employed. Among the largest studies in terms of cases included, Klein et al. calculated a PRS with 22 SNPs associated with pancreatic cancer in 3 925 pancreatic cancer cases and 3 641 controls using PanScanI-III and PanC4 data [147]. They reported an OR of 2.20 (95 % CI 1.83–2.65) when comparing individuals in the 90th with those in the 40th-60th percentiles of PRS distribution. Galeotti et al. increased the number of SNPs to 30 to calculate a PRS in 3 619 cases and 5 460 controls of European genetic ancestry from the PANcreatic Disease ReseArch (PANDoRA) consortium and reported an OR of 3.64 (95 % CI 1.97–3.54) for the first vs fifth quintile comparison. The authors validated the result in 8 769 cases and 7 055 belonging to PanScanI-III and PanC4 [144]. The integration of PRS with environmental and clinical data, generating a multifactorial risk score (MRS), resulted in a stronger association [144], with an OR of 14.37 (95 % CI 5.57–37.09) comparing individuals in the first quintile to individuals in the fifth quintile. The authors observed an area under the receiver operating characteristic ROC curve of 0.63 (95 % CI 0.59–0.67). Sharma et al. applied a model including age, diabetes onset, age at diabetes diagnosis, waist circumference, family history of digestive cancer, and a PRS of 49 SNPs from previously reported PRSs [142]. This model resulted in an AUC of 0.83 (95 % CI 0.80–0.86) in 1 042 pancreatic cancer cases and 10,420 age- and sex-matched controls from UKBB, while clinical factors, such as age at diabetes mellitus diagnosis and diabetes mellitus onset led to an AUC of 0.79 (95 % CI 0.75–0.83). Similarly, Salvatore et al. tested several models including variables from electronic health records and a PRS based on 18 SNPs associated with pancreatic cancer risk in the European population. They reported AUCs ranging from 0.74 (95 % CI 0.72–0.76) to 0.89 (95 % CI 0.87–0.91) [150]. PRS and MRS were also tested in the Japanese population [151], Chinese population [152], African population [153], and two multiethnic cohorts [146,154], although all studies were performed on a limited number of cases ($n < 700$ pancreatic cancer cases). Despite differences in study populations, such as ethnic diversity, sample sizes, and the selection of the SNPs used in the PRS calculations, individuals in the higher percentile of PRS distribution consistently exhibited a greater risk for pancreatic cancer. Furthermore, the integration of a PRS, alongside clinical and lifestyle variables, into a MRS showed promise for a better pancreatic cancer risk stratification. Such models have demonstrated greater predictive power than those relying solely on traditional clinical features or genetic data only. Nevertheless, the limited number of known pancreatic cancer risk loci currently limits the PRS and MRS approach [97]. Expanding the pool of genetic variants will enhance the predictive accuracy of these models, paving the way for targeted screening strategies for pancreatic cancer.

5. Advancing risk prediction models: integrating AI and machine learning into PDAC risk assessment

Traditional risk models primarily focus on isolated clinical factors, overlooking the complex interplay between genetic, lifestyle, and environmental variables. This limitation reduces their ability to effectively identify high-risk individuals. Furthermore, current screening guidelines heavily rely on established risk factors such as age, family history, and smoking, while emerging biomarkers, including circulating tumour cells, cell-free DNA, exosomes, and serum proteins, remain underutilized, with their full clinical potential yet to be realized. To address these limitations, there is a growing need for advanced computational models capable of integrating diverse risk factors into precise risk profiles. Such models could enable timely screening and intervention for high-risk individuals, facilitating earlier detection and personalized management strategies.

Machine learning (ML) and artificial intelligence (AI) models excel at analysing this multifaceted data, uncovering complex gene-environment interactions and polygenic effects. Their development and application may enable and improve personalized risk assessments and support evidence-based recommendations for screening and intervention, particularly for genetically predisposed individuals [47,155]

While traditional epidemiological methods, including cohort and case-control studies, have laid the foundation for identifying key PDAC risk factors, their reliance on linear models often based on a limited set of variables, limits their capacity to capture intricate interdependencies. AI overcomes these challenges by leveraging advanced algorithms to model non-linear, high-dimensional relationships across diverse

datasets. This may enable the identification of complex associations and interactions by scanning larger amounts of data.

5.1. Artificial intelligence

In the era of precision medicine, AI methodologies are gaining great attention in the landscape of PDAC risk stratification. PDAC has been the subject of 20 AI studies to date, including investigations into both the general population [156–167] and high-risk groups, such as individuals with diabetes [168–172], chronic pancreatitis [59], and impaired fasting glucose [168].

These studies present risk prediction models based on different algorithms that process a wide range of health records and known and potential PDAC risk factors, evaluating the model performances through various metrics, including accuracy, recall, precision, F1-score, and AUC. The latter one is the most commonly used metric and will serve as the primary reference for comparing model performance.

5.2. AI models in the general population

A systematic review by Mishra et al. assessed multiple machine learning approaches applied to electronic health records (EHR), highlighting their potential to improve PDAC risk stratification by leveraging vast, multi-dimensional datasets that traditional models often overlook [173]. These methods, including neural networks and logistic regression models, have achieved encouraging predictive performance, demonstrating their feasibility for population-level screening and personalised risk assessments.

To ensure higher reliability, only those studies with a large sample size ($n > 1\ 000$), a comprehensive set of over 18 variables, external validation, and AUC > 0.70 were selected for detailed analysis, as these criteria lend greater credibility and reliability to the findings. A total of five studies meeting these criteria have been conducted to date [157,159,162,167,174].

Artificial neural networks (ANNs) are a class of machine learning models inspired by the structure of the human brain, designed to recognize complex patterns within large datasets. In PDAC risk prediction, ANNs have shown promising results by integrating various demographic, clinical, and lifestyle factors to improve accuracy over traditional methods. These models excel in handling non-linear relationships and interactions between variables, making them particularly suited for multifactorial diseases like PDAC. Three studies have applied ANNs to diverse data sources, such as the Pancreatic Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trials and the National Health Interview Survey (NHIS), where they achieved significant predictive performance. For instance, a study by Muhammad et al. incorporated 18 variables (age, sex, ethnicity, smoking-related variables, physical activity, alcohol intake, family history of PC, and presence of various diseases, such as diabetes), obtaining an AUC of 0.71 in the training set and an AUC of 0.85 in the validation set (PLCO+NHIS) [157]. Placido and colleagues used a sequential neural network analysing diseases trajectories of 23 985 pancreatic cancer cases and 6 151 252 controls within the Danish National Patient Registry (DNPR). The model achieved an impressive AUC of 0.88 for predicting cancer occurrence within a 36-month timeframe. Validation was performed on a separate cohort from the US Veterans Affairs (US-VA), including 3 418 cases and 1 941,374 controls, where the model demonstrated an AUC of 0.71 [174].

The recent development of the Prism model by Kia et al. represents a significant advancement in PDAC risk prediction using EHR data across a federated network of 55 U.S. healthcare organizations [162]. Prism includes two models: PrismNN, a neural network, and PrismLR, a logistic regression model, both using 87 features to predict PDAC risk 6–18 months before diagnosis for patients aged 40 and older. PrismNN demonstrated strong predictive accuracy with a test AUC of 0.83, while PrismLR reached 0.80. Importantly, the Prism model's validation across geographic, racial, and temporal subsets shows its generalizability across diverse populations. PrismNN can detect up to 3.5 times more PDAC cases at comparable risk levels than current screening guidelines. The federated network structure enables the integration of Prism into clinical practice, offering a scalable solution for identifying high-risk individuals in the general population, facilitating earlier interventions, and placing Prism within the context of broad clinical applicability.

Appelbaum et al. developed an L2-regularised logistic regression (LR) [175] model using EHR diagnoses and validated it on an external dataset. The LR model achieved an AUC of 0.71 in the training set and an AUC of 0.68 in the test set [159].

The studies by Appelbaum, Kia, and Placido illustrate that models incorporating long-term disease history can stratify individuals at elevated risk for pancreatic cancer up to one to three years in advance. Such an approach may provide an evidence-based framework for selecting individuals for targeted pancreatic cancer screening programs.

Interestingly, AI can be used to stratify PDAC risk by exploiting differences in microbiome composition. Using 27 differentially abundant bacterial species identified by whole metagenome sequencing, an L1-regularized logistic regression model was developed to distinguish PDAC cases from controls. This model was trained on a population of 136 subjects (57 cases, 50 controls, and 29 patients with chronic pancreatitis), achieving an AUC of 0.84. Validation on a separate cohort of 76 subjects yielded an AUC of 0.83, which improved to 0.94 when CA 19–9 levels were integrated [176].

Finally, the study conducted by Cheng et al. employed two distinct machine learning models (XGBoost [177] and random survival forests [178]) to predict the occurrence of pancreatic cancer in two separate populations: Kaiser Permanente Southern California for the training dataset (1 792 pancreatic cancer cases and 1 800 139 controls) and Veterans Affairs for the validation dataset (4 582 cases and 2 686 313 controls). Variables such as age, presence or absence of different diseases (acute or chronic pancreatitis, benign pancreatic disorders etc.), weight-related variables, blood tests, *H. pylori* infection and surgical procedures were included in the models. The XGBoost model obtained the best AUC in both training and validation (AUC of 0.78 and 0.74, respectively) compared to the random survival forest (AUC of 0.77 and 0.73 respectively), with both models displaying congruent performance results [179].

Compared to regularized logistic regression and alongside artificial neural networks, XGBoost and random survival forests provide distinctive advantages in robustly handling missing data and efficiently capturing complex, non-linear relationships within data [177,180].

Most models applied for the general population to date did not account for the genetic background, as in the studies mentioned above. Notably, only the studies by Kulm et al. (2022), Ke, Lophatananon, and Muir (2023), and Peduzzi et al. (2024) incorporated genetic variability through PRS within AI models, achieving AUCs of 0.71 0.77, and 0.92, respectively [165,166,181]. The AUCs from the works of Kulm and Ke, Lophatanon and Muir are lower than those obtained in other studies without a genetic component, likely reflecting the limited sample sizes of PDAC cases in these studies (371 and 960 cases, respectively) rather than a decrease in performance directly related to the inclusion of genetic information itself. However, Peduzzi et al. suggested the PRS as the primary contributor, together with age, to the prediction of high-risk individuals in a UKBB-based study on 654 cases and 1 308 controls. The above-mentioned studies are all reported in Table 3, which also integrates the number of features used in the studies divided into different categories (Fig. 2), based on the classification reported in Supplementary Table 1.

5.3. AI Models for specific populations or contexts

Despite the promising results, the low incidence of PDAC limits these models' predictive power and cost-effectiveness for general population screening. This challenge underscores the need for more targeted

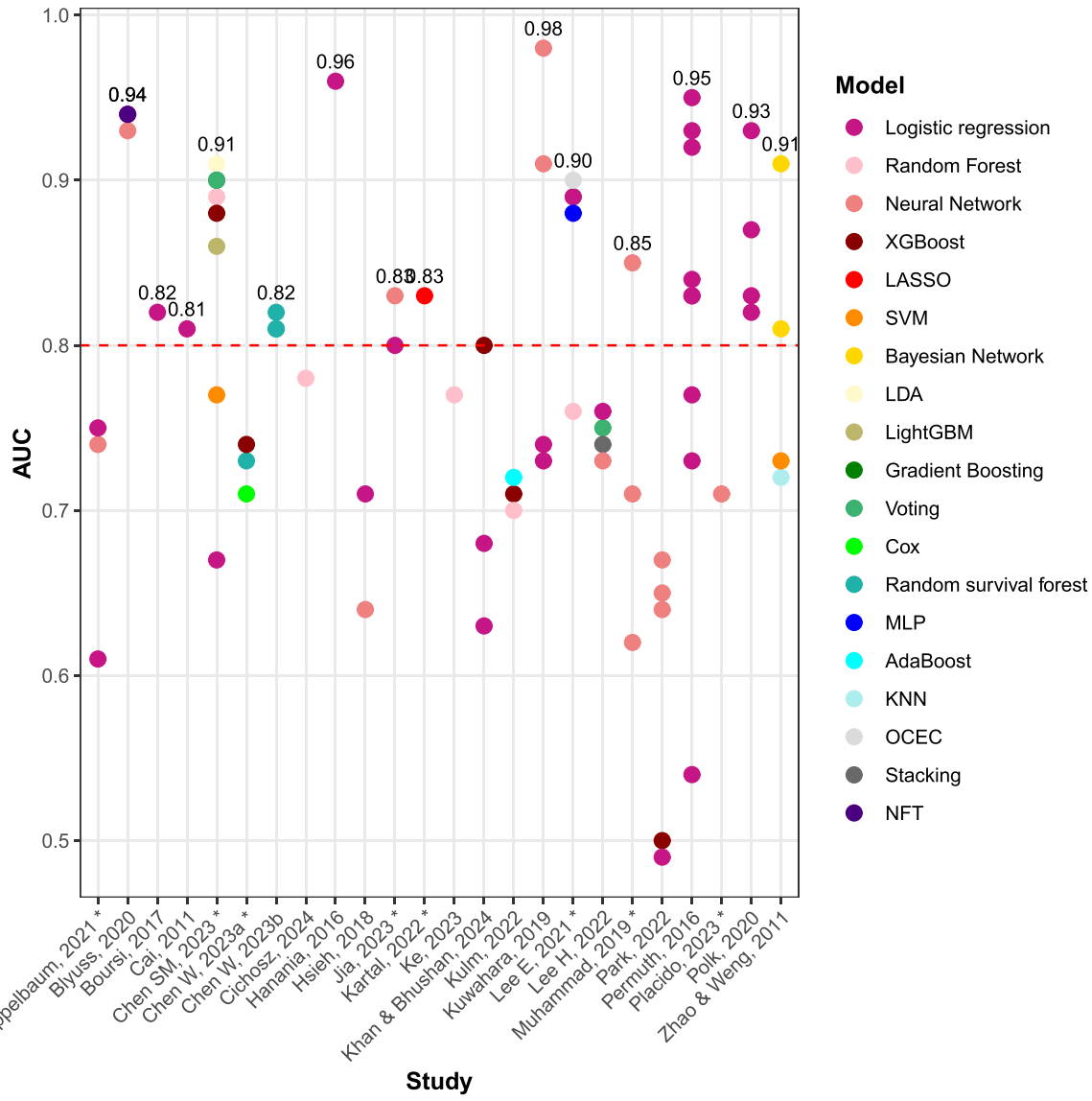

Fig. 1. Comparative representation of the various AI model types and their respective performance (AUC) across the selected studies. ***Footnotes***: Notations are only reported for AUCs higher than the median of the studies (red line, AUC = 0.80). *= AUCs from external validation. SVM = Support vector machine; LDA = Linear discriminant analysis; GBM = Gradient boosting model; MLP = Multilayer perceptron; KNN = K-nearest neighbour; OCEC = One-class embedding classifier; NFT = Neural-fuzzy technology.

screening methods, perhaps focusing on high-risk groups, such as those with diabetes, chronic pancreatitis, or impaired fasting glucose, to improve feasibility and resource allocation.

Eight studies have focused on predicting the risk of pancreatic cancer in high-risk populations, with six studies conducted among individuals with NOD that obtained AUC results ranging from 0.61 to 0.91 [168–172,183]. These findings suggest that while AI models are promising tools for PDAC risk prediction in high-risk diabetic populations, their performance varies significantly depending on several factors, such as dataset characteristics, number and informativeness of variables, and differences in algorithm design. Notably, Boursi et al. examined a cohort of 109 385 patients with new-onset diabetes (NOD) of which 0.4 % were diagnosed with PDAC within three years. They developed a predictive model incorporating 13 variables (age, BMI, BMI change per year, smoking, insulin use, PPI use, oral hypoglycaemics, metformin, Hb, HbA1c, creatinine, total cholesterol, and alkaline phosphatase), achieving an AUC of 0.82. With a PDAC risk of 1 % over 3 years, 6.19 % of NOD individuals would qualify for screening. The logistic regression model achieved a sensitivity of 44.7 % and a specificity of 94 %, indicating a good performance in identifying healthy individuals as non-cases. However, the positive predictive value of 2.6 % indicated that only a small proportion of individuals classified as positive for PDAC would actually be PDAC cases, with the remaining 87.4 % being false positives. The prediction rule showed good discrimination (AUC = 0.72), with the model classifying patients into low-risk and high-risk groups, the latter of which exhibited a significantly higher risk of pancreatic cancer (52.9 % vs. 13.2 %, $p < 0.001$) [59].

5.4. *Radiomics and imaging-driven AI for pancreatic cancer*

The AI-based systematic integration of epidemiological and clinical characteristics with morphological and textural features and variations of pancreatic imaging, obtained through automated segmentation, could significantly improve the estimation of PDAC risk. Qureshi et al., using a Bayes classifier model to retrospectively analyse CT scans conducted 3–6 months before a PDAC diagnosis, reclassified certain imaging features as precursor indicators of PDAC, demonstrating a pre-diagnostic accuracy of 85 % [184]. Chen et al. developed a multi-state risk prediction model

Table 3
Summary of the studies employing AI for pancreatic cancer risk prediction.

Method	Model	Internal validation AUC	External validation AUC	Population	Cases/Controls (overall)	Category (number of features)	Reference
Supervised learning	Linear discriminant analysis	0.91	0.91	Taipei Medical University Clinical Research Database	89/66 295	Demographics (2), anthropometric (1), comorbidities (5), drugs (2), biomarkers (3)	Chen et al., 2023 [172]
Ensemble	XGBoost	0.78	0.74	KPSC (internal), Veteran affairs (external)	6 374/4 486 452	Demographics (1), biomarkers (8), comorbidities (6), health history (2), anthropometric (2)	Chen et al., 2023 [179]
Ensemble	Random survival forest	0.77 A	0.68 A	KPSC (internal), Veteran affairs (external)	6 374/4 486 452	Demographic (1), biomarkers (9), comorbidities (10), health history (3), anthropometric (3)	Chen et al., 2023 [163]
Deep learning	Grouped neural network	0.67	-	Columbia University Irving Medical Center-New York Presbyterian Hospital	834/8 223	Biomarkers (33)	Park et al., 2022 [161]
Ensemble	Random survival forest	0.82	-	KPSC	319/108 947	Demographic (1), anthropometric (1), biomarkers (2)	Chen et al., 2023 [171]
Ensemble	AdaBoost	0.72	-	UK Biobank	371/121 507	Health history, lifestyle, comorbidities, biomarkers, demographic, genetics	Kulm et al., 2022 [166]
Deep learning	Sequential neural network	0.88	0.71	Danish National Patient Registry (internal), Veterans affairs (external)	27 403/8 092 626	Comorbidities	Placido et al., 2023 [174]
Deep learning	Artificial neural network	0.86	0.85	NHIS (internal), PLCO (external) *	898/799 246	Demographic (4), health history (3), lifestyle (11), anthropometric (1), comorbidities (11)	Muhammad et al., 2019 [157]
Knowledge representation	Bayesian network	0.91	-	Electronic health records	98/14 971	Demographic (1), lifestyle (1), comorbidities (9), biomarkers (9)	Zhao and Weng, 2011 [156]
Ensemble	Random forest	0.78	-	Danish National Patient Registry + Danish National Prescription Registry + Civil Registration System	716/716	Demographic (1), biomarkers (18)	Cichosz et al., 2024 [169]
Deep learning	Artificial neural network	0.76	0.74	Beth Israel Deaconess Medical Center (internal), Partners HealthCare (external)	1 002/260 972	Demographic (3), comorbidities	Appelbaum et al., 2021 [159]
Supervised learning	Logistic regression	0.71	-	Longitudinal Cohort of Diabetes Patients (NHI)	3 092/1 355 542	Demographic (1), comorbidities (2), drugs	Hsieh et al., 2018 [170]
Deep learning	One-class embedding classifier	0.74	0.90	NHIS: health checkup cohort (internal), national sample cohort (external)	551/235 633	Demographic (2), anthropometric (1), biomarkers (9), lifestyle(6), health history (11)	Lee et al., 2021 [164]
Supervised learning	Logistic regression	0.76	-	NHI Taiwan	738/2 214	Comorbidities (32)	Lee et al., 2022 [182]
Ensemble	XGBoost	0.80	-	EHR (TriNetX)	380/80 743	Demographic (3), biomarkers (6), anthropometric (2), drugs (4), comorbidities (3), lifestyle (2), health history (2)	Khan and Bhushan, 2024 [183]
Ensemble	Random forest	0.77	-	UK Biobank	960/257 348	Demographics (2), genetics (1), comorbidities (7), lifestyle (3), health history (2), anthropometric (2), biomarkers (1)	Ke et al., 2023 [165]
Deep learning	Artificial neural network	0.80	0.83	EHR (TriNetX)	35 387/1 500 081	Demographic (2), biomarkers (40), comorbidities (19), health history (16), drugs (2)	Jia et al., 2023 [162]
Deep learning	Neuro-fuzzy technology	0.94 ***	-	Royal London hospital, CNIO Madrid	199/180	Demographic (1), biomarkers (4)	Blyuss et al., 2020 [158]
Supervised learning	Naive bayes	NA	0.86 B	CSMC (internal), KPMC (external)	36/36	Images/CT/radiomics	Qureshi et al., 2022 [184]
Deep learning	Convolutional neural network	0.74 A	-	PanCanAtlas TCGA	NA **	Demographic (3), health history (1), genetics (2), images/CT/radiomics	Cheerla and Gevaert, 2019 [185]
Supervised learning	Logistic Regression	0.96	-	MD Anderson Cancer Center	34 high-grade IPMN/19 low-grade IPMN	Images/CT/radiomics	Hanania et al., 2016 [186]
Supervised learning	Logistic Regression	0.82	-	UK-THIN	390/108,995	Demographic (2), anthropometric (2), lifestyle (2), comorbidities (4), health history (1), drugs (13), biomarkers (20)	Boursi et al., 2017 [168]

(*continued on next page*)

Table 3 (*continued*)

Method	Model	Internal validation AUC	External validation AUC	Population	Cases/Controls (overall)	Category (number of features)	Reference
Supervised learning	LASSO	0.94	0.83	Hospital Ramón y Cajal in Madrid & Hospital Vall d'Hebron Barcelona (internal), University Hospital of Erlangen & Goethe University clinic (external)	101/82	Biomarkers (28)	Kartal et al., 2022 [176]
Supervised learning	Logistic Regression	0.93	-	H. Lee Moffitt cancer center and research institute	29/22	Images/CT/radiomics	Polk et al., 2020 [187]
Deep learning	Convolutional neural network	0.98	-	Aichi cancer center	23 malignant IPMN/ 27 benign IPMN	Images/CT/radiomics	Kuwahara et al., 2019 [188]
Supervised learning	Logistic Regression	0.95	-	H. Lee Moffitt cancer center and research institute	18 malignant IPMN/ 20 benign IPMN	Images/CT/radiomics	Permuth et al., 2016 [189]
Supervised learning	Support vector machine	0.94 C	-	Changai hospital	262/126 chronic pancreatitis	Images/CT/radiomics	Zhu et al., 2013 [190]
Supervised learning	Logistic Regression	0.81	-	Changai hospital	25/113	Demographic (1), biomarkers (2), Health history (2)	Cai et al., 2011 [59]
Ensemble	AdaBoost	0.91	-	UK Biobank	654/1 308	Demographic (3), anthropometrics (5), lifestyle (11), health history (3), comorbidities (1), genetics (1)	Peduzzi et al., 2024 [181]
Ensemble	XGBoost	0.92	-	UK Biobank	654/1 308	Demographic (3), anthropometrics (5), lifestyle (11), health history (3), comorbidities (1), genetics (1)	Peduzzi et al., 2024 [181]
Ensemble	CatBoost	0.91	-	UK Biobank	654/1 308	Demographic (3), anthropometrics (5), lifestyle (11), health history (3), comorbidities (1), genetics (1)	Peduzzi et al., 2024 [181]
Ensemble	Deep Forest	0.89	-	UK Biobank	654/1 308	Demographic (3), anthropometrics (5), lifestyle (11), health history (3), comorbidities (1), genetics (1)	Peduzzi et al., 2024 [181]
Ensemble	Random Forest	0.88	-	UK Biobank	654/1 308	Demographic (3), anthropometrics (5), lifestyle (11), health history (3), comorbidities (1), genetics (1)	Peduzzi et al., 2024 [181]

A = C-index (concordance score).
B = mean classification accuracy.
C = correct classification rate.
*= the combination of PLCO and NHIS data yielded the highest result, AUC = 0.85.
** = number of cases not reported by the authors.
*** = logistic regression achieved an equal result.
KPSC = Kaise Permanente South California; XGBoost = Extreme gradient boosting; AdaBoost = Adaptive boosting; CT = Computed tomography; CSMC = Cedars-Sinai Medical Center; KPMC = Kaiser Permanente Medical Center; CAD = Coronary artery disease; PPI = proton pump inhibitors; HbA1c = Haemoglobin A1C; CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio.

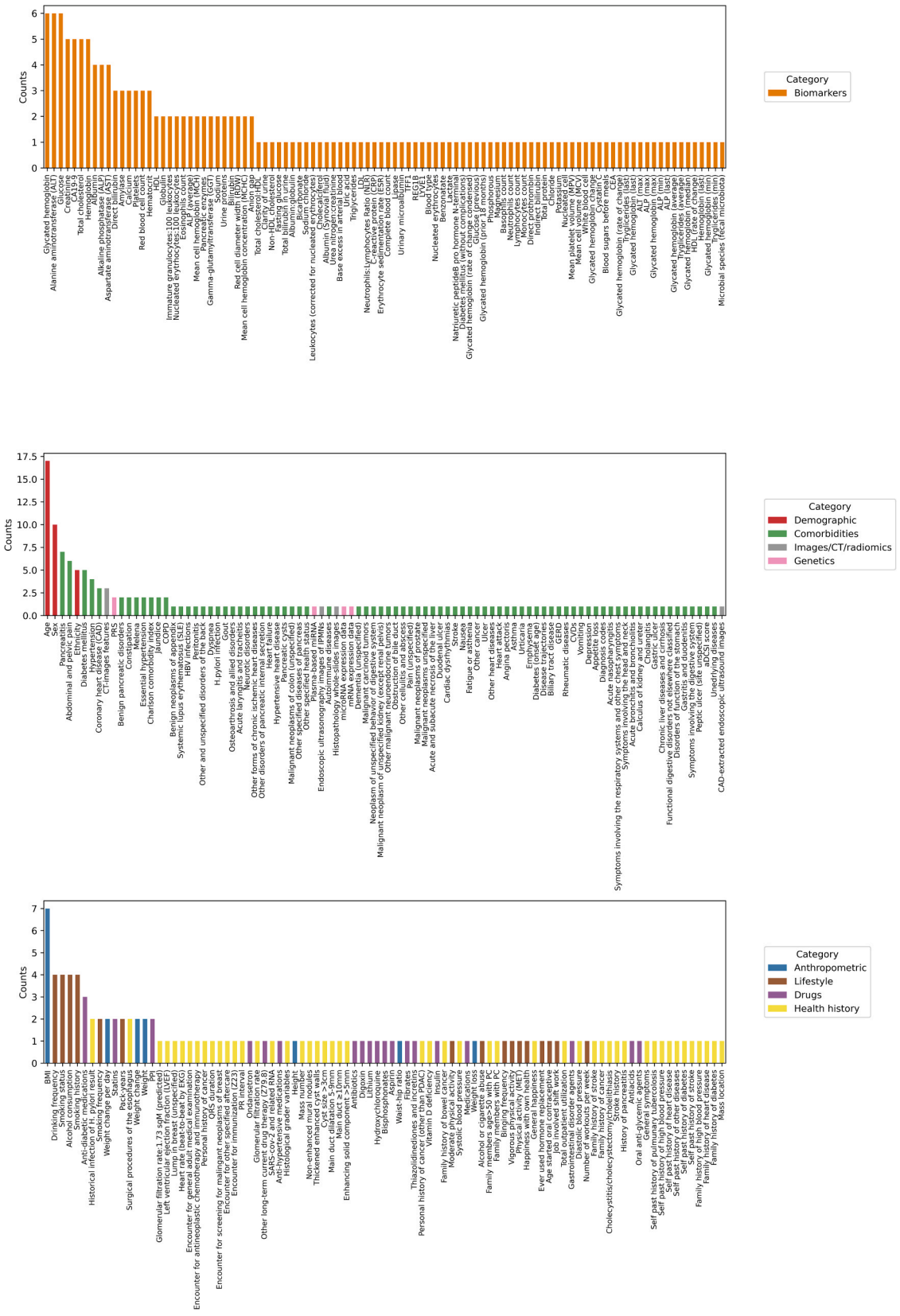

Fig. 2. Distribution of the features used in papers investigating PDAC risk using AI models. Different categories grouping similar features are colour-coded (e.g., Biomarkers in red).

for patients with pre-diagnostic pancreatic ductal dilation, incorporating morphological features from CT and MRI scans, such as pancreatic atrophy, cysts, calcifications, and pancreatic duct irregularity, along with clinical risk factors like age, sex, ethnicity, smoking, and alcohol use. The model effectively distinguished between patients who developed PDAC and those who did not, achieving a C-index of 0.825–0.833 [185]. The C-index is a statistical measure used to assess the discriminatory capability of a model. When evaluating a model for a binary outcome, the C-index and the AUC provide equivalent information [191].

Radiomics-based AI can also help clinicians to overcome the risk of overtreatment in IPMNs. Considering that only a portion of IPMNs progress into high-grade dysplasia (HGD) or invasive cancer (IC), patient management is crucial. According to the Fukuoka International Consensus guidelines, morphological imaging features guide the decision for IPMN surgical resection [192]. For instance, radiomics-based AI models correlating with the IPMN histopathological grade provided the ability to distinguish low-grade from high-grade IPMN, and high-grade from invasive IPMN with AUCs of 0.96 and 0.92, respectively [186]. Moreover, the AI-based integration of the radiomic features with the morphological features included in the Fukuoka International Consensus guidelines into a risk model for IPMN malignancy, was able to distinguish between malignant and benign IPMN lesions with an AUC varying from 0.84 to 0.93 [187]. In a recent study by Kuwahara et al., a deep neural network was used to stratify the potential IPMN malignancy based on preoperative EUS images. The integration of variables such as age, sex, symptoms, serum amylase, CEA and CA 19–9 levels, cyst location, size and mural nodule, main pancreatic duct size, and pathological features, allowed to achieve an AUC of 0.98 [188]. Permuth et al. employed an alternative approach by developing a radiogenomic model that integrated plasma miRNA expression data with radiomic data. The model was applied to 38 surgically resected IPMNs (20 benign, 18 malignant), resulting in a malignant IPMN prediction with an AUC of 0.93. Using the same population, the authors also developed a model based on the 'worrisome' features included in the international consensus guidelines, which achieved an AUC of 0.54 [189]. These findings support the use of a radiogenomic approach as a potential non-invasive tool for more accurate IPMN pathology prediction compared to conventional guidelines, while also highlighting its relevance for improved PDAC risk stratification.

5.5. AI models nearing real-world application for PDAC

Artificial intelligence is advancing PDAC risk prediction and early detection through models nearing real-world applicability. The Prism model, developed using federated electronic health record (EHR) data from 55 U.S. healthcare organizations, features two versions: PrismNN, a neural network, and PrismLR, a logistic regression model. These models predict PDAC risk 6–18 months prior to diagnosis for individuals aged 40 and older, with PrismNN achieving an AUC of 0.826 and identifying up to 3.5 times more cases than current high-risk screening criteria [162]. The federated design ensures patient privacy, making Prism scalable for diverse clinical settings.

In imaging, convolutional neural networks analyse CT, MRI, and EUS scans to detect pancreatic abnormalities with improved accuracy. For instance, a model by Zu et al. distinguished pancreatic adenocarcinoma from chronic pancreatitis with 94 % sensitivity [190]. Similarly, EHR-based approaches, like Boursi et al.'s logistic regression model for new-onset diabetes patients [168], achieved an AUC of 0.82, demonstrating the practical potential for identifying high-risk individuals [173].

AI models integrating genetic information and molecular data, such as miRNA expression, enhance personalized risk assessment by combining genetic, clinical, and lifestyle information. These approaches are particularly useful for identifying individuals with cumulative genetic risks who may not have a single high-penetrance mutation [173].

These promising models demonstrate AI's capability to integrate diverse data types, offering scalable, personalized strategies for PDAC risk stratification and early diagnosis. Continued validation and refinement in clinical settings will bring these approaches closer to widespread application.

5.6. Limitations of AI approaches for pancreatic cancer study

Despite their considerable potential, AI approaches still require overcoming a number of challenges in order to be successfully translated into clinical practice. The interpretability of the models, the lack of large and comprehensive datasets, and the presence of imbalanced classes (*i.e.,* cases and controls) represent the most significant limitations.

5.6.1. Interpretability

There is a trade-off between the accuracy and the explainability of AI models, even if a scientific consensus has yet to be reached about the most interpretable models, offering a clear and transparent binary decision process for decision-making. In the manuscript by Quinlan et al., the concept of decision trees is clearly explained [193]. However, these models are considered to be less accurate. Conversely, deep learning and transformer algorithms are considered to be the most accurate, although they are also the least interpretable due to the large number of parameters used to make predictions [194].

The use of a vast number of parameters and non-linear transformations, such as those observed in neural networks, increases the accuracy and performance of AI models. For example, the models used in the study by Muhammad described previously [157] achieved such a complexity that makes it challenging to understand how these models arrive at their decisions [195]. Thus, it has become increasingly necessary to use explainable AI (XAI), as it enables the understanding of the contribution of each variable analysed in classifying a subject as a case or control. The development of XAI strategies is also essential to enhance the trustworthiness of clinicians in AI applications [196].

The use of XAI techniques is a relatively recent phenomenon, with a considerable number of these models leveraging epidemiological data to predict PDAC risk. These models display a different degree of explainability. To date, there have been just six studies in the published literature employing XAI in this context, which underscores both the novelty of this approach and the limited scope of its current application [164,165,167,172,181,183]. The most contributory variables in predicting the risk of pancreatic cancer are haemoglobin and weight-related variables, although the studies from Kulm et al. and Peduzzi et al. also indicated the PRS as a major contributor variable [166,181]. Notably, all six studies used SHapley Additive exPlanations (SHAP) [197], which is regarded as the gold standard in this field. SHAP provides global and local interpretations with high stability, applicability to various models, and intuitive visualisations. Compared to other methods, such as Local Interpretable Model-Agnostic Explanations (LIME) or Partial Dependence Plots (PDP), it ensures greater consistency and robustness, making it ideal for critical contexts like pancreatic cancer prediction [197]. Additionally, Peduzzi et al. also included Global Model Interpretation via Recursive Partitioning (Girp) algorithm, which explains more complex AI models through simpler decision trees [198]. The combination of SHAP and Girp may be an example of how integrating multiple XAI tools increases the interpretability of AI models, with SHAP quantifying the contribution of each feature to the prediction, while Girp extracts a set of rules to define the selection of the features.

5.6.2. Available datasets

The translation of AI for PDAC management in clinical practice is hindered by the lack of multiple, similar, large and comprehensive and well-curated datasets needed for robust model deployment and validation. Firstly, the datasets currently available lack crucial variables to represent the clinical landscape of the disease and the various factors that may influence PDAC progression, including clinical, genomics,

epidemiological, and (histo)pathological data. These limitations also complicate external and independent validation, ultimately hindering the translation of AI models into clinical practice. The issue of dataset availability has been reported in literature by several authors [165,166].

5.6.3. Imbalanced data

A further significant challenge is presented by the lower number of PDAC cases than controls. A common approach to addressing the issue of imbalanced data is to apply resampling techniques, which involve selecting subjects by resampling the initial population through methods such as oversampling and under sampling [199]. Oversampling involves artificially increasing the frequency of underrepresented classes (PDAC cases), for example by duplicating or generating new samples, while under sampling entails reducing the frequency of overrepresented classes (controls) by eliminating some of their samples [200]. In the context of pancreatic cancer prediction, oversampling can result in less accurate predictions, as artificially increasing the frequency of pancreatic cancer cases may alter the original distribution of variable values. For example, Lee et al. in their study addressed data imbalance by re-sampling smaller classes (PDAC cases) to achieve a 1:1 balance during training and validation, obtaining discrete AUC values ranging from 0.73 to 0.75 depending on the algorithm used [160].

In contrast, a reduced number of pancreatic cancer cases may also result in overfitting of the models. Overfitting occurs when the model memorises the training data without learning from them, eventually resulting in an inability to generalise on the testing data [201]. Overfitted models produce unreliable results, thereby preventing their implementation and tragically reducing their applicability.

5.7. Future directions: federated learning and AI integration

As PDAC is a relatively rare disease, data from individual institutions may be insufficient to train robust predictive models. Federated learning, which involves collaborative model training across institutions without sharing patient data, is a new approach comprising several models that offer a promising solution [202]. This approach enables the pooling of diverse datasets while preserving patient privacy. The Prism model, developed through federated learning, integrates demographic and clinical data from multiple healthcare organisations to predict PDAC risk up to 18 months in advance. By enhancing model generalizability and security, federated learning provides a pathway to more accurate, population-wide PDAC risk assessments without compromising patient confidentiality.

6. Conclusion

PDAC remains one of the most challenging malignancies to diagnose and manage due to its late-stage presentation and complex aetiology. This review highlights how classical approaches, such as epidemiological studies and genetic analyses, have provided foundational insights into PDAC risk factors. Moreover, these methodologies have provided the foundational etiological knowledge that continues to underpin essential risk models, shaping current screening guidelines and prevention strategies. However, their limitations in addressing multifactorial interactions and predicting individual risk underscore the urgent need for more advanced predictive tools. Focusing on high-risk groups may further improve early PDAC diagnosis, while the introduction of new genetic approaches, including PRS, MRS and fine-mapping, may establish the basis for individual risk prediction.

The advent of AI offers unprecedented opportunities to revolutionize PDAC risk stratification and early detection. By integrating diverse datasets spanning genetic, clinical, lifestyle, and imaging data AI models can capture complex, non-linear relationships and provide dynamic, personalized risk profiles. Such promising tools have shown significant potential for improving predictive accuracy and guiding targeted screening efforts.

Despite these advancements, several challenges remain. The interpretability of AI models, the need for large, comprehensive datasets, and the inherent imbalance in PDAC case-control studies must be addressed to enable successful clinical translation. Initiatives like federated learning and explainable AI are crucial for overcoming these barriers while maintaining patient privacy and enhancing clinician trust in these technologies.

Future efforts should focus on validating AI models in diverse populations, integrating emerging biomarkers, and refining algorithms to balance precision and generalizability. Collaborative initiatives, such as international consortia, can play a pivotal role in pooling data and expertise to accelerate progress in PDAC research.

In summary, the integration of classical methodologies with cutting-edge AI approaches holds immense promise for redefining PDAC risk stratification and early detection. By bridging the gap between research and clinical application, these advancements have the potential to significantly improve patient outcomes and reduce the global burden of this devastating disease.

Declaration of Generative AI and AI-assisted technologies in the writing process

In preparing this work, the author(s) utilized AI for sentence restructuring during editing. They reviewed and refined the content as necessary, fully accepting responsibility for the publication's content

Declaration of Competing Interest

Eithne Costello is named as an inventor on GB patent GB1806002.0; PCT/GB2019/050998, submitted by the University of Liverpool, that covers the measurement of adiponectin and IL-1Ra as a biomarker for early detection of pancreatic cancer. The other authors report no declarations of interest. All the other authors report no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semcancer.2025.03.004.

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