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Review article

# Addressing the challenges of pancreatic cancer: Future directions for improving outcomes

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of all pancreatic tumours, is a devastating malignancy with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease. The low survival rates associated with PDAC primarily reflect the fact that tumours progress rapidly with few specific symptoms and are thus at an advanced stage at diagnosis in most patients. As a result, there is an urgent need to develop accurate markers of pre-invasive pancreatic neoplasms in order to facilitate prediction of cancer risk and to help diagnose the disease at an earlier stage. However, screening for early diagnosis of prostate cancer remains challenging and identifying a highly accurate, low-cost screening test for early PDAC for use in clinical practice remains an important unmet need. More effective therapies are also crucial in PDAC, since progress in identifying novel therapies has been hampered by the genetic complexity of the disease and treatment remains a major challenge. Presently, the greatest step towards improved treatment efficacy has been made in the field of palliative chemotherapy by introducing FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan and oxaliplatin) and gemcitabine/nab-paclitaxel. Strategies designed to raise the profile of PDAC in research and clinical practice are a further requirement in order to ensure the best treatment for patients. This article proposes a number of approaches that may help to accelerate progress in treating patients with PDAC, which, in turn, may be expected to improve the quality of life and survival for those suffering from this devastating disease.


## Introduction

Pancreatic ductal adenocarcinoma (PDAC), the most frequent form of pancreatic cancer, is a common malignancy, with around 280,000 new cases being diagnosed worldwide in 2008, and 70,000 cases seen in the European Union alone [1]. Although PDAC is the twelfth most common cancer worldwide, its low survival rate means that it is the fourth leading cause of cancer-related death in Western countries [1–3]. Indeed, this tumour is associated with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease, falling to less than 4% at 5 years [2]. The low survival rates associated with PDAC primarily reflect the fact that tumours progress rapidly with few specific symptoms and are thus at an advanced stage at diagnosis, with only 10% being operable. Therefore, it is not possible to survive PDAC in the way that colorectal or breast cancer can be survived [4].

While earlier diagnosis of the disease is clearly required to improve outcomes, more effective therapies are also urgently

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needed. However, progress in identifying novel therapies has been hampered by the genetic complexity of the disease and the lack of prognostic markers, underlining the need for new treatment approaches.

## Pathogenesis of pancreatic cancer

PDAC accounts for more than 90% of all pancreatic tumours, which constitute a heterogeneous set of diseases encompassing cancers of the endocrine and exocrine pancreas. Genetic studies suggest that PDAC develops from one of three known precursor lesions – pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms and mucinous cystic neoplasms – though the majority develop from PanINs, progressing from PanIN-1A and -1B through to PanIN-3 [5–7]. There is, however, some debate regarding the PanIN progression model [8,9]. Whole-exome sequencing studies have established that different precursor lesions are associated with distinct genetic alterations that mirror their histological progression (Table 1) [6,7]. Further studies into the genetic features of these initial lesions may provide an opportunity for early diagnosis of the disease while it is still in the curative stage. Genetic data have been interpreted to suggest that development of invasive disease from these precursor lesions occurs over a considerable length of time (17 years on average), with death following after 2–3 years, highlighting the importance of identifying early diagnostic markers [10–12]. Although the unavailability of early-stage tissue from patients with non-invasive precursor lesions has hampered the search for such markers, use of pancreatic cancer mouse models is likely to go some way to further the understanding of tumour initiation and progression [13,14]. Indeed, human PDAC xenografts and genetically-engineered mouse models have already been used to demonstrate the potential for the use of elevated Cath E (a protease highly and specifically expressed in PDAC) in PDAC and PanIN as an imageable, early biomarker for pancreatic cancer [15]. Nevertheless, screening for early diagnosis of pancreatic cancer remains challenging due to the low incidence of the disease, requiring a highly specific and sensitive test [16]. While focussing efforts on high-risk groups comprising those with a syndromic or familial risk of PDAC may improve accuracy, these groups represent only a minority of affected individuals [17–19]. Consequently, identifying an accurate, low-cost screening test for early PDAC for use in clinical practice remains an important unmet need. Given the cost to society, future research efforts are also likely to focus on identifying possible cancer preventative strategies. In the case of PDAC, risk factors for the disease have yet to be determined. However, the recent discovery that oncogenic K-Ras (found in almost all pancreatic cancers) is not constitutively active as previously thought, but requires activation by upstream stimulants [20], presents exciting possibilities for future prevention strategies. Since a large number of healthy individuals harbour Ras mutations [21], interventions aimed at reducing Ras activation is likely to have important cancer-preventive value, particularly in those with oncogenic Ras mutations [20].

Several core signalling pathways have been found to be genetically altered in PDAC, including apoptosis and Hedgehog, transforming growth factor-β (TGF-β) and KRAS signalling, with tumours containing an average of 63 alterations (Fig. 1) [22]. Key genes mutated in the majority of PDAC tumours include *KRAS*, *TP53*, *SMAD4* and *CDKN2A* [22,23]. *KRAS* is an early mutation occurring in PanIN-1A lesions, suggesting that this alteration may play an important role in the initiation of many PDACs [6,24]. Mutations of *CDKN2A* and *TP53* are also known to be involved in PDAC pathogenesis and their inactivation has been observed in around 80% and 50% of tumours, respectively [25,26]. *SMAD4* inactivation is a late event present in 50–60% of tumours and may be associated with more aggressive disease [27,28]. Although the complex signalling pathways underlying the development of PDAC have yet to be fully elucidated, genomic analysis of large cohorts of patients can be used to identify common mechanisms and will be key to the development of novel therapeutic strategies for the disease [23]. The tumour microenvironment may also present an opportunity for therapeutic targeting since extensive stromal cross-talk occurs with tumour cells, with stromal–epithelial interactions contributing to tumour spread and metastases [29]. However, recent studies involving elimination of stroma-promoting Hedgehog signalling in mouse models of PDAC indicate that the role of the stroma in PDAC progression is not straight-forward, with some stromal components acting to restrain tumour growth [30]. Further studies are needed, therefore, in order to clarify the value of the stroma as a therapeutic target in PDAC. Additional research is also needed into the role of cancer stem cells (CSCs) in PDAC, since available studies suggest that a small population of these cells may be responsible for tumour initiation and propagation [31,32].

**Table 1**
Selected somatic alterations in pancreatic ductal adenocarcinoma precursor lesions. Reproduced with permission from Macgregor-Das et al., 2013 [6].

| Gene | Genetic alteration | Pathway or regulatory process | Altered in PanINs | Altered in IPMNs | Altered in MCNs |
|---|---|---|---|---|---|
| *KRAS2* | Activating | GTPase-dependent signalling | Yes | Yes | Yes |
| *CDKN2A* | Inactivating | Cell cycle regulation | Yes | | |
| *TP53* | Inactivating | DNA damage response | Yes | Yes | Yes |
| *SMAD4* | Inactivating | TGF-β signalling | Yes | Yes | Yes |
| *ARID1A* | Inactivating | Chromatin remodelling | Yes | | |
| *MLL3* | Inactivating | Chromatin remodelling | Yes | | |
| *GNAS* | Activating | G protein-mediated signalling | No | Yes | |
| *RNF43* | Inactivating | Ubiquitin-dependent protein degradation | No | Yes | Yes |

PanIN: pancreatic intraepithelial neoplasia; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm.

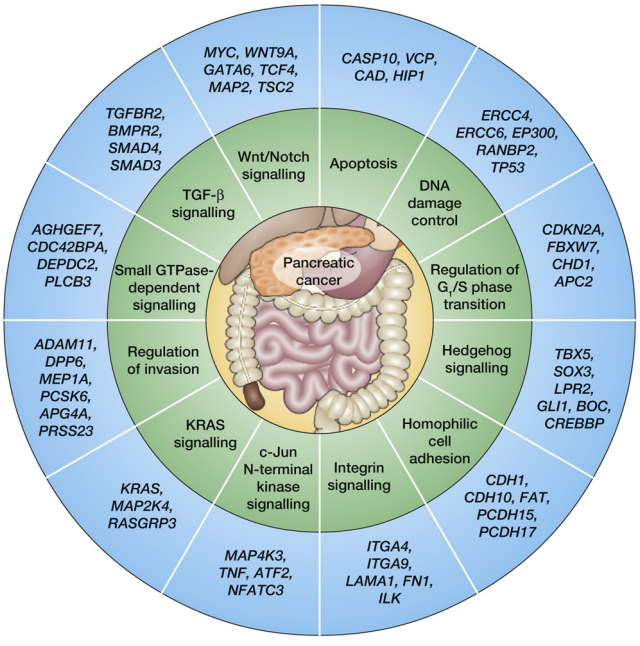


**Fig. 1.** Core signalling pathways and processes genetically altered in the majority of pancreatic cancers [22].