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Genetic Testing in Pancreatic Ductal Adenocarcinoma: Implications for Prevention and Treatment

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ABSTRACT

Purpose: This article reviews the progress to date and future directions for investigation of germline and somatic genetic testing to inform pancreatic adenocarcinoma (PDAC) treatment, screening, and prevention strategies.

Methods: We searched PubMed to identify recent articles regarding genetic testing in pancreatic cancer, including both germline and somatic testing, and recent genome-wide association studies. References were specifically hand searched as relevant. Guidelines for testing and screening high-risk individuals were included. We searched clinicaltrials.gov to review the current landscape of active clinical trials.

Findings: Approximately 10% of PDACs are associated with an identified germline mutation. Although germline mutations may inform treatment options and identify high-risk individuals for screening in other cancers, the data on PDAC are only now emerging. For example, poly adenosine diphosphate ribose polymerase (PARP) inhibitors are under investigation for BRCA-associated PDAC. Somatic mutations have also been identified in PDAC. However, current data are limited regarding treatment for potential PDAC somatic driver mutations. Although erlotinib is used in PDAC, its use is not targeted based on a tumor marker. Many tyrosine kinase inhibitors targeted toward potential driver mutations and critical pathways are in development, including BRAF/MEK, ALK, and CDK4/6. A consensus on screening strategies for individuals at high risk for PDAC is still evolving because of the relatively low prevalence of the disease, the relative invasiveness of endoscopic procedures often used as part of screening, and the lack of a clear survival benefit.

Implications: Pancreatic cancer has been slower to move toward genomic testing, partially because of a lower prevalence of mutations and partially because of a limited effect of results on treatment choices outside a clinical trial. This is an area of active investigation, and we anticipate that there will be both preventive and therapeutic implications of driver mutations in the coming decade. (*Clin Ther.* 2016;▮:▮▮▮–▮▮▮) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: genetic testing, germline mutation, pancreatic ductal adenocarcinoma, somatic mutation.

INTRODUCTION

Clinical Background

Although pancreatic adenocarcinoma (PDAC) contributes more than double its incidence rate (3% of new US cancer diagnoses per year) to cancer mortality (6.9% of US cancer deaths per year),[1] most PDAC cases are not linked to identified germline mutations.[2] However, somatic mutations, particularly in *KRAS*, are common.[3] Other risk factors, such as cigarette smoking, diabetes mellitus, and chronic pancreatitis, have consistent links to increased incidence of pancreatic cancer but with lower relative risks than for other malignant tumors.[1,4] Interestingly, PDAC has higher incidence rates in developed countries and among African Americans.[1] Although survival has modestly improved in the past 30 years, the overall 5-year survival is still only 7.2% in 2012, up from 3.6% in 1995 and 3% in 1975. Even localized disease

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that may be resectable has a 5-year survival rate of only 27%.[1]

Despite decades of research on systemic therapy for advanced PDAC, only 2 combination cytotoxic chemotherapy regimens have produced a clinically meaningful survival benefit compared with single-agent gemcitabine in the first-line setting. The FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin) regimen improved survival (11.1 vs 6.8 months) and decreased degradation quality of life at 6 months (31% vs 61%) compared with gemcitabine alone.[5] The combination of nab-paclitaxel and gemcitabine also improved survival relative to gemcitabine alone (8.5 months for the combination vs 6.7 months for gemcitabine).[6] The only targeted agent approved for PDAC treatment, the oral *EGFR* inhibitor erlotinib, improved survival by approximately 10 days when added to gemcitabine (6.24 months for the combination vs 5.91 months for gemcitabine alone).[7,8] Although there may be some association with response, *EGFR* has not proven a useful clinical tool to predict a strong erlotinib response in PDAC.[9] The choice in first-line treatment for advanced PDAC is often based on the patient's performance status and the toxicity profile of the treatment regimens.

We reviewed clinicaltrials.gov seeking active clinical trials for pancreatic cancer (accessed October 26, 2015). There are at least 90 early-stage studies of investigational therapeutic agents enrolling patients with pancreatic cancer. Most of these are early-stage, exploratory studies that include patients with a broad range of solid tumors. There are 15 later-stage studies specific to pancreatic cancer, some of which evaluate the efficacy of compounds already approved for other cancers. On the basis of historical drug development success rates,[10] it is likely that only a small proportion of these agents will be approved as anticancer therapies, and fewer still will provide clinical benefit for PDAC. Improved systemic therapy for PDAC remains a critical unmet need.

Oncogenesis of PDAC

Many PDACs appear to arise from pancreatic intraepithelial neoplasia (PanIN), an intraductal precursor lesion. As shown in Figure 1, an accumulation of genetic alterations occurs on the pathway from most well-defined PanINs to invasive carcinoma, a typical oncogenic progression.[11] Genetic predisposition syndromes act to increase the risk of oncogenesis in a variety of ways, affecting DNA repair mechanisms, microsatellite stability, or mismatch repair mechanisms. *KRAS* mutations appear to be a key somatic alteration, with low rates in pancreatitis specimens and high rates in PDAC specimens. *KRAS* mutations may also be an early mutation in the PanIN pathway because it is found in 36% to 44% of low-grade PanIN samples but up to 87% of high-grade PanIN samples.[12] *CDKN2A* is another early mutation noted in PanIN lesions. Higher-grade PanIN lesions also have *SMAD4* and *p53* mutations.[13-15]

Epigenetic alterations are also noted in PDAC. Hypermethylation is often a factor in tumor suppressor gene inactivation and increases with higher-stage pancreatic neoplasia. Overexpression of micro-RNAs is also seen in a distinct pattern in neoplastic pancreatic tissue versus normal pancreatic tissue. Although there is no current clinical application for these findings, further investigation of epigenetic markers may refine our understanding of PDAC oncogenesis and identify potential treatment targets.[15,16] This article reviews the current status of germline and somatic genetic testing in PDAC, clinical applications, and future directions for investigation.

METHODS

We performed an initial PubMed search for the terms *pancreatic cancer genetics* and *pancreatic cancer genetic testing* to identify the body of research in the last 10 years in particular. We then performed specific searches for each of the key proposed germline mutations and somatic driver mutations. Society guidelines were explicitly included. We searched clinicaltrials.gov for active clinical trials in pancreatic cancer.

DISCUSSION

Testing for PDAC genetic mutations has 2 primary purposes: (1) germline testing to identify at-risk individuals and (2) somatic and germline testing to identify potential targets for treatment. Historically, routine PDAC germline testing has been hindered by an unclear definition of the target population of at-risk individuals and the absence of proven low-risk screening strategies. For example, PDAC is not included in the Amsterdam or Bethesda guidelines that define Lynch syndrome even though these individuals have a higher PDAC risk than the general