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Editorial Board Member of *World Journal of Gastroenterology*, Oscar Teramoto-Matsubara, MD, AGAF, FACG, FACP, Associate Specialist, Department of Gastroenterology, ABC Medical Center, Mexico City 11000, Mexico. teramotomd@prodigy.net.mx

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Diagnostic biomarkers for pancreatic cancer: An update

Ming Yang, Chun-Ye Zhang

ORCID number: Ming Yang 0000-0002-4895-5864; Chun-Ye Zhang 0000-0003-2567-029X.

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Ming Yang, Department of Surgery, University of Missouri, Columbia, MO 65212, United States

Chun-Ye Zhang, Department of Veterinary Pathobiology, University of Missouri, Columbia, MO 65212, United States

Corresponding author: Ming Yang, DVM, PhD, Postdoctoral Fellow, Department of Surgery, University of Missouri, One Hospital Dr., Medical Science Building, Room M272, Columbia, MO 65212, United States. yangmin@health.missouri.edu

Abstract

Pancreatic ductal adenocarcinoma accounts for the primary type of pancreatic cancer (PC) with a 5-year survival rate of only about 10% in the United States. Early diagnosis will improve chances for curative treatment. To date, a broadly used serum marker for PC diagnosis is carbohydrate antigen 19-9, which is the only approved biomarker currently by the United States Food and Drug Administration. However, it has low specificity; therefore, development of novel biomarkers is urgently needed. Clinical trials are ongoing to evaluate candidate biomarkers for PC diagnosis, and the use of a multi-biomarker panel with current PC diagnostic biomarkers appears promising.

Key Words: Pancreatic ductal adenocarcinoma; Diagnosis; Biomarkers; Panel; Clinical trials

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Core Tip: The development of ideal diagnostic biomarkers for pancreatic cancer (PC) is critically important for early diagnosis, large-scale screening, monitoring of therapeutic response, prediction of risk, and prognosis. So far, the only approved serum marker for PC diagnosis is carbohydrate antigen 19-9 (CA 19-9) in the United States; although, many potential biomarkers have been investigated. However, CA 19-9 has low sensitivity; hence, new solutions are needed. Herein, we summarize some of the ongoing clinical trials that aim to investigate the application of biomarkers in PC diagnosis.

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TO THE EDITOR

We read with great interest a review paper recently published by O'Neill and Stoita [1], reviewing diagnostic biomarkers currently applied in pancreatic cancer (PC). The biomarkers are from serum, urinary, pancreatic, salivary, biliary, and fecal sources and comprise many different types of molecules. For example, serum biomarkers include proteins of glycolipids, growth factors, cytokines, chemokines, adhesion molecules, non-coding RNAs (long non-coding RNAs and microRNAs), and liquid biopsy (exosomes, circulating tumor DNA or ctDNA, and circulating tumor cells or CTCs)[1].

Moreover, we agree with the authors' suggestion that early diagnosis of PC improves chances for curative treatment. PC comprises two main subtypes, including the more common exocrine cancers and less common endocrine cancers. Pancreatic ductal adenocarcinoma (PDAC) accounts for the primary type of PC, consisting of around 95% in exocrine cancers and about 90% in all PCs. The 5-year survival rate of PC is relatively low and was only 10% for all patients with PC in the United States from 2010 to 2016[2]. To date, the only approved serum marker for PC diagnosis is carbohydrate antigen 19-9 (CA 19-9) in the United States, even though it has low specificity[3]. However, CA 19-9 is a non-PC-specific marker, shown to increase in colorectal, liver, lung, and ovarian cancers, as well as desmoplastic fibroblastoma[4,5]. Because of the low specificity of CA 19-9, a multi-marker panel that combines some of the currently investigated biomarkers (with CA 19-9) can be used to improve the specificity and sensitivity of PC diagnosis. For example, a multi-biomarker panel with enzyme-linked immunosorbent assay using three potential biomarkers, leucine-rich alpha-2-glycoprotein 1, transthyretin, and CA 19-9, improved the diagnosis of PDAC in normal pancreas and benign pancreatic disease and other tumors[6]. Although a multi-biomarker panel provides a better approach for early PC diagnosis, some limitations, including cost, the requirement for large sample volumes, good technique and analytical performance, and practical feasibility, may impact their broad application[3,7,8].

In addition, many of the biomarkers discussed in the abovementioned paper, including extracellular matrix-associated proteins such as matrix metalloproteinase and tissue inhibitor of metalloproteinase 1, profibrotic factors such as transforming growth factor-beta, growth factors such as vascular endothelial growth factor, cell-cell interacting protein such as intercellular adhesion molecule 1, and microRNAs such as mi-R21, are not specific markers implicated in many other cancers and diseases[9-12]. Furthermore, germline mutations in genes such as cyclin-dependent kinase inhibitor 2A, tumor protein p53, serine/threonine kinase ATM, MutL homolog 1, and breast cancer 1 and 2 have been significantly associated with PC[13]. The authors also mentioned genetic factors associated with PC, such as *KRAS* in ctDNA and *KRAS* mutation in CTCs. Therefore, genetic mutation or inherited factors may be a predisposing factor for PC and should be considered during the diagnosis.

Finally, this letter summarizes the actively recruiting and completed clinical trials to evaluate diagnostic methods or biomarkers for PC (Table 1). The data were collected from the website <https://clinicaltrials.gov> (accessed on July 18, 2021) using the keywords biomarkers and PC. Overall, the specificity and sensitivity of PC diagnosis can be increased by using multiple marker panels in combination with CA 19-9 or with novel screened biomarkers. In addition, accuracy, cost-effectiveness, and ease of application together will ensure the broad application of any new diagnostic method.

Table 1 Clinical trials for pancreatic cancer with representative diagnostic biomarkers

Trial number	Biomarkers	Status	Year to complete	Results/Trial titles
NCT03311776	HA and PRO-C3	Completed	2035	Serum HA and PRO-C3 were prognostic for overall survival in patients with PC[14]
NCT04241367	ctDNA	Recruiting	2025	Verification of predictive biomarkers for pancreatic cancer treatment using multicenter liquid biopsy
NCT04143152	sTRA and CA 19-9	Recruiting	2023	Two biomarker panels with sTRA and CA 19-9 improved sensitivity and accuracy, compared to using only CA19-9 [15]
NCT03404661	Methylated DNA markers	Recruiting	2023	Optical and biochemical biomarkers in early pancreatic cancer significance: a prospective study
NCT04584996	CircRNAs	Recruiting	2023	Circular and non-coding RNAs as clinically useful biomarkers in pancreaticobiliary cancers
NCT04636788	Circulating exosomal small RNAs	Recruiting	2022	Diagnostic and prognostic values of EUS-FNA specimens and circulating exosomal small RNA in patients with pancreatic cancer
NCT03536793	Urinary tissue factor and Endo180	Recruiting	2022	Study of uTF and Endo180 as markers of early malignancy in cystic pancreatic lesions
NCT04549064	AREG	Recruiting	2021	Identification of AREG for the detection of pancreatic cancer by the biosensor
NCT03817866	Chromogranin A	Recruiting	2021	To validate the performance of Brahms Chromogranin A II Kryptor assay to monitor the course of disease in patients with well-defined gastroentero-pancreatic neuroendocrine tumors
NCT03214991	DNA	Unknown	2021	Circulating tumor DNA as a prognostic marker in patients with pancreatic cancer
NCT01664169	VEGF-A and VEGF-R2	Completed	2018	Validation of circulating biomarkers using the immunological multiparameter chip technology (IMPACT) platform on plasma specimens collected on CALGB 80303
NCT02974764	Circulating tumor cells	Completed	2018	Alterations in circulating tumor cells predicted the progression of pancreatic ductal adenocarcinoma, treatment response, and clinical outcomes[16]
NCT00674973	AREG, EGF, sHER2, TGF- α	Completed	2015	Exploratory analyses suggested that high AREG might predict progression-free survival in patients with pancreatic cancer treated with erlotinib[17]
NCT01675258	Four messenger RNA biomarkers (KRAS, MBD3L2, ACRV1, and DPM1) in salivary samples	Completed	2013	The logistic regression model using four biomarkers yielded an area under the curve value of 0.971 (cutoff 0.433) to detect resectable pancreatic cancer with 90.0% sensitivity and 95.0% specificity[18]
NCT00899158	Caspase-3 and pAkt in muscle, and urinary 3-MH	Completed	2008	Role of caspase-3, phosphatidylinositol-3 kinase, and 3-methylhistidine in the pathophysiology of skeletal muscle loss in weight-losing pancreas cancer patients

ACRV1: Acrosomal vesicle protein 1; AREG: Amphiregulin; DPM1: Dolichyl-phosphate mannosyltransferase subunit 1; EGF: Epidermal growth factor; circRNAs: Circular RNAs; ctDNA: Circulating tumor DNA; HA: Hyaluronan; MBD3L2: Methyl-CpG binding domain protein 3 like 2; pAkt: Phosphorylated Akt; PRO-C3: Propeptide of type III collagen; sHER2: Soluble human epidermal growth factor receptor 2; sTRA: Sialylated tumor-related antigen; TGF- α : Transforming growth factor- α ; 3-MH: 3-methylhistidine.

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