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**Diagnostic biomarkers for pancreatic cancer: An update**

Yang M *et al*. Diagnostic biomarkers for PC

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**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.

**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.

**REFERENCES**

1 **O'Neill RS**, Stoita A. Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket? *World J Gastroenterol* 2021; **27**: 4045-4087 [PMID: 34326612 DOI: 10.3748/wjg.v27.i26.4045]

2 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021; **71**: 7-33 [PMID: 33433946 DOI: 10.3322/caac.21654]

3 **Choi YJ**, Yoon W, Lee A, Han Y, Byun Y, Kang JS, Kim H, Kwon W, Suh YA, Kim Y, Lee S, Namkung J, Han S, Choi Y, Heo JS, Park JO, Park JK, Kim SC, Kang CM, Lee WJ, Park T, Jang JY. Diagnostic model for pancreatic cancer using a multi-biomarker panel. *Ann Surg Treat Res* 2021; **100**: 144-153 [PMID: 33748028 DOI: 10.4174/astr.2021.100.3.144]

4 **Rasappan K**, Shaw LKRM, Chan LWM, Chuah KL, Cheng MHW. A case of raised CA 19-9 in a patient with desmoplastic fibroblastoma of the upper limb. *Int Cancer Conf J* 2021; **10**: 222-227 [PMID: 34221836 DOI: 10.1007/s13691-021-00485-z]

5 **Kim SY**, Lee HS, Bang SM, Han DH, Hwang HK, Choi GH, Chung MJ, Kim SU. Serum Dickkopf-1 in Combined with CA 19-9 as a Biomarker of Intrahepatic Cholangiocarcinoma. *Cancers (Basel)* 2021; **13** [PMID: 33921232 DOI: 10.3390/cancers13081828]

6 **Lee DH**, Yoon W, Lee A, Han Y, Byun Y, Kang JS, Kim H, Kwon W, Suh YA, Choi Y, Namkung J, Han S, Yi SG, Heo JS, Han IW, Park JO, Park JK, Kim SC, Jun E, Kang CM, Lee WJ, Lee HK, Lee H, Lee S, Jeong SY, Lee KE, Han W, Park T, Jang JY. Multi-biomarker panel prediction model for diagnosis of pancreatic cancer. *J Hepatobiliary Pancreat Sci* 2021 [PMID: 33991409 DOI: 10.1002/jhbp.986]

7 **Mellby LD**, Nyberg AP, Johansen JS, Wingren C, Nordestgaard BG, Bojesen SE, Mitchell BL, Sheppard BC, Sears RC, Borrebaeck CAK. Serum Biomarker Signature-Based Liquid Biopsy for Diagnosis of Early-Stage Pancreatic Cancer. *J Clin Oncol* 2018; **36**: 2887-2894 [PMID: 30106639 DOI: 10.1200/JCO.2017.77.6658]

8 **Park J**, Choi Y, Namkung J, Yi SG, Kim H, Yu J, Kim Y, Kwon MS, Kwon W, Oh DY, Kim SW, Jeong SY, Han W, Lee KE, Heo JS, Park JO, Park JK, Kim SC, Kang CM, Lee WJ, Lee S, Han S, Park T, Jang JY, Kim Y. Diagnostic performance enhancement of pancreatic cancer using proteomic multimarker panel. *Oncotarget* 2017; **8**: 93117-93130 [PMID: 29190982 DOI: 10.18632/oncotarget.21861]

9 **Barabás L**, Hritz I, István G, Tulassay Z, Herszényi L. The Behavior of MMP-2, MMP-7, MMP-9, and Their Inhibitors TIMP-1 and TIMP-2 in Adenoma-Colorectal Cancer Sequence. *Dig Dis* 2021; **39**: 217-224 [PMID: 32961536 DOI: 10.1159/000511765]

10 **Bar-Shai A**, Shenhar-Tsarfaty S, Ahimor A, Ophir N, Rotem M, Alcalay Y, Fireman E. A novel combined score of biomarkers in sputum may be an indicator for lung cancer: A pilot study. *Clin Chim Acta* 2018; **487**: 139-144 [PMID: 30222960 DOI: 10.1016/j.cca.2018.09.027]

11 **Wang X**, He Y, Mackowiak B, Gao B. MicroRNAs as regulators, biomarkers and therapeutic targets in liver diseases. *Gut* 2021; **70**: 784-795 [PMID: 33127832 DOI: 10.1136/gutjnl-2020-322526]

12 **Yang M**, Zhang C. The role of liver sinusoidal endothelial cells in cancer liver metastasis. *Am J Cancer Res* 2021; **11**: 1845-1860 [PMID: 34094657]

13 **Hu C**, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, Lilyquist J, Na J, Moore R, Antwi SO, Bamlet WR, Chaffee KG, DiCarlo J, Wu Z, Samara R, Kasi PM, McWilliams RR, Petersen GM, Couch FJ. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. *JAMA* 2018; **319**: 2401-2409 [PMID: 29922827 DOI: 10.1001/jama.2018.6228]

14 **Chen IM**, Willumsen N, Dehlendorff C, Johansen AZ, Jensen BV, Hansen CP, Hasselby JP, Bojesen SE, Pfeiffer P, Nielsen SE, Holländer NH, Yilmaz MK, Karsdal M, Johansen JS. Clinical value of serum hyaluronan and propeptide of type III collagen in patients with pancreatic cancer. *Int J Cancer* 2020; **146**: 2913-2922 [PMID: 31642523 DOI: 10.1002/ijc.32751]

15 **Staal B**, Liu Y, Barnett D, Hsueh P, He Z, Gao C, Partyka K, Hurd MW, Singhi AD, Drake RR, Huang Y, Maitra A, Brand RE, Haab BB. The sTRA Plasma Biomarker: Blinded Validation of Improved Accuracy Over CA19-9 in Pancreatic Cancer Diagnosis. *Clin Cancer Res* 2019; **25**: 2745-2754 [PMID: 30617132 DOI: 10.1158/1078-0432.CCR-18-3310]

16 **Gemenetzis G**, Groot VP, Yu J, Ding D, Teinor JA, Javed AA, Wood LD, Burkhart RA, Cameron JL, Makary MA, Weiss MJ, He J, Wolfgang CL. Circulating Tumor Cells Dynamics in Pancreatic Adenocarcinoma Correlate With Disease Status: Results of the Prospective CLUSTER Study. *Ann Surg* 2018; **268**: 408-420 [PMID: 30080739 DOI: 10.1097/SLA.0000000000002925]

17 **Propper D**, Davidenko I, Bridgewater J, Kupcinskas L, Fittipaldo A, Hillenbach C, Klughammer B, Ducreux M. Phase II, randomized, biomarker identification trial (MARK) for erlotinib in patients with advanced pancreatic carcinoma. *Ann Oncol* 2014; **25**: 1384-1390 [PMID: 24827134 DOI: 10.1093/annonc/mdu176]

18 **Zhang L**, Farrell JJ, Zhou H, Elashoff D, Akin D, Park NH, Chia D, Wong DT. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer. *Gastroenterology* 2010; **138**: 949-57.e1-7 [PMID: 19931263 DOI: 10.1053/j.gastro.2009.11.010]

**Footnotes**

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**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-alpha; 3-MH: 3-methylhistidine.