World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2021 July 14; 27(26): 4045-4087

DOI: 10.3748/wjg.v27.i26.4045

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Biomarkers in the diagnosis of pancreatic cancer: Are we closer to finding the golden ticket?

Robert S O'Neill, Alina Stoita

ORCID number: Robert S O'Neill 0000-0002-9576-2248; Alina Stoita 0000-0001-9460-2149.

Author contributions: O'Neill RS researched the paper and wrote the initial draft of the manuscript; Stoita A designed the paper, researched studied and reviewed the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interests relevant to this manuscript.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Robert S O'Neill, Alina Stoita, Department of Gastroenterology, St Vincent's Hospital Sydney, Sydney 2010, Australia

Robert S O'Neill, St George and Sutherland Clinical School, Faculty of Medicine, University of New South Wales, Sydney 2010, Australia

Alina Stoita, St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Sydney 2010, Australia

Corresponding author: Alina Stoita, FRACP, MBBS, Doctor, Lecturer, Department of Gastroenterology, St Vincent's Hospital Sydney, 390 Victoria Street, Sydney 2010, Australia. alina.stoita@svha.org.au

Abstract

Pancreatic cancer (PC) is a leading cause of cancer related mortality on a global scale. The disease itself is associated with a dismal prognosis, partly due to its silent nature resulting in patients presenting with advanced disease at the time of diagnosis. To combat this, there has been an explosion in the last decade of potential candidate biomarkers in the research setting in the hope that a diagnostic biomarker may provide a glimmer of hope in what is otherwise quite a substantial clinical dilemma. Currently, serum carbohydrate antigen 19-9 is utilized in the diagnostic work-up of patients diagnosed with PC however this biomarker lacks the sensitivity and specificity associated with a gold-standard marker. In the search for a biomarker that is both sensitive and specific for the diagnosis of PC, there has been a paradigm shift towards a focus on liquid biopsy and the use of diagnostic panels which has subsequently proved to have efficacy in the diagnosis of PC. Currently, promising developments in the field of early detection on PC using diagnostic biomarkers include the detection of microRNA (miRNA) in serum and circulating tumour cells. Both these modalities, although in their infancy and yet to be widely accepted into routine clinical practice, possess merit in the early detection of PC. We reviewed over 300 biomarkers with the aim to provide an in-depth summary of the current state-of-play regarding diagnostic biomarkers in PC (serum, urinary, salivary, faecal, pancreatic juice and biliary fluid).

Key Words: Pancreatic cancer; Cancer; Biomarkers; Diagnostic; Review

Country/Territory of origin: Australia

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 26, 2021
Peer-review started: January 26, 2021
First decision: February 27, 2021
Revised: March 24, 2021
Accepted: June 15, 2021
Article in press: June 15, 2021
Published online: July 14, 2021

P-Reviewer: Ruess DA
S-Editor: Gao CC
L-Editor: A
P-Editor: Liu JH

Core Tip: Circulating biomarkers are an attractive method for pancreatic cancer (PC) diagnosis. Over 300 biomarkers are presented in this review, however no gold standard biomarker exists. While carbohydrate antigen 19-9 possesses modest sensitivity in PC diagnosis, a lack of specificity is a limitation for its use. More recent studies have shifted towards the concept of a liquid biopsy along with measuring expression of RNA based markers in different mediums. Panels comprising multiple candidate biomarkers have emerged, demonstrating modest diagnostic value. Further studies are required to validate these findings, along with assessment in an asymptomatic population to determine their value in screening.

Citation: 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(26): 4045-4087
URL: https://www.wjgnet.com/1007-9327/full/v27/i26/4045.htm
DOI: https://dx.doi.org/10.3748/wjg.v27.i26.4045

INTRODUCTION

Pancreatic cancer (PC), most recently declared as a medical emergency by the United European Gastroenterology in a position paper, is a leading cause of cancer related mortality on a global scale, being the 12th most common cancer diagnosis, and the seventh leading cause of cancer related death[1-3]. The mortality associated with PC is significant compared to its solid organ tumor counterparts, accounting for approximately 4% of cancer related deaths with a Mortality/Incidence ratio of 98%, and has a dismal 5-year survival rate of approximately 9% which has only incrementally improved over the past forty years due to improvements in neoadjuvant and adjuvant therapeutic options[3-5]. This poor prognosis is attributed to patients being diagnosed with advanced disease at the time of presentation and the relatively silent nature of the disease[6]. It is estimated that, at the time of diagnosis 80%-90% of patients have unresectable disease[7]. It is postulated that diagnosis at an earlier stage would increase the 5-year survival rate as this would allow for curative resection along with adjuvant chemotherapy[8,9].

Due to the overwhelming number of patients having unresectable disease at the time of diagnosis there has been an emphasis on the identification of novel diagnostic modalities or biomarkers that can assist clinicians in detecting PC at an early stage. Currently there is no defined PC screening strategy for the general population that is comparable to screening colonoscopies for colorectal cancer (CRC) and the programs that exist are only limited to high risk patients (familial PC and hereditary PC syndromes) which represent only 5%-10% of all PC patients[10-12].

The goal of early detection of PC in otherwise asymptomatic patients is optimistic however so far impractical due to low incidence of PC in the general population, where even with a screening assay with a high specificity, implementing a screening program might result in increased levels of anxiety in the screened population with the potential for false positive results[13]. Further to this, the vast majority of studies have assessed the utility of diagnostic biomarkers in patients with symptomatic disease, rather than as a surveillance or screening biomarker in the general population.

A biomarker is defined as 'any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease'. Currently carbohydrate antigen 19-9 (CA19-9) is regarded as the best serological biomarker available so far in the diagnosis of PC, however the majority of studies endorsing the use of CA19-9 as a complementary test in the diagnosis of PC acknowledge it is not specific or sensitive enough to be used for screening[14,15]. A number of other biomarkers have been proposed and these will be reviewed here[16]. Variation exists in the biomarker domain, with studies utilizing serum, biliary fluid, pancreatic juice, urine, faeces and pancreatic cystic fluid for analysis of potential agents to determine their worth as a malignancy biomarker, however these methods of assessment vary in their invasiveness, sensitivity and specificity[17-20].

Due to the currently rapidly evolving landscape of potential biomarkers for early diagnosis of PC and the apparent lack of a gold standard diagnostic assay in the general population, the aim of this review is to provide a comprehensive update on the current diagnostic biomarkers implicated in PC with over 300 biomarkers

reviewed here.

SEROLOGICAL BIOMARKERS OF PC

Serum has been the most utilized modality for specimen collection for biomarker analysis, and it is the preferred specimen for analysis due to simplicity of collection and low risk, however it has limitations, particularly the potential for dilution of candidate tumour markers and the potential for these markers to be obscured by other serum proteins that exist within samples[21].

Glycolipids and proteins

CA19-9: CA19-9 is a tetrasaccharide expressed on the surface of cancer cells. It is the most well-known serological biomarker used in PC diagnosis, and was initially described in 1979 as a tumor antigen recognised by the monoclonal antibody NS19-9 in the case of CRC[22,23]. CA19-9 is not specific for PC alone, and has been implicated in colon, gastric and biliary tract cancer[24-26]. CA19-9 has only been reported to be elevated in only 80% of all PC patients, and has been used in monitoring disease progress or responsiveness to treatment[27,28]. CA19-9 has also been demonstrated to be elevated in benign conditions such as chronic pancreatitis (CP), biliary obstruction and cholangitis highlighting a lack of specificity[29,30]. In addition to this, CA19-9 is related to the Lewis blood group antigens and only those patients who belong to the Le (α-β+) or Le (α + β-) blood groups will express the antigen, its sensitivity in the diagnosis of PC is questionable as 10% of the population have a Le (α-β-) phenotype which lacks the enzyme 1,4-fucosyl transferase that is essential for the production of CA19-9[31,32].

Only a scarce number of studies have evaluated serum CA19-9 Levels in the general, asymptomatic population as a screening modality for PC. These studies were conducted in Japanese, Korean and Taiwanese populations and reported a low positive predictive value (PPV) of serum CA19-9 in the diagnosis of PC in a screening setting[33-35].

A recent meta-analysis assessing the diagnostic value of CA19-9 in PC compared to carcinoembryonic antigen (CEA) reported a summary sensitivity of 0.80 in the diagnosis of PC, along with a summary specificity of 0.75 and area under the curve (AUC) of 0.84[36].

To improve the diagnostic performance of CA19-9, it has been combined with a number of other biomarkers in the research setting[37,38]. This has translated to improved diagnostic value. Of note, sialylated tumor-related antigen, including sialyl-Lewis A glycan isomers, has recently been demonstrated to be superior to CA19-9 when used in isolation, as well as improving the sensitivity and specificity when used in combination with CA19-9[39-41] (Table 1).

CEA: CEA is a foetal glycoprotein that is not usually produced in large quantities after birth. Aside from its role in the surveillance and prognosis of CRC, CEA has also been implicated in ovarian, cervical, lung and breast cancer[42]. A number of studies have investigated the diagnostic value of CEA for PC, however the results reported are inconsistent throughout the literature.

The predictive value of CEA in the diagnosis and prognosis of PC has been recently evaluated in a relatively small systematic review and meta-analysis published by Meng *et al*[43] in 2017. Through the analysis of 19 studies including 3650 participants, a CEA-based panel was deemed to have greater diagnostic accuracy compared to CEA or CA19-9 alone with an AUC and *Q* value of 0.90 and 0.84 respectively, however the sensitivity of the panels demonstrated no advantage over CA19-9 or CEA when utilized in isolation[43]. A meta-analysis conducted in 2018 comparing CA19-9 to CEA included 13 studies with 4537 participants and 1277 patients diagnosed with PC[36]. This study demonstrated a superior sensitivity of CA19-9 compared to CEA (ratio of sensitivity = 1.54), along with a superior AUC (ratio of AUC = 1.24). A recommendation was made that both markers should be utilized for early diagnosis of PC due to their convenient, efficient and non-invasive properties.

CA125: CA125 is a high-molecular-weight mucin-like glycoprotein that has been associated with ovarian cancer, CRC and cholangiocarcinoma[44-46]. The role of CA125 in PC has only been established in the past decade with small studies demonstrating its superiority to CA19-9 in predicting resectability of PC, along with correlating with metastasis-associated disease burden[47,48]. There is unique clinical utility for CA125 given that serum levels do not correlate with serum bilirubin levels

Table 1 Serum protein biomarkers implicated in the diagnosis of pancreatic cancer

Class	Candidate marker
Glycolipids and proteins	CA19-9[27,28,33-38,144,160,182,187,213,221], sTRA[39-41], CEA[43], CA125[47,48,50], CA242[55,53], Osteonectin[57], Osteopontin[58-61], DUPAN-2[65-70], LAMC2[73-75], ULBP2[78-80], sCD40L[82], LRG1[84], C4BPA[86], Cofilin-1[88], sgC1qR[91], Trypsinogen-2[92,93], DKK1[96], THBS-2[99-102], THBS-1[103], AGR2[108], REG1A[108], REGIII[108], REG1β[111], REG4[114-117], SYCN[108], LOXL2[108], PARK7/DJ-1[126], TTR[129,130], TTF1[134], TTF2[134], TTF3[134], GPNMB[138], PRX-1[139], TFPI[141], TIMP-1[144], MMP-9[144], IGFBP-1[146], IGFBP-2[147-149], IGFBP-3[147,149], MSLN[148,154], C5[152], MMP-7[155-157], cathepsin-D[156], MMP-12[157], OPG[160], Kisspeptin[165], Galectin[171], MUC16[48,182], MUC5AC[37,182], PAM4[187], HSP27[190,191], CAM17.1[192,193], Fuc-Hpt[194], SAA [196], APN/CD13[200], M2-PK[203,204], APOA2[206-208], APOC1[209], APOC2[210], APOE[211-212], ITIH[213], APOA1[213], APOL1 [213]
Growth factors	TGF-B[215], VEGF[217], FGF-10/KGF-2[138], PDGF[220], TSGF[221]
Cytokines and chemokines	IP-10[220], IL-6[220,230-232], MIC-1/GDF15[227,228], IL-11[229], YKL-40[232,233], IL-8[230,234,235,237,241], IL-10[214], IL-1β[214], OSM [138], TNF-α[240-244], M-CSF[214], CXCL11[138], SCF[138,247-248], Eotaxin[250], HGF[250], MCP-1[250], CXCL10[250]
Adhesion molecules	CEACAM1[253,254], ICAM-1[160,262-263]

CEA: Carcinoembryonic antigen; TTF: Thyroid transcription factor; sTRA: Sialylated tumor-related antigen; IL: Interleukin.

and it is not significantly altered in the case of patients who are jaundiced[49].

A recent meta-analysis comprising eight studies with 1235 participants demonstrated a pooled sensitivity of 59% and specificity of 78% for CA125 in the diagnosis of PC, while the AUC and Q-value of the CA125-based diagnostic panel were 0.89 and 0.82 respectively[50]. This panel was deemed to be superior to CA125 or CA19-9 when used in isolation. Although this demonstrated a favourable result for the use of a CA125-based diagnostic panel going forward, the meta-analysis was limited by its size and heterogeneity between studies.

CA242: CA242 is a sialic acid-containing carbohydrate antigen which has been reported to have a high correlation with CA19-9 in patients diagnosed with PC[51-53]. Serum CA242 has also been demonstrated to be highest in patients diagnosed with PC compared to other solid organ malignancies, such as cervical cancer or oesophageal cancer[54].

In a 2015 meta-analysis comprising 21 studies and 3497 participants, CA242 was evaluated in conjunction with CA19-9 and CEA in diagnosing PC[55]. CA242 pooled sensitivity for detection of PC was 67.8%, with a subsequent pooled specificity of 83.0%. When combined with CA19-9, a sensitivity of 90.0% was achieved. More recently, a biomarker panel of CA19-9, serum periostin (POSTN) and CA242 was able to discriminate early stage PC from controls with an AUC of 0.98, along with benign conditions (AUC = 0.90)[53]. When utilized in isolation however, receiver operating characteristic (ROC) curve analysis returned an inferior result for CA242 in comparison to CA19-9 in distinguishing early stage PC from healthy controls.

Osteonectin: Osteonectin is a glycoprotein that has been previously demonstrated to have a key function in PC through promoting invasion and metastasis[56]. There is limited data on the use of Osteonectin in the diagnosis of PC, with a small prospective study reporting significantly elevated serum levels in those diagnosed with PC compared to controls, and a plasma level of > 100.18 ng/mL on ROC curve analysis resulting in an AUC of 86% for predicting PC[57].

Osteopontin: Osteopontin (OPN), a protein associated with the extracellular matrix (ECM), has been previously reported to be upregulated in PC preoperative serum, where when elevated it was found to have a sensitivity and specificity of 80% and 97% [58]. More recently serum levels of OPN and tissue inhibitor of metalloproteinase 1 (TIMP-1) were able to distinguish PC from CP and healthy controls. Additionally, when combined with CA19-9, diagnostic accuracy improved than compared to when used in isolation[59].

A meta-analysis published in 2014 demonstrated that the serum OPN levels in patients with PC was significantly greater compared to controls[60]. More recently, a pilot study published in 2016 identified that levels of OPN were higher in patients with PC compared to those with CP and control subjects, further affirming its potential role as a diagnostic biomarker in PC[61].

Duke pancreatic monoclonal antigen type 2: Duke pancreatic monoclonal antigen type 2 (DUPAN-2) is the precursor for CA19-9 has been reported to be elevated in patients with PC who are negative for the Lewis blood group phenotype highlighting an advantage over the conventional biomarker CA19-9[62-64]. There is minimal literature evaluating serum DUPAN-2 in the diagnosis of PC and the sensitivity of the biomarker in diagnosing PC is less than desirable, with its use shifting from diagnosis to prognosis more recently[65-70].

Laminin γ2: Laminin γ2 (LAMC2), an ECM glycoprotein, has been previously demonstrated to be inversely related to overall patient survival in patients with PC and over-expression has been proposed as a poor prognostic factor in patients diagnosed with PC[71,72]. Its value as a diagnostic biomarker has been assessed in a number of studies where when used in isolation and in conjunction with CA125 and CA19-9 in a panel, LAMC2 has demonstrated efficacy in PC diagnosis[73-75].

UL16 binding protein 2: UL16 binding protein 2 (ULBP2) is an NKG2D ligand present on NK cells that has been implicated in tumorigenesis[76,77]. Initially identified in 2011, ULBP2 was found to be elevated in PC patients compared to healthy controls [78]. ULBP2 has been utilized in combination with MIC-1, where it was reported to be significantly elevated in the serum of patients with PC compared to controls[79]. This elevation of ULBP2 in the sera of patients with PC was further validated in 2017 where in a small single centre study, serum levels of ULBP2, dickkopf-1 (DKK1) and CA19-9 were all significantly elevated in those diagnosed with PC compared to those with benign pancreatic disease and controls[80]. There is very little published with regard to the role of ULBP2 in the diagnosis of PC, with more recent data highlighting a potential role as a predictor of poor prognosis[81].

Soluble CD40 ligand: Soluble CD40 ligand (sCD40L) was first evaluated as a diagnostic and prognostic marker for PC in a study in 2014, where serum levels were significantly elevated in PC patients compared to controls[82]. Considering a lack of validation and small sample size, its routine clinical use is not recommended.

Leucine-rich a2-glycoprotein-1: Leucine-rich a2-glycoprotein-1 (LRG1) is an inflammatory protein present in human sera[83]. Although it was able to distinguish between patients with PC, CP or healthy controls, however the authors were not able to demonstrate effectiveness for LRG-1 as an early diagnostic marker[84].

C4b-binding protein a-chain: C4b-binding protein a-chain (C4BPA) is a serum protein implicated in B cell proliferation and CD40 activation which can reverse immune suppression and stimulate anti-tumour T cell responses[85]. It was demonstrated in a single study to be significantly elevated in patients with PC compared to healthy controls, with a subsequent AUC of 0.860 which was superior to CA19-9[86].

Cofilin-1: Cofilin-1 belongs to a family of proteins known as the actin depolymerizing factor/cofilin family, and has been implicated in chemotaxis, cell migration and tumor cell invasion[87]. There is minimal literature describing the role of cofilin-1 as a diagnostic biomarker of PC, with a single study in 2017 measuring the immune complex levels of cofilin-1 in sera and reporting that levels were significantly elevated in those diagnosed with PC compared to healthy controls and those with CP[88].

Soluble gC1qR: Soluble gC1qR (sgC1qR) is a multifunctional cellular protein which has previously been implicated in inflammation and malignancy[89,90]. With regard to PC, only a single small study has assessed its role as a circulating diagnostic biomarker, where it was demonstrated to be significantly increased in those diagnosed with metastatic PC compared to controls[91].

Serum trypsinogen-2: Serum trypsinogen-2 evaluation as a diagnostic biomarker is limited in the literature. A small study performed in 1996 demonstrated that high levels of serum trypsinogen-2 were present in those with BTC and PC, while also being elevated in benign obstructive disease highlighting a lack of sensitivity associated with the marker[92]. Another small single centre study showed the levels in those with PC and CP were significantly elevated compared to controls[93].

DKK1: DKK1 is a soluble inhibitor of Wnt/B-catenin signalling and has been demonstrated to be over-expressed in a number of solid organ malignancies[94,95]. DKK1 has been previously reported to be superior to CA19-9 on ROC curve analysis in differentiating patients with PC compared to controls with an AUC of 0.919 compared to 0.853 [96], while a more recent review highlights its potential as a target for cancer immuno-

therapy rather than diagnosis[97].

Thrombospondin-2 and thrombospondin-1: Thrombospondin-2 (THBS2) is a glycoprotein that mediates cell-to-cell and cell-to-matrix interactions which has previously been implicated in malignancy, particularly CRC[98]. When utilized with CA19-9, it can boost detection of PC in high-risk populations which has been more recently affirmed[99-101]. Le Large *et al*[102] reported an AUC of 0.952 for THBS2 and CA19-9 in discriminating patients with cancer compared to healthy donors, however there was no difference in plasma THBS2 expression between patients with PC and distal cholangiocarcinoma highlighting a potential diagnostic dilemma and a lack of specificity associated with the assay[102].

Serum THBS1 has been demonstrated to significantly decrease up to 24 mo prior to the diagnosis of PC and when used in combination with CA19-9, an AUC of 0.86 was achieved significantly outperforming both markers utilized in isolation[103].

Anterior gradient homolog 2 protein: Anterior gradient homolog 2 protein (AGR2) is a protein that has been previously identified as having a crucial role in embryogenesis. It is found in the endoplasmic reticulum and on the cell surface, and is expressed by multiple solid organ malignancies[104,105]. It has been previously implicated in the initiation of PC and is expressed in premalignant lesions of the pancreas[106,107]. As a diagnostic biomarker in PC, only a handful of studies exist reporting its elevation in PC compared to controls, with utilisation in a diagnostic assay with CA19-9 and REG1β resulting in modest diagnostic accuracy[108].

Regenerating protein family: REG1β, a member of the regenerating (REG) islet-derived family of proteins, which is present in pancreatic acinar cells, and subsequently is implicated in the regeneration of pancreatic islets[109]. REG family members have also been implicated in PC[110]. REG islet-derived 1 alpha (REG1A) and REGIII were initially demonstrated to be elevated in plasma in murine PC models, while REG1β was first studied in 2013 and was demonstrated to be significantly elevated in PC serum compared to healthy participants and those with benign disease [108,111].

REG4 is also over-expressed in a number of solid organ malignancies, including those of the gastrointestinal tract[112,113]. It acts an antiapoptotic factor through the Akt signalling pathway and has been demonstrated to be elevated in the serum of patient with PC compared to controls[114,115]. Serum REG4 has been reported to be superior to CA19-9 on AUC analysis, however there is inconsistencies in both sensitivity and specificity between studies[116,117].

Syncollin: Usually expressed in pancreatic acinar granules on the luminal side of the granular membrane, syncollin (SYCN) acts to concentrate and mature zymogens, while also regulating exocytosis and has previously been identified in the pancreatic juice of patients diagnosed with PC[118-120]. Initially evaluated in humans in 2013, SYCN was found to be significantly elevated in the serum of patients with PC compared to health controls and those with benign disease. In addition to this, it was also able to identify patients with PC in which serum CA19-9 was normal suggesting superior sensitivity. When combined with the serum biomarker REG1β and CA19-9, it was demonstrated to have an average AUC of 0.895 when discriminating patients with PC compared to healthy controls[108]. Although there is a lack of data to determine whether the findings of the aforementioned studies are generalisable, SYCN does display merit in terms of its sensitivity in patients diagnosed with PC compared to CA19-9.

Lysyl oxidase-like 2: Lysyl oxidase-like 2 (LOXL2) is a member of the lysyl oxidase (LOX) family of secreted, copper-dependent amine oxidases which have been implicated in malignancy due to their ability to promote epithelial-mesenchymal transition[121,122]. Additionally, its expression presents poorer overall survival and worse clinicopathological parameters irrespective of malignancy[123]. LOXL2 has been reported to be elevated in serum of patients with PC compared to controls, however was inferior to CA19-9 and its general ability to distinguish PC from controls was not deemed to be significant[108].

PARK7/DJ-1: DJ-1 is a multifunctional protein which has been implicated in Parkinson's disease, however is also an oncogene that has been demonstrated to be over-expressed in a number of solid organ malignancies[124,125]. DJ-1 was first evaluated in 47 patients with PC in 2011 and shown to be elevated in patients with PC compared to those with CP and controls, with an AUC superior to CA19-9 (0.6647)

[126]. Further studies are warranted to determine whether the results of this study can be replicated.

Transthyretin: Transthyretin (TTR) is the major carrier for the hormones thyroxin and tri-iodothyronine, and has been previously demonstrated to be elevated in patients with endocrine tumours but decreased in solid organ malignancies including epithelial ovarian carcinoma[127,128]. Studies are heterogenous, one study showing serum TTR level decreased by at least 2-fold when compared to control participants and other showing TTR is elevated in patients diagnosed with PC[129,130].

Trefoil factors: Trefoil factors (TFFs) are small, secretory mucin-associated proteins which are involved in the protection of epithelial cells, however an oncogenic role has been noted particularly in the case of gastric cancer[131-133]. In 2019 a small study demonstrated significant elevation of TFF1 and TFF2 in early PC compared to benign controls and CP patients. In addition to this, when combined with CA19-9, the panel of TFF (TFF1, TFF2 and TFF3) resulted in an AUC of 0.93 in discriminating early PC from benign controls[134].

Osteoactivin/glycoprotein nonmetastatic melanoma protein B: Glycoprotein nonmetastatic melanoma protein B (GPNMB) is a type 1 transmembrane protein which has been described as a promoter of metastasis and cellular invasion in malignancy[135-137]. A single study analyzed pre-treatment sera of patients with PC compared to controls and demonstrated modest diagnostic accuracy for PC[138].

Peroxiredoxin-1: Described as an important protector against redox damage, peroxiredoxin-1 (PRX-1) has also been implicated in PC where in the serum of patients it was significantly elevated compared to healthy controls and correlated with aggressive clinicopathological parameters. When combined with CA19-9, the AUC was significantly higher that PRX-1 when utilized in isolation[139].

Tissue factor pathway inhibitor: Tissue factor pathway inhibitor (TFPI) is a plasma Kunitz-type serine proteinase inhibitor which controls coagulation initiation, while also being implicated in malignancy[140]. An isolated study has assessed the role of TFPI in PC, where when utilized in combination with tenascin C and CA19-9 in a biomarker panel, it was demonstrated to improve the diagnostic performance of CA19-9 in discriminating early-stage cancer from healthy controls[141].

TIMP-1: TIMP-1 possesses an inhibitory effect on most MMPs along with playing a role in the regulation of cell proliferation and apoptosis[142,143]. TIMP-1 has a sensitivity of 47.1%, specificity of 69.2% and AUC of 0.64 which, in conjunction with matrix metalloproteinase-9 (MMP-9), were both deemed inferior to CA19-9 as a marker for detecting PC[144].

Insulin-like growth factor binding protein: Insulin-like growth factor binding protein 1 (IGFBP-1) is a downstream target of insulin and inhibits IGF-1 activity[145]. Wolpin *et al*[146] demonstrated that low plasma levels of IGFBP-1 predicted an increased risk of PC in a nested case-control study. In a pilot 2016 study IGFBP-2 and IGFBP-3 were shown to be able to discriminate PC patients with early stage disease from healthy controls, along with being superior to CA19-9 when utilized in combination[147]. Kendrick *et al*[148] showed that IGFBP2 and mesothelin (MSLN) were weak diagnostic classifiers individually but their utilization in a diagnostic biomarker panel was recommended. Additionally, in the case of premalignant lesions, Kim *et al*[149] reported that a biomarker panel of six candidate proteins including IGFBP-2 and IGFBP-3 had high discriminatory power in distinguishing intraductal papillary mucinous neoplasm (IPMN) and controls.

Complement component 5: Component 5 (C5) is a complement protein, which when cleaved into two fragments, C5a and C5b, is implicated in the formation of the membrane attack complex (MAC), a structure that is vital in the innate immune system[150,151]. Wingren *et al*[152] reported that C5 was differentially overexpressed, along with a number of inflammatory and growth factors in the serum of patients with PC compared to normal controls subjects.

MSLN: Initially evaluated in 2009, circulating MSLN was described as a useful biomarker for PC where it was detected in 73 of the 74 patients with PC[153]. However more recently, serum MSLN was found to be a weak diagnostic classifier of PC[148]. This supports the findings of Sharon *et al*[154] who identified that serum MSLN and megakaryocyte potentiating factor did not differ significantly between cohorts

diagnosed with PC, biliary carcinoma, benign pancreatic conditions, healthy controls and benign non-pancreatic conditions, and as such was concluded that it was not useful as a biomarker for the assessment of malignancy.

MMP: In a small study Kuhlmann *et al*[155] reported a 100% positive predictive value when MMP-7 was combined with CA19-9 in patients with periampullary carcinoma. MMP-7 has also been utilized in a panel comprising CA19-9, cathepsin D with an impressive AUC of 0.900 for discriminating patients with PC from normal healthy controls[156]. Kahlert *et al*[157] also reported that serum MMP-7 and MMP-12 were strong classifiers for the diagnosis of patients with PC compared to healthy controls.

Osteoprotegerin: Osteoprotegerin (OPG) is a member of the tumor necrosis factor (TNF) receptor superfamily and is mainly associated with regulation of bone turnover that has also been implicated in malignancy[158,159]. It has been previously combined in a biomarker panel with intercellular adhesion molecule 1 (ICAM-1) and CA19-9 and was able to discriminate PC patients from healthy controls with a sensitivity and specificity of 78% and 94% respectively[160]. This study contrasts with the findings of Nolen *et al*[161] where when combined in a panel with CA19-9 and OPN, OPG was not effective in predicting PC in prospectively collected serum samples in a large screening cohort.

Kisspeptin: Kisspeptin, initially implicated in melanoma, has been demonstrated to be expressed physiologically in a number of different tissues, suggesting it possesses antitumoral properties[162-164]. Recently, in a cohort of 128 patients with PC, serum levels of Kisspeptin were elevated in those with PC compared to healthy controls and ROC curve analysis demonstrated an AUC of 0.797 in discriminating PC from healthy controls, however it was deemed inferior to CA19-9[165].

Galectin-3: Galectin-3 is a member of the β-galactoside-binding protein family which has been previously demonstrated to be associated with a number of solid organ malignancies, including those of the gastrointestinal tract[166-169]. It has been reported to be over-expressed in PC tissue specimens and elevated in the serum of patients with PC[170]. Yi *et al*[171] further built upon this finding in a prospective screening study, where in 1850 healthy participants a single case of PC was diagnosed in a patient with elevated serum levels, a lack of specificity cited as a barrier to implementation.

Mucins: Mucins are a family of glycoproteins that serve a number of functions, and line the surface of epithelial cells in the gastrointestinal tract[172,173]. In normal pancreatic tissue, a number of mucins are expressed, these being MUC1, MUC5B, MUC6, MUC11, MUC12, MUC17, MUC20 and MUC21, while other members of the mucin family are usually undetectable[173-179]. Mucins have previously been demonstrated to have a role in PC in promoting metastasis, chemoresistance and tumorigenicity, while a recent meta-analysis identified MUC1, MUC4, MUC5AC and MUC16 as key biomarkers in the diagnosis of PC[180,181]. On peripheral blood sampling, MUC16/CA125 Levels have been previously demonstrated to be strongly associated with metastatic disease[48]. Serum MUC5AC has also been reported to have efficacy in differentiating resectable early-stage PC from healthy controls, along with median circulating levels being significantly elevated compared to benign controls and CP. Furthermore, when utilized in combination with CA19-9, diagnostic accuracy was improved significantly for resectable PC cases compared to healthy controls[37]. When combining measurements of CA19-9 assay with detection of CA19-9 on MUC5AC and MUC16, the sensitivity of PC detection improved, with greater sensitivity and near 100% specificity achieved[182].

PAM4: PAM4 antibody is a monoclonal antibody which binds to large-size mucin, and it has been previously been reported that expression of the PAM4-reactive antigen on immunohistology may provide a method for early detection of PC[183-185]. The PAM4 antigen is absent from normal pancreatic tissue or pancreatic tissue associated with benign disease[186]. A 2012 study conducted by Gold *et al*[187] reported the overall sensitivity of PAM4 detection of PC at 75%, with associated high discriminatory power with respect to benign disease, however this has yet to be replicated.

Heat shock protein 27: Heat shock protein 27 (HSP27) is a molecular chaperone which acts to prevent aggregation of misfolded proteins, along with playing a role in the degradation of these proteins[188]. Additionally, it also plays a role in promoting tumour metastasis[189]. In patients diagnosed with PC, HSP27 detection in serum has

been demonstrated to have a sensitivity of 100% and specificity of 84%, however a lack of specificity is highlighted by elevated levels also being reported in CP and cannot be recommended as a diagnostic biomarker in PC[190,191].

CAM17.1: CAM17.1 monoclonal antibody is a monoclonal antibody which detects a mucous glycoprotein that is specific for intestinal mucous, also known as CAM17.1. CAM17.1 is overexpressed in PC but has a low sensitivity and specificity of 78% and 76% respectively in diagnosing PC[192,193].

Fucosylated haptoglobin: Recently fucosylated haptoglobin (Fuc-Hpt) has emerged as a novel biomarker in PC, where it has been demonstrated to be almost equivocal to CA19-9 on ROC curve analysis and also correlates with disease stage[194]. Although this does demonstrate promise as a diagnostic biomarker, it is postulated that Fuc-Hpt is produced by metastatic deposits in the liver, and as such lacks utility in the diagnosis of early stage disease, but rather is able to identify liver metastasis that may not be detected on radiological assessment[195].

Serum amyloid A: Serum amyloid A (SAA) is an acute phase protein which has previously been implicated in a number of disease processes, however with regard to malignancy Yokoi *et al*[196] reported levels of SAA to be elevated in patients with PC compared to controls, although a sensitivity of 96.5% was observed for the detection of PC, and a specificity of 31.9% highlights a shortcoming in its use as a potential diagnostic biomarker.

Aminopeptidase N: Aminopeptidase N (APN/CD13) is a membrane bound metalloproteinase which is expressed in a number of different tumour types and cells, and has been suggested to play a role in tumor progression, proliferation, invasion and angiogenesis[197-199]. APN/CD13 was first evaluated in 2016 by Pang *et al*[200] where an AUC of 0.904 was reported in differentiating PC from benign pancreatic tumours, CP and healthy controls, however this study was limited in its size.

M2-pyruvate kinase: M2-pyruvate kinase (M2-PK) is a glycolytic enzyme that has been demonstrated to have a role in cancer metabolism[201,202]. Initially evaluated in 2004, serum M2-PK was reported to be elevated in patients with PC with a sensitivity and specificity of 85% and 41% respectively, which was subsequently validated in 2008 however elevation was also seen in patients with CP thus highlighting a lack of specificity associated with its implementation as a diagnostic biomarker[203,204].

Apolipoprotein isoforms: Apolipoproteins (APOs), which are produced in the liver and intestine, act as lipid carriers, and in doing so, act as ligands for cell membrane receptors, enzyme cofactors and structural components of lipoproteins (after binding to lipids)[205]. A large number of APOs have been reported to have a role in malignancy with serum APOA2, APOC1, APOC2 and APOE being implicated in PC diagnosis and prognosis.

APOA2, specifically APOA2-ATQ/AT has been demonstrated to be able to distinguish patients with early stage PC compared to healthy controls as well as identifying patients at high risk of pancreatic malignancy. The AUC value for APOA2-ATQ/AT was superior compared to CA19-9 in detecting early stage PC[206]. APOA2 was prospectively evaluated in 2019 where it was identified to be useful when utilized in combination with CA19-9 to improve detection of PC up to 18 mo prior to diagnosis and was suggested to be a useful first measure of PC detection prior to imaging[207]. This was built upon in 2020, where APOA2-ATQ/AT was implemented in a screening cohort in which an elevated level resulted in a PPV of 33.3% for the diagnosis of PC [208].

APOC1 has been implicated in PC where in pre-operative serum, higher levels were reported to correlate with poor prognosis highlighting the potential role of APOC1 as contributing to aggressiveness in PC[209]. Similarly, APOC2 was investigated by Xue *et al*[210] who reported that serum levels independently predicted survival in patients diagnosed with PC.

Serum APOE has been demonstrated to have a sensitivity and specificity of 76.2% and 71.4% respectively for distinguishing patients with PC compared to controls[211, 212]. This study published a superior sensitivity of APOE in diagnosing PC to CA19-9, however it lacked specificity in the diagnosis and was proposed that utilization in combination with CA19-9 could prove beneficial in the future[211]. More recently, when combined in a biomarker panel with inter-alpha-trypsin inhibitor heavy chain H3 (ITIH3), APOA1, APOL1 and CA19-9, a sensitivity and specificity of 95% and 94.1% respectively was reported for the diagnosis of PC[213].

Serum growth factors

Transforming growth factor-beta: According to the findings of Yako *et al*[214] there is a lack of a definitive consensus on the role of transforming growth factor-beta (TGF-β) as a diagnostic biomarker in PC, with serum levels varying in those diagnosed with the malignancy. In addition to this TGF-β has also been implicated in the diagnosis of PC where it has been demonstrated to be elevated in serum samples compared to benign controls, while high levels in serum also significantly correlated with reduced patient survival[215].

Vascular endothelial growth factor: Vascular endothelial growth factor (VEGF) has been reported to have an important role in PC development, while VEGF-A expression has been reported be an important predictor for both distant metastasis and poor prognosis in PC[216]. There is a lack of data affirming the role of serum VEGF as a diagnostic biomarker for PC, with biliary VEGF considered a more accurate diagnostic modality[217].

Fibroblast growth factor 10/keratinocyte growth factor-2: Fibroblast growth factor 10/keratinocyte growth factor-2 (FGF-10/KGF-2) is a regulator of the pancreatic epithelial progenitor cell proliferation and has been implicated in pancreatic morphogenesis along with epithelial mesenchymal transition[218,219]. FGF-10/KGF-2 has been demonstrated to be significantly overexpressed in the sera of patients diagnosed with PC pre-treatment compared to controls, in conjunction with a number of other novel cytokine candidate markers[138].

Platelet-derived growth factor: There is limited data pertaining to the use of platelet-derived growth factor (PDGF) in the diagnosis of PC, however it has been proposed in a panel including IP-10, interleukin (IL)-6 and CA19-9 which demonstrated diagnostic superiority in the discrimination of PC patients from patients with benign disease both in a training and independent test set[220].

Tumour specific growth factor: There is limited data pertaining to the role of tumour specific growth factor (TSGF) in the diagnosis of PC, with a single centre study reporting an increase in specificity for PC when TSGF is used in combination with CA242 and CA19-9 while another study assessed the utility of TSGF as a monitor of response to treatment[221,222].

Serum cytokines and chemokines

Macrophage inhibitory cytokine-1/Growth Differentiation Factor-15: Macrophage inhibitory cytokine-1/Growth Differentiation Factor-15 (MIC-1/GDF15) is a distant member of the TGF-β superfamily of cytokines that has been implicated with inflammation and carcinogenesis, along with serum elevation being detected in a number of pathologies including heart failure and renal failure[223-226].

A meta-analysis published in 2018 aimed to compare MIC-1/GDF15 to CA19-9 as a diagnostic biomarker in PC, identifying fourteen studies with a total of 2826 participants. MIC-1/GDF15 was reported to have a sensitivity of 80% and specificity of 88%, and a diagnostic odds ratio (DOR) of 24.57 which was superior to CA19.9 (DOR = 17.76). In addition to this the AUC of MIC-1/GDF15 in diagnosing PC was 0.8945, which was moderately superior to CA19.9. The conclusion from this study was that MIC-1/GDF15 had comparable diagnostic accuracy to CA19-9, however it was noted that there was marked heterogeneity between studies and that the results should be interpreted with caution[227].

With regard to PC, the authors of this study have recently demonstrated that in a prospective PC screening cohort deemed to be high risk for developing PC based on familial and genetic factors, MIC-1/GDF15 had moderate predictive capacity for patients who subsequently were diagnosed with PC on endoscopic ultrasound (EUS) and biopsy. However, the participants enrolled were considered high risk for developing PC, highlighting a potential issue with generalising the results of this study[228].

ILs: ILs are cytokines that constitute a substantial proportion of those cytokines present in the tumor microenvironment. With regards to their role as diagnostic biomarkers in PC, a considerable number of cytokines have been evaluated in patients diagnosed with PC with variable results (Table 1). There is heterogeneity between studies with insufficient evidence to support their use in routine clinical practice as diagnostic biomarkers, with previous studies demonstrating a lack of diagnostic capacity for PC compared to CRC or benign disease[235].

Oncostatin M (OSM) forms part of the IL-6 cytokine family and has been implicated in promoting epithelial mesenchymal transition, along with being linked to a number of solid organ malignancies[236-238]. Serum levels of OSM have been found to be significantly elevated in patients with PC compared to controls in a single centre study limiting generalisability[138]. There is limited data on the utility of CXC motif ligand 8 (CXCL8)/IL-8 as a diagnostic biomarker in PC. In a relatively small cohort study CXCL8 seems to be superior to CA19-9 and CEA[239].

TNF-α: There is variability in the data pertaining to TNF-α as a diagnostic biomarker in PC. Although the majority of studies report elevated levels of TNF-α in serum compared to healthy controls, a lack of specificity is highlighted as a pitfall in its routine use as a diagnostic biomarker[240-243].

Macrophage colony-stimulating factor: Serum macrophage colony-stimulating factor (M-CSF) has been demonstrated to be elevated in patients with PC compared to controls, along with correlating with advanced stage disease and with non-resectable tumors. Aside from those studies included in the 2016 systematic review published by Yako *et al*[214] there is limited published literature assessing the value of M-CSF as a serological biomarker in the diagnosis of PC.

CXCL11/interferon inducible T cell alpha chemokine: CXCL11 is a CXC chemokine which stimulates the phosphorylation of mitogen-activated protein kinase kinases pathways, resulting in cellular proliferation and prevention of apoptosis[244]. Initially evaluated in 2014, serum CXCL11 was found to be over-expressed in patients with PC compared to controls highlighting a potential role as a diagnostic biomarker, in addition to having a predictive role for gemcitabine and erlotinib treatment response in patients with PC[138].

Stem cell factor: Stem cell factor (SCF) is a ligand that is involved in cell proliferation, differentiation and cell survival, and aside from normal cellular physiology, SCF has been implicated in PC and CRC, with serum levels being noted to be elevated in PC compared to healthy controls, however studies are limited[138,245-248].

Eotaxin: Eotaxin is a protein which is implicated in the recruitment of eosinophils into inflammatory sites which has also been implicated in malignancy[249]. Serum eotaxin was assessed by Zeh *et al*[250] in a single centre study in 2005 in conjunction with hepatocyte growth factor, monocyte chemoattractant protein-1 and CXCL10, were it was able to distinguish PC from healthy controls with a sensitivity of 85.7% and specificity of 92.3%, which was superior to CA19-9.

Serum adhesion molecules

CEA-related cell adhesion molecules: CEA-related cell adhesion molecules (CEACAM) proteins belong to the immunoglobulin supergene family comprised of a variable-like domain as well constant C2-like Ig domains which are required for functionality as well as adhesion. The most well-known CEACAMs related to malignancy are CEACAM1, CEACAM5 (more commonly known as CEA), and CEACAM6. Both CEACAM5 and CEACAM6 are associated with the membrane through a glycosylphosphatidylinositol linkage, while CEACAM1 is anchored to the cellular membrane by transmembrane domains. CEACAM1 have been previously demonstrated to be elevated in a number of tumor entities including PC, however a lack of sensitivity and specificity has been cited as a barrier to its use[217,251-254]. More recently, the role of CEACAMs, including CEACAM1 has shifted from diagnosis to treatment, with CEACAM1 being implicated in cancer immunotherapy[255].

CEACAM6 is a cell surface adhesion receptor that has been previously reported to modulate the ECM in PC[256]. Expression of CEACAM6 was noted in 92% of PC specimens assessed in a 2005 study[257]. Although relatively specific for PC on serum analysis, there is scant evidence to suggest the CEACAM6 as a serological biomarker is useful in the detection of PC with a shift in focus to disruption of CAECAM6 as a therapeutic option in PC[258]. CEACAM5, or CEA, has been demonstrated to have limited efficacy in the diagnosis of PC as described previously, due to it being overexpressed in a number of solid organ malignancies[259,260].

ICAM-1: ICAM-1 is a glycoprotein that functions in cell-cell and cell-ECM adhesion, along with acting as a macrophage chemoattractant[261]. Serum ICAM-1 has been previously evaluated in a number of studies, where it has been demonstrated to be superior to CA19-9 in PC diagnosis. Although preliminary studies have demonstrated promise, its inability to distinguish between early and late-stage PC have been

identified as a potential dilemma limiting its implementation as a screening and diagnostic biomarker[262,263].

Serum non-coding RNAs

Long non-coding RNAs: Long non-coding RNAs (LncRNAs) belong to a group of RNAs that are longer than 200 nucleotides and are not translated into proteins. These RNAs are abundant in cells, and were previously thought to be of minimal value with minimal influence on biological behaviour[264]. This belief has however changed over the past 10 years, with more recent data suggesting that lncRNAs have a diverse range of function, including chromatin modification, gene transcription, post-translational modification and regulation of intracellular signalling pathways[265]. In addition to this, they play a role in either the promotion or suppression of tumor growth, through involvement in intracellular signalling pathways[266] (Table 2).

LncRNA in PC have the potential to modulate both intrinsic and acquired chemo-resistance. Additionally, lncRNA also possess the capacity to act as a miRNA sponge, to perform chromatin remodelling, and promote gene transcription in candidate tumour suppressor genes by binding to gene promotors[267-270]. In terms of the role of lncRNAs as a diagnostic marker in PC a number of candidates have been evaluated with mixed results, and studies are limited to single cohort studies yet to be validated [271]. Perhaps the most promising study to date in search for a lncRNA biomarker was published in 2020, which utilized analysis of the extracellular vesicle lncRNA profile by extracellular vesicle lncRNA sequencing in patients diagnosed with PC and CP. This was performed utilizing a support vector machine algorithm to detect a d-signature for eight different extracellular vesicular long RNA. This study demonstrated that through utilisation of the d-signature, an AUC of 0.949 was able to be achieved in identifying resectable stage I/II PC, while also demonstrating superiority when compared to CA19-9 when distinguishing PC from CP[272].

MiRNAs: MiRNAs are noncoding 20-25 nucleotide endogenous RNA sequences who regulate gene expression and are able to regulate the biological function of many tumors[273]. MiRNAs have become prominent in the field of oncology in the diagnosis, prognosis and monitoring of therapy of cancer. In addition to their presence in serum, miRNAs have also been detected in cerebrospinal fluid, breast milk, saliva and urine[274,275]. Although the method through which miRNA are released into the peripheral circulation from active malignancies is still being determined, their ability to withstand severe conditions along with extended storage highlights an exciting potential diagnostic biomarker. Due to the lack of a gold-standard diagnostic biomarker for PC, research into the efficacy of miRNA as a diagnostic biomarker in PC has progressed rapidly in the past decade with a large number of candidate miRNA biomarkers utilized in serum for the detection of PC as demonstrated in Table 2. Perhaps the most comprehensive analysis to date reviewing candidate miRNAs utilized in PC comes from a large meta-analysis published in 2018 encompassing 80 studies which detected miRNA in blood (including whole blood, serum and plasma samples that concluded that candidate miRNA biomarkers are useful in PC, particularly when used in combination, however no standing panel was reported to exist at this stage[276].

The rapid expansion of miRNA utilization in serum in the diagnosis of PC highlights its potential value as a future diagnostic biomarker modality which could be implemented into routine clinical practice, however determination of which miRNA possesses the greatest diagnostic accuracy is required. Panel based assays represent a very attractive methodology for miRNA detection which have been identified as having superior diagnostic accuracy, however further validation of specific candidate miRNAs is required.

Serum liquid biopsy

Exosomes: Exosomes are membrane-bound nano-capsules that transfer molecules between cells[308]. Their role in the diagnosis of PC is limited to only a handful of studies which were recently included in a relatively small systematic review meta-analysis which also assessed circulating tumor cells (CTCs) and cell-free DNA (cfDNA). In six papers included, exosomes were found to have strong diagnostic value with an AUC of 0.9819[309]. It was postulated that they possessed value in the field of PC detection due to pancreatic cells possessing a strong exocrine function, along with the high activity of PC cells. A number of different types of exosomes were analyzed as demonstrated in Table 3.

Table 2 Serum based non-coding RNA biomarkers implicated in the diagnosis of pancreatic cancer

Type	Candidate marker
LncRNA	LINC-PINT[277], SNHG15[278,279], LINC01238[280], ABHD11-AS1[281], HULC[282,283], UFC1[284]
MiRNA	miR-21[285-289], miR-25[288,290,297], miR-210-3p[289], miR-29a[290], miR-19a[290], miR-210[285,291], miR-155[285,292], miR-499a-5p[293], miR-125a-3p[294], miR-6893-5p[294], miR-125b-1-3p[294], miR-6075[294], miR-6836-3p[294], miR-1469[294], miR-6729-5p[294], miR-575[294], miR-204-3p[294], miR-6820-5p[294], miR-4294[294], miR-4476[294], miR-4792[294], miR-196a[285,295], miR-18a[296,297], miR-10b[292-298], miR-106b[292], miR-642-3p[299], miR-885-5p[299], miR-22-3p[299], miR-34a[286], miR-191[297], miR-451a[300], miR-121-5p[298], miR-30c[298], miR-483-5p[290,297], miR-1290[301,302], miR-24[290,297,301], miR-134[301], miR-146a[301], miR-378[301], miR-484[301], miR-628-4p[301], miR-1825[301], miR-1246[302], miR-482-3p[287], miR-16[295], miR-27a-3p[303], miR-192[304], miR-885-5p[299], miR-22-3p[299], miR-642b-3p[299], miR-492[305], miR-663a[305], miR-194[304], miR-223[306], miR-774-5p[307], miR-409-3p[307], miR-128-3p[307], miR-20a[290,297], miR-27a[297], miR-29c[297], miR-30a.5p[297], miR-323.3p[297], miR-345[297]

MiRNA: MicroRNA; LINC-PINT: Long intergenic non-protein coding RNA, P53 induced transcript; SNHG15: Small nucleolar RNA host gene 15; ABHD11-AS1: ABHD11 antisense RNA 1; HULC: Highly up-regulated in liver cancer.

Table 3 Serum based 'liquid biopsy' biomarkers implicated in the diagnosis of pancreatic cancer

	Biomarkers
Exosomes	Exosomes: GPC1[310,313], miR-10b[310], miR-30c[310], miR-181-a[310], miR-let7a[310], miR-17-5p[311], miR-21[311], miR-1246[312], miR-4644[312], miR-3976[312], miR-4306[312]
ctDNA	*KRAS*[314-317], *ADAMTS1*[318], *BNC1*[318]
CTC	CAPI+/CD45-[319], CK+[319], CEA+[319], CD45-/DAPI+/CEP8[320], CD45[321], CCK19[321], Pdx-1[321], Kras mutation[322], CEP8[323], CK[323], CD45[323], DAPI[323], chromosome 8[324], Folate-receptor positive CTCs[326]

Tspan8: Tetraspanin 8; EpCAM: Epithelial cell adhesion molecule; MET: mesenchymal-epithelial transition factor; CD104: Integrin 4-beta; GPC1: Glypican 1; GNAS: Guanine Nucleotide binding protein; KRAS: KRAS Proto-Oncogene, GTPase; ADAMTS1: A disintegrin and metalloproteinase with thrombospondin motifs 1; BNC1: Basonuclin 1; CD45: Leukocyte common antigen; CK19: Cytokeratin 19; Pdx-1: Pancreatic and duodenal homeobox 1; ADAMTS1: A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; BNC1: Zinc finger protein basonuclin-1.

CTCs: Initially identified in 1896 in metastatic breast cancer, CTCs are cells that are shed from primary tumor or metastatic deposits which enter the bloodstream directly and can be detected forming what is known as a real-time "liquid biopsy"[325]. In a recently published systematic review and meta-analysis, seven articles were identified which utilized CTCs in the diagnosis of PC, of which multiple methods of detection were used highlighting heterogeneity between study methodology. The pooled sensitivity and specificity of CTCs were 74% and 83% respectively, with and AUC of 0.8166. The authors' conclusion was that CTCs had moderate diagnostic value in PC [309].

CTCs demonstrated inferiority when compared to exosomes in the systematic review due to their inferior sensitivity and specificity, however their AUC was still deemed acceptable from a diagnostic capacity for PC. Folate receptor positive CTCs have also been implicated as a novel diagnostic biomarker in those patients diagnosed with periampullary malignancy on ligand-targeted polymerase chain reaction demonstrating a significant elevation compared to those with benign pancreatic disease[326]. In addition to this, when utilized in combination with CA19-9, it was reported to have a superior sensitivity and specificity of 97.8% and 83.3% respectively, compared to when used in isolation. CTCs have yet to be utilized in a prospective screening population. Decreased blood flow to malignant pancreatic tissue along with increased CTC accumulation in the liver due to the portal circulation are posed as challenges in the detection of PC related CTCs[327].

Circulating tumor DNA: cfDNA, initially identified in 1948, is fragmented DNA identified in the circulation. It has been applied to many areas of medicine, ranging from prenatal assessment, renal failure, and stroke where it has had mixed results[328-330]. In the case of medical oncology, the detection and utilisation of cfDNA secreted from tumours, referred to as circulating tumor DNA (ctDNA) has been met with a number of challenges, namely the ability to discriminate ctDNA from normal cfDNA, and low levels of ctDNA hampering detection[331].

The diagnostic value of ctDNA in PC has been deemed to be promising with a recent meta-analysis being able to identify seven articles assessing ctDNA in the

diagnosis of PC showed a pooled sensitivity and specificity were 64% and 92% respectively, with an AUC of 0.9478[309]. In this review, ctDNA was deemed inferior to CTCs from a sensitivity perspective, however the AUC was superior in diagnosing PC. This was attributable to the inability to detect low levels of circulating ctDNA in early stages of cancer when overall tumor burden was low, highlighting a dilemma in utilizing this form of diagnostic biomarker in early stages of disease and as a screening modality. A summary of the included ctDNA biomarkers can be viewed in Table 3.

Plasma ctDNA quantification of hot-spot mutations in KRAS and GNAS has also been reported to be useful in predicting tumor burden in patients diagnosed with PC. In addition to this, digital PCR (dPCR) provided accurate tumor-derived mutant KRAS detection in plasma in resectable PC and improved post-resection recurrence prediction compared to CA19-9[332].

URINARY BIOMARKERS

Urine protein biomarkers

Urine proteins have also been established as a means through which PC can be detected, with previous proof-of-concept studies demonstrating that protein signatures associated with PC can be detected in the urine[333]. Radon *et al*[334] were able to build upon this, where they reported that three proteins, lymphatic vessel endothelial hyaluronan receptor 1, REG1A and thyroid transcription factor 1, when combined in a biomarker panel, were able to detect patients with PC with an AUC of 0.89 and 0.92 in training and validation datasets respectively, compared to healthy controls. Although further validation is required, this presents an inexpensive and non-invasive option for screening in patients for PC, and was suggested to be added to the current screening modalities utilized in high-risk patients to determine its efficacy prospectively[334]. Aside from this there is relatively little published with regard to the urinary proteome in the detection of PC and other proteins implicated are limited to single centre cohort studies (Table 4).

Urine non-coding RNA

MiRNA: Urinary miRNA has previously been utilized in the detection of bladder cancer, however, there is scant literature to support the use of urinary miRNA in the detection of PC[339]. In a small British study, Debernardi *et al*[340] were able to demonstrate that miR-143, miR-223 and miR-30e were significantly over-expressed in patients with stage I PC compared to age-matched healthy individuals. MiR-1246 has also been assessed as a urinary biomarker, where significantly higher levels of expression were noted in patients with PC compared to controls, with an AUC of 0.90 which was superior to serum miR-1246 (AUC = 0.87)[18]. Considering the non-invasive capacity of urine sampling, coupled with the rapid expansion and interest in use of miRNA in the detection of malignancy, further studies should aim to determine whether experimental studies can translate into larger prospective clinical studies.

Urine liquid biopsy

Urinary cfDNA: Considering the rapid expansion of the concept of a 'liquid biopsy', the hypothesis that tumour DNA could be detected through the urine with urinary cfDNA originating from the shedding of cells directly from the genitourinary tract or *via* the circulation passing through the kidney and filtering through the glomerulus also known as transrenal DNA has emerged as a method of biomarker detection. Terasawa *et al*[341] were able to detect urine KRAS mutations in 48% of participants diagnosed with PC, which was equivocal with the serum detection rate. This method of detection however is influenced by the patient's underlying kidney function.

Exosomes: More recently, the ratio of miR-3940-5p/miR-8069 in urine exosomes has been implicated in PC. This ratio was noted to be elevated in patients diagnosed with early stage PC, with a sensitivity of 93.0% and PPV of 78.4%[342].

Other urinary markers

Detection of volatile organic compounds (VOCs) is a relatively novel area in malignancy diagnosis, which utilized odors that emanate from urine, breath and faeces. These compounds are produced by bacterial dysbiosis which is secondary to malignancy. Recently Nissinen *et al*[343] were able to demonstrate through using field asymmetric waveform ion mobility spectrometry that patients diagnosed with PC could be distinguished from healthy controls with a sensitivity and specificity of 79%

Table 4 Urinary biomarkers implicated in the detection of pancreatic cancer

Type	Candidate marker
Protein	LYVE1[334], REG1A[334], TTF1[334], TIMP1[335], MMP-2[335], NGAL[336], PGE2 metabolites[337], CD59 glycoprotein (CD59)[338], ANXA2[338], 21 kDA gelsolin fragment[338], S100A9[338]
Liquid biopsy	UcfDNA: KRAS mutation[341]; Exosomal miRNA: miR-3940-5p[342], miR-8069[342]
RNA	MiRNA: miR-143[340], miR-223[340], miR30e[340], miR-1246[18]
Metallomics	Calcium[344], magnesium[344]
Other	VOCs[343]

MiRNA: MicroRNA; ANXA2: Annexin A2; S200A9: Protein S100-A9.

and 79% respectively through the detection of VOCs in the urine. Additionally, the analysis of the metallomic signature of urine is also a relatively uncharted area in the field of PC, with a study published by Schilling *et al*[344] recently demonstrating that in those diagnosed with PC, urine calcium and magnesium were significantly lower compared to healthy controls. They were able to demonstrate through combined analysis that these metals were accurate indicators for metal dyshomeostasis in PC with a sensitivity of 99.5%.

PANCREATIC JUICE BIOMARKERS

Pancreatic juice is usually obtained during the ERCP which is an invasive procedure with potential morbidity and mortality and is not used routinely as a screening procedure. Alternatively, pancreatic juice can be collected during the endoscopy from the duodenum after secretin administration which has the risk of secretin induced pancreatitis and contamination of the sample with duodenal and gastric juice. While attractive, pancreatic juice biomarkers are unlikely to be used in large populational studies but it might be useful in selected cases in which endoscopy or ERCP is indicated (Table 5).

Protein based biomarkers

Protein biomarkers are the most well explored candidate biomarkers in the medium of pancreatic juice. Conventional markers utilized in serum, such as CA19-9 and CEA, have been implicated in pancreatic juice where the sensitivity of CA19-9 is questionable, while CEA demonstrated merit in predicting malignant transformation of IPMNs along with the diagnosis of PC[345-352]. Aside from these biomarkers, a large number of proteins have been assessed in the pancreatic juice of patients with variable results, however considering that evidence supporting these biomarkers is limited to only a handful of small cohort studies, their implementation as a diagnostic tool is not recommended.

Although mucins have been extensively investigated in the diagnosis of PC, with regard to pancreatic juice there is limited literature published on its value. Levels have been demonstrated to be elevated in the case of MUC1, and KL-6 mucin, a type of MUC1, was investigated by Matsumoto *et al*[354] and reported to be significantly elevated in the pancreatic juice of patients with PC and IPMC compared to inflammatory lesions and IPMNs however its specificity was less than desirable.

Non-coding RNA

When compared to serum and saliva, pancreatic juice has proved to be less fruitful with regard to candidate miRNA biomarkers in PC diagnosis. Both miR-21 and miR-155 have been demonstrated to be elevated in the pancreatic juice of patients diagnosed with PC compared to CP[362], while Wang *et al*[363] was also able to report a specificity of 88% and sensitivity of 87% when four circulating miRNAs in pancreatic juice (miR-205, miR-210, miR-492 and miR-1427) were used in combination for detecting PC. In addition to miRNA assessed in pancreatic juice, MSLN mRNA has also been implicated in the diagnosis of PC on pancreatic juice[364].

Table 5 Pancreatic Juice biomarkers implicated in the detection of pancreatic cancer

Type	Candidate marker
Protein	CA19-9[345-347,349], MIC-1[349], NGAL[349], CEA[347,348,350-352], AMYP[353], PRSS1[353], glycoprotein GP2-1[353], CCDC132[353], REG1A[353], REG1B[353], REG3A[353], LIPRP2[353], KL-6/MUC1[354], CPA5[355], inactive LIPRP1[355], KLK1[355], HBD[355], TTR [355], S100P[356], MMP-9[357], MMP-7[155], DJ-1[357] A1BG[357], PAP-1[358], AGR2[359], IL-8[360], Cathepsin E[361]
RNA	MiRNA: miR-21[362], miR-155[362] , miR-205[363], miR-210[363], miR-492[363], miR-1427[363]; mRNA: mesothelin[364]; Other: hTERT [365,366], telomerase activity[367-369]
Liquid biopsy	Exosomes: CEACAM1[371], CEACAM 5[371], tenascin C[371], MMP7[371], LAMB3[371], LAMC2[371], MUC1[372], MUC4[372], MUC5AC[372], MUC6[372], MUC16[372], CFTR[372], MDR1[372], ex-miR-21[373], ex-miR-155[373]; Methylated DNA: KRAS[374,377], ppENK[375,376], p16[375,376], Cyclin D2[376], FOXE1[376], NPTX2[376], TFPI2[376], CD1D[377], KCNK12[377], CLEC11A[377], NDRG4 [377], IKZF1[377], PKRCB[377], MUC1[378], MUC2[378], MUC4[378]

MiRNA: MicroRNA; PRSS1: Trypsin-1; CPA5: Carboxypeptidase A5; KLK1: Kallikrein-1; HBD: Hemoglobin Subunit Delta; LAMB3: Laminin subunit beta-3; CFTR: Cystic fibrosis transmembrane conductance regulator; MDR1: Multidrug resistance protein 1; KCNK12: Potassium channel, subfamily K, member 12; CLEC11A: C-Type lectin domain containing 11A; NDRG4: NDRG family member 4; IKZF1: Ikaros family zinc finger protein 1 gene; PKRCB: Protein kinase C beta; FOXE1: Forkhead Box E1; NPTX2: Neuronal pentraxin-2.

Liquid biopsy

Telomerase activity and human telomerase reverse transcriptase: Telomerase activity has previously been deemed a promising marker as it was shown to be elevated in pancreatic juice samples of patients with PC[365-367]. Further to this, a recent meta-analysis assessing the diagnostic utility of the four major altered genes in PC (KRAS/CDKN2A/p16, TP53, and SMAD4/DPC4), telomerase activity, and a combination assay, revealed that the most reliable biomarker in diagnosing PC in pancreatic juice samples was telomerase activity[367]. Human telomerase reverse transcriptase (hTERT) is a catalytic subunit of telomerase, and the detection of mRNA for hTERT has been postulated to aid in the diagnosis of malignancies including PC. hTERT was first detected in 10 of 11 patients diagnosed with invasive PC on pancreatic juice sampling[368]. This was further validated by Nakashima *et al*[369] and was additionally assessed in a recent systematic review assessing the role of hTERT which reported that telomerase reactivation played a significant role in the development of hepatobiliary and pancreatic tumors, along with being a diagnostic biomarker for PC[369,370].

Methylated DNA: Mutations in the KRAS oncogene are present in over 90% of resected PC specimens, with the vast majority of these mutations occurring in KRAS codon 12. A recent meta-analysis published by Patel *et al*[374], encompassing 22 studies aimed to assess the diagnostic accuracy of mutant KRAS detection from pancreatic secretions (mucus, secretions and juice) for the diagnosis of PC. They reported a wide variation in sensitivity (38%-89%) and specificity (13%-100%) for the diagnosis of PC through KRAS mutation testing in pancreatic secretions, with significant heterogeneity in diagnostic accuracy across the included studies. They also assessed whether KRAS mutation detection would be beneficial in diagnosing PC in a screening population, which similarly returned a sensitivity ranging from 21%-86%, however specificity improved remarkably to 82%-100%[374]. In addition to KRAS, Methylated ppENK and p16 were reported to be present in pancreatic juice in 90.9% and 18.2% respectively of patients diagnosed with PC, and due to normal pancreatic juice not containing methylated forms of this DNA, their presence was postulated to suggest the presence of PC[375]. Other markers investigated in single centre studies are shown in Table 5. MUC1 was also assessed in conjunction with MUC2 and MUC4 in 2014. Yokoyama *et al*[378] reported that DNA methylation status of MUC1, MUC2 and MUC4 was useful for the differential diagnosis of human pancreatic neoplasms, with a sensitivity and specificity of 87% and 80% for PC.

PANCREATIC CYST FLUID BIOMARKERS

Pancreatic cysts (PCy) are proving to be a promising area in the field of specimen sampling for biomarker identification. PCy incidence increases with age, with the most common cyst types including IPMN, mucinous cystic neoplasms (MCN), serous cystic neoplasms, and pseudocysts[379-381] (Table 6).

Table 6 Pancreatic cyst fluid biomarker studied in relation to high grade dysplasia and pancreatic cancer diagnosis

Type	Candidate marker
Protein	CEA[383,384,399,402-407], Glucose[385], MUC4[386,412], PGE2[387,388], IL-1B[386,387], PGE synthetase 2[386], IL-4[389], CA72-4[389], sFASL [389], MMP9[389] AREG[390,391], SPINK1[392], mAB Das-1[393,394], IL-10[395], GM-CSF[395], MUC1[413], MUC2[413], MUC5AC[413]
RNA	MiRNA: miR-21[396], miR-221[396], miR-18a[397,398], miR-24[397,398],miR-30a-3p[397,398], miR-92a[397,398], miR-99b[397,398], miR-106b[397, 398], miR-142-3p[397,398], miR-342-3p[397,398], and miR-532-3p[397,398]
Other	DNA based-*KRAS* mutations[399-407,409-411]*GNAS* mutations[409-411]

MiRNA: MicroRNA; CA72-4: Cancer antigen 72-4; sFASL: Soluble Fas; AREG: amphiregulin; SPINK1: serine peptidase inhibitor kazal type 1; GM-CSF: granulocyte macrophage colony-stimulating factor.

Due to IPMNs and MCNs possessing a risk of developing into PC identification of cyst fluid biomarkers in these pre-malignant lesions help to select which patients to proceed to surgery[382]. The cyst fluid is aspirated during EUS (EUS-FNA) under antibiotic cover and the amount of fluid retrieved depends on the size of the cyst therefore highlighting a potential for insufficient sampling during aspiration. Pancreatic cyst fluid analysis was initially focused on proteins isolated for biomarker assessment, however more recently there has been a transition towards the analysis of non-coding RNA, or miRNA in pancreatic cyst fluid to determine their diagnostic capacity for PC[408].

Proteins analyzed on cyst fluid, for the most part, have been reported to lack specificity in the diagnosis of PC, however mucin analysis, CEA level and VEGF-A on cystic fluid has proved to have efficacy in discriminating premalignant and malignant lesions from benign lesions. MUC4 expression has been implicated in PCy, being elevated in MCN, and has been postulated to assist in early detection of PC[412]. In addition to this, MUC1, MUC2 and MUC5AC have been demonstrated to be upregulated in patients with PC on cytology obtained during EUS-FNA but MUC7 is upregulated in PC and also in IPMN and CP, limiting its specificity in the diagnosis of PC[413,414].

Additionally, DNA-based biomarkers, including KRAS and GNAS, have been evaluated in the context of PC diagnosis and IPMN and noted to be elevated in mucin producing cysts. Recently, supervised machine learning techniques were used to develop a test to guide management of PCy based on clinical features, imaging and cyst fluid genetic and biochemical markers (CompCyst)[415]. Due to invasive nature of cyst fluid collection, the authors recommend that future studies should focus on biomarkers and algorithms that can help select which cysts have malignant potential and should proceed to surgery.

SALIVARY BIOMARKERS

Saliva is an emerging interest in the field of biomarker detection as it provides a non-invasive means through which potential diagnostic biomarkers can be sampled. It has previously been validated in the areas of drug abuse, human immunodeficiency virus infection and hormone assessment, along with detection of oral, breast, lung, ovarian and oesophageal cancer, and has been recently named the "diagnostic window to the body"[416-418] (Table 7).

The analysis of salivary fluid as a means for identification and evaluation of diagnostic biomarkers for PC is in its infancy, with proteomic biomarkers scant in the literature and due to the large amounts of salivary amylase, albumin and immunoglobulins present in saliva, their subsequent sensitivity is hampered in PC diagnosis [419,420]. Given this lack of sensitivity, there has been a shift in focus to RNA based biomarkers, namely LncRNA and miRNA . A recent systematic review reported that PC is the most investigated disease in relation to the utilization of salivary miRNA analysis. This is highlighted by 18 miRNA candidates which have been detected and studied in relation to PC, irrespective of stage, through the medium of saliva. Although miRNA analysis in saliva is in its infancy with regard to PC, the reported specificity in the diagnosis of PC is impressive and warrants further validation. Despite this reported specificity, the aforementioned systematic review concluded that there is marked heterogeneity between studies and as such meta-analysis is unachievable, highlighting the need for further research in this area[421-425].

Table 7 Salivary fluid biomarkers studied in relation to pancreatic cancer diagnosis

Type	Candidate marker
RNA	LncRNA: *HOTAIR*[428], *PVT1*[428]; MiRNA: miR-21[286,423,431], miR-23a[423], miR-23b[423], miR-29c[423], miR-1246[422], miR-4644[422], miR-34a[286], miR-155[286], miR-200b[286], miR-376a[286], miR-216[423], miR-940[424], miR-3679-5p[424], miR-17[425], miR-181b[425], miR-196a[425]
Other	Salivary polyamines: Alanine[427], N_1-acetylspermidine[427], 2-oxobutyrate[427], 2-hydroxybutyrate[427]

MiRNA: MicroRNA.

Aside from proteomic and RNA analysis of saliva, polyamine analysis has also emerged as a potential diagnostic biomarker candidate. Abnormalities in tumor-suppressor genes, deemed to play a key role in PC development, accelerate polyamine synthesis and as such, increased levels have been postulated to be a potential biomarker in PC[426]. Only a single study has assessed polyamines in PC detection with modest diagnostic accuracy[427].

BILIARY FLUID BIOMARKERS

Biliary fluid is a potential source for biomarkers, however due to sampling requiring an invasive procedure, ERCP, there are inherent risks with this mode of acquisition and is not routinely used. Currently the literature is limited to protein-based biomarkers, non-coding RNA markers and methylated DNA as a method of liquid biopsy with a recent meta-analysis highlighting minimal literature on biliary miRNA markers utilized in PC diagnosis[445] (Table 8).

There have been mixed results from these studies with a lack of large prospective studies to determine the validity of these biomarkers in clinical use. Although some biomarkers display merit in the early phases of clinical research, their role has also been deemed to be of value in the diagnosis of indeterminate biliary strictures thus highlighting a potential lack of sensitivity in the diagnosis of PC. Given the invasive nature of acquisition, less intrusive methods of biomarker acquisition should be considered for future research.

FAECAL BIOMARKERS

The concept of being able to detect PC biomarkers in stool is due to the large amount of pancreatic juice produced and excreted into the bowel on a daily basis, highlighting the potential that that precancerous or molecular changes indicative of a malignant process can be detected in faeces[447] (Table 9).

Faecal protein biomarkers

Adnab-9: Adnab-9 is a murine monoclonal antibody that has previously been implicated in the diagnosis of gastrointestinal tumors[448,449]. Adnab-9 detection in stools has a sensitivity and specificity of 80% and 87% for detection PC[450,451].

Faecal non-coding RNA

MiRNA: Faecal miRNA detection as a diagnostic biomarker has been utilized in CRC where although the environment has deemed to be more hostile than blood, miRNAs have been demonstrated to remain intact and stable for detection due to being packaged in exosomes. Faecal miRNA detection only requires 1 g of faeces in a sample, therefore presents itself as an efficacious modality as a screening test. Although there is only scant literature describing faecal miRNA analysis as a biomarker in PC[19,452,453], certain candidate markers demonstrate promise however there is heterogeneity between studies. Further studies are required to determine the relationship of faecal miRNA expression in PC to determine whether a candidate marker can be utilized in a screening population.

Faecal liquid biopsy

Faecal mutant *KRAS*: Initially detected in 1994 by Caldas *et al*[454], the presence of *K-ras* mutation in stool in patients with PC has proved to be an area of promise with regard to a non-invasive method of detection, and has also been explored in

Table 8 Biliary fluid diagnostic biomarkers studied with relation to pancreatic cancer

Type	Candidate marker
Protein	VEGF[217,429], CA19-9[431], CA125[432], CA72-4[432], CEA[432,433], sLR11[434], MUC4[435], IGF-1[217,430], NGAL[436-439], CEAM6[436,440], LG3BP[436], MMP7[436], MUC5B[436], MCM5[441,442], Trypsinogen-1[443], Trypsinogen-2[443]
Liquid biopsy	Methylated DNA: *TFP12*[444], *NPTX2*[444], *CCND2*[444]
RNA	MiRNA: miR-10b[292,445], miR-106b[292,445], miR-30c[292,445], miR-155[292,445], miR-212[292,445], miR-1247[446], miR-200a[446], miR-200b[446]

MCM5: Minichromosome maintenance protein 5; NGAL: Neutrophil gelatinase-associated lipocalin; sLR11: Soluble LDL receptor relative with 11 ligand-binding repeats; IGF1: Insulin-like growth factor 1; LG3BP: Galectin-3-binding protein; CEAM6: Carcinoembryonic cell adhesion molecule 6; TFP12: Methylated tissue factor pathway inhibitor 2; NPTX2: Neuronal pentraxin II gene; CCND2: G1/S-specific cyclin-D2; VEGF: Vascular endothelial growth factor; CEA: Carcinoembryonic antigen; MiRNA: MicroRNA.

Table 9 Faecal diagnostic biomarkers implicated in pancreatic cancer

Type	Candidate marker
Protein	Adnab-9[450,451]
RNA	MiRNA: miR-181b[452], miR-210[452], miR-155[453], miR-216a[453], miR-196a[452,453], miR-143[453]
Liquid biopsy	Mutant *KRAS*[454,455], mBMP3[456]

MiRNA: MicroRNA.

combination with methylated bone morphogenetic protein 3 (mBMP3)[454-456].

mBMP3: There is scarce literature regarding the role of BMP3 in the diagnosis of PC with a single study in 2011. Stool mBMP3 use as a biomarker for PC was first assessed in 2012, where it was able to detect 51% of PCs, compared to mutant *KRAS* which detected 50%. The AUC for mBMP3 was 0.73, however when used in combination with mutant *KRAS*, an AUC of 0.85 was achieved highlighting a potential option for non-invasive biomarker testing in a prospective cohort[456].

CONCLUSION

The literature is diverse with regard to biomarkers in the diagnosis of PC, with variation both in the medium utilized (serum, urine, saliva, pancreatic juice, cyst fluid analysis, faeces), along with the type of biomarker detected (miRNA, exosomes, proteins, CTCs, ctDNA) as demonstrated through this review, encompassing over 300 different diagnostic biomarkers in a variety of mediums. The current diagnostic biomarker utilized in the routine diagnostic work-up of PC is CA19-9, however this lacks sensitivity highlighted by phenotypic variation in the Lewis blood group antigen. Current research has focused on miRNA, ctDNA and CTCs in the detection and subsequent diagnosis of PC in experimental or feasibility studies with mixed results so far. Perhaps the most promising area of diagnostic biomarker discovery in the field of PC is the utilisation of diagnostic panels comprising a number of candidate markers rather than a single candidate protein or miRNA. These panels have proved to be efficacious in their diagnostic capacity for PC and as such should be further explored in prospective multi-centre studies to prove generalizability of results across different population groups. Very minimal research has been conducted evaluating biomarkers as a screening tool, with the low incidence of PC in the general population being cited as a barrier. This should be further explored to determine whether these candidate markers can be used as part of a screening program. A small number of studies have assessed the role of biomarkers in high-risk populations part of PC screening programs, however further research is required to determine whether their results can be extended to the general population. Future studies should aim to capitalize on the non-invasive nature of salivary, urinary, faecal and serum testing, as ultimately at a population level these are the most implementable modalities of testing and use cyst analysis and pancreatic juice in undetermined pancreatic lesions when

surgery is contemplated. Although we are yet to find the elusive 'golden ticket' for diagnosing PC, translational research is constantly opening up new doors in the search for a diagnostic biomarker that will help select the patients who need further investigations aimed at detecting PC early, similar to a positive FOBT prompting further assessment with a colonoscopy.

REFERENCES

1 **The Lancet Gastroenterology Hepatology**. Pancreatic cancer: a state of emergency? *Lancet Gastroenterol Hepatol* 2021; **6**: 81 [PMID: 33444531 DOI: 10.1016/S2468-1253(20)30397-6]
2 **Khalaf N**, El-Serag HB, Abrams HR, Thrift AP. Burden of Pancreatic Cancer: From Epidemiology to Practice. *Clin Gastroenterol Hepatol* 2021; **19**: 876-884 [PMID: 32147593 DOI: 10.1016/j.cgh.2020.02.054]
3 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
4 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]
5 **Rawla P**, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World J Oncol* 2019; **10**: 10-27 [PMID: 30834048 DOI: 10.14740/wjon1166]
6 **Ghaneh P**, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer. *Gut* 2007; **56**: 1134-1152 [PMID: 17625148 DOI: 10.1136/gut.2006.103333]
7 **Costello E**, Greenhalf W, Neoptolemos JP. New biomarkers and targets in pancreatic cancer and their application to treatment. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 435-444 [PMID: 22733351 DOI: 10.1038/nrgastro.2012.119]
8 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
9 **Klaiber U**, Leonhardt CS, Strobel O, Tjaden C, Hackert T, Neoptolemos JP. Neoadjuvant and adjuvant chemotherapy in pancreatic cancer. *Langenbecks Arch Surg* 2018; **403**: 917-932 [PMID: 30397779 DOI: 10.1007/s00423-018-1724-8]
10 **Chang MC**, Wu CH, Yang SH, Liang PC, Chen BB, Jan IS, Chang YT, Jeng YM. Pancreatic cancer screening in different risk individuals with family history of pancreatic cancer-a prospective cohort study in Taiwan. *Am J Cancer Res* 2017; **7**: 357-369 [PMID: 28337383]
11 **Henrikson NB**, Aiello Bowles EJ, Blasi PR, Morrison CC, Nguyen M, Pillarisetty VG, Lin JS. Screening for Pancreatic Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2019; **322**: 445-454 [PMID: 31386140 DOI: 10.1001/jama.2019.6190]
12 **Shi C**, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med* 2009; **133**: 365-374 [PMID: 19260742 DOI: 10.5858/133.3.365]
13 **Singhi AD**, Koay EJ, Chari ST, Maitra A. Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology* 2019; **156**: 2024-2040 [PMID: 30721664 DOI: 10.1053/j.gastro.2019.01.259]
14 **Takaori K**, Bassi C, Biankin A, Brunner TB, Cataldo I, Campbell F, Cunningham D, Falconi M, Frampton AE, Furuse J, Giovannini M, Jackson R, Nakamura A, Nealon W, Neoptolemos JP, Real FX, Scarpa A, Sclafani F, Windsor JA, Yamaguchi K, Wolfgang C, Johnson CD; IAP/EPC study group on the clinical managements of pancreatic cancer. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. *Pancreatology* 2016; **16**: 14-27 [PMID: 26699808 DOI: 10.1016/j.pan.2015.10.013]
15 **Gui JC**, Yan WL, Liu XD. CA19-9 and CA242 as tumor markers for the diagnosis of pancreatic cancer: a meta-analysis. *Clin Exp Med* 2014; **14**: 225-233 [PMID: 23456571 DOI: 10.1007/s10238-013-0234-9]
16 **Herreros-Villanueva M**, Gironella M, Castells A, Bujanda L. Molecular markers in pancreatic cancer diagnosis. *Clin Chim Acta* 2013; **418**: 22-29 [PMID: 23305796 DOI: 10.1016/j.cca.2012.12.025]
17 **Agrawal S**. Potential prognostic biomarkers in pancreatic juice of resectable pancreatic ductal adenocarcinoma. *World J Clin Oncol* 2017; **8**: 255-260 [PMID: 28638795 DOI: 10.5306/wjco.v8.i3.255]
18 **Ishige F**, Hoshino I, Iwatate Y, Chiba S, Arimitsu H, Yanagibashi H, Nagase H, Takayama W. MIR1246 in body fluids as a biomarker for pancreatic cancer. *Sci Rep* 2020; **10**: 8723 [PMID: 32457495 DOI: 10.1038/s41598-020-65695-6]
19 **Yang JY**, Sun YW, Liu DJ, Zhang JF, Li J, Hua R. MicroRNAs in stool samples as potential screening biomarkers for pancreatic ductal adenocarcinoma cancer. *Am J Cancer Res* 2014; **4**: 663-673 [PMID: 25520858]

20 **Jimenez-Luna C**, Torres C, Ortiz R, Dieguez C, Martinez-Galan J, Melguizo C, Prados JC, Caba O. Proteomic biomarkers in body fluids associated with pancreatic cancer. *Oncotarget* 2018; **9**: 16573-16587 [PMID: 29662668 DOI: 10.18632/oncotarget.24654]

21 **Pan S**, Chen R, Crispin DA, May D, Stevens T, McIntosh MW, Bronner MP, Ziogas A, Anton-Culver H, Brentnall TA. Protein alterations associated with pancreatic cancer and chronic pancreatitis found in human plasma using global quantitative proteomics profiling. *J Proteome Res* 2011; **10**: 2359-2376 [PMID: 21443201 DOI: 10.1021/pr101148r]

22 **Goonetilleke KS**, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; **33**: 266-270 [PMID: 17097848 DOI: 10.1016/j.ejso.2006.10.004]

23 **Koprowski H**, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Genet* 1979; **5**: 957-971 [PMID: 94699 DOI: 10.1007/BF01542654]

24 **Ning S**, Wei W, Li J, Hou B, Zhong J, Xie Y, Liu H, Mo X, Chen J, Zhang L. Clinical significance and diagnostic capacity of serum TK1, CEA, CA 19-9 and CA 72-4 Levels in gastric and colorectal cancer patients. *J Cancer* 2018; **9**: 494-501 [PMID: 29483954 DOI: 10.7150/jca.21562]

25 **Nikolaou S**, Qiu S, Fiorentino F, Rasheed S, Tekkis P, Kontovounisios C. Systematic review of blood diagnostic markers in colorectal cancer. *Tech Coloproctol* 2018; **22**: 481-498 [PMID: 30022330 DOI: 10.1007/s10151-018-1820-3]

26 **Liang B**, Zhong L, He Q, Wang S, Pan Z, Wang T, Zhao Y. Diagnostic Accuracy of Serum CA19-9 in Patients with Cholangiocarcinoma: A Systematic Review and Meta-Analysis. *Med Sci Monit* 2015; **21**: 3555-3563 [PMID: 26576628 DOI: 10.12659/msm.895040]

27 **Ballehaninna UK**, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012; **3**: 105-119 [PMID: 22811878 DOI: 10.3978/j.issn.2078-6891.2011.021]

28 **Kriz D**, Ansari D, Andersson R. Potential biomarkers for early detection of pancreatic ductal adenocarcinoma. *Clin Transl Oncol* 2020; **22**: 2170-2174 [PMID: 32447642 DOI: 10.1007/s12094-020-02372-0]

29 **Binicier OB**, Pakoz ZB. CA 19-9 levels in patients with acute pancreatitis due to gallstone and metabolic/toxic reasons. *Rev Assoc Med Bras (1992)* 2019; **65**: 965-970 [PMID: 31389506 DOI: 10.1590/1806-9282.65.7.965]

30 **Doğan ÜB**, Gümürdülü Y, Gölge N, Kara B. Relationship of CA 19-9 with choledocholithiasis and cholangitis. *Turk J Gastroenterol* 2011; **22**: 171-177 [PMID: 21796554 DOI: 10.4318/tjg.2011.0186]

31 **Kannagi R**. Carbohydrate antigen sialyl Lewis a--its pathophysiological significance and induction mechanism in cancer progression. *Chang Gung Med J* 2007; **30**: 189-209 [PMID: 17760270]

32 **Fahrmann JF**, Bantis LE, Capello M, Scelo G, Dennison JB, Patel N, Murage E, Vykoukal J, Kundnani DL, Foretova L, Fabianova E, Holcatova I, Janout V, Feng Z, Yip-Schneider M, Zhang J, Brand R, Taguchi A, Maitra A, Brennan P, Max Schmidt C, Hanash S. A Plasma-Derived Protein-Metabolite Multiplexed Panel for Early-Stage Pancreatic Cancer. *J Natl Cancer Inst* 2019; **111**: 372-379 [PMID: 30137376 DOI: 10.1093/jnci/djy126]

33 **Satake K**, Takeuchi T, Homma T, Ozaki H. CA19-9 as a screening and diagnostic tool in symptomatic patients: the Japanese experience. *Pancreas* 1994; **9**: 703-706 [PMID: 7846012 DOI: 10.1097/00006676-199411000-00005]

34 **Kim JE**, Lee KT, Lee JK, Paik SW, Rhee JC, Choi KW. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. *J Gastroenterol Hepatol* 2004; **19**: 182-186 [PMID: 14731128 DOI: 10.1111/j.1440-1746.2004.03219.x]

35 **Chang CY**, Huang SP, Chiu HM, Lee YC, Chen MF, Lin JT. Low efficacy of serum levels of CA 19-9 in prediction of malignant diseases in asymptomatic population in Taiwan. *Hepatogastroenterology* 2006; **53**: 1-4 [PMID: 16506366]

36 **Xing H**, Wang J, Wang Y, Tong M, Hu H, Huang C, Li D. Diagnostic Value of CA 19-9 and Carcinoembryonic Antigen for Pancreatic Cancer: A Meta-Analysis. *Gastroenterol Res Pract* 2018; **2018**: 8704751 [PMID: 30584422 DOI: 10.1155/2018/8704751]

37 **Kaur S**, Smith LM, Patel A, Menning M, Watley DC, Malik SS, Krishn SR, Mallya K, Aithal A, Sasson AR, Johansson SL, Jain M, Singh S, Guha S, Are C, Raimondo M, Hollingsworth MA, Brand RE, Batra SK. A Combination of MUC5AC and CA19-9 Improves the Diagnosis of Pancreatic Cancer: A Multicenter Study. *Am J Gastroenterol* 2017; **112**: 172-183 [PMID: 27845339 DOI: 10.1038/ajg.2016.482]

38 **Liu J**, Gao J, Du Y, Li Z, Ren Y, Gu J, Wang X, Gong Y, Wang W, Kong X. Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. *Int J Cancer* 2012; **131**: 683-691 [PMID: 21913185 DOI: 10.1002/ijc.26422]

39 **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]

40 **Tang H**, Singh S, Partyka K, Kletter D, Hsueh P, Yadav J, Ensink E, Bern M, Hostetter G, Hartman D, Huang Y, Brand RE, Haab BB. Glycan motif profiling reveals plasma sialyl-lewis x elevations in pancreatic cancers that are negative for sialyl-lewis A. *Mol Cell Proteomics* 2015; **14**: 1323-1333 [PMID: 25733690 DOI: 10.1074/mcp.M114.047837]

41 **Barnett D**, Liu Y, Partyka K, Huang Y, Tang H, Hostetter G, Brand RE, Singhi AD, Drake RR, Haab BB. The CA19-9 and Sialyl-TRA Antigens Define Separate Subpopulations of Pancreatic Cancer Cells. *Sci Rep* 2017; **7**: 4020 [PMID: 28642461 DOI: 10.1038/s41598-017-04164-z]

42 **Hall C**, Clarke L, Pal A, Buchwald P, Eglinton T, Wakeman C, Frizelle F. A Review of the Role of Carcinoembryonic Antigen in Clinical Practice. *Ann Coloproctol* 2019; **35**: 294-305 [PMID: 31937069 DOI: 10.3393/ac.2019.11.13]

43 **Meng Q**, Shi S, Liang C, Liang D, Xu W, Ji S, Zhang B, Ni Q, Xu J, Yu X. Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis. *Onco Targets Ther* 2017; **10**: 4591-4598 [PMID: 28979147 DOI: 10.2147/OTT.S145708]

44 **Jacobs I**. Screening for ovarian cancer by CA-125 measurement. *Lancet* 1988; **1**: 889 [PMID: 2895400 DOI: 10.1016/s0140-6736(88)91642-x]

45 **Giessen C**, Nagel D, Glas M, Spelsberg F, Lau-Werner U, Modest DP, Michl M, Heinemann V, Stieber P, Schulz C. Evaluation of preoperative serum markers for individual patient prognosis in stage I-III rectal cancer. *Tumour Biol* 2014; **35**: 10237-10248 [PMID: 25027407 DOI: 10.1007/s13277-014-2338-6]

46 **Wu WR**, Shi XD, Zhang R, Zhu MS, Xu LB, Yu XH, Zeng H, Wang J, Liu C. Clinicopathological significance of aberrant Notch receptors in intrahepatic cholangiocarcinoma. *Int J Clin Exp Pathol* 2014; **7**: 3272-3279 [PMID: 25031748]

47 **Luo G**, Xiao Z, Long J, Liu Z, Liu L, Liu C, Xu J, Ni Q, Yu X. CA125 is superior to CA19-9 in predicting the resectability of pancreatic cancer. *J Gastrointest Surg* 2013; **17**: 2092-2098 [PMID: 24146342 DOI: 10.1007/s11605-013-2389-9]

48 **Liu L**, Xu HX, Wang WQ, Wu CT, Xiang JF, Liu C, Long J, Xu J, Fu de L, Ni QX, Houchen CW, Postier RG, Li M, Yu XJ. Serum CA125 is a novel predictive marker for pancreatic cancer metastasis and correlates with the metastasis-associated burden. *Oncotarget* 2016; **7**: 5943-5956 [PMID: 26745601 DOI: 10.18632/oncotarget.6819]

49 **Haglund C**. Tumour marker antigen CA125 in pancreatic cancer: a comparison with CA19-9 and CEA. *Br J Cancer* 1986; **54**: 897-901 [PMID: 3467786 DOI: 10.1038/bjc.1986.259]

50 **Meng Q**, Shi S, Liang C, Xiang J, Liang D, Zhang B, Qin Y, Ji S, Xu W, Xu J, Ni Q, Yu X. Diagnostic Accuracy of a CA125-Based Biomarker Panel in Patients with Pancreatic Cancer: A Systematic Review and Meta-Analysis. *J Cancer* 2017; **8**: 3615-3622 [PMID: 29151947 DOI: 10.7150/jca.18901]

51 **Haglund C**, Lindgren J, Roberts PJ, Kuusela P, Nordling S. Tissue expression of the tumour associated antigen CA242 in benign and malignant pancreatic lesions. A comparison with CA 50 and CA 19-9. *Br J Cancer* 1989; **60**: 845-851 [PMID: 2557879 DOI: 10.1038/bjc.1989.377]

52 **Kuusela P**, Haglund C, Roberts PJ. Comparison of a new tumour marker CA 242 with CA 19-9, CA 50 and carcinoembryonic antigen (CEA) in digestive tract diseases. *Br J Cancer* 1991; **63**: 636-640 [PMID: 2021550 DOI: 10.1038/bjc.1991.146]

53 **Dong D**, Jia L, Zhang L, Ma N, Zhang A, Zhou Y, Ren L. Periostin and CA242 as potential diagnostic serum biomarkers complementing CA19.9 in detecting pancreatic cancer. *Cancer Sci* 2018; **109**: 2841-2851 [PMID: 29945294 DOI: 10.1111/cas.13712]

54 **Dou H**, Sun G, Zhang L. CA242 as a biomarker for pancreatic cancer and other diseases. *Prog Mol Biol Transl Sci* 2019; **162**: 229-239 [PMID: 30905452 DOI: 10.1016/bs.pmbts.2018.12.007]

55 **Zhang Y**, Yang J, Li H, Wu Y, Zhang H, Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. *Int J Clin Exp Med* 2015; **8**: 11683-11691 [PMID: 26380005]

56 **Rossi MK**, Gnanamony M, Gondi CS. The 'SPARC' of life: Analysis of the role of osteonectin/SPARC in pancreatic cancer (Review). *Int J Oncol* 2016; **48**: 1765-1771 [PMID: 26983777 DOI: 10.3892/ijo.2016.3417]

57 **Papapanagiotou A**, Sgourakis G, Karkoulias K, Raptis D, Parkin E, Brotzakis P, Panchal S, Papavassiliou AG. Osteonectin as a screening marker for pancreatic cancer: A prospective study. *J Int Med Res* 2018; **46**: 2769-2779 [PMID: 29756486 DOI: 10.1177/0300060518772413]

58 **Koopmann J**, Fedarko NS, Jain A, Maitra A, Iacobuzio-Donahue C, Rahman A, Hruban RH, Yeo CJ, Goggins M. Evaluation of osteopontin as biomarker for pancreatic adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 487-491 [PMID: 15006928]

59 **Poruk KE**, Firpo MA, Scaife CL, Adler DG, Emerson LL, Boucher KM, Mulvihill SJ. Serum osteopontin and tissue inhibitor of metalloproteinase 1 as diagnostic and prognostic biomarkers for pancreatic adenocarcinoma. *Pancreas* 2013; **42**: 193-197 [PMID: 23407481 DOI: 10.1097/MPA.0b013e31825e354d]

60 **Li JJ**, Li HY, Gu F. Diagnostic significance of serum osteopontin level for pancreatic cancer: a meta-analysis. *Genet Test Mol Biomarkers* 2014; **18**: 580-586 [PMID: 24950303 DOI: 10.1089/gtmb.2014.0102]

61 **Rychlíková J**, Vecka M, Jáchymová M, Macášek J, Hrabák P, Zeman M, Vávrová L, Řoupal J, Krechler T, Ák A. Osteopontin as a discriminating marker for pancreatic cancer and chronic pancreatitis. *Cancer Biomark* 2016; **17**: 55-65 [PMID: 27314293 DOI: 10.3233/CBM-160617]

62 **Takasaki H**, Uchida E, Tempero MA, Burnett DA, Metzgar RS, Pour PM. Correlative study on expression of CA 19-9 and DU-PAN-2 in tumor tissue and in serum of pancreatic cancer patients. *Cancer Res* 1988; **48**: 1435-1438 [PMID: 3162196]

63 **Kawa S**, Oguchi H, Kobayashi T, Tokoo M, Furuta S, Kanai M, Homma T. Elevated serum levels of Dupan-2 in pancreatic cancer patients negative for Lewis blood group phenotype. *Br J Cancer* 1991;

64: 899-902 [PMID: 1931612 DOI: 10.1038/bjc.1991.422]

64 **Narimatsu H**, Iwasaki H, Nakayama F, Ikehara Y, Kudo T, Nishihara S, Sugano K, Okura H, Fujita S, Hirohashi S. Lewis and secretor gene dosages affect CA19-9 and DU-PAN-2 serum levels in normal individuals and colorectal cancer patients. *Cancer Res* 1998; **58**: 512-518 [PMID: 9458099]

65 **Chung YS**, Ho JJ, Kim YS, Tanaka H, Nakata B, Hiura A, Motoyoshi H, Satake K, Umeyama K. The detection of human pancreatic cancer-associated antigen in the serum of cancer patients. *Cancer* 1987; **60**: 1636-1643 [PMID: 3476183 DOI: 10.1002/1097-0142(19871001)60:7<1636::aid-cncr2820600736>3.0.co;2-c]

66 **Cooper EH**, Forbes MA, Taylor M. An evaluation of DUPAN-2 in pancreatic cancer and gastrointestinal disease. *Br J Cancer* 1990; **62**: 1004-1005 [PMID: 2257202 DOI: 10.1038/bjc.1990.426]

67 **Satake K**, Chung YS, Umeyama K, Takeuchi T, Kim YS. The possibility of diagnosing small pancreatic cancer (less than 4.0 cm) by measuring various serum tumor markers. A retrospective study. *Cancer* 1991; **68**: 149-152 [PMID: 2049735 DOI: 10.1002/1097-0142(19910701)68:1<149::aid-cncr2820680127>3.0.co;2-9]

68 **Saito S**, Taguchi K, Nishimura N, Watanabe A, Ogoshi K, Niwa M, Furukawa T, Takahashi M. Clinical usefulness of computer-assisted diagnosis using combination assay of tumor markers for pancreatic carcinoma. *Cancer* 1993; **72**: 381-388 [PMID: 8319169 DOI: 10.1002/1097-0142(19930715)72:2<381::aid-cncr2820720212>3.0.co;2-l]

69 **Satake K**, Takeuchi T. Comparison of CA19-9 with other tumor markers in the diagnosis of cancer of the pancreas. *Pancreas* 1994; **9**: 720-724 [PMID: 7846015 DOI: 10.1097/00006676-199411000-00008]

70 **Sunagawa Y**, Yamada S, Sato Y, Morimoto D, Sonohara F, Takami H, Inokawa Y, Hayashi M, Kanda M, Tanaka C, Kobayashi D, Nakayama G, Koike M, Fujiwara M, Fujii T, Kodera Y. Novel Prognostic Implications of DUPAN-2 in the Era of Initial Systemic Therapy for Pancreatic Cancer. *Ann Surg Oncol* 2020; **27**: 2081-2089 [PMID: 31673938 DOI: 10.1245/s10434-019-07981-w]

71 **Badea L**, Herlea V, Dima SO, Dumitrascu T, Popescu I. Combined gene expression analysis of whole-tissue and microdissected pancreatic ductal adenocarcinoma identifies genes specifically overexpressed in tumor epithelia. *Hepatogastroenterology* 2008; **55**: 2016-2027 [PMID: 19260470]

72 **Mitsunaga S**, Fujii S, Ishii G, Kinoshita T, Hasebe T, Aoyagi K, Sasaki H, Ochiai A. Nerve invasion distance is dependent on laminin gamma2 in tumors of pancreatic cancer. *Int J Cancer* 2010; **127**: 805-819 [PMID: 20013810 DOI: 10.1002/ijc.25104]

73 **Kosanam H**, Prassas I, Chrystoja CC, Soleas I, Chan A, Dimitromanolakis A, Blasutig IM, Rückert F, Gruetzmann R, Pilarsky C, Maekawa M, Brand R, Diamandis EP. Laminin, gamma 2 (LAMC2): a promising new putative pancreatic cancer biomarker identified by proteomic analysis of pancreatic adenocarcinoma tissues. *Mol Cell Proteomics* 2013; **12**: 2820-2832 [PMID: 23798558 DOI: 10.1074/mcp.M112.023507]

74 **Chan A**, Prassas I, Dimitromanolakis A, Brand RE, Serra S, Diamandis EP, Blasutig IM. Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer. *Clin Cancer Res* 2014; **20**: 5787-5795 [PMID: 25239611 DOI: 10.1158/1078-0432.CCR-14-0289]

75 **Yang C**, Liu Z, Zeng X, Wu Q, Liao X, Wang X, Han C, Yu T, Zhu G, Qin W, Peng T. Evaluation of the diagnostic ability of laminin gene family for pancreatic ductal adenocarcinoma. *Aging (Albany NY)* 2019; **11**: 3679-3703 [PMID: 31182680 DOI: 10.18632/aging.102007]

76 **Champsaur M**, Lanier LL. Effect of NKG2D ligand expression on host immune responses. *Immunol Rev* 2010; **235**: 267-285 [PMID: 20536569 DOI: 10.1111/j.0105-2896.2010.00893.x]

77 **Unni AM**, Bondar T, Medzhitov R. Intrinsic sensor of oncogenic transformation induces a signal for innate immunosurveillance. *Proc Natl Acad Sci USA* 2008; **105**: 1686-1691 [PMID: 18223157 DOI: 10.1073/pnas.0701675105]

78 **Chang YT**, Wu CC, Shyr YM, Chen TC, Hwang TL, Yeh TS, Chang KP, Liu HP, Liu YL, Tsai MH, Chang YS, Yu JS. Secretome-based identification of ULBP2 as a novel serum marker for pancreatic cancer detection. *PLoS One* 2011; **6**: e20029 [PMID: 21625447 DOI: 10.1371/journal.pone.0020029]

79 **Zhou YF**, Xu LX, Huang LY, Guo F, Zhang F, He XY, Yuan YZ, Yao WY. Combined detection of serum UL16-binding protein 2 and macrophage inhibitory cytokine-1 improves early diagnosis and prognostic prediction of pancreatic cancer. *Oncol Lett* 2014; **8**: 2096-2102 [PMID: 25295097 DOI: 10.3892/ol.2014.2429]

80 **Cui D**, Zhang Y, Lian J, Liu B, Liu F, Han L, Wang Y, Gao S. Value analysis of CA19-9, s-ULBP2 and Dkk1 in the diagnosis of pancreatic cancer. *Shiyong Yixue Zazhi* 2017; **33**: 4086-4089 [DOI: 10.3969/j.issn.1006-5725.2017.24.016]

81 **Kegasawa T**, Tatsumi T, Yoshioka T, Suda T, Ikezawa K, Nakabori T, Yamada R, Kodama T, Shigekawa M, Hikita H, Sakamori R, Takehara T. Soluble UL16-binding protein 2 is associated with a poor prognosis in pancreatic cancer patients. *Biochem Biophys Res Commun* 2019; **517**: 84-88 [PMID: 31303272 DOI: 10.1016/j.bbrc.2019.07.020]

82 **Chung HW**, Lim JB. Clinical significance of elevated serum soluble CD40 ligand levels as a diagnostic and prognostic tumor marker for pancreatic ductal adenocarcinoma. *J Transl Med* 2014; **12**: 102 [PMID: 24745825 DOI: 10.1186/1479-5876-12-102]

83 **Haupt H**, Baudner S. [Isolation and characterization of an unknown, leucine-rich 3.1-S-alpha2-glycoprotein from human serum (author's transl)]. *Hoppe Seylers Z Physiol Chem* 1977; **358**: 639-646 [PMID: 69600]

84 **Furukawa K**, Kawamoto K, Eguchi H, Tanemura M, Tanida T, Tomimaru Y, Akita H, Hama N, Wada H, Kobayashi S, Nonaka Y, Takamatsu S, Shinzaki S, Kumada T, Satomura S, Ito T, Serada S, Naka T, Mori M, Doki Y, Miyoshi E, Nagano H. Clinicopathological Significance of Leucine-Rich α2-Glycoprotein-1 in Sera of Patients With Pancreatic Cancer. *Pancreas* 2015; **44**: 93-98 [PMID: 25058884 DOI: 10.1097/MPA.0000000000000205]

85 **Brodeur SR**, Angelini F, Bacharier LB, Blom AM, Mizoguchi E, Fujiwara H, Plebani A, Notarangelo LD, Dahlback B, Tsitsikov E, Geha RS. C4b-binding protein (C4BP) activates B cells through the CD40 receptor. *Immunity* 2003; **18**: 837-848 [PMID: 12818164 DOI: 10.1016/s1074-7613(03)00149-3]

86 **Sogawa K**, Takano S, Iida F, Satoh M, Tsuchida S, Kawashima Y, Yoshitomi H, Sanda A, Kodera Y, Takizawa H, Mikata R, Ohtsuka M, Shimizu H, Miyazaki M, Yokosuka O, Nomura F. Identification of a novel serum biomarker for pancreatic cancer, C4b-binding protein α-chain (C4BPA) by quantitative proteomic analysis using tandem mass tags. *Br J Cancer* 2016; **115**: 949-956 [PMID: 27657339 DOI: 10.1038/bjc.2016.295]

87 **Wang W**, Eddy R, Condeelis J. The cofilin pathway in breast cancer invasion and metastasis. *Nat Rev Cancer* 2007; **7**: 429-440 [PMID: 17522712 DOI: 10.1038/nrc2148]

88 **Satoh M**, Takano S, Sogawa K, Noda K, Yoshitomi H, Ishibashi M, Mogushi K, Takizawa H, Otsuka M, Shimizu H, Miyazaki M, Nomura F. Immune-complex level of cofilin-1 in sera is associated with cancer progression and poor prognosis in pancreatic cancer. *Cancer Sci* 2017; **108**: 795-803 [PMID: 28161904 DOI: 10.1111/cas.13181]

89 **Peerschke EI**, Ghebrehiwet B. The contribution of gC1qR/p33 in infection and inflammation. *Immunobiology* 2007; **212**: 333-342 [PMID: 17544818 DOI: 10.1016/j.imbio.2006.11.011]

90 **Peerschke EI**, Ghebrehiwet B. cC1qR/CR and gC1qR/p33: observations in cancer. *Mol Immunol* 2014; **61**: 100-109 [PMID: 25044096 DOI: 10.1016/j.molimm.2014.06.011]

91 **Peerschke EI**, Brandwijk RJ, Dembitzer FR, Kinoshita Y, Ghebrehiwet B. Soluble gC1qR in Blood and Body Fluids: Examination in a Pancreatic Cancer Patient Cohort. *Int J Cancer Res Mol Mech* 2015; **1** [PMID: 26973884]

92 **Hedström J**, Haglund C, Haapiainen R, Stenman UH. Serum trypsinogen-2 and trypsin-2-alpha(1)-antitrypsin complex in malignant and benign digestive-tract diseases. Preferential elevation in patients with cholangiocarcinomas. *Int J Cancer* 1996; **66**: 326-331 [PMID: 8621252 DOI: 10.1002/(SICI)1097-0215(19960503)66:3<326::AID-IJC10>3.0.CO;2-9]

93 **Cao J**, Xia C, Cui T, Guo H, Li H, Ren Y, Wang S. Correlations between serum trypsinogen-2 and pancreatic cancer. *Hepatogastroenterology* 2015; **62**: 435-440 [PMID: 25916077]

94 **Osada H**, Tomida S, Yatabe Y, Tatematsu Y, Takeuchi T, Murakami H, Kondo Y, Sekido Y, Takahashi T. Roles of achaete-scute homologue 1 in DKK1 and E-cadherin repression and neuroendocrine differentiation in lung cancer. *Cancer Res* 2008; **68**: 1647-1655 [PMID: 18339843 DOI: 10.1158/0008-5472.CAN-07-5039]

95 **Voorzanger-Rousselot N**, Goehrig D, Journe F, Doriath V, Body JJ, Clézardin P, Garnero P. Increased Dickkopf-1 expression in breast cancer bone metastases. *Br J Cancer* 2007; **97**: 964-970 [PMID: 17876334 DOI: 10.1038/sj.bjc.6603959]

96 **Han SX**, Zhou X, Sui X, He CC, Cai MJ, Ma JL, Zhang YY, Zhou CY, Ma CX, Varela-Ramirez A, Zhu Q. Serum dickkopf-1 is a novel serological biomarker for the diagnosis and prognosis of pancreatic cancer. *Oncotarget* 2015; **6**: 19907-19917 [PMID: 26101916 DOI: 10.18632/oncotarget.4529]

97 **Igbinigie E**, Guo F, Jiang SW, Kelley C, Li J. Dkk1 involvement and its potential as a biomarker in pancreatic ductal adenocarcinoma. *Clin Chim Acta* 2019; **488**: 226-234 [PMID: 30452897 DOI: 10.1016/j.cca.2018.11.023]

98 **Wang X**, Zhang L, Li H, Sun W, Zhang H, Lai M. THBS2 is a Potential Prognostic Biomarker in Colorectal Cancer. *Sci Rep* 2016; **6**: 33366 [PMID: 27632935 DOI: 10.1038/srep33366]

99 **Kim J**, Bamlet WR, Oberg AL, Chaffee KG, Donahue G, Cao XJ, Chari S, Garcia BA, Petersen GM, Zaret KS. Detection of early pancreatic ductal adenocarcinoma with thrombospondin-2 and CA19-9 blood markers. *Sci Transl Med* 2017; **9** [PMID: 28701476 DOI: 10.1126/scitranslmed.aah5583]

100 **Peng HY**, Chang MC, Hu CM, Yang HI, Lee WH, Chang YT. Thrombospondin-2 is a Highly Specific Diagnostic Marker and is Associated with Prognosis in Pancreatic Cancer. *Ann Surg Oncol* 2019; **26**: 807-814 [PMID: 30569296 DOI: 10.1245/s10434-018-07109-6]

101 **Berger AW**, Schwerdel D, Reinacher-Schick A, Uhl W, Algül H, Friess H, Janssen KP, König A, Ghadimi M, Gallmeier E, Bartsch DK, Geissler M, Staib L, Tannapfel A, Kleger A, Beutel A, Schulte LA, Kornmann M, Ettrich TJ, Seufferlein T. A Blood-Based Multi Marker Assay Supports the Differential Diagnosis of Early-Stage Pancreatic Cancer. *Theranostics* 2019; **9**: 1280-1287 [PMID: 30867830 DOI: 10.7150/thno.29247]

102 **Le Large TYS**, Meijer LL, Paleckyte R, Boyd LNC, Kok B, Wurdinger T, Schelfhorst T, Piersma SR, Pham TV, van Grieken NCT, Zonderhuis BM, Daams F, van Laarhoven HWM, Bijlsma MF, Jimenez CR, Giovannetti E, Kazemier G. Combined Expression of Plasma Thrombospondin-2 and CA19-9 for Diagnosis of Pancreatic Cancer and Distal Cholangiocarcinoma: A Proteome Approach. *Oncologist* 2020; **25**: e634-e643 [PMID: 31943574 DOI: 10.1634/theoncologist.2019-0680]

103 **Jenkinson C**, Elliott VL, Evans A, Oldfield L, Jenkins RE, O'Brien DP, Apostolidou S, Gentry-Maharaj A, Fourkala EO, Jacobs IJ, Menon U, Cox T, Campbell F, Pereira SP, Tuveson DA, Park BK, Greenhalf W, Sutton R, Timms JF, Neoptolemos JP, Costello E. Decreased Serum

Thrombospondin-1 Levels in Pancreatic Cancer Patients Up to 24 Months Prior to Clinical Diagnosis: Association with Diabetes Mellitus. *Clin Cancer Res* 2016; **22**: 1734-1743 [PMID: 26573598 DOI: 10.1158/1078-0432.CCR-15-0879]

104 **Fritzsche FR**, Dahl E, Pahl S, Burkhardt M, Luo J, Mayordomo E, Gansukh T, Dankof A, Knuechel R, Denkert C, Winzer KJ, Dietel M, Kristiansen G. Prognostic relevance of AGR2 expression in breast cancer. *Clin Cancer Res* 2006; **12**: 1728-1734 [PMID: 16551856 DOI: 10.1158/1078-0432.CCR-05-2057]

105 **Chen YT**, Ho CL, Chen PK, Chen YL, Chang CF. Anterior gradient 2: a novel sensitive tumor marker for metastatic oral cancer. *Cancer Lett* 2013; **339**: 270-278 [PMID: 23834814 DOI: 10.1016/j.canlet.2013.06.025]

106 **Ramachandran V**, Arumugam T, Wang H, Logsdon CD. Anterior gradient 2 is expressed and secreted during the development of pancreatic cancer and promotes cancer cell survival. *Cancer Res* 2008; **68**: 7811-7818 [PMID: 18829536 DOI: 10.1158/0008-5472.CAN-08-1320]

107 **Dumartin L**, Whiteman HJ, Weeks ME, Hariharan D, Dmitrovic B, Iacobuzio-Donahue CA, Brentnall TA, Bronner MP, Feakins RM, Timms JF, Brennan C, Lemoine NR, Crnogorac-Jurcevic T. AGR2 is a novel surface antigen that promotes the dissemination of pancreatic cancer cells through regulation of cathepsins B and D. *Cancer Res* 2011; **71**: 7091-7102 [PMID: 21948970 DOI: 10.1158/0008-5472.CAN-11-1367]

108 **Makawita S**, Dimitromanolakis A, Soosaipillai A, Soleas I, Chan A, Gallinger S, Haun RS, Blasutig IM, Diamandis EP. Validation of four candidate pancreatic cancer serological biomarkers that improve the performance of CA19.9. *BMC Cancer* 2013; **13**: 404 [PMID: 24007603 DOI: 10.1186/1471-2407-13-404]

109 **Wu H**, Zheng Q, Rengabhashyam P, Zenilman ME. A Brief History of Pancreatic Reg: Implications as to its Clinical Importance. *Einstein Q J Biol Med* 2000; **17**: 178 [PMID: 21687811]

110 **Li Q**, Wang H, Zogopoulos G, Shao Q, Dong K, Lv F, Nwilati K, Gui XY, Cuggia A, Liu JL, Gao ZH. Reg proteins promote acinar-to-ductal metaplasia and act as novel diagnostic and prognostic markers in pancreatic ductal adenocarcinoma. *Oncotarget* 2016; **7**: 77838-77853 [PMID: 27788482 DOI: 10.18632/oncotarget.12834]

111 **Faca VM**, Song KS, Wang H, Zhang Q, Krasnoselsky AL, Newcomb LF, Plentz RR, Gurumurthy S, Redston MS, Pitteri SJ, Pereira-Faca SR, Ireton RC, Katayama H, Glukhova V, Phanstiel D, Brenner DE, Anderson MA, Misek D, Scholler N, Urban ND, Barnett MJ, Edelstein C, Goodman GE, Thornquist MD, McIntosh MW, DePinho RA, Bardeesy N, Hanash SM. A mouse to human search for plasma proteome changes associated with pancreatic tumor development. *PLoS Med* 2008; **5**: e123 [PMID: 18547137 DOI: 10.1371/journal.pmed.0050123]

112 **Oue N**, Mitani Y, Aung PP, Sakakura C, Takeshima Y, Kaneko M, Noguchi T, Nakayama H, Yasui W. Expression and localization of Reg IV in human neoplastic and non-neoplastic tissues: Reg IV expression is associated with intestinal and neuroendocrine differentiation in gastric adenocarcinoma. *J Pathol* 2005; **207**: 185-198 [PMID: 16086444 DOI: 10.1002/path.1827]

113 **Violette S**, Festor E, Pandrea-Vasile I, Mitchell V, Adida C, Dussaulx E, Lacorte JM, Chambaz J, Lacasa M, Lesuffleur T. Reg IV, a new member of the regenerating gene family, is overexpressed in colorectal carcinomas. *Int J Cancer* 2003; **103**: 185-193 [PMID: 12455032 DOI: 10.1002/ijc.10788]

114 **Takehara A**, Eguchi H, Ohigashi H, Ishikawa O, Kasugai T, Hosokawa M, Katagiri T, Nakamura Y, Nakagawa H. Novel tumor marker REG4 detected in serum of patients with resectable pancreatic cancer and feasibility for antibody therapy targeting REG4. *Cancer Sci* 2006; **97**: 1191-1197 [PMID: 16918991 DOI: 10.1111/j.1349-7006.2006.00297.x]

115 **Bishnupuri KS**, Luo Q, Murmu N, Houchen CW, Anant S, Dieckgraefe BK. Reg IV activates the epidermal growth factor receptor/Akt/AP-1 signaling pathway in colon adenocarcinomas. *Gastroenterology* 2006; **130**: 137-149 [PMID: 16401477 DOI: 10.1053/j.gastro.2005.10.001]

116 **Takayama R**, Nakagawa H, Sawaki A, Mizuno N, Kawai H, Tajika M, Yatabe Y, Matsuo K, Uehara R, Ono K, Nakamura Y, Yamao K. Serum tumor antigen REG4 as a diagnostic biomarker in pancreatic ductal adenocarcinoma. *J Gastroenterol* 2010; **45**: 52-59 [PMID: 19789838 DOI: 10.1007/s00535-009-0114-y]

117 **Saukkonen K**, Hagström J, Mustonen H, Lehtinen L, Carpen O, Andersson LC, Seppänen H, Haglund C. Prognostic and diagnostic value of REG4 serum and tissue expression in pancreatic ductal adenocarcinoma. *Tumour Biol* 2018; **40**: 1010428318761494 [PMID: 29542402 DOI: 10.1177/1010428318761494]

118 **Antonin W**, Wagner M, Riedel D, Brose N, Jahn R. Loss of the zymogen granule protein syncollin affects pancreatic protein synthesis and transport but not secretion. *Mol Cell Biol* 2002; **22**: 1545-1554 [PMID: 11839820 DOI: 10.1128/MCB.22.5.1545-1554.2002]

119 **Kalus I**, Hodel A, Koch A, Kleene R, Edwardson JM, Schrader M. Interaction of syncollin with GP-2, the major membrane protein of pancreatic zymogen granules, and association with lipid microdomains. *Biochem J* 2002; **362**: 433-442 [PMID: 11853552 DOI: 10.1042/0264-6021:3620433]

120 **Grønborg M**, Bunkenborg J, Kristiansen TZ, Jensen ON, Yeo CJ, Hruban RH, Maitra A, Goggins MG, Pandey A. Comprehensive proteomic analysis of human pancreatic juice. *J Proteome Res* 2004; **3**: 1042-1055 [PMID: 15473694 DOI: 10.1021/pr0499085]

121 **Saito H**, Papaconstantinou J, Sato H, Goldstein S. Regulation of a novel gene encoding a lysyl oxidase-related protein in cellular adhesion and senescence. *J Biol Chem* 1997; **272**: 8157-8160 [PMID: 9079631 DOI: 10.1074/jbc.272.13.8157]

122 **Cano A**, Santamaría PG, Moreno-Bueno G. LOXL2 in epithelial cell plasticity and tumor progression. *Future Oncol* 2012; **8**: 1095-1108 [PMID: 23030485 DOI: 10.2217/fon.12.105]

123 **Zhang X**, Huang J, You F, Li W, Zou Z. Prognostic and clinicopathological significance of LOXL2 in cancers: A systematic review and meta-analysis. *J Cell Physiol* 2019; **234**: 21369-21379 [PMID: 31032923 DOI: 10.1002/jcp.28746]

124 **Cao J**, Lou S, Ying M, Yang B. DJ-1 as a human oncogene and potential therapeutic target. *Biochem Pharmacol* 2015; **93**: 241-250 [PMID: 25498803 DOI: 10.1016/j.bcp.2014.11.012]

125 **Vasseur S**, Afzal S, Tomasini R, Guillaumond F, Tardivel-Lacombe J, Mak TW, Iovanna JL. Consequences of DJ-1 upregulation following p53 Loss and cell transformation. *Oncogene* 2012; **31**: 664-670 [PMID: 21725356 DOI: 10.1038/onc.2011.268]

126 **He XY**, Liu BY, Yao WY, Zhao XJ, Zheng Z, Li JF, Yu BQ, Yuan YZ. Serum DJ-1 as a diagnostic marker and prognostic factor for pancreatic cancer. *J Dig Dis* 2011; **12**: 131-137 [PMID: 21401899 DOI: 10.1111/j.1751-2980.2011.00488.x]

127 **Zhang Z**, Bast RC Jr, Yu Y, Li J, Sokoll LJ, Rai AJ, Rosenzweig JM, Cameron B, Wang YY, Meng XY, Berchuck A, Van Haaften-Day C, Hacker NF, de Bruijn HW, van der Zee AG, Jacobs IJ, Fung ET, Chan DW. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res* 2004; **64**: 5882-5890 [PMID: 15313933 DOI: 10.1158/0008-5472.CAN-04-0746]

128 **Jacobsson B**. In situ localization of transthyretin-mRNA in the adult human liver, choroid plexus and pancreatic islets and in endocrine tumours of the pancreas and gut. *Histochemistry* 1989; **91**: 299-304 [PMID: 2659558 DOI: 10.1007/BF00493004]

129 **Ehmann M**, Felix K, Hartmann D, Schnölzer M, Nees M, Vorderwülbecke S, Bogumil R, Büchler MW, Friess H. Identification of potential markers for the detection of pancreatic cancer through comparative serum protein expression profiling. *Pancreas* 2007; **34**: 205-214 [PMID: 17312459 DOI: 10.1097/01.mpa.0000250128.57026.b2]

130 **Chen J**, Chen LJ, Xia YL, Zhou HC, Yang RB, Wu W, Lu Y, Hu LW, Zhao Y. Identification and verification of transthyretin as a potential biomarker for pancreatic ductal adenocarcinoma. *J Cancer Res Clin Oncol* 2013; **139**: 1117-1127 [PMID: 23546595 DOI: 10.1007/s00432-013-1422-4]

131 **Perry JK**, Kannan N, Grandison PM, Mitchell MD, Lobie PE. Are trefoil factors oncogenic? *Trends Endocrinol Metab* 2008; **19**: 74-81 [PMID: 18054496 DOI: 10.1016/j.tem.2007.10.003]

132 **Zhang CX**, Wu CT, Xiao L, Tang SH. The diagnostic and clinicopathological value of trefoil factor 3 in patients with gastric cancer: a systematic review and meta-analysis. *Biomarkers* 2021; **26**: 95-102 [PMID: 33401971 DOI: 10.1080/1354750X.2020.1871411]

133 **Taupin D**, Podolsky DK. Trefoil factors: initiators of mucosal healing. *Nat Rev Mol Cell Biol* 2003; **4**: 721-732 [PMID: 14506475 DOI: 10.1038/nrm1203]

134 **Jahan R**, Ganguly K, Smith LM, Atri P, Carmicheal J, Sheinin Y, Rachagani S, Natarajan G, Brand RE, Macha MA, Grandgenett PM, Kaur S, Batra SK. Trefoil factor(s) and CA19.9: A promising panel for early detection of pancreatic cancer. *EBioMedicine* 2019; **42**: 375-385 [PMID: 30956167 DOI: 10.1016/j.ebiom.2019.03.056]

135 **Weterman MA**, Ajubi N, van Dinter IM, Degen WG, van Muijen GN, Ruitter DJ, Bloemers HP. nmb, a novel gene, is expressed in low-metastatic human melanoma cell lines and xenografts. *Int J Cancer* 1995; **60**: 73-81 [PMID: 7814155 DOI: 10.1002/ijc.2910600111]

136 **Onaga M**, Ido A, Hasuike S, Uto H, Moriuchi A, Nagata K, Hori T, Hayash K, Tsubouchi H. Osteoactivin expressed during cirrhosis development in rats fed a choline-deficient, L-amino acid-defined diet, accelerates motility of hepatoma cells. *J Hepatol* 2003; **39**: 779-785 [PMID: 14568261 DOI: 10.1016/s0168-8278(03)00361-1]

137 **Rose AA**, Grosset AA, Dong Z, Russo C, Macdonald PA, Bertos NR, St-Pierre Y, Simantov R, Hallett M, Park M, Gaboury L, Siegel PM. Glycoprotein nonmetastatic B is an independent prognostic indicator of recurrence and a novel therapeutic target in breast cancer. *Clin Cancer Res* 2010; **16**: 2147-2156 [PMID: 20215530 DOI: 10.1158/1078-0432.CCR-09-1611]

138 **Torres C**, Perales S, Alejandre MJ, Iglesias J, Palomino RJ, Martin M, Caba O, Prados JC, Aránega A, Delgado JR, Irigoyen A, Ortuño FM, Rojas I, Linares A. Serum cytokine profile in patients with pancreatic cancer. *Pancreas* 2014; **43**: 1042-1049 [PMID: 24979617 DOI: 10.1097/MPA.0000000000000155]

139 **Cai CY**, Zhai LL, Wu Y, Tang ZG. Expression and clinical value of peroxiredoxin-1 in patients with pancreatic cancer. *Eur J Surg Oncol* 2015; **41**: 228-235 [PMID: 25434328 DOI: 10.1016/j.ejso.2014.11.037]

140 **Lwaleed BA**, Bass PS. Tissue factor pathway inhibitor: structure, biology and involvement in disease. *J Pathol* 2006; **208**: 327-339 [PMID: 16261634 DOI: 10.1002/path.1871]

141 **Balasenthil S**, Huang Y, Liu S, Marsh T, Chen J, Stass SA, KuKuruga D, Brand R, Chen N, Frazier ML, Jack Lee J, Srivastava S, Sen S, McNeill Killary A. A Plasma Biomarker Panel to Identify Surgically Resectable Early-Stage Pancreatic Cancer. *J Natl Cancer Inst* 2017; **109** [PMID: 28376184 DOI: 10.1093/jnci/djw341]

142 **Lee SJ**, Yoo HJ, Bae YS, Kim HJ, Lee ST. TIMP-1 inhibits apoptosis in breast carcinoma cells *via* a pathway involving pertussis toxin-sensitive G protein and c-Src. *Biochem Biophys Res Commun* 2003; **312**: 1196-1201 [PMID: 14652000 DOI: 10.1016/j.bbrc.2003.11.050]

143 **Hayakawa T**, Yamashita K, Tanzawa K, Uchijima E, Iwata K. Growth-promoting activity of tissue inhibitor of metalloproteinases-1 (TIMP-1) for a wide range of cells. A possible new growth factor in serum. *FEBS Lett* 1992; **298**: 29-32 [PMID: 1544418 DOI: 10.1016/0014-5793(92)80015-9]

144 **Joergensen MT**, Brünner N, De Muckadell OB. Comparison of circulating MMP-9, TIMP-1 and CA19-9 in the detection of pancreatic cancer. *Anticancer Res* 2010; **30**: 587-592 [PMID: 20332475]

145 **Mohan S**, Baylink DJ. IGF-binding proteins are multifunctional and act *via* IGF-dependent and -independent mechanisms. *J Endocrinol* 2002; **175**: 19-31 [PMID: 12379487 DOI: 10.1677/joe.0.1750019]

146 **Wolpin BM**, Michaud DS, Giovannucci EL, Schernhammer ES, Stampfer MJ, Manson JE, Cochrane BB, Rohan TE, Ma J, Pollak MN, Fuchs CS. Circulating insulin-like growth factor binding protein-1 and the risk of pancreatic cancer. *Cancer Res* 2007; **67**: 7923-7928 [PMID: 17699799 DOI: 10.1158/0008-5472.CAN-07-0373]

147 **Yoneyama T**, Ohtsuki S, Honda K, Kobayashi M, Iwasaki M, Uchida Y, Okusaka T, Nakamori S, Shimahara M, Ueno T, Tsuchida A, Sata N, Ioka T, Yasunami Y, Kosuge T, Kaneda T, Kato T, Yagihara K, Fujita S, Huang W, Yamada T, Tachikawa M, Terasaki T. Identification of IGFBP2 and IGFBP3 As Compensatory Biomarkers for CA19-9 in Early-Stage Pancreatic Cancer Using a Combination of Antibody-Based and LC-MS/MS-Based Proteomics. *PLoS One* 2016; **11**: e0161009 [PMID: 27579675 DOI: 10.1371/journal.pone.0161009]

148 **Kendrick ZW**, Firpo MA, Repko RC, Scaife CL, Adler DG, Boucher KM, Mulvihill SJ. Serum IGFBP2 and MSLN as diagnostic and prognostic biomarkers for pancreatic cancer. *HPB (Oxford)* 2014; **16**: 670-676 [PMID: 24308545 DOI: 10.1111/hpb.12199]

149 **Kim Y**, Kang M, Han D, Kim H, Lee K, Kim SW, Kim Y, Park T, Jang JY. Biomarker Development for Intraductal Papillary Mucinous Neoplasms Using Multiple Reaction Monitoring Mass Spectrometry. *J Proteome Res* 2016; **15**: 100-113 [PMID: 26561977 DOI: 10.1021/acs.jproteome.5b00553]

150 **Merle NS**, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement System Part II: Role in Immunity. *Front Immunol* 2015; **6**: 257 [PMID: 26074922 DOI: 10.3389/fimmu.2015.00257]

151 **Merle NS**, Church SE, Fremeaux-Bacchi V, Roumenina LT. Complement System Part I - Molecular Mechanisms of Activation and Regulation. *Front Immunol* 2015; **6**: 262 [PMID: 26082779 DOI: 10.3389/fimmu.2015.00262]

152 **Wingren C**, Sandström A, Segersvärd R, Carlsson A, Andersson R, Löhr M, Borrebaeck CA. Identification of serum biomarker signatures associated with pancreatic cancer. *Cancer Res* 2012; **72**: 2481-2490 [PMID: 22589272 DOI: 10.1158/0008-5472.CAN-11-2883]

153 **Johnston FM**, Tan MC, Tan BR Jr, Porembka MR, Brunt EM, Linehan DC, Simon PO Jr, Plambeck-Suess S, Eberlein TJ, Hellstrom KE, Hellstrom I, Hawkins WG, Goedegebuure P. Circulating mesothelin protein and cellular antimesothelin immunity in patients with pancreatic cancer. *Clin Cancer Res* 2009; **15**: 6511-6518 [PMID: 19843662 DOI: 10.1158/1078-0432.CCR-09-0565]

154 **Sharon E**, Zhang J, Hollevoet K, Steinberg SM, Pastan I, Onda M, Gaedcke J, Ghadimi BM, Ried T, Hassan R. Serum mesothelin and megakaryocyte potentiating factor in pancreatic and biliary cancers. *Clin Chem Lab Med* 2012; **50**: 721-725 [PMID: 22149739 DOI: 10.1515/CCLM.2011.816]

155 **Kuhlmann KF**, van Till JW, Boermeester MA, de Reuver PR, Tzvetanova ID, Offerhaus GJ, Ten Kate FJ, Busch OR, van Gulik TM, Gouma DJ, Crawford HC. Evaluation of matrix metalloproteinase 7 in plasma and pancreatic juice as a biomarker for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 886-891 [PMID: 17507610 DOI: 10.1158/1055-9965.EPI-06-0779]

156 **Park HD**, Kang ES, Kim JW, Lee KT, Lee KH, Park YS, Park JO, Lee J, Heo JS, Choi SH, Choi DW, Kim S, Lee JK, Lee SY. Serum CA19-9, cathepsin D, and matrix metalloproteinase-7 as a diagnostic panel for pancreatic ductal adenocarcinoma. *Proteomics* 2012; **12**: 3590-3597 [PMID: 23065739 DOI: 10.1002/pmic.201200101]

157 **Kahlert C**, Fiala M, Musso G, Halama N, Keim S, Mazzone M, Lasitschka F, Pecqueux M, Klupp F, Schmidt T, Rahbari N, Schölch S, Pilarsky C, Ulrich A, Schneider M, Weitz J, Koch M. Prognostic impact of a compartment-specific angiogenic marker profile in patients with pancreatic cancer. *Oncotarget* 2014; **5**: 12978-12989 [PMID: 25483099 DOI: 10.18632/oncotarget.2651]

158 **Tsuda E**, Goto M, Mochizuki S, Yano K, Kobayashi F, Morinaga T, Higashio K. Isolation of a novel cytokine from human fibroblasts that specifically inhibits osteoclastogenesis. *Biochem Biophys Res Commun* 1997; **234**: 137-142 [PMID: 9168977 DOI: 10.1006/bbrc.1997.6603]

159 **Holen I**, Cross SS, Neville-Webbe HL, Cross NA, Balasubramanian SP, Croucher PI, Evans CA, Lippitt JM, Coleman RE, Eaton CL. Osteoprotegerin (OPG) expression by breast cancer cells *in vitro* and breast tumours in vivo--a role in tumour cell survival? *Breast Cancer Res Treat* 2005; **92**: 207-215 [PMID: 16155791 DOI: 10.1007/s10549-005-2419-8]

160 **Brand RE**, Nolen BM, Zeh HJ, Allen PJ, Eloubeidi MA, Goldberg M, Elton E, Arnoletti JP, Christein JD, Vickers SM, Langmead CJ, Landsittel DP, Whitcomb DC, Grizzle WE, Lokshin AE. Serum biomarker panels for the detection of pancreatic cancer. *Clin Cancer Res* 2011; **17**: 805-816 [PMID: 21325298 DOI: 10.1158/1078-0432.CCR-10-0248]

161 **Nolen BM**, Brand RE, Prosser D, Velikokhatnaya L, Allen PJ, Zeh HJ, Grizzle WE, Huang Y, Lomakin A, Lokshin AE. Prediagnostic serum biomarkers as early detection tools for pancreatic cancer in a large prospective cohort study. *PLoS One* 2014; **9**: e94928 [PMID: 24747429 DOI: 10.1371/journal.pone.0094928]

162 **Lee JH**, Welch DR. Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KiSS-1. *Cancer Res* 1997; **57**: 2384-2387 [PMID:

9192814]
163 **Bhattacharya M**, Babwah AV. Kisspeptin: beyond the brain. *Endocrinology* 2015; **156**: 1218-1227 [PMID: 25590245 DOI: 10.1210/en.2014-1915]
164 **Ji K**, Ye L, Mason MD, Jiang WG. The Kiss-1/Kiss-1R complex as a negative regulator of cell motility and cancer metastasis (Review). *Int J Mol Med* 2013; **32**: 747-754 [PMID: 23969598 DOI: 10.3892/ijmm.2013.1472]
165 **Loosen SH**, Luedde M, Lurje G, Spehlmann M, Paffenholz P, Ulmer TF, Tacke F, Vucur M, Trautwein C, Neumann UP, Luedde T, Roderburg C. Serum Levels of Kisspeptin Are Elevated in Patients with Pancreatic Cancer. *Dis Markers* 2019; **2019**: 5603474 [PMID: 31772690 DOI: 10.1155/2019/5603474]
166 **Zhao W**, Ajani JA, Sushovan G, Ochi N, Hwang R, Hafley M, Johnson RL, Bresalier RS, Logsdon CD, Zhang Z, Song S. Galectin-3 Mediates Tumor Cell-Stroma Interactions by Activating Pancreatic Stellate Cells to Produce Cytokines via Integrin Signaling. *Gastroenterology* 2018; **154**: 1524-1537.e6 [PMID: 29274868 DOI: 10.1053/j.gastro.2017.12.014]
167 **Lee KM**, Nam K, Oh S, Lim J, Kim YP, Lee JW, Yu JH, Ahn SH, Kim SB, Noh DY, Lee T, Shin I. Extracellular matrix protein 1 regulates cell proliferation and trastuzumab resistance through activation of epidermal growth factor signaling. *Breast Cancer Res* 2014; **16**: 479 [PMID: 25499743 DOI: 10.1186/s13058-014-0479-6]
168 **Arfaoui-Toumi A**, Kria-Ben Mahmoud L, Ben Hmida M, Khalfallah MT, Regaya-Mzabi S, Bouraoui S. Implication of the Galectin-3 in colorectal cancer development (about 325 Tunisian patients). *Bull Cancer* 2010; **97**: E1-E8 [PMID: 20080461 DOI: 10.1684/bdc.2010.1032]
169 **Lin TW**, Chang HT, Chen CH, Lin SW, Hsu TL, Wong CH. Galectin-3 Binding Protein and Galectin-1 Interaction in Breast Cancer Cell Aggregation and Metastasis. *J Am Chem Soc* 2015; **137**: 9685-9693 [PMID: 26168351 DOI: 10.1021/jacs.5b04744]
170 **Xie L**, Ni WK, Chen XD, Xiao MB, Chen BY, He S, Lu CH, Li XY, Jiang F, Ni RZ. The expressions and clinical significances of tissue and serum galectin-3 in pancreatic carcinoma. *J Cancer Res Clin Oncol* 2012; **138**: 1035-1043 [PMID: 22367363 DOI: 10.1007/s00432-012-1178-2]
171 **Yi N**, Zhao X, Ji J, Xu M, Jiao Y, Qian T, Zhu S, Jiang F, Chen J, Xiao M. Serum galectin-3 as a biomarker for screening, early diagnosis, prognosis and therapeutic effect evaluation of pancreatic cancer. *J Cell Mol Med* 2020; **24**: 11583-11591 [PMID: 32886424 DOI: 10.1111/jcmm.15775]
172 **Reid CJ**, Harris A. Developmental expression of mucin genes in the human gastrointestinal system. *Gut* 1998; **42**: 220-226 [PMID: 9536947 DOI: 10.1136/gut.42.2.220]
173 **Wang S**, You L, Dai M, Zhao Y. Mucins in pancreatic cancer: A well-established but promising family for diagnosis, prognosis and therapy. *J Cell Mol Med* 2020; **24**: 10279-10289 [PMID: 32745356 DOI: 10.1111/jcmm.15684]
174 **Balagué C**, Audié JP, Porchet N, Real FX. In situ hybridization shows distinct patterns of mucin gene expression in normal, benign, and malignant pancreas tissues. *Gastroenterology* 1995; **109**: 953-964 [PMID: 7657125 DOI: 10.1016/0016-5085(95)90406-9]
175 **Balagué C**, Gambús G, Carrato C, Porchet N, Aubert JP, Kim YS, Real FX. Altered expression of MUC2, MUC4, and MUC5 mucin genes in pancreas tissues and cancer cell lines. *Gastroenterology* 1994; **106**: 1054-1061 [PMID: 8143972 DOI: 10.1016/0016-5085(94)90767-6]
176 **Gum JR Jr**, Crawley SC, Hicks JW, Szymkowski DE, Kim YS. MUC17, a novel membrane-tethered mucin. *Biochem Biophys Res Commun* 2002; **291**: 466-475 [PMID: 11855812 DOI: 10.1006/bbrc.2002.6475]
177 **Williams SJ**, McGuckin MA, Gotley DC, Eyre HJ, Sutherland GR, Antalis TM. Two novel mucin genes down-regulated in colorectal cancer identified by differential display. *Cancer Res* 1999; **59**: 4083-4089 [PMID: 10463611]
178 **Higuchi T**, Orita T, Nakanishi S, Katsuya K, Watanabe H, Yamasaki Y, Waga I, Nanayama T, Yamamoto Y, Munger W, Sun HW, Falk RJ, Jennette JC, Alcorta DA, Li H, Yamamoto T, Saito Y, Nakamura M. Molecular cloning, genomic structure, and expression analysis of MUC20, a novel mucin protein, up-regulated in injured kidney. *J Biol Chem* 2004; **279**: 1968-1979 [PMID: 14565953 DOI: 10.1074/jbc.M304558200]
179 **Itoh Y**, Kamata-Sakurai M, Denda-Nagai K, Nagai S, Tsuiji M, Ishii-Schrade K, Okada K, Goto A, Fukayama M, Irimura T. Identification and expression of human epiglycanin/MUC21: a novel transmembrane mucin. *Glycobiology* 2008; **18**: 74-83 [PMID: 17977904 DOI: 10.1093/glycob/cwm118]
180 **Wang S**, You L, Dai M, Zhao Y. Quantitative assessment of the diagnostic role of mucin family members in pancreatic cancer: a meta-analysis. *Ann Transl Med* 2021; **9**: 192 [PMID: 33708819 DOI: 10.21037/atm-20-5606]
181 **Kaur S**, Kumar S, Momi N, Sasson AR, Batra SK. Mucins in pancreatic cancer and its microenvironment. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 607-620 [PMID: 23856888 DOI: 10.1038/nrgastro.2013.120]
182 **Yue T**, Maupin KA, Fallon B, Li L, Partyka K, Anderson MA, Brenner DE, Kaul K, Zeh H, Moser AJ, Simeone DM, Feng Z, Brand RE, Haab BB. Enhanced discrimination of malignant from benign pancreatic disease by measuring the CA 19-9 antigen on specific protein carriers. *PLoS One* 2011; **6**: e29180 [PMID: 22220206 DOI: 10.1371/journal.pone.0029180]
183 **Gold DV**, Karanjawala Z, Modrak DE, Goldenberg DM, Hruban RH. PAM4-reactive MUC1 is a biomarker for early pancreatic adenocarcinoma. *Clin Cancer Res* 2007; **13**: 7380-7387 [PMID: 18094420 DOI: 10.1158/1078-0432.CCR-07-1488]

184 **Gold DV**, Lew K, Maliniak R, Hernandez M, Cardillo T. Characterization of monoclonal antibody PAM4 reactive with a pancreatic cancer mucin. *Int J Cancer* 1994; **57**: 204-210 [PMID: 7512537 DOI: 10.1002/ijc.2910570213]

185 **Gold DV**, Cardillo T, Goldenberg DM, Sharkey RM. Localization of pancreatic cancer with radiolabeled monoclonal antibody PAM4. *Crit Rev Oncol Hematol* 2001; **39**: 147-154 [PMID: 11418312 DOI: 10.1016/s1040-8428(01)00114-7]

186 **Shi C**, Merchant N, Newsome G, Goldenberg DM, Gold DV. Differentiation of pancreatic ductal adenocarcinoma from chronic pancreatitis by PAM4 immunohistochemistry. *Arch Pathol Lab Med* 2014; **138**: 220-228 [PMID: 24476519 DOI: 10.5858/arpa.2013-0056-OA]

187 **Gold DV**, Gaedcke J, Ghadimi BM, Goggins M, Hruban RH, Liu M, Newsome G, Goldenberg DM. PAM4 enzyme immunoassay alone and in combination with CA 19-9 for the detection of pancreatic adenocarcinoma. *Cancer* 2013; **119**: 522-528 [PMID: 22898932 DOI: 10.1002/cncr.27762]

188 **Cheng J**, Lv Z, Weng X, Ye S, Shen K, Li M, Qin Y, Hu C, Zhang C, Wu J, Zheng S. Hsp27 Acts as a Master Molecular Chaperone and Plays an Essential Role in Hepatocellular Carcinoma Progression. *Digestion* 2015; **92**: 192-202 [PMID: 26381739 DOI: 10.1159/000431254]

189 **Xu L**, Chen S, Bergan RC. MAPKAPK2 and HSP27 are downstream effectors of p38 MAP kinase-mediated matrix metalloproteinase type 2 activation and cell invasion in human prostate cancer. *Oncogene* 2006; **25**: 2987-2998 [PMID: 16407830 DOI: 10.1038/sj.onc.1209337]

190 **Melle C**, Ernst G, Escher N, Hartmann D, Schimmel B, Bleul A, Thieme H, Kaufmann R, Felix K, Friess HM, Settmacher U, Hommann M, Richter KK, Daffner W, Täubig H, Manger T, Claussen U, von Eggeling F. Protein profiling of microdissected pancreas carcinoma and identification of HSP27 as a potential serum marker. *Clin Chem* 2007; **53**: 629-635 [PMID: 17303689 DOI: 10.1373/clinchem.2006.079194]

191 **Liao WC**, Wu MS, Wang HP, Tien YW, Lin JT. Serum heat shock protein 27 is increased in chronic pancreatitis and pancreatic carcinoma. *Pancreas* 2009; **38**: 422-426 [PMID: 19214136 DOI: 10.1097/MPA.0b013e318198281d]

192 **Gansauge F**, Gansauge S, Parker N, Beger MI, Poch B, Link KH, Safi F, Beger HG. CAM 17.1--a new diagnostic marker in pancreatic cancer. *Br J Cancer* 1996; **74**: 1997-2002 [PMID: 8980403 DOI: 10.1038/bjc.1996.666]

193 **Parker N**, Makin CA, Ching CK, Eccleston D, Taylor OM, Milton JD, Rhodes JM. A new enzyme-linked lectin/mucin antibody sandwich assay (CAM 17.1/WGA) assessed in combination with CA 19-9 and peanut lectin binding assay for the diagnosis of pancreatic cancer. *Cancer* 1992; **70**: 1062-1068 [PMID: 1515982 DOI: 10.1002/1097-0142(19920901)70:5<1062::aid-cncr2820700509>3.0.co;2-p]

194 **Kamada Y**, Kinoshita N, Tsuchiya Y, Kobayashi K, Fujii H, Terao N, Kamihagi K, Koyama N, Yamada S, Daigo Y, Nakamura Y, Taniguchi N, Miyoshi E. Reevaluation of a lectin antibody ELISA kit for measuring fucosylated haptoglobin in various conditions. *Clin Chim Acta* 2013; **417**: 48-53 [PMID: 23262369 DOI: 10.1016/j.cca.2012.12.014]

195 **Miyoshi E**, Kamada Y. Application of glycoscience to the early detection of pancreatic cancer. *Cancer Sci* 2016; **107**: 1357-1362 [PMID: 27418030 DOI: 10.1111/cas.13011]

196 **Yokoi K**, Shih LC, Kobayashi R, Koomen J, Hawke D, Li D, Hamilton SR, Abbruzzese JL, Coombes KR, Fidler IJ. Serum amyloid A as a tumor marker in sera of nude mice with orthotopic human pancreatic cancer and in plasma of patients with pancreatic cancer. *Int J Oncol* 2005; **27**: 1361-1369 [PMID: 16211233]

197 **Bhagwat SV**, Lahdenranta J, Giordano R, Arap W, Pasqualini R, Shapiro LH. CD13/APN is activated by angiogenic signals and is essential for capillary tube formation. *Blood* 2001; **97**: 652-659 [PMID: 11157481 DOI: 10.1182/blood.v97.3.652]

198 **Kido A**, Krueger S, Haeckel C, Roessner A. Inhibitory effect of antisense aminopeptidase N (APN/CD13) cDNA transfection on the invasive potential of osteosarcoma cells. *Clin Exp Metastasis* 2003; **20**: 585-592 [PMID: 14669789 DOI: 10.1023/a:1027383729767]

199 **Curnis F**, Arrigoni G, Sacchi A, Fischetti L, Arap W, Pasqualini R, Corti A. Differential binding of drugs containing the NGR motif to CD13 isoforms in tumor vessels, epithelia, and myeloid cells. *Cancer Res* 2002; **62**: 867-874 [PMID: 11830545]

200 **Pang L**, Zhang N, Xia Y, Wang D, Wang G, Meng X. Serum APN/CD13 as a novel diagnostic and prognostic biomarker of pancreatic cancer. *Oncotarget* 2016; **7**: 77854-77864 [PMID: 27788483 DOI: 10.18632/oncotarget.12835]

201 **Vander Heiden MG**, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029-1033 [PMID: 19460998 DOI: 10.1126/science.1160809]

202 **Zhu H**, Wu J, Zhang W, Luo H, Shen Z, Cheng H, Zhu X. PKM2 enhances chemosensitivity to cisplatin through interaction with the mTOR pathway in cervical cancer. *Sci Rep* 2016; **6**: 30788 [PMID: 27492148 DOI: 10.1038/srep30788]

203 **Novotný I**, Dítě P, Dastych M, Záková A, Trna J, Novotná H, Nechutová H. Tumor marker M2-pyruvate-kinase in differential diagnosis of chronic pancreatitis and pancreatic cancer. *Hepatogastroenterology* 2008; **55**: 1475-1477 [PMID: 18795715]

204 **Ventrucci M**, Cipolla A, Racchini C, Casadei R, Simoni P, Gullo L. Tumor M2-pyruvate kinase, a new metabolic marker for pancreatic cancer. *Dig Dis Sci* 2004; **49**: 1149-1155 [PMID: 15387337 DOI: 10.1023/b:ddas.0000037803.32013.aa]

205 **Terentes-Printzios D**, Vlachopoulos C, Vyssoulis G, Alexopoulos N, Aznaouridis K, Ioakeimidis

N, Pietri P, Dima I, Samentzas A, Stefanadis C. Lipids, apolipoproteins and their ratios in relation to arterial stiffness in never-treated hypertensives. *Eur Heart J* 2010; **31**: 102-103

206 **Honda K**, Kobayashi M, Okusaka T, Rinaudo JA, Huang Y, Marsh T, Sanada M, Sasajima Y, Nakamori S, Shimahara M, Ueno T, Tsuchida A, Sata N, Ioka T, Yasunami Y, Kosuge T, Miura N, Kamita M, Sakamoto T, Shoji H, Jung G, Srivastava S, Yamada T. Plasma biomarker for detection of early stage pancreatic cancer and risk factors for pancreatic malignancy using antibodies for apolipoprotein-AII isoforms. *Sci Rep* 2015; **5**: 15921 [PMID: 26549697 DOI: 10.1038/srep15921]

207 **Honda K**, Katzke VA, Hüsing A, Okaya S, Shoji H, Onidani K, Olsen A, Tjønneland A, Overvad K, Weiderpass E, Vineis P, Muller D, Tsilidis K, Palli D, Pala V, Tumino R, Naccarati A, Panico S, Aleksandrova K, Boeing H, Bueno-de-Mesquita HB, Peeters PH, Trichopoulou A, Lagiou P, Khaw KT, Wareham N, Travis RC, Merino S, Duell EJ, Rodríguez-Barranco M, Chirlaque MD, Barricarte A, Rebours V, Boutron-Ruault MC, Romana Mancini F, Brennan P, Scelo G, Manjer J, Sund M, Öhlund D, Canzian F, Kaaks R. CA19-9 and apolipoprotein-A2 isoforms as detection markers for pancreatic cancer: a prospective evaluation. *Int J Cancer* 2019; **144**: 1877-1887 [PMID: 30259989 DOI: 10.1002/ijc.31900]

208 **Sato Y**, Kobayashi T, Nishiumi S, Okada A, Fujita T, Sanuki T, Kobayashi M, Asahara M, Adachi M, Sakai A, Shiomi H, Masuda A, Yoshida M, Takeuchi K, Kodama Y, Kutsumi H, Nagashima K, Honda K. Prospective Study Using Plasma Apolipoprotein A2-Isoforms to Screen for High-Risk Status of Pancreatic Cancer. *Cancers (Basel)* 2020; **12** [PMID: 32937962 DOI: 10.3390/cancers12092625]

209 **Takano S**, Yoshitomi H, Togawa A, Sogawa K, Shida T, Kimura F, Shimizu H, Tomonaga T, Nomura F, Miyazaki M. Apolipoprotein C-1 maintains cell survival by preventing from apoptosis in pancreatic cancer cells. *Oncogene* 2008; **27**: 2810-2822 [PMID: 18037960 DOI: 10.1038/sj.onc.1210951]

210 **Xue A**, Chang JW, Chung L, Samra J, Hugh T, Gill A, Butturini G, Baxter RC, Smith RC. Serum apolipoprotein C-II is prognostic for survival after pancreatic resection for adenocarcinoma. *Br J Cancer* 2012; **107**: 1883-1891 [PMID: 23169340 DOI: 10.1038/bjc.2012.458]

211 **Chen J**, Chen LJ, Yang RB, Xia YL, Zhou HC, Wu W, Lu Y, Hu LW, Zhao Y. Expression and clinical significance of apolipoprotein E in pancreatic ductal adenocarcinoma. *Med Oncol* 2013; **30**: 583 [PMID: 23609192 DOI: 10.1007/s12032-013-0583-y]

212 **Yu KH**, Rustgi AK, Blair IA. Characterization of proteins in human pancreatic cancer serum using differential gel electrophoresis and tandem mass spectrometry. *J Proteome Res* 2005; **4**: 1742-1751 [PMID: 16212428 DOI: 10.1021/pr050174l]

213 **Liu X**, Zheng W, Wang W, Shen H, Liu L, Lou W, Wang X, Yang P. A new panel of pancreatic cancer biomarkers discovered using a mass spectrometry-based pipeline. *Br J Cancer* 2017; **117**: 1846-1854 [PMID: 29123261 DOI: 10.1038/bjc.2017.365]

214 **Yako YY**, Kruger D, Smith M, Brand M. Cytokines as Biomarkers of Pancreatic Ductal Adenocarcinoma: A Systematic Review. *PLoS One* 2016; **11**: e0154016 [PMID: 27170998 DOI: 10.1371/journal.pone.0154016]

215 **Zhao J**, Liang Y, Yin Q, Liu S, Wang Q, Tang Y, Cao C. Clinical and prognostic significance of serum transforming growth factor-beta1 levels in patients with pancreatic ductal adenocarcinoma. *Braz J Med Biol Res* 2016; **49** [PMID: 27464025 DOI: 10.1590/1414-431X20165485]

216 **Ai KX**, Lu LY, Huang XY, Chen W, Zhang HZ. Prognostic significance of S100A4 and vascular endothelial growth factor expression in pancreatic cancer. *World J Gastroenterol* 2008; **14**: 1931-1935 [PMID: 18350635 DOI: 10.3748/wjg.14.1931]

217 **Abdel-Razik A**, ElMahdy Y, Hanafy EE, Elhelaly R, Elzehery R, M Tawfik A, Eldars W. Insulin-Like Growth Factor-1 and Vascular Endothelial Growth Factor in Malignant and Benign Biliary Obstructions. *Am J Med Sci* 2016; **351**: 259-264 [PMID: 26992254 DOI: 10.1016/j.amjms.2015.12.013]

218 **Bhushan A**, Itoh N, Kato S, Thiery JP, Czernichow P, Bellusci S, Scharfmann R. Fgf10 is essential for maintaining the proliferative capacity of epithelial progenitor cells during early pancreatic organogenesis. *Development* 2001; **128**: 5109-5117 [PMID: 11748146]

219 **Nomura S**, Yoshitomi H, Takano S, Shida T, Kobayashi S, Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Miyazaki M. FGF10/FGFR2 signal induces cell migration and invasion in pancreatic cancer. *Br J Cancer* 2008; **99**: 305-313 [PMID: 18594526 DOI: 10.1038/sj.bjc.6604473]

220 **Shaw VE**, Lane B, Jenkinson C, Cox T, Greenhalf W, Halloran CM, Tang J, Sutton R, Neoptolemos JP, Costello E. Serum cytokine biomarker panels for discriminating pancreatic cancer from benign pancreatic disease. *Mol Cancer* 2014; **13**: 114 [PMID: 24884871 DOI: 10.1186/1476-4598-13-114]

221 **Jiang JT**, Wu CP, Deng HF, Lu MY, Wu J, Zhang HY, Sun WH, Ji M. Serum level of TSGF, CA242 and CA19-9 in pancreatic cancer. *World J Gastroenterol* 2004; **10**: 1675-1677 [PMID: 15162550 DOI: 10.3748/wjg.v10.i11.1675]

222 **Chen Y**, Gao SG, Chen JM, Wang GP, Wang ZF, Zhou B, Jin CH, Yang YT, Feng XS. Serum CA242, CA199, CA125, CEA, and TSGF are Biomarkers for the Efficacy and Prognosis of Cryoablation in Pancreatic Cancer Patients. *Cell Biochem Biophys* 2015; **71**: 1287-1291 [PMID: 25486903 DOI: 10.1007/s12013-014-0345-2]

223 **Bootcov MR**, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, Zhang HP, Donnellan M, Mahler S, Pryor K, Walsh BJ, Nicholson RC, Fairlie WD, Por SB, Robbins JM, Breit SN. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. *Proc Natl Acad Sci USA* 1997; **94**: 11514-11519 [PMID: 9326641 DOI: 10.1073/pnas.94.21.11514]

224 **Fairlie WD**, Zhang HP, Wu WM, Pankhurst SL, Bauskin AR, Russell PK, Brown PK, Breit SN. The propeptide of the transforming growth factor-beta superfamily member, macrophage inhibitory cytokine-1 (MIC-1), is a multifunctional domain that can facilitate protein folding and secretion. *J Biol Chem* 2001; **276**: 16911-16918 [PMID: 11278594 DOI: 10.1074/jbc.M010000200]

225 **Skipworth RJ**, Deans DA, Tan BH, Sangster K, Paterson-Brown S, Brown DA, Hunter M, Breit SN, Ross JA, Fearon KC. Plasma MIC-1 correlates with systemic inflammation but is not an independent determinant of nutritional status or survival in oesophago-gastric cancer. *Br J Cancer* 2010; **102**: 665-672 [PMID: 20104227 DOI: 10.1038/sj.bjc.6605532]

226 **Kempf T**, von Haehling S, Peter T, Allhoff T, Cicoira M, Doehner W, Ponikowski P, Filippatos GS, Rozentryt P, Drexler H, Anker SD, Wollert KC. Prognostic utility of growth differentiation factor-15 in patients with chronic heart failure. *J Am Coll Cardiol* 2007; **50**: 1054-1060 [PMID: 17825714 DOI: 10.1016/j.jacc.2007.04.091]

227 **Yang Y**, Yan S, Tian H, Bao Y. Macrophage inhibitory cytokine-1 *vs* carbohydrate antigen 19-9 as a biomarker for diagnosis of pancreatic cancer: A PRISMA-compliant meta-analysis of diagnostic accuracy studies. *Medicine (Baltimore)* 2018; **97**: e9994 [PMID: 29489701 DOI: 10.1097/MD.0000000000009994]

228 **O'Neill RS**, Emmanuel S, Williams D, Stoita A. Macrophage inhibitory cytokine-1/growth differentiation factor-15 in premalignant and neoplastic tumours in a high-risk pancreatic cancer cohort. *World J Gastroenterol* 2020; **26**: 1660-1673 [PMID: 32327914 DOI: 10.3748/wjg.v26.i14.1660]

229 **Ren C**, Chen Y, Han C, Fu D, Chen H. Plasma interleukin-11 (IL-11) levels have diagnostic and prognostic roles in patients with pancreatic cancer. *Tumour Biol* 2014; **35**: 11467-11472 [PMID: 25123265 DOI: 10.1007/s13277-014-2459-y]

230 **Mroczko B**, Groblewska M, Gryko M, Kedra B, Szmitkowski M. Diagnostic usefulness of serum interleukin 6 (IL-6) and C-reactive protein (CRP) in the differentiation between pancreatic cancer and chronic pancreatitis. *J Clin Lab Anal* 2010; **24**: 256-261 [PMID: 20626020 DOI: 10.1002/jcla.20395]

231 **Okada S**, Okusaka T, Ishii H, Kyogoku A, Yoshimori M, Kajimura N, Yamaguchi K, Kakizoe T. Elevated serum interleukin-6 levels in patients with pancreatic cancer. *Jpn J Clin Oncol* 1998; **28**: 12-15 [PMID: 9491135 DOI: 10.1093/jjco/28.1.12]

232 **Schultz NA**, Christensen IJ, Werner J, Giese N, Jensen BV, Larsen O, Bjerregaard JK, Pfeiffer P, Calatayud D, Nielsen SE, Yilmaz MK, Holländer NH, Wøjdemann M, Bojesen SE, Nielsen KR, Johansen JS. Diagnostic and Prognostic Impact of Circulating YKL-40, IL-6, and CA 19.9 in Patients with Pancreatic Cancer. *PLoS One* 2013; **8**: e67059 [PMID: 23840582 DOI: 10.1371/journal.pone.0067059]

233 **Koca YS**, Bulbul M, Barut I. The Diagnostic Roles of Cytokines in Hepatobiliary Cancers. *Biomed Res Int* 2017; **2017**: 2979307 [PMID: 29410961 DOI: 10.1155/2017/2979307]

234 **Chen Y**, Shi M, Yu GZ, Qin XR, Jin G, Chen P, Zhu MH. Interleukin-8, a promising predictor for prognosis of pancreatic cancer. *World J Gastroenterol* 2012; **18**: 1123-1129 [PMID: 22416189 DOI: 10.3748/wjg.v18.i10.1123]

235 **Sakamoto H**, Kimura H, Sekijima M, Matsumoto K, Arao T, Chikugo T, Yamada Y, Kitano M, Ito A, Takeyama Y, Kudo M, Nishio K. Plasma concentrations of angiogenesis-related molecules in patients with pancreatic cancer. *Jpn J Clin Oncol* 2012; **42**: 105-112 [PMID: 22167663 DOI: 10.1093/jjco/hyr178]

236 **West NR**, Murray JI, Watson PH. Oncostatin-M promotes phenotypic changes associated with mesenchymal and stem cell-like differentiation in breast cancer. *Oncogene* 2014; **33**: 1485-1494 [PMID: 23584474 DOI: 10.1038/onc.2013.105]

237 **Queen MM**, Ryan RE, Holzer RG, Keller-Peck CR, Jorcyk CL. Breast cancer cells stimulate neutrophils to produce oncostatin M: potential implications for tumor progression. *Cancer Res* 2005; **65**: 8896-8904 [PMID: 16204061 DOI: 10.1158/0008-5472.CAN-05-1734]

238 **Benson DD**, Meng X, Fullerton DA, Moore EE, Lee JH, Ao L, Silliman CC, Barnett CC Jr. Activation state of stromal inflammatory cells in murine metastatic pancreatic adenocarcinoma. *Am J Physiol Regul Integr Comp Physiol* 2012; **302**: R1067-R1075 [PMID: 22422663 DOI: 10.1152/ajpregu.00320.2011]

239 **Litman-Zawadzka A**, Łukaszewicz-Zając M, Gryko M, Kulczyńska-Przybik A, Mroczko B. Serum chemokine CXCL8 as a better biomarker for diagnosis and prediction of pancreatic cancer than its specific receptor CXCR2, C-reactive protein, and classic tumor markers CA 19-9 and CEA. *Pol Arch Intern Med* 2018; **128**: 524-531 [PMID: 30057378 DOI: 10.20452/pamw.4307]

240 **Błogowski W**, Deskur A, Budkowska M, Sałata D, Madej-Michniewicz A, Dąbkowski K, Dołęgowska B, Starzyńska T. Selected cytokines in patients with pancreatic cancer: a preliminary report. *PLoS One* 2014; **9**: e97613 [PMID: 24849506 DOI: 10.1371/journal.pone.0097613]

241 **Zhang P**, Zou M, Wen X, Gu F, Li J, Liu G, Dong J, Deng X, Gao J, Li X, Jia X, Dong Z, Chen L, Wang Y, Tian Y. Development of serum parameters panels for the early detection of pancreatic cancer. *Int J Cancer* 2014; **134**: 2646-2655 [PMID: 24615168 DOI: 10.1002/ijc.28584]

242 **Dima SO**, Tanase C, Albulescu R, Herlea V, Chivu-Economescu M, Purnichescu-Purtan R, Dumitrascu T, Duda DG, Popescu I. An exploratory study of inflammatory cytokines as prognostic biomarkers in patients with ductal pancreatic adenocarcinoma. *Pancreas* 2012; **41**: 1001-1007 [PMID: 22722257 DOI: 10.1097/MPA.0b013e3182546e13]

243 **Gabitass RF**, Annels NE, Stocken DD, Pandha HA, Middleton GW. Elevated myeloid-derived

suppressor cells in pancreatic, esophageal and gastric cancer are an independent prognostic factor and are associated with significant elevation of the Th2 cytokine interleukin-13. *Cancer Immunol Immunother* 2011; **60**: 1419-1430 [PMID: 21644036 DOI: 10.1007/s00262-011-1028-0]

244 **Miekus K**, Jarocha D, Trzyna E, Majka M. Role of I-TAC-binding receptors CXCR3 and CXCR7 in proliferation, activation of intracellular signaling pathways and migration of various tumor cell lines. *Folia Histochem Cytobiol* 2010; **48**: 104-111 [PMID: 20529825 DOI: 10.2478/v10042-008-0091-7]

245 **Yasuda A**, Sawai H, Takahashi H, Ochi N, Matsuo Y, Funahashi H, Sato M, Okada Y, Takeyama H, Manabe T. The stem cell factor/c-kit receptor pathway enhances proliferation and invasion of pancreatic cancer cells. *Mol Cancer* 2006; **5**: 46 [PMID: 17044945 DOI: 10.1186/1476-4598-5-46]

246 **Mroczko B**, Szmitkowski M, Wereszczyńska-Siemiatkowska U, Jurkowska G. Hematopoietic cytokines in the sera of patients with pancreatic cancer. *Clin Chem Lab Med* 2005; **43**: 146-150 [PMID: 15843207 DOI: 10.1515/CCLM.2005.024]

247 **Mroczko B**, Szmitkowski M, Wereszczynska-Siemiatkowska U, Jurkowska G. Stem cell factor and macrophage-colony stimulating factor in patients with pancreatic cancer. *Clin Chem Lab Med* 2004; **42**: 256-260 [PMID: 15080556 DOI: 10.1515/CCLM.2004.047]

248 **Mroczko B**, Szmitkowski M, Wereszczyńska-Siemiatkowska U, Okulczyk B, Kedra B. Pretreatment serum levels of hematopoietic cytokines in patients with colorectal adenomas and cancer. *Int J Colorectal Dis* 2007; **22**: 33-38 [PMID: 16520929 DOI: 10.1007/s00384-006-0099-4]

249 **Gutierrez-Ramos JC**, Lloyd C, Gonzalo JA. Eotaxin: from an eosinophilic chemokine to a major regulator of allergic reactions. *Immunol Today* 1999; **20**: 500-504 [PMID: 10529777 DOI: 10.1016/s0167-5699(99)01522-4]

250 **Zeh HJ**, Winikoff S, Landsittel DP, Gorelik E, Marrangoni AM, Velikokhatnaya L, Winans MT, Lee K, Moser A, Bartlett D, Lotze MT, Siegfried JM, Whitcomb D, Papacristou G, Slivka A, Bigbee WL, Lokshin AE. Multianalyte profiling of serum cytokines for detection of pancreatic cancer. *Cancer Biomark* 2005; **1**: 259-269 [PMID: 17192050 DOI: 10.3233/cbm-2005-1601]

251 **Gebauer F**, Wicklein D, Horst J, Sundermann P, Maar H, Streichert T, Tachezy M, Izbicki JR, Bockhorn M, Schumacher U. Carcinoembryonic antigen-related cell adhesion molecules (CEACAM) 1, 5 and 6 as biomarkers in pancreatic cancer. *PLoS One* 2014; **9**: e113023 [PMID: 25409014 DOI: 10.1371/journal.pone.0113023]

252 **Arabzadeh A**, Chan C, Nouvion AL, Breton V, Benlolo S, DeMarte L, Turbide C, Brodt P, Ferri L, Beauchemin N. Host-related carcinoembryonic antigen cell adhesion molecule 1 promotes metastasis of colorectal cancer. *Oncogene* 2013; **32**: 849-860 [PMID: 22469976 DOI: 10.1038/onc.2012.112]

253 **Simeone DM**, Ji B, Banerjee M, Arumugam T, Li D, Anderson MA, Bamberger AM, Greenson J, Brand RE, Ramachandran V, Logsdon CD. CEACAM1, a novel serum biomarker for pancreatic cancer. *Pancreas* 2007; **34**: 436-443 [PMID: 17446843 DOI: 10.1097/MPA.0b013e3180333ae3]

254 **Gong DY**, Fu HX, Peng Y, You YQ, Li ZP. [Diagnostic value of serum CEACAM1 in patients with pancreatic cancer]. *Nan Fang Yi Ke Da Xue Xue Bao* 2011; **31**: 164-166 [PMID: 21269981]

255 **Dankner M**, Gray-Owen SD, Huang YH, Blumberg RS, Beauchemin N. CEACAM1 as a multi-purpose target for cancer immunotherapy. *Oncoimmunology* 2017; **6**: e1328336 [PMID: 28811966 DOI: 10.1080/2162402X.2017.1328336]

256 **Chiang WF**, Cheng TM, Chang CC, Pan SH, Changou CA, Chang TH, Lee KH, Wu SY, Chen YF, Chuang KH, Shieh DB, Chen YL, Tu CC, Tsui WL, Wu MH. Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) promotes EGF receptor signaling of oral squamous cell carcinoma metastasis *via* the complex N-glycosylation. *Oncogene* 2018; **37**: 116-127 [PMID: 28892050 DOI: 10.1038/onc.2017.303]

257 **Duxbury MS**, Matros E, Clancy T, Bailey G, Doff M, Zinner MJ, Ashley SW, Maitra A, Redston M, Whang EE. CEACAM6 is a novel biomarker in pancreatic adenocarcinoma and PanIN lesions. *Ann Surg* 2005; **241**: 491-496 [PMID: 15729073 DOI: 10.1097/01.sla.0000154455.86404.e9]

258 **Pandey R**, Zhou M, Islam S, Chen B, Barker NK, Langlais P, Srivastava A, Luo M, Cooke LS, Weterings E, Mahadevan D. Carcinoembryonic antigen cell adhesion molecule 6 (CEACAM6) in Pancreatic Ductal Adenocarcinoma (PDA): An integrative analysis of a novel therapeutic target. *Sci Rep* 2019; **9**: 18347 [PMID: 31797958 DOI: 10.1038/s41598-019-54545-9]

259 **Blumenthal RD**, Leon E, Hansen HJ, Goldenberg DM. Expression patterns of CEACAM5 and CEACAM6 in primary and metastatic cancers. *BMC Cancer* 2007; **7**: 2 [PMID: 17201906 DOI: 10.1186/1471-2407-7-2]

260 **Beauchemin N**, Arabzadeh A. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in cancer progression and metastasis. *Cancer Metastasis Rev* 2013; **32**: 643-671 [PMID: 23903773 DOI: 10.1007/s10555-013-9444-6]

261 **Roland CL**, Dineen SP, Toombs JE, Carbon JG, Smith CW, Brekken RA, Barnett CC Jr. Tumor-derived intercellular adhesion molecule-1 mediates tumor-associated leukocyte infiltration in orthotopic pancreatic xenografts. *Exp Biol Med (Maywood)* 2010; **235**: 263-270 [PMID: 20404043 DOI: 10.1258/ebm.2009.009215]

262 **mohamed A**, Saad Y, Saleh D, Elawady R, Eletreby R, Kharalla AS, Badr E. Can Serum ICAM 1 distinguish pancreatic cancer from chronic pancreatitis? *Asian Pac J Cancer Prev* 2016; **17**: 4671-4675 [PMID: 27892682 DOI: 10.22034/apjcp.2016.17.10.4671]

263 **Markocka-Maczka K**. [Concentration of serum soluble forms of ICAM-1 (sVCAM-1) and VCAM-1 (sVCAM-1) in patients with chronic pancreatitis and in patients with pancreatic carcinoma]. *Wiad Lek* 2003; **56**: 147-151 [PMID: 12923961]

264 **Cabili MN**, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, Rinn JL. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. *Genes Dev* 2011; **25**: 1915-1927 [PMID: 21890647 DOI: 10.1101/gad.17446611]

265 **McDonel P**, Guttman M. Approaches for Understanding the Mechanisms of Long Noncoding RNA Regulation of Gene Expression. *Cold Spring Harb Perspect Biol* 2019; **11** [PMID: 31791999 DOI: 10.1101/cshperspect.a032151]

266 **Chi Y**, Wang D, Wang J, Yu W, Yang J. Long Non-Coding RNA in the Pathogenesis of Cancers. *Cells* 2019; **8** [PMID: 31480503 DOI: 10.3390/cells8091015]

267 **Lv Y**, Huang S. Role of non-coding RNA in pancreatic cancer. *Oncol Lett* 2019; **18**: 3963-3973 [PMID: 31579086 DOI: 10.3892/ol.2019.10758]

268 **Xiong G**, Liu C, Yang G, Feng M, Xu J, Zhao F, You L, Zhou L, Zheng L, Hu Y, Wang X, Zhang T, Zhao Y. Long noncoding RNA GSTM3TV2 upregulates LAT2 and OLR1 by competitively sponging let-7 to promote gemcitabine resistance in pancreatic cancer. *J Hematol Oncol* 2019; **12**: 97 [PMID: 31514732 DOI: 10.1186/s13045-019-0777-7]

269 **Xiong G**, Feng M, Yang G, Zheng S, Song X, Cao Z, You L, Zheng L, Hu Y, Zhang T, Zhao Y. The underlying mechanisms of non-coding RNAs in the chemoresistance of pancreatic cancer. *Cancer Lett* 2017; **397**: 94-102 [PMID: 28254409 DOI: 10.1016/j.canlet.2017.02.020]

270 **Hu H**, Wang Y, Ding X, He Y, Lu Z, Wu P, Tian L, Yuan H, Liu D, Shi G, Xia T, Yin J, Cai B, Miao Y, Jiang K. Long non-coding RNA XLOC_000647 suppresses progression of pancreatic cancer and decreases epithelial-mesenchymal transition-induced cell invasion by down-regulating NLRP3. *Mol Cancer* 2018; **17**: 18 [PMID: 29386037 DOI: 10.1186/s12943-018-0761-9]

271 **Wang Y**, Zhou L, Lu J, Jiang B, Liu C, Guo J, Xiao GG. Research progress on long non-coding RNAs and their roles as potential biomarkers for diagnosis and prognosis in pancreatic cancer. *Cancer Cell Int* 2020; **20**: 457 [PMID: 32973402 DOI: 10.1186/s12935-020-01550-y]

272 **Yu S**, Li Y, Liao Z, Wang Z, Qian L, Zhao J, Zong H, Kang B, Zou WB, Chen K, He X, Meng Z, Chen Z, Huang S, Wang P. Plasma extracellular vesicle long RNA profiling identifies a diagnostic signature for the detection of pancreatic ductal adenocarcinoma. *Gut* 2020; **69**: 540-550 [PMID: 31562239 DOI: 10.1136/gutjnl-2019-318860]

273 **Baradaran B**, Shahbazi R, Khordadmehr M. Dysregulation of key microRNAs in pancreatic cancer development. *Biomed Pharmacother* 2019; **109**: 1008-1015 [PMID: 30551350 DOI: 10.1016/j.biopha.2018.10.177]

274 **Chen X**, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Zen K, Zhang CY. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 2008; **18**: 997-1006 [PMID: 18766170 DOI: 10.1038/cr.2008.282]

275 **Weber JA**, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, Galas DJ, Wang K. The microRNA spectrum in 12 body fluids. *Clin Chem* 2010; **56**: 1733-1741 [PMID: 20847327 DOI: 10.1373/clinchem.2010.147405]

276 **Sun X**, Zhou X, Zhang Y, Zhu X, Liu H. Systematic Review and Meta-Analysis of Diagnostic Accuracy of miRNAs in Patients with Pancreatic Cancer. *Dis Markers* 2018; **2018**: 6292396 [PMID: 29887920 DOI: 10.1155/2018/6292396]

277 **Li L**, Zhang GQ, Chen H, Zhao ZJ, Chen HZ, Liu H, Wang G, Jia YH, Pan SH, Kong R, Wang YW, Sun B. Plasma and tumor levels of Linc-pint are diagnostic and prognostic biomarkers for pancreatic cancer. *Oncotarget* 2016; **7**: 71773-71781 [PMID: 27708234 DOI: 10.18632/oncotarget.12365]

278 **Guo XB**, Yin HS, Wang JY. Evaluating the diagnostic and prognostic value of long non-coding RNA SNHG15 in pancreatic ductal adenocarcinoma. *Eur Rev Med Pharmacol Sci* 2018; **22**: 5892-5898 [PMID: 30280769 DOI: 10.26355/eurrev_201809_15917]

279 **Shuai Y**, Ma Z, Lu J, Feng J. LncRNA SNHG15: A new budding star in human cancers. *Cell Prolif* 2020; **53**: e12716 [PMID: 31774607 DOI: 10.1111/cpr.12716]

280 **Lu H**, Ye J, Zhang L, Li M, Lu S, Yang D, Hu W. Downregulation of LINC01638 lncRNA inhibits migration and invasion of pancreatic ductal adenocarcinoma cells by reducing TGFβ signaling. *Mol Med Rep* 2019; **20**: 4533-4539 [PMID: 31702018 DOI: 10.3892/mmr.2019.10699]

281 **Liu Y**, Feng W, Liu W, Kong X, Li L, He J, Wang D, Zhang M, Zhou G, Xu W, Chen W, Gong A, Xu M. Circulating lncRNA ABHD11-AS1 serves as a biomarker for early pancreatic cancer diagnosis. *J Cancer* 2019; **10**: 3746-3756 [PMID: 31333792 DOI: 10.7150/jca.32052]

282 **Takahashi K**, Ota Y, Kogure T, Suzuki Y, Iwamoto H, Yamakita K, Kitano Y, Fujii S, Haneda M, Patel T, Ota T. Circulating extracellular vesicle-encapsulated HULC is a potential biomarker for human pancreatic cancer. *Cancer Sci* 2020; **111**: 98-111 [PMID: 31715081 DOI: 10.1111/cas.14232]

283 **Ou ZL**, Luo Z, Lu YB. Long non-coding RNA HULC as a diagnostic and prognostic marker of pancreatic cancer. *World J Gastroenterol* 2019; **25**: 6728-6742 [PMID: 31857775 DOI: 10.3748/wjg.v25.i46.6728]

284 **Liu P**, Sun QQ, Liu TX, Lu K, Zhang N, Zhu Y, Chen M. Serum lncRNA-UFC1 as a potential biomarker for diagnosis and prognosis of pancreatic cancer. *Int J Clin Exp Pathol* 2019; **12**: 4125-4129 [PMID: 31933809]

285 **Wang J**, Chen J, Chang P, LeBlanc A, Li D, Abbruzzesse JL, Frazier ML, Killary AM, Sen S. MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. *Cancer Prev Res (Phila)* 2009; **2**: 807-813 [PMID: 19723895 DOI:

10.1158/1940-6207.CAPR-09-0094]
286 **Alemar B**, Izetti P, Gregório C, Macedo GS, Castro MA, Osvaldt AB, Matte U, Ashton-Prolla P. miRNA-21 and miRNA-34a Are Potential Minimally Invasive Biomarkers for the Diagnosis of Pancreatic Ductal Adenocarcinoma. *Pancreas* 2016; **45**: 84-92 [PMID: 26262588 DOI: 10.1097/MPA.0000000000000383]
287 **Abue M**, Yokoyama M, Shibuya R, Tamai K, Yamaguchi K, Sato I, Tanaka N, Hamada S, Shimosegawa T, Sugamura K, Satoh K. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. *Int J Oncol* 2015; **46**: 539-547 [PMID: 25384963 DOI: 10.3892/ijo.2014.2743]
288 **Yu Y**, Tong Y, Zhong A, Wang Y, Lu R, Guo L. Identification of Serum microRNA-25 as a novel biomarker for pancreatic cancer. *Medicine (Baltimore)* 2020; **99**: e23863 [PMID: 33350781 DOI: 10.1097/MD.0000000000023863]
289 **Guz M**, Jeleniewicz W, Cybulski M, Kozicka J, Kurzepa J, Mądro A. Serum miR-210-3p can be used to differentiate between patients with pancreatic ductal adenocarcinoma and chronic pancreatitis. *Biomed Rep* 2021; **14**: 10 [PMID: 33235725 DOI: 10.3892/br.2020.1386]
290 **Dai X**, Pang W, Zhou Y, Yao W, Xia L, Wang C, Chen X, Zen K, Zhang CY, Yuan Y. Altered profile of serum microRNAs in pancreatic cancer-associated new-onset diabetes mellitus. *J Diabetes* 2016; **8**: 422-433 [PMID: 25991015 DOI: 10.1111/1753-0407.12313]
291 **Ho AS**, Huang X, Cao H, Christman-Skieller C, Bennewith K, Le QT, Koong AC. Circulating miR-210 as a Novel Hypoxia Marker in Pancreatic Cancer. *Transl Oncol* 2010; **3**: 109-113 [PMID: 20360935 DOI: 10.1593/tlo.09256]
292 **Cote GA**, Gore AJ, McElyea SD, Heathers LE, Xu H, Sherman S, Korc M. A pilot study to develop a diagnostic test for pancreatic ductal adenocarcinoma based on differential expression of select miRNA in plasma and bile. *Am J Gastroenterol* 2014; **109**: 1942-1952 [PMID: 25350767 DOI: 10.1038/ajg.2014.331]
293 **Shi Q**, Feng K, Xia L, Wang C, Zhu J. Combined use of Serum miR-499a-5p and CA199 Increases the Diagnostic Sensitivity of Pancreatic Cancer. *Clin Lab* 2019; **65** [PMID: 31710444 DOI: 10.7754/Clin.Lab.2019.190416]
294 **Yan Q**, Hu D, Li M, Chen Y, Wu X, Ye Q, Wang Z, He L, Zhu J. The Serum MicroRNA Signatures for Pancreatic Cancer Detection and Operability Evaluation. *Front Bioeng Biotechnol* 2020; **8**: 379 [PMID: 32411694 DOI: 10.3389/fbioe.2020.00379]
295 **Liu R**, Chen X, Du Y, Yao W, Shen L, Wang C, Hu Z, Zhuang R, Ning G, Zhang C, Yuan Y, Li Z, Zen K, Ba Y, Zhang CY. Serum microRNA expression profile as a biomarker in the diagnosis and prognosis of pancreatic cancer. *Clin Chem* 2012; **58**: 610-618 [PMID: 22194634 DOI: 10.1373/clinchem.2011.172767]
296 **Morimura R**, Komatsu S, Ichikawa D, Takeshita H, Tsujiura M, Nagata H, Konishi H, Shiozaki A, Ikoma H, Okamoto K, Ochiai T, Taniguchi H, Otsuji E. Novel diagnostic value of circulating miR-18a in plasma of patients with pancreatic cancer. *Br J Cancer* 2011; **105**: 1733-1740 [PMID: 22045190 DOI: 10.1038/bjc.2011.453]
297 **Johansen JS**, Calatayud D, Albieri V, Schultz NA, Dehlendorff C, Werner J, Jensen BV, Pfeiffer P, Bojesen SE, Giese N, Nielsen KR, Nielsen SE, Yilmaz M, Holländer NH, Andersen KK. The potential diagnostic value of serum microRNA signature in patients with pancreatic cancer. *Int J Cancer* 2016; **139**: 2312-2324 [PMID: 27464352 DOI: 10.1002/ijc.30291]
298 **Duell EJ**, Lujan-Barroso L, Sala N, Deitz McElyea S, Overvad K, Tjonneland A, Olsen A, Weiderpass E, Busund LT, Moi L, Muller D, Vineis P, Aune D, Matullo G, Naccarati A, Panico S, Tagliabue G, Tumino R, Palli D, Kaaks R, Katzke VA, Boeing H, Bueno-de-Mesquita HBA, Peeters PH, Trichopoulou A, Lagiou P, Kotanidou A, Travis RC, Wareham N, Khaw KT, Ramon Quiros J, Rodríguez-Barranco M, Dorronsoro M, Chirlaque MD, Ardanaz E, Severi G, Boutron-Ruault MC, Rebours V, Brennan P, Gunter M, Scelo G, Cote G, Sherman S, Korc M. Plasma microRNAs as biomarkers of pancreatic cancer risk in a prospective cohort study. *Int J Cancer* 2017; **141**: 905-915 [PMID: 28542740 DOI: 10.1002/ijc.30790]
299 **Ganepola GA**, Rutledge JR, Suman P, Yiengpruksawan A, Chang DH. Novel blood-based microRNA biomarker panel for early diagnosis of pancreatic cancer. *World J Gastrointest Oncol* 2014; **6**: 22-33 [PMID: 24578785 DOI: 10.4251/wjgo.v6.i1.22]
300 **Goto T**, Fujiya M, Konishi H, Sasajima J, Fujibayashi S, Hayashi A, Utsumi T, Sato H, Iwama T, Ijiri M, Sakatani A, Tanaka K, Nomura Y, Ueno N, Kashima S, Moriichi K, Mizukami Y, Kohgo Y, Okumura T. An elevated expression of serum exosomal microRNA-191, - 21, -451a of pancreatic neoplasm is considered to be efficient diagnostic marker. *BMC Cancer* 2018; **18**: 116 [PMID: 29385987 DOI: 10.1186/s12885-018-4006-5]
301 **Li A**, Yu J, Kim H, Wolfgang CL, Canto MI, Hruban RH, Goggins M. MicroRNA array analysis finds elevated serum miR-1290 accurately distinguishes patients with low-stage pancreatic cancer from healthy and disease controls. *Clin Cancer Res* 2013; **19**: 3600-3610 [PMID: 23697990 DOI: 10.1158/1078-0432.CCR-12-3092]
302 **Wei J**, Yang L, Wu YN, Xu J. Serum miR-1290 and miR-1246 as Potential Diagnostic Biomarkers of Human Pancreatic Cancer. *J Cancer* 2020; **11**: 1325-1333 [PMID: 32047539 DOI: 10.7150/jca.38048]
303 **Wang WS**, Liu LX, Li GP, Chen Y, Li CY, Jin DY, Wang XL. Combined serum CA19-9 and miR-27a-3p in peripheral blood mononuclear cells to diagnose pancreatic cancer. *Cancer Prev Res (Phila)* 2013; **6**: 331-338 [PMID: 23430754 DOI: 10.1158/1940-6207.CAPR-12-0307]

304 **Zhang J**, Zhao CY, Zhang SH, Yu DH, Chen Y, Liu QH, Shi M, Ni CR, Zhu MH. Upregulation of miR-194 contributes to tumor growth and progression in pancreatic ductal adenocarcinoma. *Oncol Rep* 2014; **31**: 1157-1164 [PMID: 24398877 DOI: 10.3892/or.2013.2960]

305 **Lin MS**, Chen WC, Huang JX, Gao HJ, Sheng HH. Aberrant expression of microRNAs in serum may identify individuals with pancreatic cancer. *Int J Clin Exp Med* 2014; **7**: 5226-5234 [PMID: 25664025]

306 **Komatsu S**, Ichikawa D, Miyamae M, Kawaguchi T, Morimura R, Hirajima S, Okajima W, Ohashi T, Imamura T, Konishi H, Shiozaki A, Ikoma H, Okamoto K, Taniguchi H, Otsuji E. Malignant potential in pancreatic neoplasm; new insights provided by circulating miR-223 in plasma. *Expert Opin Biol Ther* 2015; **15**: 773-785 [PMID: 25819175 DOI: 10.1517/14712598.2015.1029914]

307 **Kim K**, Yoo D, Lee HS, Lee KJ, Park SB, Kim C, Jo JH, Jung DE, Song SY. Identification of potential biomarkers for diagnosis of pancreatic and biliary tract cancers by sequencing of serum microRNAs. *BMC Med Genomics* 2019; **12**: 62 [PMID: 31096984 DOI: 10.1186/s12920-019-0521-8]

308 **Song Z**, Wang S, Liu Y. The diagnostic accuracy of liquid exosomes for lung cancer detection: a meta-analysis. *Onco Targets Ther* 2019; **12**: 181-192 [PMID: 30636881 DOI: 10.2147/OTT.S188832]

309 **Zhu Y**, Zhang H, Chen N, Hao J, Jin H, Ma X. Diagnostic value of various liquid biopsy methods for pancreatic cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e18581 [PMID: 32011436 DOI: 10.1097/MD.0000000000018581]

310 **Lai X**, Wang M, McElyea SD, Sherman S, House M, Korc M. A microRNA signature in circulating exosomes is superior to exosomal glypican-1 Levels for diagnosing pancreatic cancer. *Cancer Lett* 2017; **393**: 86-93 [PMID: 28232049 DOI: 10.1016/j.canlet.2017.02.019]

311 **Que R**, Ding G, Chen J, Cao L. Analysis of serum exosomal microRNAs and clinicopathologic features of patients with pancreatic adenocarcinoma. *World J Surg Oncol* 2013; **11**: 219 [PMID: 24007214 DOI: 10.1186/1477-7819-11-219]

312 **Madhavan B**, Yue S, Galli U, Rana S, Gross W, Müller M, Giese NA, Kalthoff H, Becker T, Büchler MW, Zöller M. Combined evaluation of a panel of protein and miRNA serum-exosome biomarkers for pancreatic cancer diagnosis increases sensitivity and specificity. *Int J Cancer* 2015; **136**: 2616-2627 [PMID: 25388097 DOI: 10.1002/ijc.29324]

313 **Melo SA**, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, LeBleu VS, Mittendorf EA, Weitz J, Rahbari N, Reissfelder C, Pilarsky C, Fraga MF, Piwnica-Worms D, Kalluri R. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature* 2015; **523**: 177-182 [PMID: 26106858 DOI: 10.1038/nature14581]

314 **Castells A**, Puig P, Móra J, Boadas J, Boix L, Urgell E, Solé M, Capellà G, Lluís F, Fernández-Cruz L, Navarro S, Farré A. K-ras mutations in DNA extracted from the plasma of patients with pancreatic carcinoma: diagnostic utility and prognostic significance. *J Clin Oncol* 1999; **17**: 578-584 [PMID: 10080602 DOI: 10.1200/JCO.1999.17.2.578]

315 **Yamada T**, Nakamori S, Ohzato H, Oshima S, Aoki T, Higaki N, Sugimoto K, Akagi K, Fujiwara Y, Nishisho I, Sakon M, Gotoh M, Monden M. Detection of K-ras gene mutations in plasma DNA of patients with pancreatic adenocarcinoma: correlation with clinicopathological features. *Clin Cancer Res* 1998; **4**: 1527-1532 [PMID: 9626473]

316 **Maire F**, Micard S, Hammel P, Voitot H, Lévy P, Cugnenc PH, Ruszniewski P, Puig PL. Differential diagnosis between chronic pancreatitis and pancreatic cancer: value of the detection of KRAS2 mutations in circulating DNA. *Br J Cancer* 2002; **87**: 551-554 [PMID: 12189555 DOI: 10.1038/sj.bjc.6600475]

317 **Sefrioui D**, Blanchard F, Toure E, Basile P, Beaussire L, Dolfus C, Perdrix A, Paresy M, Antonietti M, Iwanicki-Caron I, Alhameedi R, Lecleire S, Gangloff A, Schwarz L, Clatot F, Tuech JJ, Frébourg T, Jardin F, Sabourin JC, Sarafan-Vasseur N, Michel P, Di Fiore F. Diagnostic value of CA19.9, circulating tumour DNA and circulating tumour cells in patients with solid pancreatic tumours. *Br J Cancer* 2017; **117**: 1017-1025 [PMID: 28772284 DOI: 10.1038/bjc.2017.250]

318 **Eissa MAL**, Lerner L, Abdelfatah E, Shankar N, Canner JK, Hasan NM, Yaghoobi V, Huang B, Kerner Z, Takaesu F, Wolfgang C, Kwak R, Ruiz M, Tam M, Pisanic TR 2nd, Iacobuzio-Donahue CA, Hruban RH, He J, Wang TH, Wood LD, Sharma A, Ahuja N. Promoter methylation of ADAMTS1 and BNC1 as potential biomarkers for early detection of pancreatic cancer in blood. *Clin Epigenetics* 2019; **11**: 59 [PMID: 30953539 DOI: 10.1186/s13148-019-0650-0]

319 **Ankeny JS**, Court CM, Hou S, Li Q, Song M, Wu D, Chen JF, Lee T, Lin M, Sho S, Rochefort MM, Girgis MD, Yao J, Wainberg ZA, Muthusamy VR, Watson RR, Donahue TR, Hines OJ, Reber HA, Graeber TG, Tseng HR, Tomlinson JS. Circulating tumour cells as a biomarker for diagnosis and staging in pancreatic cancer. *Br J Cancer* 2016; **114**: 1367-1375 [PMID: 27300108 DOI: 10.1038/bjc.2016.121]

320 **Liu H**, Sun B, Wang S, Liu C, Lu Y, Li D, Liu X. Circulating Tumor Cells as a Biomarker in Pancreatic Ductal Adenocarcinoma. *Cell Physiol Biochem* 2017; **42**: 373-382 [PMID: 28558380 DOI: 10.1159/000477481]

321 **Rhim AD**, Thege FI, Santana SM, Lannin TB, Saha TN, Tsai S, Maggs LR, Kochman ML, Ginsberg GG, Lieb JG, Chandrasekhara V, Drebin JA, Ahmad N, Yang YX, Kirby BJ, Stanger BZ. Detection of circulating pancreas epithelial cells in patients with pancreatic cystic lesions. *Gastroenterology* 2014; **146**: 647-651 [PMID: 24333829 DOI: 10.1053/j.gastro.2013.12.007]

322 **Kulemann B**, Pitman MB, Liss AS, Valsangkar N, Fernández-Del Castillo C, Lillemoe KD,

Hoeppner J, Mino-Kenudson M, Warshaw AL, Thayer SP. Circulating tumor cells found in patients with localized and advanced pancreatic cancer. *Pancreas* 2015; **44**: 547-550 [PMID: 25822154 DOI: 10.1097/MPA.0000000000000324]

323 **Zhang Y**, Wang F, Ning N, Chen Q, Yang Z, Guo Y, Xu D, Zhang D, Zhan T, Cui W. Patterns of circulating tumor cells identified by CEP8, CK and CD45 in pancreatic cancer. *Int J Cancer* 2015; **136**: 1228-1233 [PMID: 25042121 DOI: 10.1002/ijc.29070]

324 **Xu Y**, Qin T, Li J, Wang X, Gao C, Xu C, Hao J, Liu J, Gao S, Ren H. Detection of Circulating Tumor Cells Using Negative Enrichment Immunofluorescence and an In Situ Hybridization System in Pancreatic Cancer. *Int J Mol Sci* 2017; **18**: 622 [PMID: 28333072 DOI: 10.3390/ijms18040622]

325 **Ashworth T**. A case of cancer in which cells similar to those in the tumours were seen in the blood after death. *Aust Med J* 1869; **14**: 146

326 **Cheng H**, He W, Yang J, Ye Q, Cheng L, Pan Y, Mao L, Chu X, Lu C, Li G, Qiu Y, He J. Ligand-targeted polymerase chain reaction for the detection of folate receptor-positive circulating tumour cells as a potential diagnostic biomarker for pancreatic cancer. *Cell Prolif* 2020; **53**: e12880 [PMID: 32707596 DOI: 10.1111/cpr.12880]

327 **Nguyen NC**, Taalab K, Osman MM. Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. *Clin Cancer Res* 2010; **16**: 367; author reply 567 [PMID: 20028758 DOI: 10.1158/1078-0432.CCR-09-2512]

328 **Lo YM**, Chiu RW. Genomic analysis of fetal nucleic acids in maternal blood. *Annu Rev Genomics Hum Genet* 2012; **13**: 285-306 [PMID: 22657389 DOI: 10.1146/annurev-genom-090711-163806]

329 **Tsai NW**, Lin TK, Chen SD, Chang WN, Wang HC, Yang TM, Lin YJ, Jan CR, Huang CR, Liou CW, Lu CH. The value of serial plasma nuclear and mitochondrial DNA levels in patients with acute ischemic stroke. *Clin Chim Acta* 2011; **412**: 476-479 [PMID: 21130757 DOI: 10.1016/j.cca.2010.11.036]

330 **Bethel K**, Luttgen MS, Damani S, Kolatkar A, Lamy R, Sabouri-Ghomi M, Topol S, Topol EJ, Kuhn P. Fluid phase biopsy for detection and characterization of circulating endothelial cells in myocardial infarction. *Phys Biol* 2014; **11**: 016002 [PMID: 24406475 DOI: 10.1088/1478-3975/11/1/016002]

331 **Diaz LA Jr**, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol* 2014; **32**: 579-586 [PMID: 24449238 DOI: 10.1200/JCO.2012.45.2011]

332 **Okada T**, Mizukami Y, Ono Y, Sato H, Hayashi A, Kawabata H, Koizumi K, Masuda S, Teshima S, Takahashi K, Katanuma A, Omori Y, Iwano H, Yamada M, Yokochi T, Asahara S, Kawakubo K, Kuwatani M, Sakamoto N, Enomoto K, Goto T, Sasajima J, Fujiya M, Ueda J, Matsumoto S, Taniue K, Sugitani A, Karasaki H, Okumura T. Digital PCR-based plasma cell-free DNA mutation analysis for early-stage pancreatic tumor diagnosis and surveillance. *J Gastroenterol* 2020; **55**: 1183-1193 [PMID: 32939577 DOI: 10.1007/s00535-020-01724-5]

333 **Weeks ME**, Hariharan D, Petronijevic L, Radon TP, Whiteman HJ, Kocher HM, Timms JF, Lemoine NR, Crnogorac-Jurcevic T. Analysis of the urine proteome in patients with pancreatic ductal adenocarcinoma. *Proteomics Clin Appl* 2008; **2**: 1047-1057 [PMID: 21136905 DOI: 10.1002/prca.200780164]

334 **Radon TP**, Massat NJ, Jones R, Alrawashdeh W, Dumartin L, Ennis D, Duffy SW, Kocher HM, Pereira SP, Guarner posthumous L, Murta-Nascimento C, Real FX, Malats N, Neoptolemos J, Costello E, Greenhalf W, Lemoine NR, Crnogorac-Jurcevic T. Identification of a Three-Biomarker Panel in Urine for Early Detection of Pancreatic Adenocarcinoma. *Clin Cancer Res* 2015; **21**: 3512-3521 [PMID: 26240291 DOI: 10.1158/1078-0432.CCR-14-2467]

335 **Roy R**, Zurakowski D, Wischhusen J, Frauenhoffer C, Hooshmand S, Kulke M, Moses MA. Urinary TIMP-1 and MMP-2 levels detect the presence of pancreatic malignancies. *Br J Cancer* 2014; **111**: 1772-1779 [PMID: 25137018 DOI: 10.1038/bjc.2014.462]

336 **Hogendorf P**, Durczyński A, Skulimowski A, Kumor A, Poznańska G, Strzelczyk J. Neutrophil Gelatinase-Associated Lipocalin (NGAL) concentration in urine is superior to CA19-9 and Ca 125 in differentiation of pancreatic mass: Preliminary report. *Cancer Biomark* 2016; **16**: 537-543 [PMID: 27002756 DOI: 10.3233/CBM-160595]

337 **Cui Y**, Shu XO, Li HL, Yang G, Wen W, Gao YT, Cai Q, Rothman N, Yin HY, Lan Q, Xiang YB, Zheng W. Prospective study of urinary prostaglandin E2 metabolite and pancreatic cancer risk. *Int J Cancer* 2017; **141**: 2423-2429 [PMID: 28815606 DOI: 10.1002/ijc.31007]

338 **Chuang LY**, Hung WC, Yang ML, Chang CC, Tsai JF. Urinary epidermal growth factor receptor-binding growth factors in patients with cancers of the digestive tract. *Clin Biochem* 1994; **27**: 485-489 [PMID: 7697894 DOI: 10.1016/0009-9120(94)00053-x]

339 **Juracek J**, Peltanova B, Dolezel J, Fedorko M, Pacik D, Radova L, Vesela P, Svoboda M, Slaby O, Stanik M. Genome-wide identification of urinary cell-free microRNAs for non-invasive detection of bladder cancer. *J Cell Mol Med* 2018; **22**: 2033-2038 [PMID: 29363887 DOI: 10.1111/jcmm.13487]

340 **Debernardi S**, Massat NJ, Radon TP, Sangaralingam A, Banissi A, Ennis DP, Dowe T, Chelala C, Pereira SP, Kocher HM, Young BD, Bond-Smith G, Hutchins R, Crnogorac-Jurcevic T. Noninvasive urinary miRNA biomarkers for early detection of pancreatic adenocarcinoma. *Am J Cancer Res* 2015; **5**: 3455-3466 [PMID: 26807325]

341 **Terasawa H**, Kinugasa H, Ako S, Hirai M, Matsushita H, Uchida D, Tomoda T, Matsumoto K, Horiguchi S, Kato H, Nouso K, Okada H. Utility of liquid biopsy using urine in patients with pancreatic ductal adenocarcinoma. *Cancer Biol Ther* 2019; **20**: 1348-1353 [PMID: 31328611 DOI: 10.1080/15384047.2019.1638685]

342 **Yoshizawa N**, Sugimoto K, Tameda M, Inagaki Y, Ikejiri M, Inoue H, Usui M, Ito M, Takei Y. miR-3940-5p/miR-8069 ratio in urine exosomes is a novel diagnostic biomarker for pancreatic ductal adenocarcinoma. *Oncol Lett* 2020; **19**: 2677-2684 [PMID: 32218818 DOI: 10.3892/ol.2020.11357]

343 **Nissinen SI**, Roine A, Hokkinen L, Karjalainen M, Venäläinen M, Helminen H, Niemi R, Lehtimäki T, Rantanen T, Oksala N. Detection of Pancreatic Cancer by Urine Volatile Organic Compound Analysis. *Anticancer Res* 2019; **39**: 73-79 [PMID: 30591442 DOI: 10.21873/anticanres.13081]

344 **Schilling K**, Larner F, Saad A, Roberts R, Kocher HM, Blyuss O, Halliday AN, Crnogorac-Jurcevic T. Urine metallomics signature as an indicator of pancreatic cancer. *Metallomics* 2020; **12**: 752-757 [PMID: 32211672 DOI: 10.1039/d0mt00061b]

345 **Nishida K**, Tasaki N, Miyagawa H, Yoshikawa T, Kondo M. Estimation of carbohydrate antigen (CA) 19-9 levels in pure pancreatic juice of patients with pancreatic cancer. *Am J Gastroenterol* 1988; **83**: 126-129 [PMID: 3422536]

346 **Wakabayashi T**, Sawabu N, Takemori Y, Satomura Y, Kidani H, Ohta H, Watanabe H, Yamakawa O, Takahashi H, Watanabe K. Diagnostic significance of cancer-associated carbohydrate antigen (CA19-9) concentrations in pancreatic juice: analysis in pure pancreatic juice collected by endoscopic aspiration and immunohistochemical study in chronic pancreatitis. *Pancreas* 1993; **8**: 151-159 [PMID: 8460089 DOI: 10.1097/00006676-199303000-00003]

347 **Matsumoto S**, Harada H, Tanaka J, Ochi K, Seno T, Tsurumi T, Kunichika K. Evaluation of cytology and tumor markers of pure pancreatic juice for the diagnosis of pancreatic cancer at early stages. *Pancreas* 1994; **9**: 741-747 [PMID: 7846018 DOI: 10.1097/00006676-199411000-00012]

348 **Futakawa N**, Kimura W, Yamagata S, Zhao B, Ilsoo H, Inoue T, Sata N, Kawaguchi Y, Kubota Y, Muto T. Significance of K-ras mutation and CEA level in pancreatic juice in the diagnosis of pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2000; **7**: 63-71 [PMID: 10982594 DOI: 10.1007/s005340050156]

349 **Kaur S**, Baine MJ, Guha S, Ochi N, Chakraborty S, Mallya K, Thomas C, Crook J, Wallace MB, Woodward TA, Jain M, Singh S, Sasson AR, Skinner V, Raimondo M, Batra SK. Neutrophil gelatinase-associated lipocalin, macrophage inhibitory cytokine 1, and carbohydrate antigen 19-9 in pancreatic juice: pathobiologic implications in diagnosing benign and malignant disease of the pancreas. *Pancreas* 2013; **42**: 494-501 [PMID: 23146921 DOI: 10.1097/MPA.0b013e31826a8597]

350 **Sharma MP**, Gregg JA, Loewenstein MS, McCabe RP, Zamcheck N. Carcinoembryonic antigen (CEA) activity in pancreatic juice of patients with pancreatic carcinoma and pancreatitis. *Cancer* 1976; **38**: 2457-2461 [PMID: 1000475 DOI: 10.1002/1097-0142(197612)38:6<2457::aid-cncr2820380634>3.0.co;2-3]

351 **Nakaizumi A**, Uehara H, Takenaka A, Uedo N, Sakai N, Yano H, Ohigashi H, Ishikawa O, Ishiguro S, Sugano K, Tatsuta M. Diagnosis of pancreatic cancer by cytology and measurement of oncogene and tumor markers in pure pancreatic juice aspirated by endoscopy. *Hepatogastroenterology* 1999; **46**: 31-37 [PMID: 10228761]

352 **Hayakawa H**, Fukasawa M, Sato T, Takano S, Kadokura M, Shindo H, Takahashi E, Hirose S, Kawakami S, Fukasawa Y, Maekawa S, Inoue T, Yamaguchi T, Nakayama Y, Kawaida H, Kono H, Mochizuki K, Kondo T, Ichikawa D, Enomoto N. Carcinoembryonic antigen level in the pancreatic juice is effective in malignancy diagnosis and prediction of future malignant transformation of intraductal papillary mucinous neoplasm of the pancreas. *J Gastroenterol* 2019; **54**: 1029-1037 [PMID: 31111221 DOI: 10.1007/s00535-019-01592-8]

353 **Porterfield M**, Zhao P, Han H, Cunningham J, Aoki K, Von Hoff DD, Demeure MJ, Pierce JM, Tiemeyer M, Wells L. Discrimination between adenocarcinoma and normal pancreatic ductal fluid by proteomic and glycomic analysis. *J Proteome Res* 2014; **13**: 395-407 [PMID: 24328148 DOI: 10.1021/pr400422g]

354 **Matsumoto K**, Takeda Y, Harada K, Onoyama T, Kawata S, Horie Y, Sakamoto T, Ueki M, Miura N, Murawaki Y. Clinical Impact of the KL-6 Concentration of Pancreatic Juice for Diagnosing Pancreatic Masses. *Biomed Res Int* 2015; **2015**: 528304 [PMID: 26451373 DOI: 10.1155/2015/528304]

355 **Marchegiani G**, Paulo JA, Sahora K, Fernández-Del Castillo C. The proteome of postsurgical pancreatic juice. *Pancreas* 2015; **44**: 574-582 [PMID: 25875796 DOI: 10.1097/MPA.0000000000000304]

356 **Matsunaga T**, Ohtsuka T, Asano K, Kimura H, Ohuchida K, Kitada H, Ideno N, Mori Y, Tokunaga S, Oda Y, Guha S, Raimondo M, Nakamura M, Tanaka M. S100P in Duodenal Fluid Is a Useful Diagnostic Marker for Pancreatic Ductal Adenocarcinoma. *Pancreas* 2017; **46**: 1288-1295 [PMID: 28984789 DOI: 10.1097/MPA.0000000000000940]

357 **Tian M**, Cui YZ, Song GH, Zong MJ, Zhou XY, Chen Y, Han JX. Proteomic analysis identifies MMP-9, DJ-1 and A1BG as overexpressed proteins in pancreatic juice from pancreatic ductal adenocarcinoma patients. *BMC Cancer* 2008; **8**: 241 [PMID: 18706098 DOI: 10.1186/1471-2407-8-241]

358 **Rosty C**, Christa L, Kuzdzal S, Baldwin WM, Zahurak ML, Carnot F, Chan DW, Canto M, Lillemoe KD, Cameron JL, Yeo CJ, Hruban RH, Goggins M. Identification of hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I as a biomarker for pancreatic ductal adenocarcinoma by protein biochip technology. *Cancer Res* 2002; **62**: 1868-1875 [PMID: 11912167]

359 **Chen R**, Pan S, Duan X, Nelson BH, Sahota RA, de Rham S, Kozarek RA, McIntosh M, Brentnall

TA. Elevated level of anterior gradient-2 in pancreatic juice from patients with pre-malignant pancreatic neoplasia. *Mol Cancer* 2010; **9**: 149 [PMID: 20550709 DOI: 10.1186/1476-4598-9-149]

360 **Noh KW**, Pungpapong S, Wallace MB, Woodward TA, Raimondo M. Do cytokine concentrations in pancreatic juice predict the presence of pancreatic diseases? *Clin Gastroenterol Hepatol* 2006; **4**: 782-789 [PMID: 16713745 DOI: 10.1016/j.cgh.2006.03.026]

361 **Uno K**, Azuma T, Nakajima M, Yasuda K, Hayakumo T, Mukai H, Sakai T, Kawai K. Clinical significance of cathepsin E in pancreatic juice in the diagnosis of pancreatic ductal adenocarcinoma. *J Gastroenterol Hepatol* 2000; **15**: 1333-1338 [PMID: 11129230]

362 **Sadakari Y**, Ohtsuka T, Ohuchida K, Tsutsumi K, Takahata S, Nakamura M, Mizumoto K, Tanaka M. MicroRNA expression analyses in preoperative pancreatic juice samples of pancreatic ductal adenocarcinoma. *JOP* 2010; **11**: 587-592 [PMID: 21068491]

363 **Wang J**, Raimondo M, Guha S, Chen J, Diao L, Dong X, Wallace MB, Killary AM, Frazier ML, Woodward TA, Wang J, Sen S. Circulating microRNAs in Pancreatic Juice as Candidate Biomarkers of Pancreatic Cancer. *J Cancer* 2014; **5**: 696-705 [PMID: 25258651 DOI: 10.7150/jca.10094]

364 **Watanabe H**, Okada G, Ohtsubo K, Yamaguchi Y, Mouri H, Motoo Y, Wakabayashi T, Sawabu N. Expression of mesothelin mRNA in pure pancreatic juice from patients with pancreatic carcinoma, intraductal papillary mucinous neoplasm of the pancreas, and chronic pancreatitis. *Pancreas* 2005; **30**: 349-354 [PMID: 15841046 DOI: 10.1097/01.mpa.0000160281.56828.76]

365 **Suehara N**, Mizumoto K, Tanaka M, Niiyama H, Yokohata K, Tominaga Y, Shimura H, Muta T, Hamasaki N. Telomerase activity in pancreatic juice differentiates ductal carcinoma from adenoma and pancreatitis. *Clin Cancer Res* 1997; **3**: 2479-2483 [PMID: 9815650]

366 **Myung SJ**, Kim MH, Kim YS, Kim HJ, Park ET, Yoo KS, Lim BC, Wan Seo D, Lee SK, Min YI, Kim JY. Telomerase activity in pure pancreatic juice for the diagnosis of pancreatic cancer may be complementary to K-ras mutation. *Gastrointest Endosc* 2000; **51**: 708-713 [PMID: 10840305 DOI: 10.1067/mge.2000.104654]

367 **Hata T**, Ishida M, Motoi F, Yamaguchi T, Naitoh T, Katayose Y, Egawa S, Unno M. Telomerase activity in pancreatic juice differentiates pancreatic cancer from chronic pancreatitis: A meta-analysis. *Pancreatology* 2016; **16**: 372-381 [PMID: 26899542 DOI: 10.1016/j.pan.2016.01.007]

368 **Hashimoto Y**, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Fukuda E, Sueda T, Hiyama E. Detection of human telomerase reverse transcriptase (hTERT) expression in tissue and pancreatic juice from pancreatic cancer. *Surgery* 2008; **143**: 113-125 [PMID: 18154939 DOI: 10.1016/j.surg.2007.07.042]

369 **Nakashima A**, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Ohge H, Oda M, Sueda T, Hiyama E. Usefulness of human telomerase reverse transcriptase in pancreatic juice as a biomarker of pancreatic malignancy. *Pancreas* 2009; **38**: 527-533 [PMID: 19342980 DOI: 10.1097/MPA.0b013e3181a16d28]

370 **Sansone V**, Le Grazie M, Roselli J, Polvani S, Galli A, Tovoli F, Tarocchi M. Telomerase reactivation is associated with hepatobiliary and pancreatic cancers. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 420-428 [PMID: 32386990 DOI: 10.1016/j.hbpd.2020.04.007]

371 **Zheng J**, Hernandez JM, Doussot A, Bojmar L, Zambirinis CP, Costa-Silva B, van Beek EJAH, Mark MT, Molina H, Askan G, Basturk O, Gonen M, Kingham TP, Allen PJ, D'Angelica MI, DeMatteo RP, Lyden D, Jarnagin WR. Extracellular matrix proteins and carcinoembryonic antigen-related cell adhesion molecules characterize pancreatic duct fluid exosomes in patients with pancreatic cancer. *HPB (Oxford)* 2018; **20**: 597-604 [PMID: 29339034 DOI: 10.1016/j.hpb.2017.12.010]

372 **Osteikoetxea X**, Benke M, Rodriguez M, Pálóczi K, Sódar BW, Szvicsek Z, Szabó-Taylor K, Vukman KV, Kittel Á, Wiener Z, Vékey K, Harsányi L, Szűcs Á, Turiák L, Buzás EI. Detection and proteomic characterization of extracellular vesicles in human pancreatic juice. *Biochem Biophys Res Commun* 2018; **499**: 37-43 [PMID: 29550476 DOI: 10.1016/j.bbrc.2018.03.107]

373 **Nakamura S**, Sadakari Y, Ohtsuka T, Okayama T, Nakashima Y, Gotoh Y, Saeki K, Mori Y, Nakata K, Miyasaka Y, Onishi H, Oda Y, Goggins M, Nakamura M. Pancreatic Juice Exosomal MicroRNAs as Biomarkers for Detection of Pancreatic Ductal Adenocarcinoma. *Ann Surg Oncol* 2019; **26**: 2104-2111 [PMID: 30820789 DOI: 10.1245/s10434-019-07269-z]

374 **Patel N**, Petrinic T, Silva M, Soonawalla Z, Reddy S, Gordon-Weeks A. The Diagnostic Accuracy of Mutant KRAS Detection from Pancreatic Secretions for the Diagnosis of Pancreatic Cancer: A Meta-Analysis. *Cancers (Basel)* 2020; **12** [PMID: 32825312 DOI: 10.3390/cancers12092353]

375 **Fukushima N**, Walter KM, Uek T, Sato N, Matsubayashi H, Cameron JL, Hruban RH, Canto M, Yeo CJ, Goggins M. Diagnosing pancreatic cancer using methylation specific PCR analysis of pancreatic juice. *Cancer Biol Ther* 2003; **2**: 78-83 [PMID: 12673124 DOI: 10.4161/cbt.183]

376 **Matsubayashi H**, Canto M, Sato N, Klein A, Abe T, Yamashita K, Yeo CJ, Kalloo A, Hruban R, Goggins M. DNA methylation alterations in the pancreatic juice of patients with suspected pancreatic disease. *Cancer Res* 2006; **66**: 1208-1217 [PMID: 16424060 DOI: 10.1158/0008-5472.CAN-05-2664]

377 **Kisiel JB**, Raimondo M, Taylor WR, Yab TC, Mahoney DW, Sun Z, Middha S, Baheti S, Zou H, Smyrk TC, Boardman LA, Petersen GM, Ahlquist DA. New DNA Methylation Markers for Pancreatic Cancer: Discovery, Tissue Validation, and Pilot Testing in Pancreatic Juice. *Clin Cancer Res* 2015; **21**: 4473-4481 [PMID: 26023084 DOI: 10.1158/1078-0432.CCR-14-2469]

378 **Yokoyama S**, Kitamoto S, Higashi M, Goto Y, Hara T, Ikebe D, Yamaguchi T, Arisaka Y, Niihara T, Nishimata H, Tanaka S, Takaori K, Batra SK, Yonezawa S. Diagnosis of pancreatic neoplasms

using a novel method of DNA methylation analysis of mucin expression in pancreatic juice. *PLoS One* 2014; **9**: e93760 [PMID: 24714692 DOI: 10.1371/journal.pone.0093760]

379 **de Jong K**, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, van Heel E, Klass G, Fockens P, Bruno MJ. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol* 2010; **8**: 806-811 [PMID: 20621679 DOI: 10.1016/j.cgh.2010.05.017]

380 **Elta GH**, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. *Am J Gastroenterol* 2018; **113**: 464-479 [PMID: 29485131 DOI: 10.1038/ajg.2018.14]

381 **Jabbar KS**, Arike L, Verbeke CS, Sadik R, Hansson GC. Highly Accurate Identification of Cystic Precursor Lesions of Pancreatic Cancer Through Targeted Mass Spectrometry: A Phase IIc Diagnostic Study. *J Clin Oncol* 2018; **36**: 367-375 [PMID: 29166170 DOI: 10.1200/JCO.2017.73.7288]

382 **Anand N**, Sampath K, Wu BU. Cyst features and risk of malignancy in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 913-921; quiz e59 [PMID: 23416279 DOI: 10.1016/j.cgh.2013.02.010]

383 **Park WG**, Mascarenhas R, Palaez-Luna M, Smyrk TC, O'Kane D, Clain JE, Levy MJ, Pearson RK, Petersen BT, Topazian MD, Vege SS, Chari ST. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts. *Pancreas* 2011; **40**: 42-45 [PMID: 20966811 DOI: 10.1097/MPA.0b013e3181f69f36]

384 **Ngamruengphong S**, Bartel MJ, Raimondo M. Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis. *Dig Liver Dis* 2013; **45**: 920-926 [PMID: 23790480 DOI: 10.1016/j.dld.2013.05.002]

385 **Carr RA**, Yip-Schneider MT, Simpson RE, Dolejs S, Schneider JG, Wu H, Ceppa EP, Park W, Schmidt CM. Pancreatic cyst fluid glucose: rapid, inexpensive, and accurate diagnosis of mucinous pancreatic cysts. *Surgery* 2018; **163**: 600-605 [PMID: 29241991 DOI: 10.1016/j.surg.2017.09.051]

386 **Maker AV**, Hu V, Kadkol SS, Hong L, Brugge W, Winter J, Yeo CJ, Hackert T, Büchler M, Lawlor RT, Salvia R, Scarpa A, Bassi C, Green S. Cyst Fluid Biosignature to Predict Intraductal Papillary Mucinous Neoplasms of the Pancreas with High Malignant Potential. *J Am Coll Surg* 2019; **228**: 721-729 [PMID: 30794864 DOI: 10.1016/j.jamcollsurg.2019.02.040]

387 **Simpson RE**, Yip-Schneider MT, Flick KF, Wu H, Colgate CL, Schmidt CM. Pancreatic Fluid Interleukin-1β Complements Prostaglandin E2 and Serum Carbohydrate Antigen 19-9 in Prediction of Intraductal Papillary Mucinous Neoplasm Dysplasia. *Pancreas* 2019; **48**: 1026-1031 [PMID: 31404023 DOI: 10.1097/MPA.0000000000001377]

388 **Schmidt CM**, Yip-Schneider MT, Ralstin MC, Wentz S, DeWitt J, Sherman S, Howard TJ, McHenry L, Dutkevitch S, Goggins M, Nakeeb A, Lillemoe KD. PGE(2) in pancreatic cyst fluid helps differentiate IPMN from MCN and predict IPMN dysplasia. *J Gastrointest Surg* 2008; **12**: 243-249 [PMID: 18027059 DOI: 10.1007/s11605-007-0404-8]

389 **Al Efishat MA**, Attiyeh MA, Eaton AA, Gönen M, Prosser D, Lokshin AE, Castillo CF, Lillemoe KD, Ferrone CR, Pergolini I, Mino-Kenudson M, Rezaee N, Dal Molin M, Weiss MJ, Cameron JL, Hruban RH, D'Angelica MI, Kingham TP, DeMatteo RP, Jarnagin WR, Wolfgang CL, Allen PJ. Multi-institutional Validation Study of Pancreatic Cyst Fluid Protein Analysis for Prediction of High-risk Intraductal Papillary Mucinous Neoplasms of the Pancreas. *Ann Surg* 2018; **268**: 340-347 [PMID: 28700444 DOI: 10.1097/SLA.0000000000002421]

390 **Pham K**, Dong A, Wodziak D, Banerjee S, Friedland S, Poultsides GA, Visser B, Norton JA, Lowe AW, Park W. Su1351 Amphiregulin in Pancreatic Cyst Fluid is Elevated in High-Risk Pancreatic Cysts. *Gastroenterology* 2016; **150**: S500-S501

391 **Tun MT**, Pai RK, Kwok S, Dong A, Gupta A, Visser BC, Norton JA, Poultsides GA, Banerjee S, Van Dam J, Chen AM, Friedland S, Scott BA, Verma R, Lowe AW, Park WG. Diagnostic accuracy of cyst fluid amphiregulin in pancreatic cysts. *BMC Gastroenterol* 2012; **12**: 15 [PMID: 22333441 DOI: 10.1186/1471-230X-12-15]

392 **Räty S**, Sand J, Laukkarinen J, Vasama K, Bassi C, Salvia R, Nordback I. Cyst fluid SPINK1 may help to differentiate benign and potentially malignant cystic pancreatic lesions. *Pancreatology* 2013; **13**: 530-533 [PMID: 24075519 DOI: 10.1016/j.pan.2013.06.008]

393 **Das KK**, Xiao H, Geng X, Fernandez-Del-Castillo C, Morales-Oyarvide V, Daglilar E, Forcione DG, Bounds BC, Brugge WR, Pitman MB, Mino-Kenudson M, Das KM. mAb Das-1 is specific for high-risk and malignant intraductal papillary mucinous neoplasm (IPMN). *Gut* 2014; **63**: 1626-1634 [PMID: 24277729 DOI: 10.1136/gutjnl-2013-306219]

394 **Das KK**, Geng X, Brown JW, Morales-Oyarvide V, Huynh T, Pergolini I, Pitman MB, Ferrone C, Al Efishat M, Haviland D, Thompson E, Wolfgang C, Lennon AM, Allen P, Lillemoe KD, Fields RC, Hawkins WG, Liu J, Castillo CF, Das KM, Mino-Kenudson M. Cross Validation of the Monoclonal Antibody Das-1 in Identification of High-Risk Mucinous Pancreatic Cystic Lesions. *Gastroenterology* 2019; **157**: 720-730. e2 [PMID: 31175863 DOI: 10.1053/j.gastro.2019.05.014]

395 **Siu L**, Paredes J, Kurbatov V, Ramachandran R, Serafini F, Grossman E, Gress F, Martello L. Clinical Utility of Cytokine Biomarker Analysis of Pancreatic Cyst Fluid Obtained by Endoscopic Ultrasound Fine Needle Aspiration: A Pilot Study. *Pancreas* 2019; **48**: e60-e61 [PMID: 31425485 DOI: 10.1097/MPA.0000000000001365]

396 **Farrell JJ**, Toste P, Wu N, Li L, Wong J, Malkhassian D, Tran LM, Wu X, Li X, Dawson D, Wu H, Donahue TR. Endoscopically acquired pancreatic cyst fluid microRNA 21 and 221 are associated

with invasive cancer. *Am J Gastroenterol* 2013; **108**: 1352-1359 [PMID: 23752880 DOI: 10.1038/ajg.2013.167]

397 **Matthaei H**, Wylie D, Lloyd MB, Dal Molin M, Kemppainen J, Mayo SC, Wolfgang CL, Schulick RD, Langfield L, Andruss BF, Adai AT, Hruban RH, Szafranska-Schwarzbach AE, Maitra A. miRNA biomarkers in cyst fluid augment the diagnosis and management of pancreatic cysts. *Clin Cancer Res* 2012; **18**: 4713-4724 [PMID: 22723372 DOI: 10.1158/1078-0432.CCR-12-0035]

398 **Utomo WK**, Looijenga LH, Bruno MJ, Hansen BE, Gillis A, Biermann K, Peppelenbosch MP, Fuhler GM, Braat H. A MicroRNA Panel in Pancreatic Cyst Fluid for the Risk Stratification of Pancreatic Cysts in a Prospective Cohort. *Mol Ther Nucleic Acids* 2016; **5**: e350 [PMID: 28131248 DOI: 10.1038/mtna.2016.61]

399 **Khalid A**, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, Moser AJ, Lee KK, Slivka A, Whitcomb DC, Finkelstein S. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. *Clin Gastroenterol Hepatol* 2005; **3**: 967-973 [PMID: 16234041 DOI: 10.1016/s1542-3565(05)00409-x]

400 **Schoedel KE**, Finkelstein SD, Ohori NP. K-Ras and microsatellite marker analysis of fine-needle aspirates from intraductal papillary mucinous neoplasms of the pancreas. *Diagn Cytopathol* 2006; **34**: 605-608 [PMID: 16900481 DOI: 10.1002/dc.20511]

401 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]

402 **Sawhney MS**, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; **69**: 1106-1110 [PMID: 19249035 DOI: 10.1016/j.gie.2008.08.015]

403 **Shen J**, Brugge WR, Dimaio CJ, Pitman MB. Molecular analysis of pancreatic cyst fluid: a comparative analysis with current practice of diagnosis. *Cancer* 2009; **117**: 217-227 [PMID: 19415731 DOI: 10.1002/cncy.20027]

404 **Sreenarasimhaiah J**, Lara LF, Jazrawi SF, Barnett CC, Tang SJ. A comparative analysis of pancreas cyst fluid CEA and histology with DNA mutational analysis in the detection of mucin producing or malignant cysts. *JOP* 2009; **10**: 163-168 [PMID: 19287110]

405 **Talar-Wojnarowska R**, Pazurek M, Durko L, Degowska M, Rydzewska G, Smigielski J, Janiak A, Olakowski M, Lampe P, Grzelak P, Stefanczyk L, Smolarz B, Malecka-Panas E. A comparative analysis of K-ras mutation and carcinoembryonic antigen in pancreatic cyst fluid. *Pancreatology* 2012; **12**: 417-420 [PMID: 23127529 DOI: 10.1016/j.pan.2012.08.001]

406 **Nikiforova MN**, Khalid A, Fasanella KE, McGrath KM, Brand RE, Chennat JS, Slivka A, Zeh HJ, Zureikat AH, Krasinskas AM, Ohori NP, Schoedel KE, Navina S, Mantha GS, Pai RK, Singhi AD. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. *Mod Pathol* 2013; **26**: 1478-1487 [PMID: 23743931 DOI: 10.1038/modpathol.2013.91]

407 **Al-Haddad M**, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, Coté G, El Chafic AH, Luz L, Stuart JS, Johnson CS, Klochan C, Imperiale TF. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. *Gastrointest Endosc* 2014; **79**: 79-87 [PMID: 23845445 DOI: 10.1016/j.gie.2013.05.026]

408 **Thiruvengadam N**, Park WG. Systematic Review of Pancreatic Cyst Fluid Biomarkers: The Path Forward. *Clin Transl Gastroenterol* 2015; **6**: e88 [PMID: 26065716 DOI: 10.1038/ctg.2015.17]

409 **Wu J**, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, Goggins M, Canto MI, Schulick RD, Edil BH, Wolfgang CL, Klein AP, Diaz LA Jr, Allen PJ, Schmidt CM, Kinzler KW, Papadopoulos N, Hruban RH, Vogelstein B. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. *Sci Transl Med* 2011; **3**: 92ra66 [PMID: 21775669 DOI: 10.1126/scitranslmed.3002543]

410 **Siddiqui AA**, Kowalski TE, Kedika R, Roy A, Loren DE, Ellsworth E, Adler D, Finkelstein SD. EUS-guided pancreatic fluid aspiration for DNA analysis of KRAS and GNAS mutations for the evaluation of pancreatic cystic neoplasia: a pilot study. *Gastrointest Endosc* 2013; **77**: 669-670 [PMID: 23498145 DOI: 10.1016/j.gie.2012.11.009]

411 **Singhi AD**, Nikiforova MN, Fasanella KE, McGrath KM, Pai RK, Ohori NP, Bartholow TL, Brand RE, Chennat JS, Lu X, Papachristou GI, Slivka A, Zeh HJ, Zureikat AH, Lee KK, Tsung A, Mantha GS, Khalid A. Preoperative GNAS and KRAS testing in the diagnosis of pancreatic mucinous cysts. *Clin Cancer Res* 2014; **20**: 4381-4389 [PMID: 24938521 DOI: 10.1158/1078-0432.CCR-14-0513]

412 **Etekpo A**, Alghawalby A, Alghawalby M, Soliman A, Hablas A. Differences in MUC4 Expression in Pancreatic Cancers and Pancreatic Cysts in Egypt. *J Carcinog Mutagen* 2018; **9**: 2 [DOI: 10.4172/2157-2518.1000312]

413 **Wang Y**, Gao J, Li Z, Jin Z, Gong Y, Man X. Diagnostic value of mucins (MUC1, MUC2 and MUC5AC) expression profile in endoscopic ultrasound-guided fine-needle aspiration specimens of the pancreas. *Int J Cancer* 2007; **121**: 2716-2722 [PMID: 17708554 DOI: 10.1002/ijc.22997]

414 **Carrara S**, Cangi MG, Arcidiacono PG, Perri F, Petrone MC, Mezzi G, Boemo C, Talarico A, Cin ED, Grassini G, Doglioni C, Testoni PA. Mucin expression pattern in pancreatic diseases: findings from EUS-guided fine-needle aspiration biopsies. *Am J Gastroenterol* 2011; **106**: 1359-1363 [PMID: 21647207 DOI: 10.1038/ajg.2011.22]

415 **Springer S**, Masica DL, Dal Molin M, Douville C, Thoburn CJ, Afsari B, Li L, Cohen JD,

Thompson E, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Simpson RE, Fernandez-Del Castillo C, Mino-Kenudson M, Brugge W, Brand RE, Singhi AD, Scarpa A, Lawlor R, Salvia R, Zamboni G, Hong SM, Hwang DW, Jang JY, Kwon W, Swan N, Geoghegan J, Falconi M, Crippa S, Doglioni C, Paulino J, Schulick RD, Edil BH, Park W, Yachida S, Hijioka S, van Hooft J, He J, Weiss MJ, Burkhart R, Makary M, Canto MI, Goggins MG, Ptak J, Dobbyn L, Schaefer J, Sillman N, Popoli M, Klein AP, Tomasetti C, Karchin R, Papadopoulos N, Kinzler KW, Vogelstein B, Wolfgang CL, Hruban RH, Lennon AM. A multimodality test to guide the management of patients with a pancreatic cyst. *Sci Transl Med* 2019; **11** [PMID: 31316009 DOI: 10.1126/scitranslmed.aav4772]

416 **Lee YH**, Wong DT. Saliva: an emerging biofluid for early detection of diseases. *Am J Dent* 2009; **22**: 241-248 [PMID: 19824562]

417 **Xie ZJ**, Chen G, Zhang XC, Li DF, Huang J, Li ZJ. Saliva supernatant miR-21: a novel potential biomarker for esophageal cancer detection. *Asian Pac J Cancer Prev* 2012; **13**: 6145-6149 [PMID: 23464420 DOI: 10.7314/apjcp.2012.13.12.6145]

418 **Zhang Y**, Sun J, Lin CC, Abemayor E, Wang MB, Wong DT. The emerging landscape of salivary diagnostics. *Periodontol 2000* 2016; **70**: 38-52 [PMID: 26662481 DOI: 10.1111/prd.12099]

419 **Vitorino R**, Lobo MJ, Ferrer-Correira AJ, Dubin JR, Tomer KB, Domingues PM, Amado FM. Identification of human whole saliva protein components using proteomics. *Proteomics* 2004; **4**: 1109-1115 [PMID: 15048992 DOI: 10.1002/pmic.200300638]

420 **Hu S**, Xie Y, Ramachandran P, Ogorzalek Loo RR, Li Y, Loo JA, Wong DT. Large-scale identification of proteins in human salivary proteome by liquid chromatography/mass spectrometry and two-dimensional gel electrophoresis-mass spectrometry. *Proteomics* 2005; **5**: 1714-1728 [PMID: 15800970 DOI: 10.1002/pmic.200401037]

421 **Setti G**, Pezzi ME, Viani MV, Pertinhez TA, Cassi D, Magnoni C, Bellini P, Musolino A, Vescovi P, Meleti M. Salivary MicroRNA for Diagnosis of Cancer and Systemic Diseases: A Systematic Review. *Int J Mol Sci* 2020; **21** [PMID: 32019170 DOI: 10.3390/ijms21030907]

422 **Machida T**, Tomofuji T, Maruyama T, Yoneda T, Ekuni D, Azuma T, Miyai H, Mizuno H, Kato H, Tsutsumi K, Uchida D, Takaki A, Okada H, Morita M. miR1246 and miR4644 in salivary exosome as potential biomarkers for pancreatobiliary tract cancer. *Oncol Rep* 2016; **36**: 2375-2381 [PMID: 27573701 DOI: 10.3892/or.2016.5021]

423 **Humeau M**, Vignolle-Vidoni A, Sicard F, Martins F, Bournet B, Buscail L, Torrisani J, Cordelier P. Salivary MicroRNA in Pancreatic Cancer Patients. *PLoS One* 2015; **10**: e0130996 [PMID: 26121640 DOI: 10.1371/journal.pone.0130996]

424 **Xie Z**, Yin X, Gong B, Nie W, Wu B, Zhang X, Huang J, Zhang P, Zhou Z, Li Z. Salivary microRNAs show potential as a noninvasive biomarker for detecting resectable pancreatic cancer. *Cancer Prev Res (Phila)* 2015; **8**: 165-173 [PMID: 25538087 DOI: 10.1158/1940-6207.CAPR-14-0192]

425 **Gao S**, Chen LY, Wang P, Liu LM, Chen Z. MicroRNA expression in salivary supernatant of patients with pancreatic cancer and its relationship with ZHENG. *Biomed Res Int* 2014; **2014**: 756347 [PMID: 25126577 DOI: 10.1155/2014/756347]

426 **Gerner EW**, Meyskens FL Jr. Polyamines and cancer: old molecules, new understanding. *Nat Rev Cancer* 2004; **4**: 781-792 [PMID: 15510159 DOI: 10.1038/nrc1454]

427 **Asai Y**, Itoi T, Sugimoto M, Sofuni A, Tsuchiya T, Tanaka R, Tonozuka R, Honjo M, Mukai S, Fujita M, Yamamoto K, Matsunami Y, Kurosawa T, Nagakawa Y, Kaneko M, Ota S, Kawachi S, Shimazu M, Soga T, Tomita M, Sunamura M. Elevated Polyamines in Saliva of Pancreatic Cancer. *Cancers (Basel)* 2018; **10** [PMID: 29401744 DOI: 10.3390/cancers10020043]

428 **Xie Z**, Chen X, Li J, Guo Y, Li H, Pan X, Jiang J, Liu H, Wu B. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. *Oncotarget* 2016; **7**: 25408-25419 [PMID: 27028998 DOI: 10.18632/oncotarget.8323]

429 **Navaneethan U**, Gutierrez NG, Jegadeesan R, Venkatesh PG, Poptic E, Liu X, Sanaka MR, Jang S, Vargo JJ, Parsi MA. Vascular endothelial growth factor levels in bile distinguishes pancreatic cancer from other etiologies of biliary stricture: a pilot study. *Dig Dis Sci* 2013; **58**: 2986-2992 [PMID: 23828141 DOI: 10.1007/s10620-013-2764-0]

430 **Alvaro D**, Macarri G, Mancino MG, Marzioni M, Bragazzi M, Onori P, Corradini SG, Invernizzi P, Franchitto A, Attili AF, Gaudio E, Benedetti A. Serum and biliary insulin-like growth factor I and vascular endothelial growth factor in determining the cause of obstructive cholestasis. *Ann Intern Med* 2007; **147**: 451-459 [PMID: 17909206 DOI: 10.7326/0003-4819-147-7-200710020-00003]

431 **Brockmann J**, Emparan C, Hernandez CA, Sulkowski U, Dietl KH, Menzel J, Wolters H, Glodny B, Senninger N. Gallbladder bile tumor marker quantification for detection of pancreato-biliary malignancies. *Anticancer Res* 2000; **20**: 4941-4947 [PMID: 11326643]

432 **Natsios A**, Vezakis A, Kaparos G, Fragulidis G, Karakostas N, Kouskouni E, Logothetis E, Polydorou A. Significance of serum and bile tumor markers in the diagnostic approach of patients with malignant pancreatobiliary disease. *J BUON* 2015; **20**: 1030-1036 [PMID: 26416052]

433 **Joo KR**, Kim DH, Park JH, Bang SJ, Shin JW, Park NH. The role of bile carcinoembryonic antigen in diagnosing bile duct cancer. *J Korean Med Sci* 2003; **18**: 855-858 [PMID: 14676443 DOI: 10.3346/jkms.2003.18.6.855]

434 **Terai K**, Jiang M, Tokuyama W, Murano T, Takada N, Fujimura K, Ebinuma H, Kishimoto T, Hiruta N, Schneider WJ, Bujo H. Levels of soluble LR11/SorLA are highly increased in the bile of patients with biliary tract and pancreatic cancers. *Clin Chim Acta* 2016; **457**: 130-136 [PMID:

27079357 DOI: 10.1016/j.cca.2016.04.010]

435 **Matull WR**, Andreola F, Loh A, Adiguzel Z, Deheragoda M, Qureshi U, Batra SK, Swallow DM, Pereira SP. MUC4 and MUC5AC are highly specific tumour-associated mucins in biliary tract cancer. *Br J Cancer* 2008; **98**: 1675-1681 [PMID: 18475301 DOI: 10.1038/sj.bjc.6604364]

436 **Adrait A**, Dumonceau JM, Delhaye M, Annessi-Ramseyer I, Frossard JL, Couté Y, Farina A. Liquid Biopsy of Bile based on Targeted Mass Spectrometry for the Diagnosis of Malignant Biliary Strictures. *Clin Transl Sci* 2021; **14**: 148-152 [PMID: 33048472 DOI: 10.1111/cts.12890]

437 **Budzynska A**, Nowakowska-Dulawa E, Marek T, Boldys H, Nowak A, Hartleb M. Differentiation of pancreatobiliary cancer from benign biliary strictures using neutrophil gelatinase-associated lipocalin. *J Physiol Pharmacol* 2013; **64**: 109-114 [PMID: 23568978]

438 **Zabron AA**, Horneffer-van der Sluis VM, Wadsworth CA, Laird F, Gierula M, Thillainayagam AV, Vlavianos P, Westaby D, Taylor-Robinson SD, Edwards RJ, Khan SA. Elevated levels of neutrophil gelatinase-associated lipocalin in bile from patients with malignant pancreatobiliary disease. *Am J Gastroenterol* 2011; **106**: 1711-1717 [PMID: 21670771 DOI: 10.1038/ajg.2011.187]

439 **Roli L**, Pecoraro V, Trenti T. Can NGAL be employed as prognostic and diagnostic biomarker in human cancers? *Int J Biol Markers* 2017; **32**: e53-e61 [PMID: 28106227 DOI: 10.5301/jbm.5000245]

440 **Farina A**, Dumonceau JM, Antinori P, Annessi-Ramseyer I, Frossard JL, Hochstrasser DF, Delhaye M, Lescuyer P. Bile carcinoembryonic cell adhesion molecule 6 (CEAM6) as a biomarker of malignant biliary stenoses. *Biochim Biophys Acta* 2014; **1844**: 1018-1025 [PMID: 23806607 DOI: 10.1016/j.bbapap.2013.06.010]

441 **Ayaru L**, Stoeber K, Webster GJ, Hatfield AR, Wollenschlaeger A, Okoturo O, Rashid M, Williams G, Pereira SP. Diagnosis of pancreaticobiliary malignancy by detection of minichromosome maintenance protein 5 in bile aspirates. *Br J Cancer* 2008; **98**: 1548-1554 [PMID: 18414413 DOI: 10.1038/sj.bjc.6604342]

442 **Keane MG**, Huggett MT, Chapman MH, Johnson GJ, Webster GJ, Thorburn D, Mackay J, Pereira SP. Diagnosis of pancreaticobiliary malignancy by detection of minichromosome maintenance protein 5 in biliary brush cytology. *Br J Cancer* 2017; **116**: 349-355 [PMID: 28081547 DOI: 10.1038/bjc.2016.447]

443 **Hedström J**, Haglund C, Leinonen J, Nordling S, Stenman UH. Trypsinogen-1, -2 and tumour-associated trypsin-inhibitor in bile and biliary tract tissues from patients with biliary tract diseases and pancreatic carcinomas. *Scand J Clin Lab Invest* 2001; **61**: 111-118 [PMID: 11347977 DOI: 10.1080/00365510151097584]

444 **Parsi MA**, Li A, Li CP, Goggins M. DNA methylation alterations in endoscopic retrograde cholangiopancreatography brush samples of patients with suspected pancreaticobiliary disease. *Clin Gastroenterol Hepatol* 2008; **6**: 1270-1278 [PMID: 18995218 DOI: 10.1016/j.cgh.2008.07.007]

445 **Pei Z**, Liu SM, Huang JT, Zhang X, Yan D, Xia Q, Ji C, Chen W, Xu J, Wang J. Clinically relevant circulating microRNA profiling studies in pancreatic cancer using meta-analysis. *Oncotarget* 2017; **8**: 22616-22624 [PMID: 28186984 DOI: 10.18632/oncotarget.15148]

446 **Ohtsubo K**, Miyake K, Arai S, Fukuda K, Yanagimura N, Suzuki C, Otani S, Adachi Y, Tanimoto A, Nishiyama A, Yamashita K, Takeuchi S, Notohara K, Yoshimura K, Yano S. Aberrant Methylation of Tumor Suppressive miRNAs in Bile from Patients With Pancreaticobiliary Diseases. *Anticancer Res* 2019; **39**: 5449-5459 [PMID: 31570439 DOI: 10.21873/anticanres.13738]

447 **Haug U**, Wente MN, Seiler CM, Jesenofsky R, Brenner H. Stool testing for the early detection of pancreatic cancer: rationale and current evidence. *Expert Rev Mol Diagn* 2008; **8**: 753-759 [PMID: 18999925 DOI: 10.1586/14737159.8.6.753]

448 **Tobi M**, Elitsur Y, Moyer MP, Halline A, Deutsch M, Nochomovitz L, Luk GD. Mucosal origin and shedding of an early colonic tumor marker defined by Adnab-9 monoclonal antibody. *Scand J Gastroenterol* 1993; **28**: 1025-1034 [PMID: 8303203 DOI: 10.3109/00365529309098304]

449 **Qiao SX**, Yuan M, Liu YL, Lin XS, Zhang XP, Tobi M. Detection of gastric cancer and premalignant lesions by novel marker glycoprotein 87 using monoclonal antibody Adnab-9. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 1095-1099 [PMID: 14578149]

450 **Tobi M**, Kim M, Weinstein DH, Rambus MA, Hatfield J, Adsay NV, Levi E, Evans D, Lawson MJ, Fligiel S. Prospective markers for early diagnosis and prognosis of sporadic pancreatic ductal adenocarcinoma. *Dig Dis Sci* 2013; **58**: 744-750 [PMID: 23001406 DOI: 10.1007/s10620-012-2387-x]

451 **Tobi M**, Hatfield J, Adsay V, Galagan K, Kozarek R, Inagaki M, Kasai S, Tokusashi Y, Obara T, Hruban R, Lough J, Barkun A, Jabbari M, Sheikh R, Ruebner B, Lawson M, Ben-Josef E, Fligiel S. Prognostic Significance of the Labeling of Adnab-9 in Pancreatic Intraductal Papillary Mucinous Neoplasms. *Int J Gastrointest Cancer* 2001; **29**: 141-150 [PMID: 12754384]

452 **Ren Y**, Gao J, Liu JQ, Wang XW, Gu JJ, Huang HJ, Gong YF, Li ZS. Differential signature of fecal microRNAs in patients with pancreatic cancer. *Mol Med Rep* 2012; **6**: 201-209 [PMID: 22504911 DOI: 10.3892/mmr.2012.862]

453 **Link A**, Becker V, Goel A, Wex T, Malfertheiner P. Feasibility of fecal microRNAs as novel biomarkers for pancreatic cancer. *PLoS One* 2012; **7**: e42933 [PMID: 22905187 DOI: 10.1371/journal.pone.0042933]

454 **Caldas C**, Hahn SA, Hruban RH, Redston MS, Yeo CJ, Kern SE. Detection of K-ras mutations in the stool of patients with pancreatic adenocarcinoma and pancreatic ductal hyperplasia. *Cancer Res* 1994; **54**: 3568-3573 [PMID: 8012983]

455 **Haug U**, Hillebrand T, Bendzko P, Löw M, Rothenbacher D, Stegmaier C, Brenner H. Mutant-enriched PCR and allele-specific hybridization reaction to detect K-ras mutations in stool DNA: high prevalence in a large sample of older adults. *Clin Chem* 2007; **53**: 787-790 [PMID: 17317884 DOI: 10.1373/clinchem.2006.078188]

456 **Kisiel JB**, Yab TC, Taylor WR, Chari ST, Petersen GM, Mahoney DW, Ahlquist DA. Stool DNA testing for the detection of pancreatic cancer: assessment of methylation marker candidates. *Cancer* 2012; **118**: 2623-2631 [PMID: 22083596 DOI: 10.1002/cncr.26558]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com