

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 July 14; 27(26): 3951-4251



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**INDEXING/ABSTRACTING**

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Ji-Hong Lin*; Production Department Director: *Yun-Jie Ma*; Editorial Office Director: *Ze-Mao Gong*.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

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

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

July 14, 2021

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**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



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

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**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.

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**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

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### 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

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**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 12<sup>th</sup> 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 ( $\alpha$ - $\beta$ +) or Le ( $\alpha$  +  $\beta$ -) blood groups will express the antigen, its sensitivity in the diagnosis of PC is questionable as 10% of the population have a Le ( $\alpha$ - $\beta$ -) 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 <sup>[146]</sup> , 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-β[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  $\gamma$ 2:** Laminin  $\gamma$ 2 (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  $\alpha$ 2-glycoprotein-1:** Leucine-rich  $\alpha$ 2-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  $\alpha$ -chain:** C4b-binding protein  $\alpha$ -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 REG1 $\beta$  resulting in modest diagnostic accuracy[108].

**Regenerating protein family:** REG1 $\beta$ , 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 REG1 $\beta$  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 REG1 $\beta$  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 thyroxine 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 than 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 periaampullary 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  $\beta$ -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 metallo-proteinase 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- $\beta$ ) as a diagnostic biomarker in PC, with serum levels varying in those diagnosed with the malignancy. In addition to this TGF- $\beta$  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 to 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- $\beta$  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- $\alpha$ :** There is variability in the data pertaining to TNF- $\alpha$  as a diagnostic biomarker in PC. Although the majority of studies report elevated levels of TNF- $\alpha$  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 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, where 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 as 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 CEACAM6 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 chemoresistance. 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 promoters[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 an 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 periaampullary 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], TFP12[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: <i>HOTAIR</i> [428], <i>PVT1</i> [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 <sub>1</sub> -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: <i>TFPI2</i> [444], <i>NPTX2</i> [444], <i>CCND2</i> [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; TFPI2: 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 <i>KRAS</i> [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.

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