Table S1 Comparison of PC derived EVs *vs.* other cancer biomarkers

Potential biomarker	Sample type	Diagnostic value in PC patients	Advantages	Disadvantages	References
Carbohydrate antigen 19-9 (CA19-9)	Serum	Sensitivity: 79-81%; Specificity: 82-90%	Relatively easy collection; reliable marker for treatment response and monitoring	Poor screening marker; elevated expression in benign jaundice, pancreatitis, ovarian cancer or other malignancies	(1)
Circulating tumour cells (CTCs)	Serum/plasma	Sensitivity: 75%; Specificity: 96.4%; AUC: 0.867; 95% CI: 0.798-0.935	Correlated with poor prognosis	Low concentration in serum/plasma; Lack of evidence in large scale clinical setting; variable in isolation techniques	(2-4)
Cell free DNA (cfDNA)	Plasma	Combination of 5mC and 5hmC prediction model: Sensitivity: 93.8%; Specificity: 95.5%; AUC: 0.99	Correlated with poor prognosis	Utility is limited to identifying existing mutation in clinical setting; Lacks evidence in large scale clinical setting	(5)
Extracellular vesicles (EVs)	Plasma/serum/pancreatic juice	GPC1+ study: Sensitivity: 95-100%; Specificity: 95-100%	Correlated to early detection, prognostic marker and potential tumour staging marker	Variability in isolation techniques; Lacks evidence in high quality isolation in clinical setting	(6-17)

AUC, area under curve.

Table S2 Potential EV biomarkers in pancreatic cancer

Type of EV cargo	EV content	Experimental Approach	Sample Type	PC patient sample size	Sensitivity and specificity	Relevance to PC	Reference
Micro RNA (miRNA)	miR-1246, miR-3976, miR-4644, miR-4306	RT-PCR, qRT-PCR	Serum samples and PC cell lines	miR-1246, miR-4644 and miR-4306: Patients: 12. miR-3976: Patients: 131	miR-1246: Sensitivity: 66.7%, Specificity:100%, AUC: 0.814. miR-4644: Sensitivity: 75%, Specificity: 76.9%, AUC: 0.76	Elevated expression	(13,15,18)
	miR-18a	qRT-PCR	Patient plasma samples	Patients: 36	Not available	Elevated expression	(19,20)
	miR-17-5p	qRT-PCR	Patient serum samples	Patients: 22	Sensitivity: 72.7%, Specificity: 92.6%	Correlated to advanced stage of PC	(21)
	miR-122-5p	qRT-PCR	Patient plasma samples	Patients: 216	AUC: 0.81	Diagnostic marker	(7)
	miR-let7a	LC-MS/MS, qRT-PCR	Patient plasma samples	Patients: 29	Sensitivity: 100%, Specificity	Lower expression linked to PC progression	(22,23)
	miR-191, miR-451a and miR-21	qRT-PCR	Patient plasma samples	Patients: 32	miR-191: Sensitivity: 71.9%, Specificity: 84.2%. miR-451a: Sensitivity: 65.6%, Specificity: 85.7%. miR-21: Sensitivity: 80.7%, Specificity: 81.0%	Elevated expression	(24)
	miR-21	Western Blotting, TCLN biochip	Patient plasma and mouse serum samples	Patients: 36	Sensitivity: 95.5%, Specificity: 81.5%	Elevated expression	(25)
	miR-451a	qRT-PCR	Patient serum samples	Patients: 6	Sensitivity: 69.2%, Specificity: 70.8%	Elevated expression	(26)
	miR-196b/LCN2/TIMP1	RT-PCR	Patient serum and duodenal juice	Patients: 50	Sensitivity: 80%, Specificity: 80%, AUC: 0.93	Elevated expression	(27)
	miR-214	qRT-PCR	Patient plasma samples	Patients: 20	Not available	Lower expression linked to better survival rate. Diagnostic marker	(28)
	Ratio of miR-3940-5p/miR-8069	3D digital PCR	Patient urine samples	Patients: 43	Sensitivity: 58.1%, Specificity: 89.2%	Diagnostic marker	(29)
	miR-192-5p, miR-19a-3p, and miR-19b-3p	qRT-PCR	Patient serum samples	Patients: 159	Not available	Elevated expression; Diagnostic and prognostic value	(30)
	miR-10b, miR-21, miR-30c, miR-181a	LSPR-based assay	Patient plasma samples	Patients: 29	Sensitivity: 100%, Specificity: 100%	Diagnostic marker	(22)
Circular RNA (circ RNA)	has_circ_0000896 and has_circ_0000128	qRT-PCR	Patient plasma and cell culture samples	Patients: 8	Not available	Elevated expression	(31)
	circRNA-PDE8A	RNA binding protein immunoprecipitation assay, Biotinylated RNA pulldown assays	Patient plasma samples	Patients: 93	Not available	Elevated expression; correlated PC progression	(32)
	circ-IARS	qRT-PCR	Patient plasma, tissue and cell culture samples	Patients: 92	Not available	Elevated expression	(33)
	circRNA-0000069	Flow-cytometry, Western blotting, RT-qPCR	Patient tissue and cell culture samples	Patients: 179	Not available	Elevated expression	(34)

Table S2 *(continued)*

Table S2 *(continued)*

Type of EV cargo	EV content	Experimental Approach	Sample Type	PC patient sample size	Sensitivity and specificity	Relevance to PC	Reference
mRNA	CK18, CD63	Next Generation sequencing and qRT-PCR	Patient plasma samples	Patients: 89	AUC: 0.93	Detected in PDAC patients	(35)
	FGA, KRT19, HIST1H2BK, ITIH2, MARCH2, CLDN1, MAL2 and *TIMP1*	RNA sequencing analysis	Patient plasma samples	Patients: 284	AUC: 0.949	Detected in PDAC patients	(36)
Proteins	Glypican-1	UPLC-MS, Western Blot Analysis, qRT-PCR	Patient serum and tissue samples, Animal studies, cell lines	Patients: 190	Sensitivity: 100%, Specificity: 100%	Diagnostic/Screening tool	(6)
	MIF	Proteomics, RNA sequencing, tissue processing, immunofluorescence, SDS-PAGE, Western Blot, flow cytometry	Human peripheral blood samples, animal studies and Cell lines	Patients: 18	Not available	Initiates formation of pre- metastatic niche in the liver	(37)
DNA	NOTCH1, BRCA2	Next generation sequencing	Patient pleural fluid, blood, plasma	Patient: 3	Not available	Detected in patient exoDNA samples	(38)
	KRAS^{G12D} and *TP53*^{R273H}	ddPCR	Patient serum samples	Patients: 171	Not available	Elevated expression	(39)
	KRAS	ddPCR	Patient plasma samples	Patients: 194	Not available	Detected in PC patients	(40)
	KRAS	ddPCR	Patient plasma samples	Patients: 88	Not available	Elevated expression	(41)

GPC1+, glypican-1; RT-PCR, reverse transcriptase polymerase chain reaction; qRT-PCR, quantitative real time polymerase chain reaction; LC-MS/MS, Liquid chromatography-mass spectrometry; TCLN biochip, tethered cationic lipoplex nanoparticle biochip; LSPR-based assay, localized surface plasmon resonance based assay; UPLC-MS, ultra performance liquid chromatography mass spectrometry; SDS-PAGE, sodium dodecyl-sulfate polyacrylamide gel electrophoresis; ddPCR, droplet digital polymerase chain reaction; MIF, migration inhibitory factor; AUC, area under curve.

Table S3 Preclinical and clinical trials of PC derived EVs

Disease Model	Trial	Pharmacological drug	Administration	References
Mouse	Preclinical	siPAK4	Intratumoral injection	(42)
Mouse	Preclinical	Gemcitabine	Intravenous injection	(43)
Mouse	Preclinical	siKRASG12D	Intraperitoneal injection	(44)
Mouse	Preclinical	siKRASG12D	Intraperitoneal injection	(45)
Mouse	Preclinical	siKRASG12D and miRNA-145-5p	Intratumoral injection	(46)
Human	Clinical (Phase 1)	siRNA KrasG12D	Intravenous injection	(47)

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