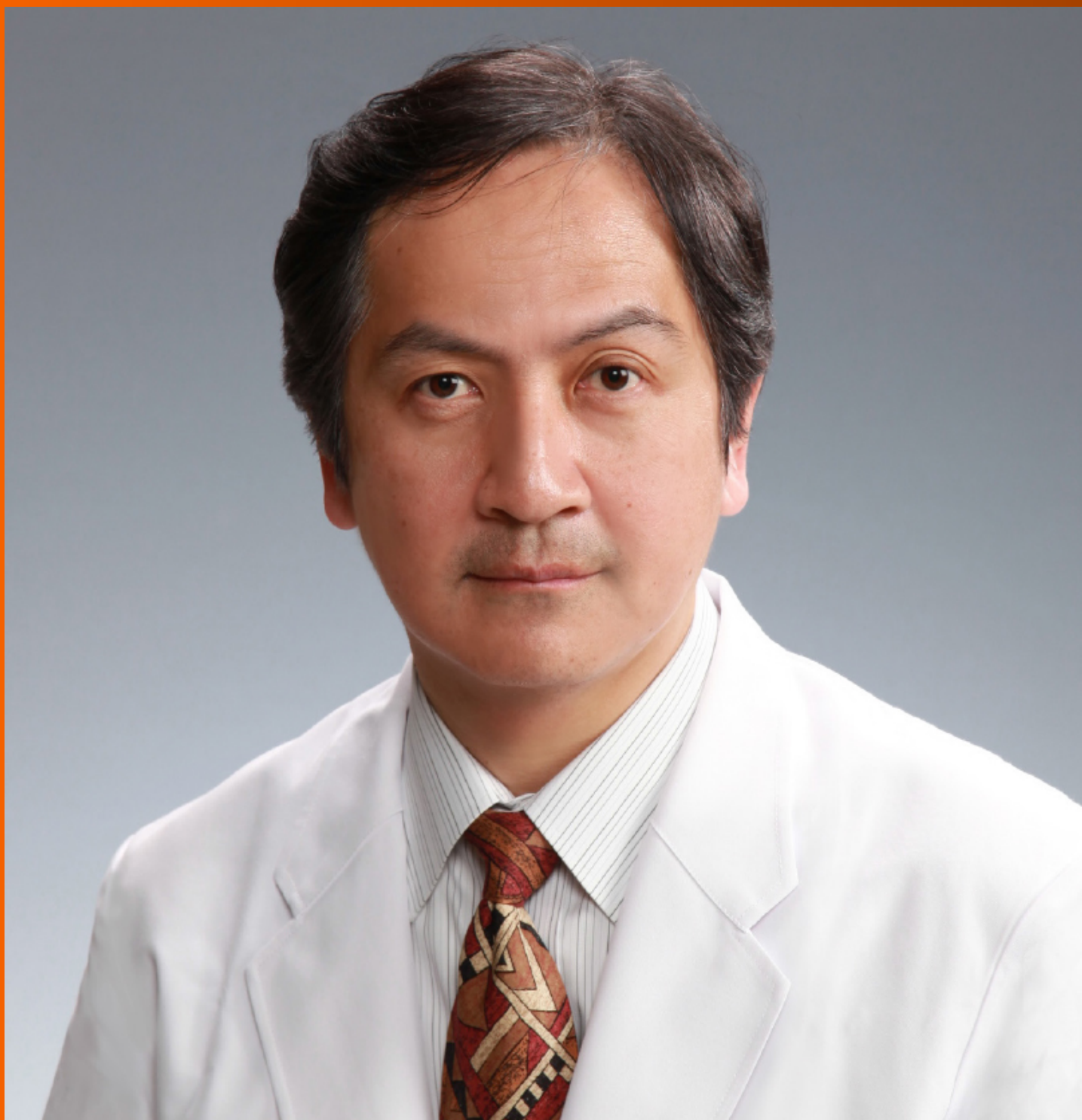


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## Molecular advances in pancreatic cancer: A genomic, proteomic and metabolomic approach

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### Abstract

Pancreatic ductal adenocarcinoma (PDAC) represents a challenging pathology with very poor outcomes and is increasing in incidence within the general population. The majority of patients are diagnosed incidentally with insidious symptoms and hence present late in the disease process. This significantly affects patient outcomes: the only cure is surgical resection but only up to 20% of patients present with resectable disease at the time of clinical presentation. The use of "omic" technology is expanding rapidly in the field of personalised medicine - using genomic, proteomic and metabolomic approaches allows researchers and clinicians to delve deep into the core molecular processes of this difficult disease. This review gives an overview of the current findings in PDAC using these "omic" approaches and summarises useful markers in aiding clinicians treating PDAC. Future strategies incorporating these findings and potential application of these methods are presented in this review article.

**Key Words:** Pancreatic ductal adenocarcinoma, Pancreatic adenocarcinoma; Genomic; Proteomic; Metabolomic

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**Core Tip:** Treatment for pancreatic ductal adenocarcinoma is limited by the severity of the pathology, limited biomarkers and late presentation of patients. Utilising genomic, proteomic and metabolomic research into pancreatic ductal adenocarcinoma has provided insight into understanding the disease process as well as providing suitable markers of diagnosis and treatment to improve clinical outcomes.

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## INTRODUCTION

Pancreatic adenocarcinoma or pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a 1-year and 5-year survival rate of 24% and 9% respectively and make up the majority of pancreatic cancers (PC) (85%) with others arising from the endocrine tissue of the pancreas[1]. According to the GLOBOCAN statistics in 2020, PC were the 12<sup>th</sup> most commonly diagnosed cancer in the world with the incidence increasing with the Human Development Index; the highest cumulative risks being in North America and Europe[2]. Unfortunately, developments in treatment have not progressed as rapidly as other cancers and PC are projected to become the second leading cause of cancer related death in the United States by 2030[3]. Majority of PDAC cases are diagnosed at a late stage owing to the lack of clinical features early on in its course. Currently the only curative option is through surgical resection, but only roughly 20% of all cases are operable at the time of diagnosis, with limited chemotherapy and radiotherapy options at present[4]. However, with the emergence of "omics" research, new advances have been made in improving the treatment of PC.

## GENOMICS, PROTEOMICS AND METABOLOMICS

The field of "omics" research refers to the use of high throughput technologies to globally analyse a biological system at the molecular level. This takes place on multiple "levels" depending on the nature of the molecules being studied i.e. genetic material, proteins and metabolites[5].

The first of these fields to emerge was genomics, with the goal of characterising the genome and the variations of its structure and expression leading to pathogenesis[5]. Cancer being essentially a disease of the genome, occurring through the accumulation of genetic mutations, the insights gleaned from such analysis is invaluable for cancer research[6].

With the advent of next-generation sequencing [whole-genome sequencing (WGS), whole-exome sequencing (WES) and RNA sequencing], this can now be done quicker and more accurately than traditional methods[7]. WES, which sequences all protein coding exons, is more abundantly utilised as it is more accurate and relatively less expensive compared to WGS, which also has the issue of complex data analysis and interpretation[6].

At the protein level, proteomic studies identify and quantify the proteome of a biological system, their interactions and post-translational modifications[5]. Proteomics technologies are largely based in protein separation (gel-based techniques and chromatography) and mass spectrometry (MS) for high throughput analysis of proteins in tissues and fluids[8,9]. Quantification methods include isobaric tags for relative and absolute quantification, isotope coded affinity tag and differential image gel electrophoresis, with tandem MS[8,9]. Modifications can also be detected by MS through the corresponding change in mass brought on by the modifying process[5].

Metabolomics involves the study of all the low molecular weight metabolites within a sample that gives a comprehensive reflection of the sample's phenotype at a given time[10]. Identification and quantification of these metabolites can indicate the metabolic processes occurring and changes in these can then be associated with disease processes. Like proteomics, metabolomics is largely driven by MS and chromatography, however there is added complexity due to the variation of the physical properties of these metabolites. Due to this, the metabolites need to be stratified along these properties followed by the application of analytic methods optimised for each type of metabolite[10].

## MOLECULAR SUBTYPES FOR PERSONALISED MEDICINE

### Genomic subtypes

Waddell *et al*[11] utilised WGS to map the genome of 100 PDAC specimens. Their findings reinforced the known main drivers of PDAC (KRAS, TP53, CDKN2A and

SMAD4) and also found multiple other mutations at much lower prevalence. The authors described four subtypes of PDAC based on the quantity of variations in chromosome structure: (1) Stable (20%; < 50 structural variations and widespread aneuploidy); (2) Locally rearranged (30%; significant events on 1-2 chromosomes); (3) Scattered (36%; < 200 structural variations and moderate chromosomal damage); and (4) Unstable (14%; large number of structural variation and defects in DNA damage repair). The unstable subtype was associated with a high BReast CAncer gene (BRCA) mutational signature, suggesting defects in DNA damage repair, possibly sensitising these to platinum based chemotherapy or poly (ADP-ribose) polymerase inhibitors (PARPi). Indeed, from their sample, 4 out of 5 of these patients treated with platinum based chemotherapy showed response to treatment[11].

Singhi *et al*[12] utilised real time targeted sequencing of exons and introns of 3594 PDAC specimens during the course of clinical care and reported that 17% of these may be susceptible to current therapies based on this genomic data. They found genetic alterations in receptor tyrosine kinase (RTK)/Ras/mitogen-activated protein kinase (MAPK) activation, DNA damage repair, cell cycle control, TGF- $\beta$  signalling, histone modification, SWI/SNF protein complex, PI3L/mTOR signalling, WNT/B-catenin pathway, RNA splicing, NOTCH pathway, angiogenesis and Hedgehog signalling. Interestingly, the investigators also found that 14% of their sample exhibited mutations in DNA damage repair genes (BRCA-FANC family). Further to this, they identified genetic alterations in receptor tyrosine kinases as potential targets on a background of wild-type KRAS PDAC (12% of the sample)[12].

Aguirre *et al*[13] performed deep WES of PDAC primaries and metastases for 73 patients having clinically indicated biopsies. Average time for the results of WES to return to the clinicians was 39 d, longer than that of research only biopsies (28 d) due to the need for histological diagnosis prior to sequencing. Analysis of these findings resulted in three mutational signatures: SigA (homologous recombination deficiency), SigB (aging) and SigC (unknown aetiology). Around 40% of these patients had potentially targetable genomic findings, when excluding KRAS or CDKN2A, 48% were eligible for clinical trials or off-label use of other therapeutic agents and 24% of patients were indeed enrolled onto a clinical trial or treated with an off-label agent. This shows the feasibility of implementing WES clinically to guide treatment choice. Clinically relevant findings included DNA damage repair (DDR) mutations and BRAF mutations in KRAS wild-type PDAC which may confer sensitivity to platinum-based chemotherapy/PARPi and MAPK inhibition respectively. The authors also presented two such case studies with significant responses to treatment[13].

### Proteomic subtypes

Using 56 PDAC liver metastases specimens, Law *et al*[14] performed liquid chromatography-mass spectrometry (LC-MS/MS) to identify 30811 peptides that mapped to 916 proteins comprising of at least 5 peptides in 80% of the sample. Functional analysis of these proteins showed that they play a role in, “extracellular matrix organization, protein processing and transport, translation, glycolytic processes, NADPH metabolism, cell migration, immune response, fibronectin binding, and cell homeostasis”[14].

These proteins were analysed to categorise four PDAC subtypes and three protein clusters. The matched subtypes and clusters are: “Inflammatory” (cluster 3 - pentose phosphate pathway, adaptive immune response, complement activation, IL8 production and extracellular fibril organisation), “proliferative” (cluster 2 - translation, cell proliferation and telomere maintenance), “progenitor-like” (cluster 1 - ethanol oxidation pathways, mitochondrial fatty acid  $\beta$ -oxidation and retinoic acid signaling pathways) and “metabolic” (cluster 1). Both the “progenitor-like” and “metabolic” subtypes exhibit cluster 1 proteins however, the latter shows higher expression of these proteins. The authors were also able to map these subtypes onto previously defined transcriptomic subtypes, making this the first proteomic study with data robust enough to make such a correlation[14].

Clinically, the “proliferative” subtype was associated with a history of alcohol use and the “metabolic” subtype was associated with tobacco use. The “metabolic” and “progenitor-like” subtypes had a decreased risk of death when treated with FOL-FIRINOX + gemcitabine compared to the other two subtypes. Further analysis also showed that there was a significant increase in survival when “progenitor-like” subtypes are treated with gemcitabine and that the “metabolic” subtype had a negative correlation between survival probability and abraxane/paclitaxel treatment. These analyses support the use of proteomics derived subtypes as a method for selecting targeted therapeutics however more robust trials are needed to validate these findings [14].

Another interesting finding from this study is the role of serine hydroxymethyltransferase (SHMT1) (involved in the folic acid cycle) in gemcitabine resistance. Comparison of untreated samples and samples treated with only gemcitabine showed that SHMT1 was significantly down-regulated in the treatment group. The investigators further displayed increased EC50 of gemcitabine in cell lines with SHMT1 knockdown compared to the control group, showing that SHMT1 is a potential mediator of gemcitabine resistance. Expression of SHMT1 was higher in “metabolic” and “progenitor-like” subtypes compared to the other two subtypes regardless of gemcitabine treatment. Expression of this protein may potentially guide the choice of gemcitabine as treatment or monitor those on gemcitabine for resistance to treatment [14].

Humphrey *et al* [15] used liquid chromatography-mass spectrometry (LC-MS/MS) to stratify two cohorts of PDAC cell lines American Type Culture Collection (ATCC) and The Kinghorn Cancer Centre (TKCC), along tyrosine phosphorylation (pTyr) sites. The authors produced a list of 1622 pTyr sites from 797 proteins. Of these, 144 had significant subtype specificity. ATCC subtype 1 showed hypophosphorylation of 65 pTyr sites and the enriched proteins were involved in formation and regulation cell-cell adheren junctions and tight junctions. ATCC subtype 2 contained 54 up-regulated pTyr sites (specifically increased relative phosphorylation rather than increased protein levels) with enrichment of proteins involved in mRNA processing and spliceosome pathways. ATCC subtype 3 showed significantly increased phosphorylation (in both relative phosphorylation and protein expression) in 15 pTyr sites of RTKs including EGFR, MET, RON, EPHA4, EPHB2/3/4 and DDR2 [15].

When this methodology was applied to the TKCC cohorts, 1220 pTyr sites were identified, of which 383 were subtype specific. TKCC subtypes 1 and 2 showed 101 and 73 down-regulated pTyr sites, while TKCC subtype 3 showed up-regulation of 209 pTyr sites and was enriched for Ephrin and EGFR signalling. Targeting RTK pTyr sites in the TKCC cohort showed increased phosphorylation of RTKs in subtype 3 including sites on EGFR, EPHA2, DDR1, FGFR1, INSR, MERTK, MET, and RON [15].

Of the subtype specific pTyr sites identified, 8 were identified as “common classifier sites”, able to predict the subtype in the ATCC cohort. Subtypes 1, 2 and 3 were identified to exhibit low medium and high phosphorylation of these sites respectively. As both cohorts had subtypes that were “RTK-enriched”, the investigators tested the cell lines in this cohort against erlotinib, an EGFR kinase inhibitor. Indeed, the cell lines in this subtype showed increased sensitivity to erlotinib. The authors recognised that the pTyr signature of these RTKs are what conferred sensitivity to RTK blockade rather than expression levels and so stratifying patients with such a signature can potentially allow targeted therapeutic regimes to be studied [15].

### Metabolomic subtypes

Metabolomics profiling by Daemen *et al* [16] using LC-MS/MS and gas chromatography-MS represents the only metabolomic study to stratify PDAC. The investigators examined 38 “PDAC-derived” cell lines to quantify 256 metabolites. Analysis of these metabolites revealed three subtypes of PDAC, described as: (1) Slow proliferating (34%); (2) Glycolytic (27%); and (3) Lipogenic (39%). The slow proliferating subtype was low in amino acids and carbohydrates, and the cells had a significantly longer doubling time than the other two subtypes. The glycolytic subtype showed increased levels of metabolites of the glycolytic and serine pathways (phosphoenolpyruvate, glyceraldehyde-3-phosphate, lactate, and serine) and decreased redox balance metabolites (NAD, NADH, NADP, NADPH, GSSG, GSH and flavin adenine dinucleotide). The lipogenic pathway showed increased levels of lipid metabolites (palmitic acid, oleic acid, palmitoleic acid and myristic acid), oxidative phosphorylation (OXPHOS) metabolites (coenzymes Q9 and Q10) and aspartate-malate shuttle metabolites (aspartate and glutamate) [16].

Moreover, the authors predicted and demonstrated *in vitro*, sensitivity of the glycolytic subtypes to aerobic glycolysis inhibitors (oxamate and the LDHA inhibitor GNE-140), glutaminolysis inhibitor (BPTES) and inhibitors of gamma-glutamyl-cysteine synthetase (BSO) and cystine transporter [(S)-4-CPG], and also demonstrated sensitivity of the lipogenic subtype to lipid synthesis inhibitors (FASN inhibitor GSK1195010, SCD inhibitor, cerulenin, and orlistat). They also performed *in vivo* confirmatory tests, inducing 68% tumour growth inhibition of the glycolytic cell line with LDHA inhibition and 52% tumour growth inhibition in the lipogenic cell line with SCD inhibition [16]. Table 1 summarises these studies and the clinically significant findings.



Table 1 Summary of molecular subtyping studies

Ref.	Subtypes	Clinical significance
	Genomic	
Waddell <i>et al</i> [11]	Stable, locally re-arranged, scattered and unstable	High BRCA mutational signature in the unstable subtype, sensitizing to PARPi and PBC.
Singhi <i>et al</i> [12]	-	Real time genetic sequencing. 17% of specimens found to have sensitivities to available treatments. Potential therapeutic targets.
Aguirre <i>et al</i> [13]	SigA, SigB and SigC	Potential targets in 40% of patients. 48% eligible for trials/off-label use. Of 24% enrolled onto a clinical trial.
	Proteomic	
Law <i>et al</i> [14]	Inflammatory, proliferative, progenitor-like and metabolic	↓Risk of death in metabolic and progenitor-like subtypes treated with FOLFIRINOX+Gemcitabine. ↑Survival in progenitor-like subtype treated with gemcitabine. SHMT1 a potential mediator of gemcitabine resistance.
Humphrey <i>et al</i> [15]	TKCC subtypes 1, 2 and 3 ATCC subtypes 1, 2 and 3 Metabolomic	Subtypes 3 in both cohorts showed increased sensitivity to erlotinib, potentially mediated by tyrosine phosphorylation of RTK sites.
Daemen <i>et al</i> [16]	Slow proliferating, glycolytic and lipogenic	Glycolytic subtype sensitive to inhibitors of aerobic glycolysis, glutaminolysis, γ-glutamylcysteine and Xct. Lipogenic subtype sensitive to lipid synthesis inhibitors.

BRCA; Breast cancer gene; RTK: Receptor tyrosine kinase; PBC: Platinum-based chemotherapy; PARPi: Poly (ADP-ribose) polymerase inhibitors; xCT: Cystine transporter; SHMT1: Serine hydroxymethyltransferase 1.

## BIOMARKER DISCOVERY

Currently, the only biomarker for PDAC is carbohydrate antigen 19-9 (CA19-9), approved by the Food and Drug Administration for use in clinical practice[17]. Unfortunately, the median sensitivity and specificity of CA19-9 is 79% and 82% respectively, making it unsuitable for use as a diagnostic marker, with it being raised in other gastrointestinal pathology[18]. Further complicating this is the fact that roughly 10% of the population with a Lewis-negative genotype do not express CA19-9 (a sialyl-Lewis A tetrasaccharide) at all. Its use currently is limited to monitoring CA19-9 positive PDAC for progression or recurrence after resection[17]. There is an obvious need for further investigation for potential biomarkers for early diagnosis, prognosis and sensitivity/resistance to therapeutics. "Omics" techniques have the capability to produce large amounts of data which can be correlated with specific states of the biological system and so there is great potential for this data to be used for biomarker discovery.

As mentioned earlier, one of the main factors that influence the outcomes in PDAC is that the majority are diagnosed at an advanced stage. With surgical resection currently being the only curative option, improving the proportion of patients eligible for surgery would drastically improve outcomes. The use of "omics" technologies to screen for potential diagnostic markers that can accurately differentiate PDAC from other pathologies or normal healthy tissue can lead the way to targeted diagnostic panels that can be implemented clinically.

An emerging area of research is the use of "liquid biopsy", which is the sampling of tumour material which spills into the circulation[19]. The main components of such a biopsy include circulating tumour cells (CTC), cell-free DNA (cfDNA) and circulating exosomes. cfDNA is genetic material released into the circulation from benign and malignant cells during cell death, circulating tumour DNA (ctDNA) being the subset of this derived from malignant cells. Exosomes are extracellular vesicles released from cells into various bodily fluids and can contain proteins and genetic material for analysis. They have a longer half-life and are constantly being produced by cells making them more readily available for isolation than cfDNA[19].

Zhu *et al* [20] conducted a systematic review and meta-analysis of 19 studies utilising ctDNA, CTCs and exosomes to diagnose "pancreatic adenocarcinoma", "pancreatic ductal adenocarcinoma" or "pancreatic cancer". They found that the overall sensitivity, specificity and area under the curve (AUC) for liquid biopsy was 0.8 [95% confidence interval (CI): 0.77-0.82], 0.89 (95%CI: 0.87-0.91) and 0.93 respectively, demonstrating the feasibility of liquid biopsy as a diagnostic tool. Of the three components,

exosomes were found to have the highest accuracy with a sensitivity, specificity and AUC of 0.93 (95%CI: 0.90-0.95), 0.92 (95%CI: 0.88-0.95), and 0.9819 respectively. The authors suggested that the high sensitivity of the exosomes was due to the exocrine function of the pancreases and the high specificity due to the methods used to analyse the exosomes in these studies [polymerase chain reaction (PCR) and flow cytometry] [20].

Overall sensitivity, specificity and AUC of the CTC studies was 0.74 (95%CI: 0.68-0.79), 0.83 (95%CI: 0.78-0.88), and 0.8166[20]. This was thought to be due to hepatic trapping of CTCs and due to reduced blood flow in pancreatic malignancies compared to normal tissue (decreasing the chances of cell shedding into the circulation)[20]. Indeed, it was found that for PC, the levels of CTC was the lowest compared to other types of cancer[21].

ctDNA's overall sensitivity, specificity and AUC was 0.64 (95%CI: 0.58-0.70), 0.92 (95%CI: 0.88-0.95), and 0.9478[20]. All of the ctDNA studies utilised PCR of KRAS mutations to distinguish PC from either healthy controls, pancreatitis or benign lesions. As mentioned before, KRAS is the most common genetic driver of PDAC and so utilising this as the marker for detection may be the reason for the high specificity. The relatively low sensitivity however may have been due to the abundance of ctDNA in the circulation[20]. It has been found that the abundance of ctDNA has a positive correlation with tumour load, supported by the physiology of ctDNA mentioned above: It is released through cell death[22]. Due to this, ctDNA may not be an ideal candidate for use in early detection of PDAC but may have a role as a prognostic biomarker or a marker of response to treatment, especially in those that are CA19-9 negative.

In terms of protein biomarkers, many studies have been done to characterise the differences in the proteomes of PDAC and normal control (NC) specimens from various sources including tissue samples, cell lines, serum/plasma and pancreatic juice[8]. While quite a few studies have been done, only a few of the biomarkers described overlap between studies. Further to this, none of these biomarkers have been put to use clinically, mainly due to the lack of validation in clinical trials, and standardised, reproducible and cost-effective analytical methods.

MS data combined with the results of a literature review by Capello *et al*[23] yielded 17 plasma protein biomarkers to distinguish early stage PDAC from benign pancreatic disease and NC. They tested these biomarkers using ELISA, first in a triage set which narrowed these down to 7 biomarkers, followed by validation of these 7 biomarkers in three independent plasma sample sets. Statistical analysis of the performance of these 7 biomarkers led to the development of a 3 biomarker panel of metalloproteinase inhibitor 1, leucine rich alpha-2-glycoprotein 1 and CA 19-9 which was able to differentiate PDAC cases from healthy controls with an AUC of 0.887 (95%CI: 0.817-0.957) in a blinded test set, which was a statistically significant improvement compared to CA 19-9 alone. The sensitivities at a fixed 95% and 99% specificity were 0.667 and 0.410 respectively, compared to the sensitivities of 0.538 and 0.462 respectively for CA 19-9 [23].

In terms of prognostic biomarkers, de Oliveira *et al*[24] recently conducted a meta-analysis of MS data from two systematic reviews of PDAC secretome and proteome. No protein was found to be present in all the studies and so the authors selected those that were presented in at least 2 studies, generating a list of 39 secreted proteins. Further gene expression analysis of 4747 tumours (of 10 types of cancers) and 2737 corresponding normal tissues for these proteins revealed that 31 of these were unregulated in PDAC, and when analysed for 10 cancer types showed that all 39 genes were enriched in PDAC *vs* the other types, with an opposite expression profile in acute myeloid leukaemia. Further to this, the authors displayed a correlation between the gene expression for these proteins and significantly shorter survival (hazard ratio = 5.36) in PDAC patients, which was validated in three independent data sets[24].

Peng *et al*[25] developed a protein signature to predict response to chemotherapy through LC-MS/MS of prepared serum samples from 16 stage IV PDAC patients. The three protein biomarker candidates vitamin-K dependent protein Z, sex hormone-binding globulin and von Willebrand factor, combined with CA 19-9 were used to make a biomarker panel, with biomarker positive patients having significantly shorter median survival in both stage III and stage IV patients [8.7 mo (95%CI: 6-11.7) for biomarker negative *vs* 19.2 mo (95%CI: 11.4-22.1) for biomarker positive].

A meta-analysis of metabolomic biomarkers for PC by Mehta *et al*[26] yielded 21 deregulated blood based biomarkers that appeared in at least 2 studies. The authors developed a 10 metabolite diagnostic panel from these biomarkers which was tested on plasma samples of 192 patients from four diagnostic groups: PC ( $n = 59$ ), NC ( $n = 48$ ), colorectal cancer (CRC,  $n = 66$ ) and type 2 diabetes mellitus (T2DM,  $n = 19$ ). The

**Table 2 Summary of biomarker discovery studies**

Ref.	Biomarkers	Sensitivity	Specificity	AUC
Zhu <i>et al</i> [20]	ctDNA	0.64	0.92	0.9478
	CTC	0.74	0.83	0.8166
	Exosome	0.93	0.92	0.9819
Capello <i>et al</i> [23]	TIMP1, LRG1 and CA19-9	0.667/0.410	0.95/0.99	0.887
Mehta <i>et al</i> [26]	Panel of: Lactate, LysoPC (18:2), Alanine, Choline, Threonine, Asparagine, Tyrosine, Lysine, Palmitate and 3-hydroxybutyrate	-	-	0.992 <i>vs</i> NC
				0.957 <i>vs</i> T2DM
				0.653 <i>vs</i> CRC
		Biomarker + ve median survival		Biomarker - ve median survival
Peng <i>et al</i> [25]	Panel of: PZ, SHBG, VWF and CA19-9	19.2 mo		8.7 mo
			AUC	
Martín-Blázquez <i>et al</i> [27]	Panel of: PS (12:0/15:1), TG (22:2/15:0/18:3), 4-oxo-Retinoic acid, Androsterone sulfate, LysoPE (18:2), Phenylalanylphenylalanine, all-trans-Decaprenyldiphosphate, LysoPC (18:2) and Dehydroepiandrosterone sulfate		0.992 (CI: 0.972-1.000)	

ctDNA: Circulating tumour DNA; CTC: Circulating tumour cells; TIMP1: Metalloproteinase inhibitor 1; LRG1: Leucine rich alpha-2-glycoprotein 1; CA19-9: Carbohydrate antigen 19-9; CI: Confidence interval; NC: Normal control; T2DM: Type 2 Diabetes mellitus; CRC: Colorectal cancer.

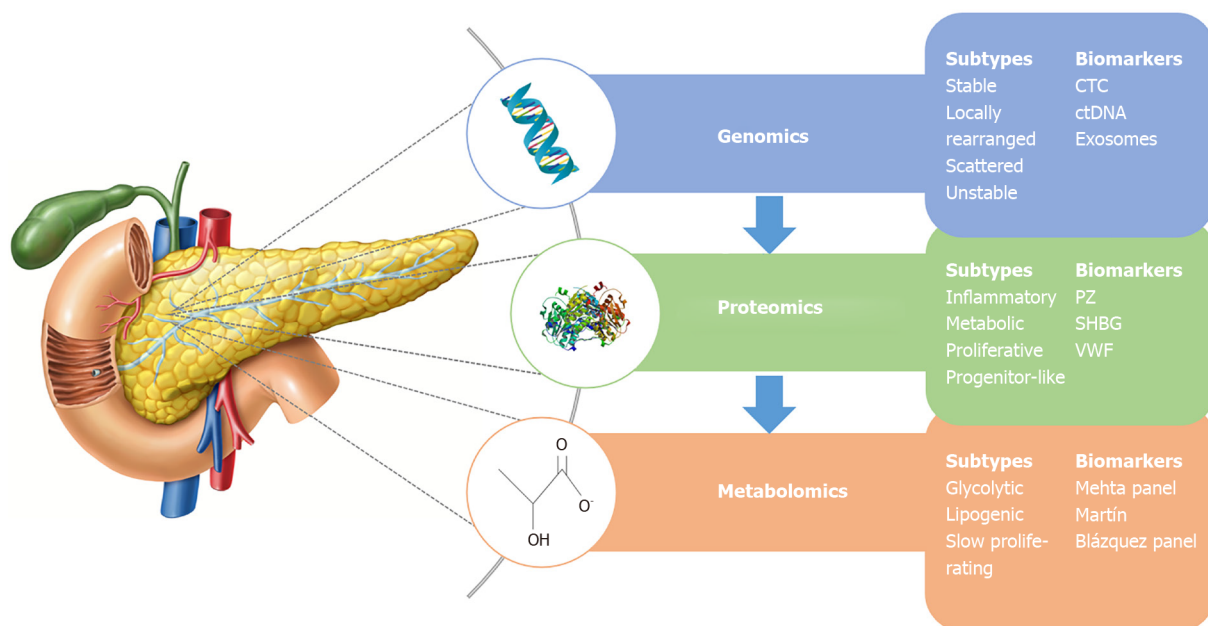
AUC of PC, T2DM and CRC *vs* NC were 0.992 (95%CI: 0.977-1), 0.957 (95%CI: 0.868-1) and 0.986 (95%CI: 0.967-1) respectively. The AUC of PC *vs* CRC was only 0.653 (95%CI: 0.543-0.757), suggesting a lack of specificity of the panel between these two groups. An index of the 10 metabolite panel showed that higher index values correlated with increased risk of malignancy, with a value of  $\geq 12.5$  representing a 100% risk of PC [26]. While the authors used the term “pancreatic cancer”, in their study, the authors manually curated the literature to ensure the comparison groups were PDAC patients and controls.

More recently, Martín-Blázquez *et al* [27] analysed serum from unresectable PDAC patients and NC using reverse-phase liquid chromatography and high-resolution MS to identify 86 significant metabolites. With these, the researchers proposed a model of 9 markers that discriminated PDAC from healthy controls with an AUC of 0.992 (95%CI: 0.972-1.000). Table 2 summarises these molecular subtyping studies while Figure 1 demonstrates subtypes and biomarkers by “Omics” level [28].

## CONCLUSION

### Closing thoughts and future considerations

“Omics” technologies have allowed mining of massive amounts of data, giving new insights into the complex, heterogeneous nature of PDAC. As described above, many studies have been done to describe molecular classifications and potential biomarkers, but none of these have yet been translated into clinical practice [28]. Several trials, as reviewed by Du *et al* [29], faced difficulties in sample procurement, low quality of samples and waiting time for sample analysis leading to patient deterioration or withdrawal. The authors suggest a multi-disciplinary approach with specialist input in sample acquisition in designated centres with high levels of experience. Issues regarding the technology should improve as these become more accessible to the clinical setting. Indeed, these difficulties were echoed by lessons learnt from the Individualized Molecular Pancreatic Cancer Therapy trial, a study that aimed to match patients with recurrent or metastatic PDAC to treatment based on genomic data [30]. Unfortunately, no patients were able to be enrolled into the study largely due to the quick progression of PDAC and due to inadequate numbers meeting the eligibility criteria. The investigators described four criteria that would need to be met for such a study to take place: (1) Screening of a sufficient number of patients; (2) Timely acquisition of tumour material for analysis; (3) Quick turnaround time of usable data; and (4)



**Figure 1 Genomic, proteomic and metabolomic subtypes and biomarkers of pancreatic cancer.** Double stranded DNA image[28]. CTC: Circulating tumour cells; ctDNA: Circulating tumour DNA; PZ: Vitamin-K dependent protein Z; SHBG: Sex hormone-binding globulin; VWF: Von Willebrand Factor.

Effective treatments or clinical trials for enrollment[30]. Currently, there is an exciting initiative by PrecisionPanc in the United Kingdom, where through a “Master Protocol”, patients suspected or diagnosed with PDAC will undergo prospective molecular profiling to guide enrollment into one of their five PRIMUS trials[31].

Additionally, many of these studies are largely comparative, most of them describing the difference in data between disease and normal states. Few studies have correlated their findings with upstream/downstream “omics” data and so there is an obvious need for integrated analysis of multiple “omics” levels. An example of integrated analysis is seen in the study by The Cancer Genome Atlas Research Network, who performed genomic, transcriptomic and proteomic analysis of 150 PDAC specimens using whole-exon sequencing, DNA methylation assays, RNA sequencing and reverse phase protein arrays[32]. The authors described molecular profiles along each of these “omic” levels, potential subtypes along transcriptomic and proteomic lines, potential therapeutic targets and through integrated analysis were able to describe some of the interplay between these levels, giving further insight into the complexity of PDAC. Another example is the study by Follia *et al*[33] who used genomic and transcriptomic data to describe four metabolic subtypes of PDAC (2 glycolytic and 2 non-glycolytic) which they correlated with the subtypes described by Daemen *et al*[16].

Finally, with such high throughput technologies being used, cancer research is moving into the realm of “big data”. “Wide” data sets (where the number of variables exceed the number of subjects) such as those produced by “omics” technologies are better analysed through machine learning/artificial intelligence than traditional statistical analysis[34]. Over the past few years, many studies have been done using machine learning methods for molecular subtyping and biomarker discovery in other types of malignancies, simultaneously using data from multiple “omics” levels and there is great potential for machine learning and artificial intelligence applications in PDAC research[35].

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