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Diagnostic Potential of Biosensors and Biomarkers in Pancreatic Cancer: A Comprehensive Review

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ABSTRACT

Pancreatic cancer (PC) being the primary cause of cancer-related fatalities across the globe is a hard and aggressive type of cancer that is typically diagnosed in the patients at the last phase. Currently, the average chance of surviving pancreatic cancer five years after detection is just 6 percent which highlights the need for early diagnosis and monitoring. Pancreatic cancer is traditionally diagnosed through imaging techniques such as CT scans, PET scans, magnetic resonance imaging, ultrasound, and biopsy. To get precise and understandable results, these methods are prolonged, expensive, and need the knowledge of experts in the field. Biosensors are emerging at a rapid pace that are used in the diagnosis of pancreatic cancer owing to their easy accessibility, cost-effectiveness accompanied with a high degree of precision. The present review investigated various biomarkers and biosensors along with their benefits and shortcomings which are extensively used in cancer detection. The study found that CA 19-9 biomarkers are best suited for diagnosis of pancreatic cancer due to its better performance and sensitivity. This review primarily helps biomedical engineers, doctors, and others researchers working in same domain in identification of potential research gaps and selection of most suitable biosensors for diagnosing pancreatic cancer.

Keywords: *Biomarker; Biosensor; Imaging techniques; Diagnosis; Cancer detection.*

1. INTRODUCTION

Pancreatic cancer (PC) is the most stubborn cancer of the digestive tract. The survival rate for pancreatic cancer is less than 5%, making it life-threatening[1]. PC is a very destructive disease that quickly spreads to surrounding organs and tissues[2], [3]. Due to the lack of symptoms in the early stages, over 80% of PC patients are not diagnosed until the advanced stage. Due to the risk of metastases, surgical treatment is not possible in advanced stages[4]. Around the world, it ranks as the 12th most common cancer diagnosis and the seventh most common cause of cancer-related death[5], [6]. Both genetic and environmental factors play a role in the development of pancreatic cancer (PC)[7]. People with a family history of the disease have a higher risk of developing pancreatic cancer than people without a family history[8]. Smoking is one of the main environmental factors that cause pancreatic cancer[9]. Based on origin, pancreatic cancer is classified into two major types: i) Exocrine, and ii) Neuroendocrine (as shown in figure 1). Approximately 95% of cases of pancreatic cancer are exocrine cancers, which can have different subtypes, and rest 5% are neuroendocrine. This cancer is a fatal disease, aggressive pancreatic ductal adenocarcinoma (PDAC), which is responsible for most cases (more than 90%) of pancreatic destruction. This cancer has a 5-year survival rate of 1.3-6%. [10]. PDAC affects both exocrine and endocrine pancreatic cancer[11]. It is very difficult to detect pancreatic cancer in its early stages because it often shows symptoms in its advanced stages[12]. Pancreatic cancer is mainly associated with weight loss, jaundice, and malaise[13]. Various imaging techniques such as a) positron emission tomography(PET), b) computed tomography(CT), c) multidetector computed tomography (MDCT), d) endoscopic ultrasound (EUS), and e) magnetic resonance imaging (MRI) are used to diagnose a solid mass in the pancreas[14]. Early detection of pancreatic cancer is difficult, so the main goal is to find new diagnostic biomarkers or modalities that can help in early cancer detection[15]. It is needed to construct a biosensor for early detection of pancreatic cancer biomarkers. A biomarker is a biological molecule (also called a molecular marker) that is found in fluids or tissues

and is calculated in the body to predict the occurrence of a disease process. The best serological biomarker for the diagnosis of pancreatic cancer is carbohydrate antigen 19-9 (CA 19-9)[16], [17]. We will go through some other biomarkers that have been suggested here. However, the invasiveness, sensitivity, and specificity of these assessment methods vary[18], [19]. The goal is to find biomarkers to diagnose early-stage pancreatic cancer by constructing biosensors that can detect these biomarkers[20].

There is currently a rapid development of various nanomaterials that are increasingly being used in clinical settings and improving the diagnosis of pancreatic cancer. Nanomaterials have many advantages over conventional methods and also have considerable development potential. At the nanoscale, nanomaterials are used to increase detection sensitivity. With technological advances, the manufacturing cost of these nanosensors can be reduced, resulting in reduced patient burden and medical costs associated with cancer diagnosis and treatment[21]. In recent years, studies have focused on testing and developing nanotechnology that can improve the detection of current diseases.

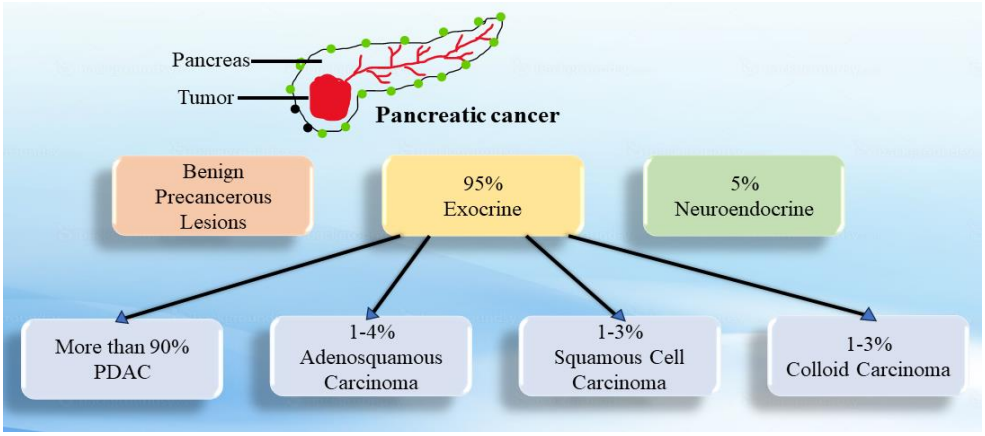

Figure 1. Classification of pancreatic cancer.

Biomarkers for Early Diagnosis of Pancreatic Cancer

Due to the poor prognosis, pancreatic cancer typically occurs at an advanced stage of the disease. However, when the diagnosis is made early enough to allow surgical resection, the 5-year survival rate of PDACs increases to 30-60 percent[22]. Approximately 15% of patients can still undergo surgical resection[23]. Early-stage biomarkers would enable curative resection and improve 5-year survival for a large number of patients undergoing additional chemotherapy. Biomarkers are biologically derived molecules found in body fluids that can be used to identify abnormal processes or diseases. Using biomarkers, it is possible to track the body's response to therapy [24]. Biomarkers serve as important indicators for detecting early tumors, disease progression, and cancer response to therapy. These are inexpensive, non-invasive, have high sensitivity and specificity help in the early detection of cancer and increase survival rates (as shown in Figure 2) [16]. Biomarkers are often found in blood, urine, serum, or cerebrospinal fluid, but also on or in tumor cells [11]. Biomarkers related to PDAC can be divided into three main categories: predictive (which predicts the success of a treatment), prognostic (which informs us about the consequences), and diagnostic (which helps diagnose cancer).

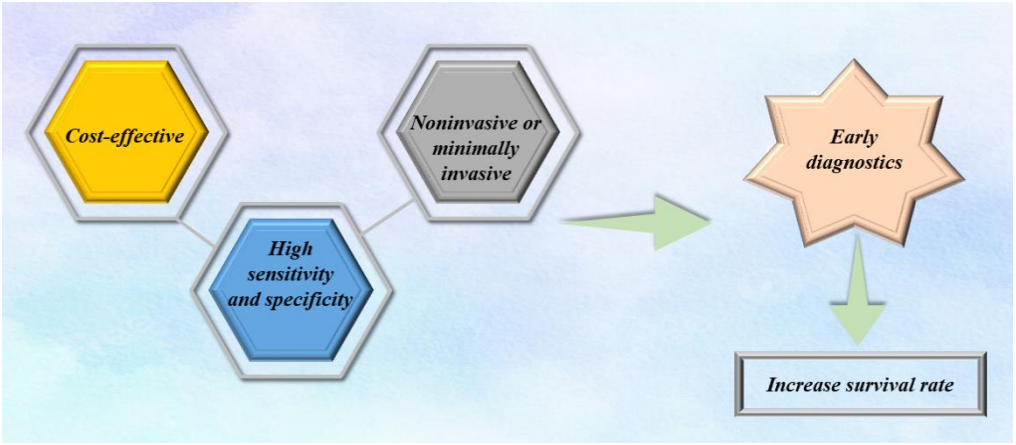

Figure 2. Various characteristics of pancreatic cancer biomarkers.

It is critical to comprehend the processes that underlie the onset and spread of pancreatic cancer. The substances that cancer cells produce are used to assess the presence and severity of the disease[25]. A range of biomarkers, including long noncoding RNAs (lncRNAs), Mucin 1 (MUC1)[26], Mucin 4 (MUC4)[27], MicroRNA-21 (miR-21) and MicroRNA-155 (miR-155)[28], Alpha-enolase (ENO1)[29], Chaperonin containing TCP1 subunit 8 (CCT8)[30], Carcinoembryonic antigen-related cell adhesion molecule (CEACAM) [31], Fucosylated haptoglobin (Fuc-Hpt)[32], and Carbohydrate antigen 19–9 (CA19-9)[33] can all be used in appropriate biosensor studies to support pancreas diagnosis (Figure 3).

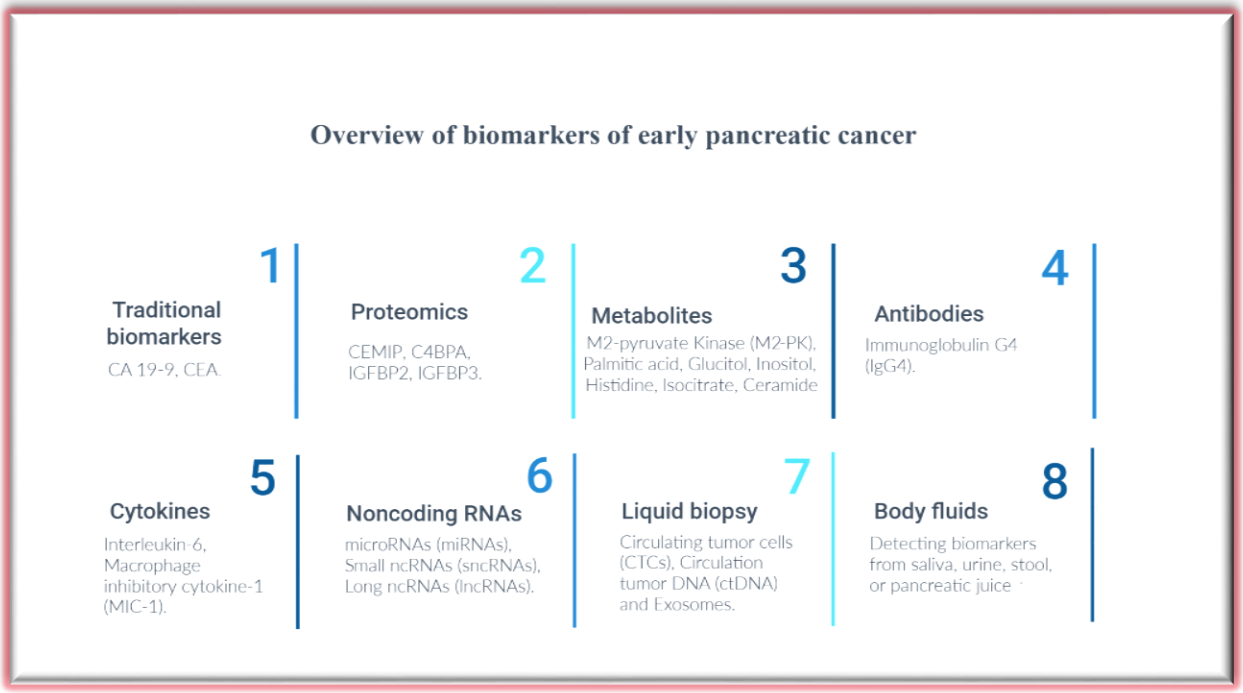

Figure 3. Various biomarkers for early detection of pancreatic cancer.

Traditional biomarkers

PDAC has been linked to several protein biomarkers, such as Pulse amplitude modulation 4-level (PAM4), CA 19-9, mucin family members (MUC1, MUC4), Cancer Antigen 242 (CA242), Cancer Antigen 494 (CA494), haptoglobin (Hp), Neutrophil gelatinase-associated lipocalin (NGAL), etc. The CA 19-9 is a promising biomarker for the treatment of pancreatic cancer, with elevated levels (>37 U/mL) associated with a better prognosis[34]. CA 19-9 is a protein biomarker that helps detect pancreatic cancer early in patients. With an average sensitivity of 79 percent and specificity of 82 percent, it's pretty good at it. Another serum protein is called haptoglobin and also includes a group of other proteins such as OPN, CA 242, CA 494, MIC-1, TPA, and HE4 that have also been discovered, but none appear to be better for the pancreas than CA 19-9 Cancer detection. The mucoprotein carbohydrate antigen CA 242 is found in saliva and is not normally present in healthy tissues. According to Haglund et al. CA242 can help diagnose PDAC. They found that the biomarker CA 242 has a sensitivity of 74 percent and a specificity of 91 percent, as well as an overall accuracy rate of 84 percent for diagnosing PDAC. Compared to the biomarker CA 19-9, CA242 has lower sensitivity but higher specificity for detecting pancreatic cancer. Some recent studies have investigated that using a combination of different biomarker panels could help improve the accuracy and specificity of pancreatic cancer detection[34]. In combination with newly discovered protein biomarkers, CA 19-9 leads to increased sensitivity and specificity. However, the association of CA19-9 and CA242, with a sensitivity of 89 percent, offers a greater chance of early detection of pancreatic cancer[35].

Proteomics

Protein biomarkers are commonly studied biomarkers in pancreatic juice. Pancreatic juice and conventional serum markers such as CA19-9 and CEA have been linked[36], [37]. In addition to these biomarkers, several other proteins have been tested in patients' pancreatic juice, with varying degrees of success. Matsumoto, in conjunction with other studies, showed that a particular type of protein called Krebs von den Lungen 6 mucin, although its specificity was not that good, acted as a notable indicator and was significantly higher in pancreatic juice in patients with pancreatic cancer compared to inflammatory diseases[38].

Metabolites

By Novotny et al. in 2008. [39] investigate a potential tumor marker called M2-pyruvate kinase (M2-PK) that could help distinguish between healthy people, people with pancreatic cancer (PC), and chronic pancreatitis (ChP). Patients with advanced PDAC disease had higher serum M2-PK levels among the 132 patients in the group. When comparing the results with patients with early-stage pancreatic cancer, healthy individuals, and chronic pancreatitis, the researchers found that M2-PK levels were significantly higher in all cases. However, M2-PK could not successfully distinguish between ChP and PC. Jorgensen and others wanted to see how well the diagnostic effectiveness of M2-PK compared to CA 19-9[40]. In detecting pancreatic cancer, the sensitivity and specificity of M2-PK were worse and did not perform well compared with the CA 19-9 biomarker[39], [41].

Antibodies

IgG4

There is a link between elevated blood serum levels of immunoglobulin G4 (IgG4) and IgG4-related diseases[42]. Immunoglobulin G4-related disease (IgG4-RD) manifests pancreatically as autoimmune pancreatitis (AIP)[43]. Some researchers investigated a possible link between pancreatic cancer and elevated serum IgG4[44]. Small elevations in IgG4 levels do not help distinguish PDAC from AIP, and the high IgG4 level is not indicative of pancreatic cancer. However, an increase in serum IgG4 of more than twice the normal amount appears to be associated with AIP.

Cytokines

In 2016 Yako and others. examined 65 articles that examined various cytokines of PDAC in a comprehensive review[45]. Multiple studies consistently reported increases in six cytokines in PDAC, including four interleukins (IL-6, IL-8, IL-10), vascular endothelial growth factor (VEGF), and transforming growth factor (TGF). On the other hand, PDAC can be distinguished from other benign pancreatic diseases or healthy individuals based on several cytokines[46], [47]. Furthermore, tumor progression is associated with increased MIC-1 levels[48]. A large analysis in 2017 comparing 14 studies involving a total of 2,800 people found that MIC-1 in the blood achieved similar diagnostic accuracy to CA19-9 in detecting pancreatic cancer[49]. However, using an association of CA 19-9 and MIC-1 can make the diagnosis more specific, but MIC-1 alone is not always accurate enough[50].

Noncoding RNAs (ncRNAs)

Depending on their length, non-coding RNAs are divided into two groups: long ncRNAs (lncRNAs) are more than 200 bases long, while short ncRNAs (sncRNAs) are up to 200 bases long[51], [52]. Another type of noncoding RNA called microRNA (miRNA) is not involved in making proteins. Instead, they control the expression of genes (transcription regulation) by degrading the RNA (transcript destruction) or preventing it from being converted into proteins (translational repression). MicroRNA consists of 18-25 building blocks called nucleotides. In recent years, miRNA has attracted the attention of researchers regarding the role of miRNA as a potential biomarker for early detection of pancreatic cancer [51]. As a result, researchers observed that miRNA in different parts of the body is affected by pancreatic tumors. Their findings suggest that miRNAs or miRNA clusters detected in PDAC patients' serum or plasma could have additional diagnostic uses besides CA19-9[53], [54].

Liquid biopsy

Many cancers, including PDAC, may benefit from liquid biopsy, and researchers have looked into the possible roles of exosomes, circulating tumor DNA (ctDNA), and circulating tumor cells (CTCs).

Circulating Tumor Cells (CTCs)

Circulating tumor cells (CTCs) originate from the main tumor and after breaking away from the primary origin, these cancer cells enter the blood, travel through the bloodstream, and attempt to spread to other organs[55], [56]. In cancer patients, CTCs are present at incredibly low frequencies – about one CTC per billion blood cells[57], To date, identifying and isolating pancreatic cancer has proven difficult [58]. Some studies have shown that cancer cells can also get into the bloodstream in the early stages of PDAC [59]–[61]. A recent study by Kulemann et al. conducted a study that found that most pancreatic cancer patients may have CTCs in their blood. They used a method that filters blood and studies a specific mutation called KRAS[62]. Regardless of tumor stage, they found CTCs in 73% of PDAC patients. The blood of nine healthy donors did not contain CTCs, while CTCs were identified in three of four patients with early-stage PDAC (detection rate: 75%). In 2016, Ankeny and colleagues used a special method (NanoVelcro microfluidic CTC chip) to detect pancreatic cancer with a specificity of 96.5% and a sensitivity of 75% in detecting PDAC[63], [64]. Due to their diversity and rarity, they are not always the best choice as a detection method for liquid biopsy[64]. Before clinical use, we need a standardized method and comprehensive validation[65].

Circulating Tumor DNA (ctDNA)

The tiny double-stranded DNA fragments called circulating free DNA (cfDNA) are found in the blood. In healthy people,

the majority of cfDNA comes from the liver and bone marrow, among other things[66]. Circulating tumor DNA (ctDNA), first described in 1989, is another type of DNA fragment released by tumor cells[67].

The ctDNA represents a fluctuating proportion of the cfDNA and accounts for between 0 and 50 percent of the total cell-free DNA[68]. It is possible to distinguish between normal cfDNA and ctDNA because of mutations linked to cancer. [59]. A common genetic feature of PDAC is a high frequency of KRAS mutations, directly related to the grade of PanINs. Since KRAS mutations are common in both precancerous lesions such as PaniNs and PDAC, ctDNA with these mutations can be used as a biomarker for early detection of PDAC[69]. Digital PCR techniques have found ctDNA in about half of early-stage PDAC cases, according to several research groups[70], [71].

Exosomes

Nano capsules called exosomes are membrane-bound and are used by cells to transport molecules. Inside, they contain proteins, RNAs, and fats that could help predict, prognosticate, or diagnose pancreatic cancer. The miRNA is one of the most researched exosome components, but some surface proteins are also used in medical diagnostics. The exosomes secreted by PDAC tumour cells contain a protein called glypican-1 (GPC1) on their surface, which helps in the early detection of PDAC and signalling cell growth[72], [73].

Body Fluids

Body fluids such as pancreatic juice, urine, and saliva play a vital role in detecting pancreatic cancer. Because the salivary glands have a high blood supply, the molecules in saliva are virtually the same as those in serum, making it a simple aim for PDAC diagnosis[74], [75]. PDAC diagnosis can be aided by useful biomarkers in urine, a plasma ultrafiltrate[76]. Researchers studied a special type of molecule called urinary miRNA to identify PDAC early[77]. Accordingly, Yang et al. demonstrated the effectiveness of miRNA extraction and detection from pancreatic juice serving as biomarkers for PDAC screening[78], [79].

Biosensors for Detection of Pancreatic Cancer

By using biologically active material in proximity to an appropriate transduction element, a biosensor is a self-contained analytical device that can selectively and reversibly measure the concentration or activity of species in each sample. A biological reaction is converted into an electrical signal[80].

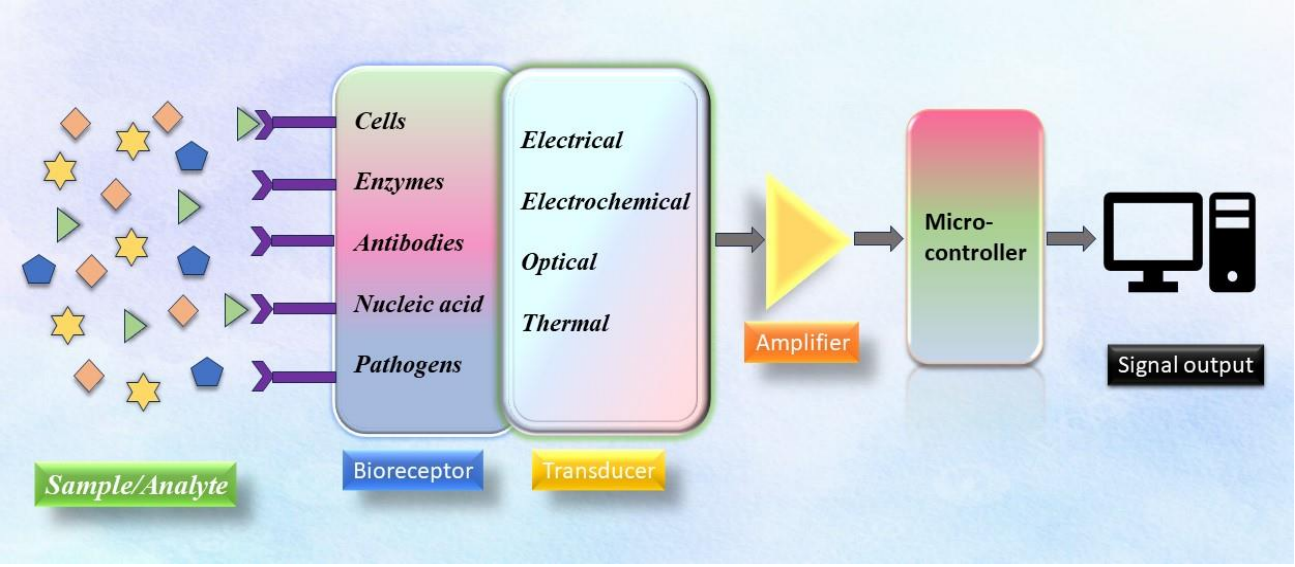

Figure 4. The general structure of a biosensor circuit diagram

A biosensor is a device that uses a biological recognition element with a sensor to provide specific analytical information. This is called a biosensor according to IUPAC[81]."

A biosensor consists of three main parts: bioreceptor, transducer, and measuring device (as shown in figure 4)[82]. Based on the type of transducer or bioreceptor, biosensors are categorized (as shown in Figure 5). Many types of sensors are composed of biomolecules such as cells, aptamers, enzymes, antibodies, etc. After the target recognizes the analyte, it selectively binds to it[83], [84]. Biosensors should have high levels of selectivity, sensitivity, repeatability, stability, and accurate post-processing results [85]. The immobilization process ensures that the biological element remains on the biosensor surface[86]. The healthcare system tries to identify disease-specific indicators to improve people's quality of life. A sensible and

economical strategy is therefore required. Enzyme-linked immunosensor tests (ELISA) are often used to identify biomarkers[87]. To identify Fuc-Hpt, a marker for pancreatic cancer, an ELISA test was performed. According to the results of the ELISA test performed on patients without healthy controls, patients with pancreatic cancer produce ten times more Fuc-Hpt[88], [89]. Therefore, routine ELISA is unable to detect complex and extremely small molecules, including cancer markers[26]. ELISA was used as the first method to detect pancreatic cancer but this method has some disadvantages. Therefore, single-stage instruments that are more cost-effective, provide faster results, and can detect even trace markers are preferred[90]. Because early detection of cancer reduces mortality rates and improves treatment options, biosensors and similar devices are essential for early detection of pancreatic cancer[91]–[93].

Immunosensors for Diagnosing Pancreatic Cancer

An immunological sensor consists of a transducer and a sensor element. To facilitate detection, antigen antibodies are immobilized on the biosensor surface. The transducer produces a signal that can be measured based on the interaction between antigens and antibodies. The biosensor transducer categorizes optical immunosensors into numerous types, including electrochemical immunosensors[94]. The interaction of an antibody and an immobilized antigen generates an electrochemical signal on the surface of the electrode. We call this type of immunosensor an electrochemical immunosensor. The main advantages of this technique are its remarkable specificity and robust stability against trace analytes. The detection of weak signals and long-range signals are characteristics of optical immunosensors. The interaction between antigen and antibody in optical immunosensors produces an optical signal, which can be fluorescent or coloured, and alters the optical properties of the medium. When detecting antibody-antigen contact, a photodetector converts optical changes into an electrical signal [95]. Immunosensors were used to identify the pancreatic cancer marker CA19-9. To identify CA19–9 biomarkers, the researchers developed immunosensors with a simple film design that could be used with electrical impedance spectroscopy. Active anti-CA19-9 is applied in a single layer to the intended electrode surface. CA19-9 levels were successfully determined using patient serum samples. This showed that pancreatic cancer can be detected accurately, easily, and effectively[96]. Using screen printing electrodes (SPE), CA19-9 could be detected in low concentration. By modifying graphene oxide (GO) sheets to produce silver (Ag) screen-printed nested electrodes (SPIDEs), researchers were able to develop an immunosensor to detect CA19-9 and CNOs. This detection technique is simple, reliable, and has high specificity for CA19-9[97]. Naturally occurring materials such as graphene that could be used in immune sensors[98], metallic nanoparticles[99], carbon nanotubes (CNTs), and chitosan[100], act as a matrix for the immobilization of biomolecules and then increase the sensitivity of the detected signal[101]. The gold nanoparticles (AuNPs) are used in a single detection reaction to amplify the analytical signal due to their large number of active sites[102]. This creates an electrical signal that is converted into light using a photomultiplier tube (PMT) and recorded in a computer[103]. The application of the biosensor in clinical diagnostics is promising[104]. Moreover, in recent years, nanomaterials have been exploited for surface modifications of biosensors to enhance the loading capacity of the biomolecules, improving sensitivity and limits of detection[105].

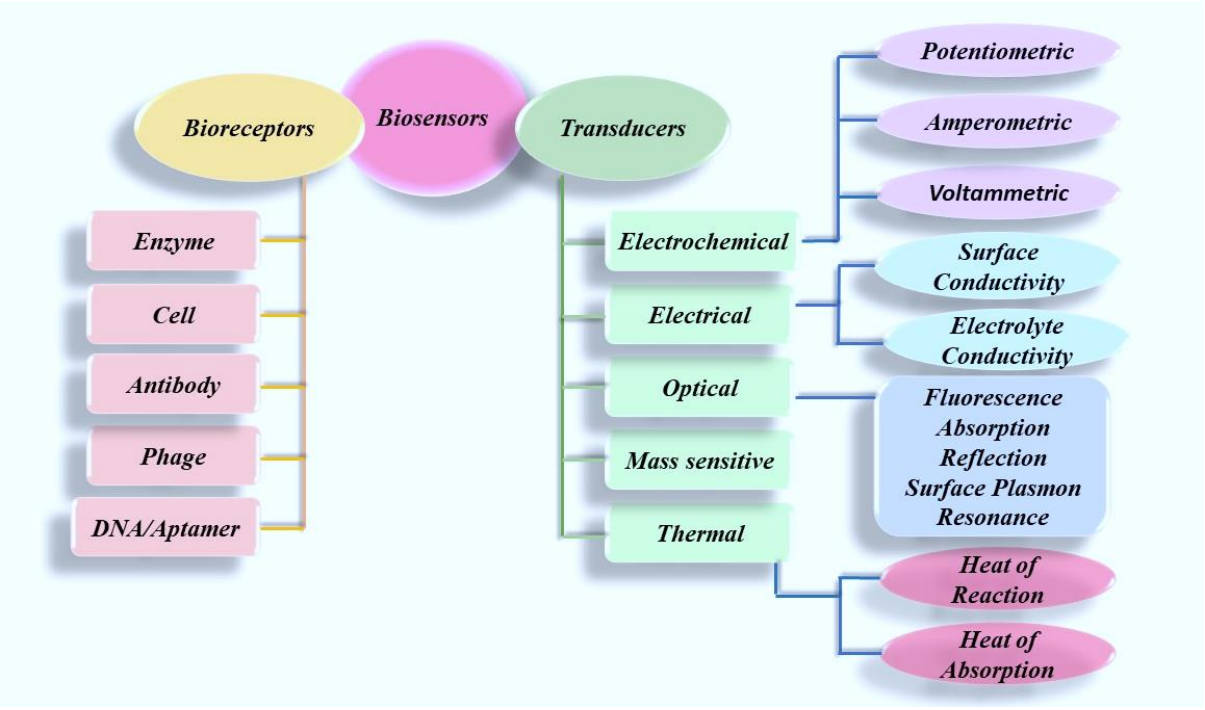

Figure 5. Biosensors are categorized according to the type of their transducer or bioreceptor.

Electrochemical biosensors for Diagnosing Pancreatic Cancer

Electrochemical biosensors are now widely used due to their simple structure, mass production capability, productivity, accessibility, possibility of miniaturization, and flexibility, which make them an attractive option for cancer prevention as a powerful device[90]. Amperometry[106], potentiometry[107], electrochemical impedance spectroscopy (EIS)[108], square wave voltammetry[109], and dielectrophoresis spectroscopy were used to quantify how the biosensors respond to PDAC biomarkers[110], [111]. Electrochemical biosensors (due to their high sensitivity) based on differential pulse voltammetry and square wave voltammetry can identify low concentrations of proteins and markers of the pancreatic cancer gene[112], [113].

Guo and others. disclosed a novel technique that utilizes the porous shells of Au@CuxOS yolk-shell nanostructures as amplification labels for the ultrasensitive detection of CA 19-9 (as shown in Table 1). The combination of disposable electrochemical biosensors and microfluidic devices represents a potentially useful tool for early PDAC diagnosis. It has been reported that electrochemical devices are becoming smaller, allowing them to fit into small pockets and be used at home, on the doctor's table, or during surgery[114].

Optical biosensors

Light wavelength fluctuations are measured by optical biosensors. These transducers are available in fluorescent, luminescent, colorimetric, and interferometric variants. Optical transducers translate wavelength changes in response to the perception of the analyte into electrical measurements and digital data. Many biological and chemical substances can be detected directly, immediately, and without labelling using optical biosensors, which represents a significant advantage over conventional analysis methods[115]. Griffin, Bohunicky Mousa, and Mittal et al. have investigated the use of optical biosensors in cancer diagnosis [116], [117]. Optical biosensors are used for early detection of pancreatic cancer. The study also provides information on the latest developments in lateral flow biosensors (LFBs), surface plasmon resonance (SPR), and other methods for identifying PDAC biomarkers[118].

Colorimetric biosensors

Colorimetric biosensors have gained popularity due to their affordability, ease of use, fast response time, and freedom from labelling. Due to their low sensitivity and limited experimental conditions, colorimetric biosensors have not been used to detect cancer biomarkers[119]. The colorimetric biosensors used to detect cancer biomarkers are enabled by the emergence of new colorimetric platforms based on hybrid nanocomposites[120]. Xiao et al. used highly catalytically active AuNP-decorated Bi2Se3 nanosheets to develop a colorimetric biosensor for the detection of the cancer biomarker CEA[121]. Due to their low sensitivity and interference from the complex matrix, only a small number of colorimetric biosensors have been used to identify pancreatic cancer biomarkers[122].

Mass sensitive biosensors

Mass change-based biosensors include piezoelectric and acoustic biosensors. The basis of piezoelectric sensors is how applying potential energy to quartz crystals results in changes in their mass. Signals can be generated by converting the frequencies produced by mass changes. Piezoelectric biosensors such as immunosensors and microcantilevers can be used to find tumour biomarkers[123].

Other types of biosensors

It is possible to identify biomarkers linked to pancreatic cancer using alternative biosensors. Feng et al. created an electrochemiluminescence biosensor based on paper to identify cancer cells. The researchers were able to analyse HL-60 cancer cells at impressively low concentrations by using a piece of porous chromatography paper bonded to glass coated with indium tin oxide. This kind of biosensor is comparable to LFBs in terms of portability, simplicity of manufacture, and low cost of production. According to Corso et al., mesothelin may be instantly detected in the supernatant of pancreatic cancer cell lines using an acoustic wave immunosensor[124]. The sensors exhibit considerable potential as a screening tool for pancreatic cancer and other malignancies because of their capacity to detect mesothelin protein nanograms in a complicated mixture at room temperature[125].

Sr. No.	Immunosensors	Type of Electrode	Biomarker	Modification	Detection Limit	Linear Range	Ref.
1.	Electrochemical	GCE	CA 19-9	PPPD-Au/Pt	2.3 × 10− 4 U/mL	0.001–40 U/mL	[126]
2.	Electrochemical	GCE	CA 19-9	rGO-Au-Pd	1.54 × 10− 3 U/mL	0.01 U/mL and 10,000 U/mL	[127]
3.	Electrochemical	GCE	CA 19-9	AuNPs@PThi	0.26 U/mL	6.5 and 520 U/mL	[128]
4.	Electrochemical	Au	CA 19-9	CeO_2/FeOx@mC	10 µU/mL	0.1 mU·mL^{-1}-10 U·mL^{-1}	[129]
5.	Electrochemical	GCE	CA 19-9	PThi–SDS/AuNPs	0.45 U/mL	5–400 U/mL	[130]
6.	Electrochemical	ITO	CA 19-9	PA6 (polyamide 6)/PAH (poly (allylamine))/MWCNT and PA6/PAH/AuNPs	1.84 and 1.57 U/mL	Up to 2 U/mL	[101]
7.	Electrochemical	GCE	CA 19-9	CS-MWCNT-Fe_3O_4	0.163 pg/mL	1.0 pg/mL-100 ng/mL	[131]
8.	Electrochemical	GCE	CA 19-9	Au@CuxOS	0.0005 U/mL	0.001-12 U/mL	[107]
9.	Electrochemical	SPIDEs	CA 19-9	Carbon nano-onions and graphene oxide films (CNO-GO)	0.12 U mL^{-1}	0.3-100 U mL^{-1}	[24]
10.	Electrochemical	Au	CA 19-9	Polyethyleneimine and carbon nanotubes (PEI-CNT)	0.35 U/mL	-	[132]
11.	Fluorescence Immunosensor	-	CA 19-9	CQDs/Au-Ab–HRP	0.007 U mL^{-1}	0.01-350 U mL^{-1}	[133]

12.	Field-effect transistor immunosensor	Au	CA 19-9	MoS_2 nanosheets	2.8×10-13 U/ml	1.0×10-12 U/ml-1.0×10-4	[134]
13.	Electrochemical	GCE	CA 19-9	Fe_3O_4@SiO_2–Au@mSiO_2	0.004 U/mL	0.01-1.11 U/mL and 11.11-476.11 U/mL	[135]
14.	Electrochemical	Au	CA 19-9	11-mercaptoundecanoic acid (11-MUA)	0.68 U mL^{-1}		[96]
15.	Electrochemical	Screen-printed carbon electrodes (SPCEs)	CA 19-9	Carboxyl-functionalized magnetic microsupports (HOOC-MBs)	1.5 U mL^{-1}	5.0-500 U mL^{-1}	[136]
16.	Electrochemical	GCE	CA 19-9	Multiwalled carbon nanotube and magnetite nanoparticle (MWCNT-Fe_3O_4)	0.163 pg mL^{-1}	1.0 pg mL^{-1}-100 ng mL^{-1}	[131]
17.	Electrochemical	ITO	CA 19-9	rGO-CNT	0.54 nU/mL	0.1 mU/mL-100 U/mL	[137]
18.	Electrochemical	GCE	CA 19-9	Ferroferric oxide nanoparticles-loaded mesoporous silica nanoparticles (Fe_3O_4–MSN)	0.0001 U/mL	0.0005-40 U/mL	[138]
19.	Electrochemical	SPCEs	CA 19-9	Carbon black (CB) and polyelectrolytes	0.07 U mL^{-1}	0.01-40 U mL^{-1}	[97]
20.	Electrochemical	GCE	CA 19-9	Graphene and gold nanoparticles	0.01 U/mL	0.05-20 U/mL	[139]
21.	Electrochemical	ITO	CA 19-9	PA6/PAH modified with either MWCNTs or AuNPs	1.84 and 1.57 U mL^{-1}	2 U mL^{-1}	[101]
22.	Electrochemical	3D cactus-like NiCo-LDH/CuSe/CC sensing	CA 19-9	ZnS@MSN-Glu	0.0005 U/mL	0.001-100 U/mL	[140]

		platform					
23.	Near-infrared (NIR) photothermal immunosensor	3D-printed device	CA 19-9	Prussian blue nanoparticles (PBNPs)-encapsulated $CaCO_3$ microspheres	0.83 U mL^{-1}	1.0 U mL^{-1} - 100 U mL^{-1}	[141]
24.	Electrochemical	GCE	CA 19-9	Zn-Co-S@G	0.82 U·mL^{-1}	6.3 U·mL^{-1} -300 U·mL^{-1}	[93]
25.	Electrochemical	Au	CA 19-9	3-mercaptopropionic acid (MPA)/β-mercaptoethanol (ME)	0.01 U/mL	0.05-500 U/mL	[142]
26.	Electrochemical	ITO	CA 19-9	Bipolar silica nanochannel array (bp-SNA)	3 μU/mL	10 μU/mL - 50 U/mL	[143]
27.	Colorimetric Immunosensor	gold nanorod (GNR)	CA 19-9	Magnetic iron oxide (IO)	3.5 × 10−5 U/mL	8.6 × 10−5 U/mL-1.4 × 10−2 U/mL	[103]
28.	Electrochemical	GCE	CA 19-9	Polyoxometalate - incorporated gold nanoparticles (AuNPs@POM)	0.030 μU mL^{-1}	0.1-10.0 μU mL^{-1}	[144]
29.	Electrochemical	Au	CA 19-9	BSA/Graphene Nanocomposites	13.5 U/mL	13.5 U/mL-1000 U/mL	[145]
30.	Electrochemical	GCE	CA 19-9	Graphene oxide-melamine (GO-MA) and polydopamine-Ag nanoparticles (PDA-Ag NPs) composite	0.032 mU mL^{-1}	0.0001-100 U mL^{-1}	[146]
31.	Electrochemi-luminescence	Magnetic glassy carbon electrode (MGCE)	CA 19-9	Ag@BSA core/shell microspheres	0.0002 U mL^{-1}	0.0005 -150 U mL^{-1}	[147]
32.	Photoelectro-chemical immunoassay	ITO	CA 19-9	TiO_2NWs/Au/CdSe@ZnS	0.0039 U/mL	0.01 U/mL-200 U/mL	[148]

33.	Electrochemical	3DOMM	CA 19-9	Au–SiO_2@Fe_3O_4 nanospheres	0.01 U mL^{-1}	0.05-15.65 U mL^{-1}	[149]
34.	Electrochemical	GCE	CA 19-9	AuPt nano-calliandras	0.03 U/mL	0.05-50 U/mL	[130]
35.	Photoelectro-chemical	SPE	CA 19-9	Au-SnSe QDs	0.0011 U mL^{-1}	0.005-100 U mL^{-1}	[150]
36.	Electrochemical	GCE	CA 19-9	ZnO QDs	0.04 U/ml	0.1–180 U/ml	[113]
37.	Electrochemical	GCE	CA 19-9	Au@Pd-Gra	0.006 U mL^{-1}	0.015-150 U mL^{-1}	[151]
38.	Electrochemical	GCE	CA 19-9	Ag/g-C_3N_4	1.2 mU mL^{-1}	5.0 mU mL^{-1} - 50 U mL^{-1}	[29]

Table 1. Comparative evaluation of multiple immunosensors using the pancreatic cancer biomarker CA 19-9 based on modified electrodes.

Conclusion and future prospectives:

The early detection of pancreatic cancer (PC) has significantly increased patient survival times. This paper covers biomarkers and current biosensor research for early detection of pancreatic cancer. This cancer is associated with several biomarkers. Many biosensor experiments have been and are being conducted to identify these biomarkers. The most sensitive types of biosensors were electrochemical and optical. The most cost-effective and reliable instrument currently available is the biosensor. Early and accurate diagnosis can lead to a reduction in cancer-related death rates. In addition to using additional biomarkers to track treatment progress, biosensors can also provide information about how well a treatment is working. Although there are other types of cancer, CA19-9 is the best-known biomarker for pancreatic cancer and remains elevated. However, the newly identified disease biomarkers offer hope. More specifically, the specificity and sensitivity of early PDAC identification could be significantly increased by combining these novel biomarkers with the traditional CA 19-9. Although it is difficult to predict how the field will change in the future, the most promising methods appear to be proteomics, metabolomics, liquid biopsies, and miRNAs. The specific set of helpful indicators should be determined by future research, and comprehensive recommendations for their routine clinical practice adoption should be provided.

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