The potential implementation of biosensors for the diagnosis of biomarkers of various cancer

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Abstract:

In the era of nanotechnology, researchers are implementing point to care service to cancer patients to detect malignancy beforehand and to reduce the mortality rate of cancers. Cancer is known to be the most fatal disease among all other diseases and the survivability from cancer is quite impossible if the stage of the cancer is an advanced level. Though the early detection of cancer can increase the chances of survival with a double fold. Biosensor is a part of nanotechnology which is capable to provide point to care service in the field of medicine. With the rising number of cancer occurrences being identified around the world and the increasing number of deaths because of the identification of advanced cancer, biosensors can play a significant part in the early detection of cancer. New molecular methods, including as genomic and proteomic approaches, are increasingly being used to study patient molecular profiles. When such diagnosis method is paired with bioinformatics tools, they generate new data that can be used to discover new disease biomarkers. Finding precise and sensitive indicators that are corelated to a specific disease, as with many other diseases, can be challenging. Furthermore, the concentration of biomarkers in biological fluids varies according to illness states and phases. Peptides, proteins, up or down regulated expression of gene markers, and gene alternation are all examples of molecular markers that are commonly used to diagnose cancer. In this article, we have highlighted six different deadliest cancers such as Ovarian, Breast, Prostrate, Lung, Colorectal and Liver cancer. The article contains distinct types of biomarkers which are normally found in these kinds of cancer and generally used as a potential diagnostic target in the medicine field. The article mainly summarized the application of different types of biosensors devices in the detection of the mostly found biomarkers in the above cancer types.

Keywords:

Biosensor, Breast Cancer, Ovarian Cancer, Lung Cancer, Prostrate Cancer, Liver Cancer, Colorectal Cancer, Nanobiotechnology .

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Highlights:

1. Biomarkers can be used as potential diagnostics target in cancer detection.
2. Nanotechnology has a flourishing future in the medical health.
3. Cancer is the most lethal disease after cardio-vascular disease.
4. Biosensor devices are able to provide point of care services.
5. Biomarkers is a great diagnostic tool in the detection of cancer.

Introduction:

Nano sensor-based technology is the new-sprung of rising star in the field of medicine. In recent years, there has been numerous research on developing this technology to contribute significantly to human health monitoring. A biosensor is a device that can measure the concentration of an analyte in a biological or chemical reaction by providing signals which can be change by the quantity of the it. Biosensors are used for many purposes like monitoring of the disease, drug research, and the diagnosis of disease-causing microorganisms, pollutants, and biomarkers that are signs of a disease in bodily fluids (urine, saliva, sweat and blood) [1]. Cammann was the first scientist who used the term "biosensor" for the first time, and later the accurate definition of biosensors came from International Union of Pure and Applied Chemistry (IUPAC).[2]. Clark and Lyons, two of the first researcher to start using biosensors in the 1960s, were also the first to use them. A biosensor connects chemistry, biology, and engineering when it is made. Based on the mechanism that how biosensors function, the materials which are utilized in biosensors are: antibodies, antigens, and nucleic acids from bio affinity group, enzymes from biocatalytic section and microorganisms from micro centered group. Microbe-based, cell-based, enzyme-based, immunosensors, protein, tissue-based, DNA, and genetically encoded biosensors are some of the variants of biosensors that have been used so far in the health care system. Each biosensor has a shape and uniqueness in how it is made and used. The biosensor-based detection system is comprised of three primary factors: the bioreceptor and transducer, the signal processing unit, and the visual representation unit.

Biosensors are tools that are used to analyze protein, RNA, and DNA materials [3]. The bioreceptors recognize the analyte, while the transducer translates the recognition to electrical impulses. Biosensor development is affected by biological and electronic factors that work together to provide a specific signal throughout the detecting process. It is critical to immobilize or bind the significant molecule to the electrical element. Additionally, biological element attachment and stability are crucial [4]. Bioreceptors' responsiveness and selectivity make them ideal for detecting malignant cells. Filters, amplifiers, and an analog-to-digital converter compose the signal processing unit. After the signal is translated via the transducer, it is being processed. To produce a correct signal, the signal is filtered, and noise cancellation is performed. Following filtration,

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amplification is used to boost the signal's intensity. Analog to digital conversion transfers the signal to a digital format that is comprehensible and suitable for visual representation.

Biosensors has been applied to multiple areas in health care system. The diagnosis of cancer biomarkers through biosensors has significant impact on the survival rate of cancer patients. Cancer is often termed as malignant tumor and neoplasms. Cancer has an unique characteristic, it can infect a certain area of cells and can metastasizes to other organs of human body which makes it different than other diseases. The effect of cancer on human body does not only affect physical state, it also put a huge amount of stress on mental health as the costing of cancer treatment is pretty much expensive. To increase the survival rate of patients, early detection and treatment of cancer biomarkers can elevate the durability of life. Biomarkers, on the other hand, can be used to pinpoint the exact location of tumors for accurate treatment delivery. In the morphological aspect, routine cancer screening approaches include study of surgically excised tissue and aspirated and exfoliated cells. X-ray, Computed tomography (CT), and nuclear magnetic resonance imaging (NMRI) are the traditional modalities for cancer detection in hospitals [5]. These techniques can detect cancer by imaging the tumor within the human body. These techniques have the problem of being unable to detect the mechanical features of cancer cells that correlate with cancer growth. Additionally, the histological study disregards cancer cells that exhibit insufficient symptoms. For single cell research, analytical techniques such as micropipette aspiration, magnetic bead twisting, and atomic force microscopy (AFM) has been frequently utilized [6]. To investigate cancer cell movement, cancer cells were detected using local interest point detectors [7]. Regrettably, these detection systems exhibit the disadvantage of being hard to use. The advancement of a simple, selective and sensitive approach for cancer diagnosis has gotten a lot of attention recently. Numerous biosensors have been developed in the area of cancer diagnosis and biomolecular imaging using nanomaterials as probes [8]. When nanomaterials and biological recognition molecules are combined, the detection technique for cancer biomarkers based on biosensors is extremely sensitive and selective [9]. Among these biosensors, nanomaterials with varying optical and electrochemical properties significantly enhance the sensitivity of the developed biosensing method, whereas biological recognition molecules such as aptamers and antibodies benefit the developed biosensing detection method by increasing its selectivity. This level of specificity is ideal for assessing multiple types of cancer biomarkers in complex biological samples.

Biosensors are widely employed to produce diverse diagnosis methods for cancer monitoring using cancer biomarkers as detection targets, leveraging the advantages of nanomaterials and biological recognition molecules [10]. This article is an summary of the application of biosensor in the detection of biomarkers in various types of cancer. The article covers the six major cancers' (eg: lung cancer, ovarian cancer, breast cancer, prostrate and liver and colorectal cancer) biomarkers

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detection with the implementation of distinct biosensors. The article has briefly illustrated the analytical data of these six different cancer biomarker detections by the application of distinct biosensor technology.

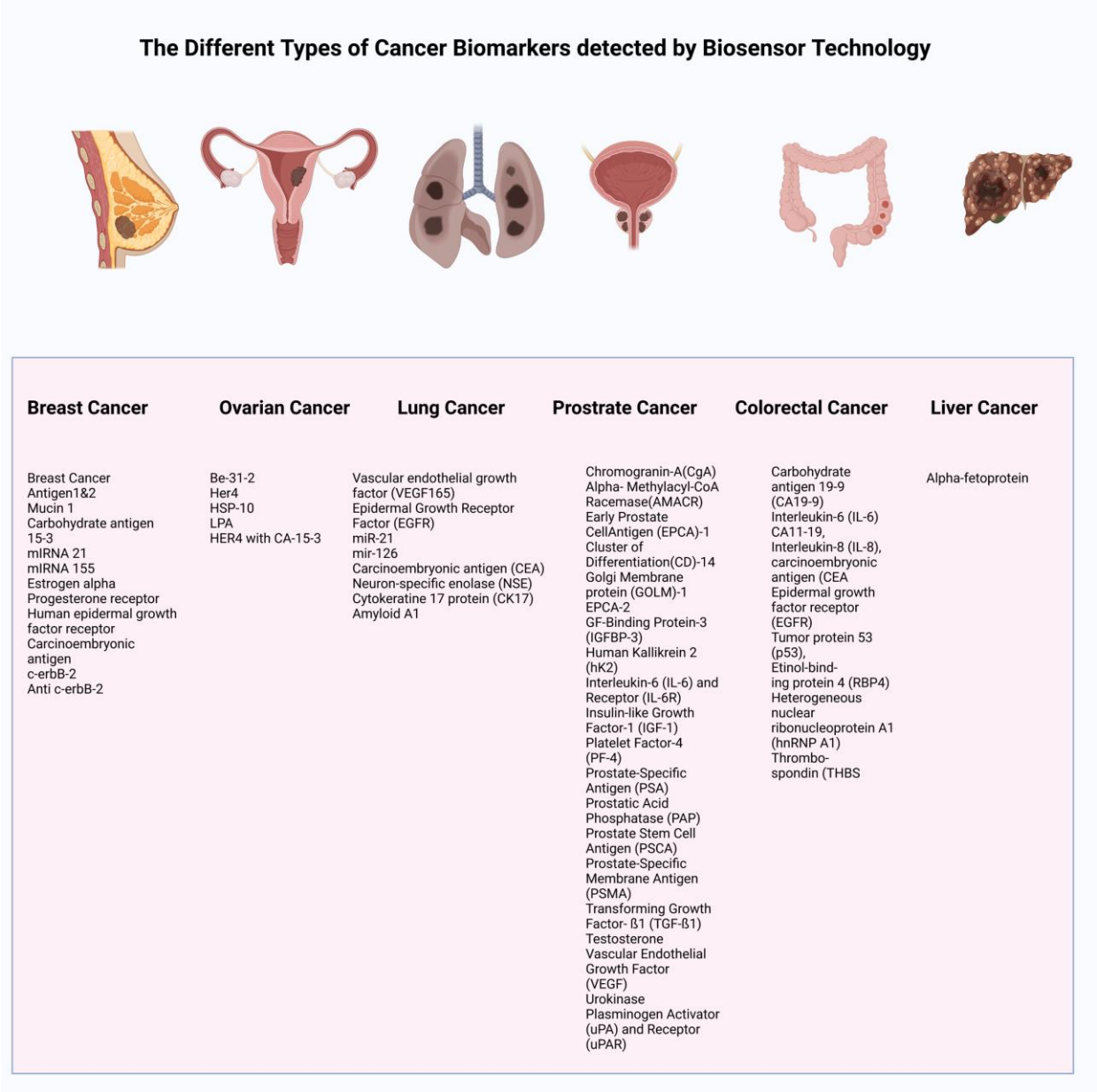

Figure 1: The detectable biomarkers of six different cancer types by distinct biosensor technology.

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Biosensors: The new diagnosis system in medical field:

Biosensor is a device which can detect biological analytes, pathogens and also can monitor environmental system and food quality. The vast application of biosensor in the molecular diagnostic systems has risen up to a new level. With the advantages of the application of biosensors, many diseases can be diagnosed at a early stage. Different characteristics of biosensors has taken its' performance to another level and Figure 2 (Table 1).

Table 1 : The distinct characteristics of biosensors

Names of Features	**Characteristics**
1. Selectivity	When designing a biosensor, selectivity is the first factor to consider when selecting bioreceptors. The most critical part of a biosensor is its selectivity ability. It refers to the capability of bioreceptors' to find a single analyte in the presence of different commixture and impurities. The best description of selectivity is the connection of antigen and antibody. Generally, the function of antibodies serves as bioreceptors which are immobilized on the surface of transducer. A mixed solution of buffer with salts is then applied to the transducer where the antigen and antibodies get bonded with each other.
2. Reproducibility	The term reproducibility defines the capability of biosensors to generate similar responses for a duplicated research setup. The definition of reproducibility of a biosensor also refers the precision and accuracy of then electronics and transducer. Precision refers to the sensor's ability to produce consistent findings every time a sample is measured, while accuracy refers to the sensor's ability to produce a mean value that is close to the true value when a sample is measured multiple times. The inference made on the response of a biosensor is more reliable and robust when the signals are reproducible.
3. Sensitivity	A biosensor's limit of detection (LOD) or sensitivity refers to the smallest amount of analyte that it can detect. A biosensor is required in several medical and environmental monitoring applications to detect analyte concentrations as low as ng/ml or even fg/ml in order to verify the existence of analytes in a sample. A prostate-specific antigen (PSA) value of 4 ng/ml in blood, for example, is linked to prostate cancer, prompting clinicians to

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	recommend biopsy tests. As a result, sensitivity is regarded as a critical attribute of a biosensor.
4. Stability	The degree of vulnerability to environmental disturbances in and around the biosensing system is referred to as stability. The output signals of a biosensor under measurement may wander as a result of these disruptions. This can impact the precision and accuracy of the biosensor by causing an inaccuracy in the measured concentration. When a biosensor is used in applications that need long incubation times or continuous monitoring, the most important feature is stability. Temperature can affect the reaction of transducers and electronics, which can affect the stability of a biosensor. As a result, proper electronics tuning is essential to assure a reliable sensor response. The affinity of the bioreceptor, which is the degree to which the analyte binds to the bioreceptor, is another aspect that might affect stability. The stability of a biosensor is enhanced by bioreceptors with high affinities, which induce either strong electrostatic bonding or covalent binding of the analyte. The degradation of the bioreceptor over time is another element that impacts the measurement's stability.
5. Linearity	Linearity is a property that describes the accuracy of the measured response (for a collection of measurements with varied analyte concentrations) to a straight line, mathematically defined as y=mc, where c is the analyte concentration, y is the output signal, and m is the biosensor's sensitivity. The resolution of the biosensor and the range of analyte concentrations under test are linked to the biosensor's linearity. The resolution of a biosensor is defined as the lowest change in analyte concentration required to cause a change in the biosensor's response. A strong resolution is necessary depending on the application, as most biosensor applications require not only analyte detection but also monitoring of analyte concentrations over a large working range. The linear range, which is defined as the range of analyte concentrations for which the biosensor response changes linearly with concentration, is another phrase linked with linearity.

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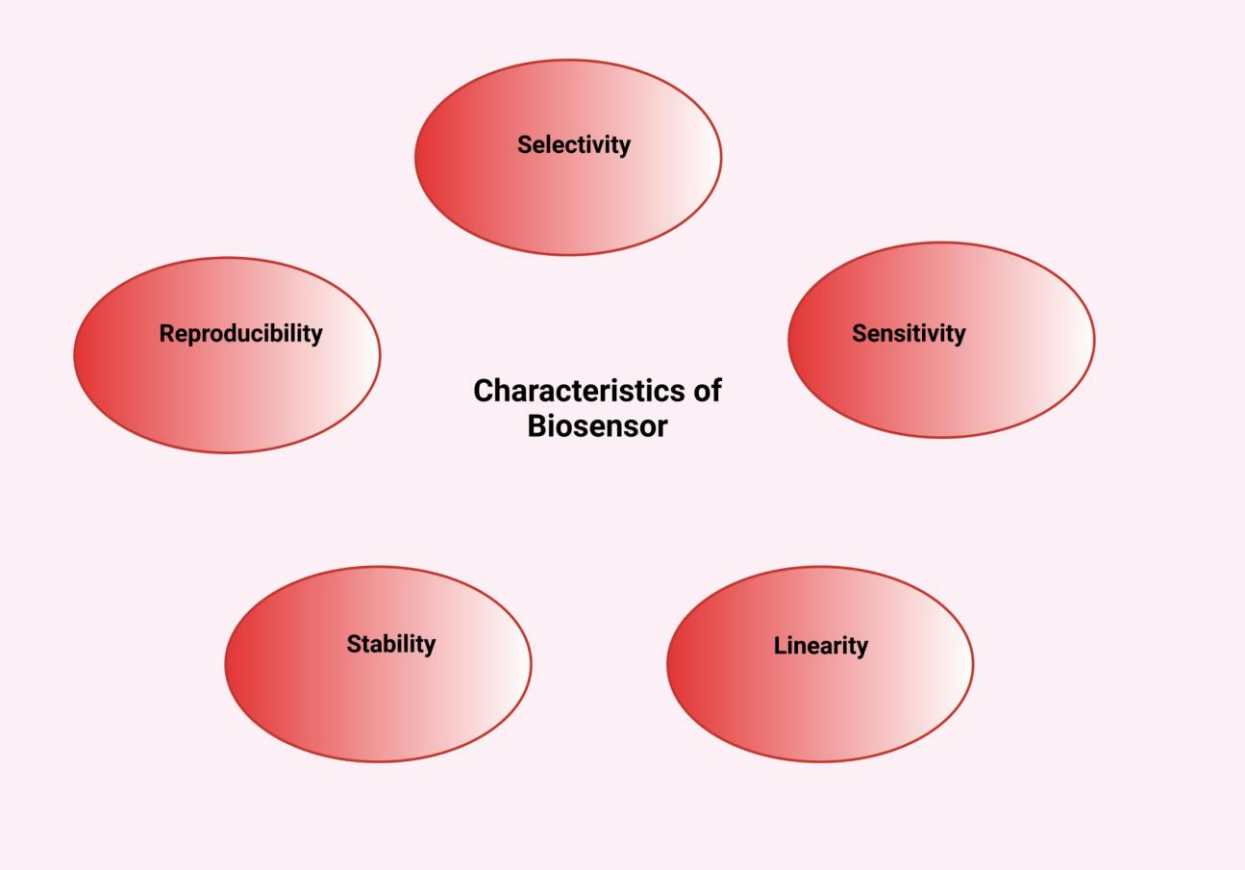

Figure 2: The five distinct characteristics of biosensors.

The first application of biosensors in the field of molecular diagnostics was glucose measurement [3]. In cardiovascular patients, a biosensor based on hafnium oxide (HfO2) is utilized to detect human interleukin (IL)-10 [4]. In addition, biosensors are used to diagnose infectious illnesses and antimicrobial susceptibility. Quantitative measurement of cardiac markers microfluidic impedance assay for controlling endothelin-induced cardiac hypertrophy, in undiluted serum, histone decyclase (HDAC) inhibitor assay from resonance energy transfer, in dental disease the effect of oxazaborolidines on immobilized fructosyltransferase, clinical immunophenotyping of blood cancer, biochip for a quick and accurate detection of multiple variants of cancer markers. Biosensors has been also developed to detect various diseases such as influenza, Hendra, Nipah, COVID-19 etc. Most biosensors created for detecting microorganisms that cause infectious disease work on the electrochemical reaction principle. This type of biosensor is the most popular since it is inexpensive, independent of solution turbidity, requires minimal power, and has a high sensitivity, and is easy to use [11].

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To evaluate the changes that occur during disease detection, various electrochemical approaches such as amperometric, impedance, and potentiometric are applied [12]. Biosensor marker, antibody–antigen, and DNA hybridization processes are typically used in amperometric biosensors, which use an electrochemical transducer to amplify the signal to a meaningful level for detection [13]. A glucometer is one of the most used amperometric sensors [14]. Research has created an immunosensor which was amperometric-based for the diagnosis of Newcastle disease [16]. Another amperometric-based immunosensor has been developed for highly precise diagnosis of forest-spring encephalitis [17]. For the Japanese B encephalitis vaccination, amperometric immunosensors (label free) have been created [19]. Another set of researchers created an optical biosensor with a sensitivity of 10 ng/ml for detecting the presence of Newcastle disease virus [20].

Immunosensors linked to SPR have also been created to detect the coronavirus that causes severe acute respiratory syndrome (SARS) [21]. The research group has also developed another sort of biosensor, piezoelectric biosensors, to assess the food and mouth disease virus [22]. A group of researchers has also created a piezoelectric-associated DNA biosensor to detect hepatitis B viral infection with a concentration range of 0.02–0.14 g/ml [24].
A numerous immunosensors has been invented to detect various pathogenic bacterial strains. An immunosensor was reported to be effective for identifying two Salmonella species (*S. gallinarum and S. pullorum*) in chicken flesh and eggs [25]. To detect *E. coli* O157:H7 and *Salmonella typhimurium* in chicken and milk samples with a CFU/mL concentration of 10^3–10^6 a screen-printed interdigitated microelectrode was created [26]. Another enzyme-based biosensor was created in which an enzyme acts as a bioreceptor for detection. One of the most often used enzyme-based biosensors is the glucometer, which detects glucose levels using an immobilized glucose oxidase enzyme [27]. A study developed an enzyme-based biosensor capable of detecting *E. coli* contamination in drinking water with high sensitivity [28]. Another type of biosensor has been created for the detection of toxins or pathogens which are labeled with fluorescent compounds, when in contact with a surface-based sensor, are intrigued by a laser pulse and generate a signal for detection [29]. A study has developed an optical biosensor to detect *S. aureus* with DL of 10^2–10^3 CFU/mL [30].

Biosensors centered on FRET are another type of optical biosensor. This sensor has been demonstrated to be successful in the detection of *S. aureus* in buffer solutions and spilled milk [31] . Additionally, Zhang and his collaborators developed a SPR biosensor for quick diagnosis of *Listeria monocytogenes*, *E. coli* O157:H7, and *Salmonella enteritidis* in food products [32]. Another type of optical biosensor mainly a colorimetric biosensor, has enabled us to detect pathogens such as *Listeria spp.* and *S. aureus* in food goods and the environment with high sensitivity.

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In the following context of this review article, the detection of various cancer biomarkers with the application of different biosensors has been briefly described:

Multiple Breast Cancer Biomarker Detection:

The incidence of breast cancer has been steadily rising in the world. Breast cancer accounted for roughly 11 percent of all cancers worldwide in 2008, and by 2012, that percentage had risen to 12 percent [33]. The data in American Cancer Society [34] illustrated that there are around three hundred thousand cases of breast cancer patients were predicted to be detected in the year of 2015 which will be new ones, with approximately forty thousand and two hundred ninety women and four hundred forty men dying from the disease. In 2018, there were around two million new cases and 626,700 deaths, accounting for 25% of all cancer cases and 15% of all women. Cancer-related mortality in women [35,36]. Early detection of breast cancer lowers long-term death rates, however it has limits in terms of identifying early-stage cancer cells [37]. The rising number of incidences of breast cancer is not due to a single source. There are several dangers associated with it. Given the variability in genotypic and phenotypic traits, it's likely that each people will have varying levels of sensitivity to breast cancer. However, when looking at the community, other risk variables have been discovered, including , family history, pregnancies, age or genetics, geographic variance, and way of life. The types of breast cancer can be classified by two kinds;

I. Noninvasive or in-situ breast cancer
II. Invasive Breast Cancer

Noninvasive Breast Cancers: This type of Breast Cancer is generally classified by observing the tumor site and its cellular activity. There are two types of breast cancer which are in this category. Ductal Carcinoma In situ (DCIS) and Lobular Carcinoma In situ (LCIS).
In the noninvasive category, DCIS is known to be the one most frequent kind of breast cancer. The milk ducts are the most affected in this type of cancer the lining of it does not breach the duct walls into the breast tissue or spread to lymph nodes or other parts of the body. Ductal Carcinoma In situ does not show any specific symptoms as it is asymptomatic and cannot be sensed with the hands. Mammography is the best exam to detect such for breast cancer, and the optimum medication is usually excision of the lump, followed by radiotherapy or hormonal medication if the cancer is hormone receptor positive. Generally, it is a type of primary level of breast cancer that responds well to medication. It can, however, recur, increasing the risk of developing invasive breast cancer in the future. It is given a higher grade than zero in certain circumstances. On the contrary, the formation of aberrant tissues in the lobules without breaching the lobules' wall and metastasizing is referred to as lobular carcinoma in situ (LCIS). A mass or morphological alteration in the tissues

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occurs infrequently. As a result, to assess the presence of additional suspected breast abnormalities, a biopsy is the preferred method of diagnosis. This type of cancer does not have the risk to develop into the advance level of life taking breast cancer for which a numerous case of such cancer goes untreated for years with no symptoms of any health issues. Even though LCIS seldom progresses to aggressive breast cancer, patients are routinely examined, by mammography and, in certain condition they are also tested by magnetic resonance imaging (MRI). Hormonal therapeutics is occasionally indicated as a prophylactic intervention due to LCIS's hormone receptor positivity.

Invasive Breast Cancer: This type of breast cancer is fully characterized by the gene expression of cell. HER2 positive luminal, Luminal A, B or B like, and TNBC or triple negative breast cancer are in this category. In the luminal A type of cancer, it is often seen that the progesterone receptor (PR) or estrogen alpha (ERα) receptor are expressed whereas the human epidermal growth factor receptor 2 (HER2) is not expressed due to the small quantity of protein Ki-67. This protein Ki-67 controls the multiplication of cancer cells which allow the cells to grow slowly, and it has the best recovery results. Conversely, in the subtypes of luminal B and B like cancer, the progesterone receptor (PR) or estrogen alpha (ERα) receptor are not expressed but the HER2 is seen to be released. Both subtypes have elevated levels of protein Ki-67 which mean that these cancers grow faster than luminal A and has less recovery rates [34,38,39].

In HER2 positive cancer type the expression of PR and ERα are not seen. This type of malignancies is only positive for HER2 receptors, and they generally multiply and spread faster than other luminal cancer and also it has a worse recovery rate but in studies where these subtypes of cancers were treated with targeted therapeutics pertuzumab, trastuzumab,ado-trastuzumab emtansine and lapatinib has shown high recovery rates [34,37,38].

The triple negative breast cancer is completely different from other invasive cancer cells. It is known as the deadliest type of breast cancer as it is generally diagnosed at very advanced stage with metastasized brain and lungs. Here in the triple negative type of breast cancer, the cells do not express HER2 or PR, ERα receptors for which targeted therapies and hormone treatment is not effective. It has the case of re-currency after every five years. The effective treatment for this cancer type is chemotherapy, radiotherapy, or surgery [34,37-39]

The best diagnosis for breast cancer is the early detection of it. Finding specific biomarkers of breast cancer may allow better prognosis. Several serum biomarkers are used in medicine to diagnose breast cancer in early stages. These biomarkers are carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), circulating cyto keratins eg: TPA (tissue polypeptide antigen), CIFRA-21-1 (cytokeratin 19 fragment and TPS (tissue polypeptide specific antigens) and also the proteolytically cleaved ectodomain of epidermal growth factor receptor 2 of human (S-HER) [40]. Among all serum biomarkers, CA15-3 is the most common serum biomarker, but it is not effective

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at detecting cancer in its early stages. Due to the advancement in the biomarkers screening technology, the new developing strategies has given opportunity to screen and diagnose breast cancer earlier [41]. DNA methylation, alternation in histones and miRNAs are the significant up-regulators of gene expression of pathological and normal development and they are known as prognostic biomarkers that are being examined by scientist to be function as targeted therapeutics.

Table 2 : Distinct variety of Breast Cancer Biomarkers

Types of Breast Cancer Biomarkers
Breast Cancer Antigen 1 (BRCA 1)
Breast Cancer Antigen 2 (BRCA 2)
Mucin 1
Carbohydrate antigen 15-3 (CA15-3)
mIRNA 21
mIRNA 155
Estrogen alpha (ERα)
Progesterone receptor (PR)
Human epidermal growth factor receptor 2(HER2)
Carcinoembryonic antigen (CEA)
c-erbB-2
Anti c-erbB-2

FDA has approved the serum biomarkers to observe the re-currency and the treatment efficiency of breast cancer, but it was not recommended to detect the cancer [42]. There are numerous conventional screening methods for breast cancer. Mammography, MRI, Breast Ultrasounds are some of those which are used to screen breast cancer in women who are at normal risk of developing cancer. Though these types of diagnostic methods are of low sensitivity. There are also some screening tests who are used to screen specific oncogene mutation such as BRCA1 and 2 mutations. These genetic mutation screening tests are used to screen heredity of breast cancer in patients. Another gene screening test Oncotype DX uses qPCR for the measurement of mRNA levels to examine the expression of twenty-one genes, among that sixteen of the genes are tumor

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specific and left-over fives are normal housekeeping one. MammaPrint is just another multianalysis test for predicting the fate of breast cancer patients [37,43-46]. This diagnostic method generally examines the levels of mRNAs of 70 genes linked to the six most common cancer symptoms. Prosigna, EndoPredict, Breast Cancer Index and the Genomic Grade Index, are some of the other multianalyte assays, with EndoPredict and Prosigna being the most studied ones [43,45]. Such two types of tests can help with the treatment decisions for patients with HER2-negative,metastatic lymph nodes and ER-positive[44,47].

Considering the expanding benefits of discovering breast cancer biomarkers, routinely used diagnostic tests are insensitive, time-consuming, and expensive, with a significant risk of false positive and negative results. As a result, there is still a pressing demand for sensitive and particular approaches that are simple and quick. Until now, oncogenetic biomarkers have been identified by analyzing biological material obtained from tumor tissue biopsy. Chemically modified electrodes were used in biosensor and electroanalysis research. It is a relatively new electrode system approach with a wide range of scientific and therapeutic applications. Biosensors are designed with exceptional principle which will cover cost and time effective, portable, sensitive and specific. Even though the majority is not in the advanced stage where they can be regarded viable for clinical and/or commercial applications. Several techniques have shown promising and cost-effective results in terms of sensitivity and specificity for recognized breast cancer biomarkers. In the near future, such researches will have a significant outcome on early breast cancer identification. Following in the next part of this article, the detection of various breast cancer biomarkers with distinct biosensor application has been briefly described:

Breast Cancer Antigen: The Breast Cancer Antigen genes are known to be tumor suppressor genes which are very efficient in fighting cancer. They control the rapid growth of cancer cells and also prohibit them to get metastasized. The expression of these genes are only visible when there are presence of cancerous cells which tend to bind with the receptors of the antigen. There are several techniques to detect the BRCA1 genes but it was observed that all of them have extremely low detection limits. Research was led by Tiwari et al. And his colleagues, where they have made utilized chitosan-co-polyaniline, which is known as cost effective and stable electroactive polymer, to invent an electrochemical biosensor as a long-term support matrix on an indiumtin-oxide (ITO) support [50]. In the presence of single stranded DNA, a probe adsorbed on the surface with BRCA1-associated cDNA sequences gave an electrochemical response [48]. In the experiment it was monitored that the limit of detection of the biosensor was 0.05 fmol, with good repeatability and good sensitivity, and it was considered as a potential detection method of breast cancer at an early stage [48]. Later another research team also made an electrochemical biosensor that can

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diagnose BRCA1 in blood samples at concentration of 1.72 fM which was very low [49]. To create this label free biosensor, a glassy carbon electrode (GCE) was produced with a strongly oppositely related polyethylene glycol layer comprising of groups of amines. The device was then altered using nanoparticles of gold, which resulted in exceptional sensitivity and accurate readings [49]. By focusing on this polyaniline/polyethylene glycol nanofibers, another study invented an ultrasensitive electrochemical biosensor to diagnose the breast cancer antigen 1 gene [50]. The device was capable to detect the gene in blood samples of human without being discontinued by nonspecific surface assimilation in complex biological situations. To capture probes, the nanofibers in the device have antifouling properties due to their high immobilization ability [50]. Research was performed by scientists [51] where they have created an electrochemical biosensor with good conductivity and strong antifouling ability for subsequent binding of a suitable DNA probe as the BRE using peptides altered with a polymer of PEDOT. The peptides which were used in this research was zwitterionic .The limit of detection of this biosensor was 0.03 fM vs1.72 fM, which was lower than Wang et al. [49].

To detect BRCA1 genes, another research team has [52] used carbon dots and AuNPs with the help of a hairpin structure to create a fluorescent dual channel biosensor model. In the biosensor the RNA/DNA targets of BRCA1 gene tends to bind to the AuNPs' corresponding sequence and release carbon dots, which results in a positive fluorescence signal with a LR of 4120 nM [53].

A "sandwich-like" biosensor was created by Yang and his research team on the surface of a bead platform which was magnetic. A tetrahedron-shaped reporter probe with three and fourth vertices labeled with a labeled with digoxin and detecting probe was constructed in this study respectively. The antidigoxin antibody has three locations to get attach for each detection probe after being tagged with appropriate enzymes, resulting in signal amplification [56]. This method was also capable of discriminating sequences of DNA with only one base mismatch, and the results were comparable to those of PCR products [55]. In the below table 3 , the studies related to BRCA1 detection are listed below:

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Table 3 :The application of Electrochemical and Optical Biosensors in the detection of BRCA1

Biosensor Technique	Biomarker Type	Linear Range	Detection Limit	References
Fluorescence	Breast Cancer Antigen 1	4 - 120 nM	-	52
Colorimetric	Breast Cancer Antigen 1	10 fM -10 nM	10 fM;	53
Electrochemical	Breast Cancer Antigen 1	0.01 pM - 1 nM	0.0038 pM	50
Electrochemical	Breast Cancer Antigen 1	-	0.03 fM	51
Electrochemical impedance spectroscopy	Breast Cancer Antigen 1	50.0 fM - 1.0 nM	1.72 fM	49
Electrochemical impedance spectroscopy and cyclic voltammetry	Breast Cancer Antigen 1	0.05- 25 fmol	2.104 μA/fmol;	48

Mucin 1: The MUC1 gene is a protein coding gene which directs the production of a protein known as mucin 1. Mucus, a slippery fluid that lubricates and protects the lining of the lungs, digestive system, reproductive system, and other organs and tissues, is made up of numerous mucin proteins. Due to genetic alternation and transcriptional dysfunctionality, MUC1 can be over expressed and cause cancer. It is often seen that 90% of breast tumors inherit the overexpression of this gene. Studies have been found where modified biosensors have been created to detect MUC1 from breast cancer sample (Table4).

To find mucin in Michigan cancer foundation-7 (MCF-7) a study was performed which have utilized an aptamer-cell aptamer sandwich architectural technique (figure 3) [54]. The biosensor has a sandwich construction that can only form when the targeted cancerous cells are present in sample. The electrochemical reaction is triggered by the enzyme HRP-labeled on the MUC1 aptamer, which is later observed to determine the electron mediator thionine [54]. The aptamer's

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twofold recognition ability boosts specificity even more of the detection process [54]. Another research team has chosen an electromagnetic technique with SPR as the MUC1 detection method on the Michigan Cancer Foundation 7 cells [55]. In this research it took approximately 30 minutes for the Au nanodes to allow an outstanding dynamical reach of 100 to 105 cells/mL . The limit of detection of 100 cells/mL [55].

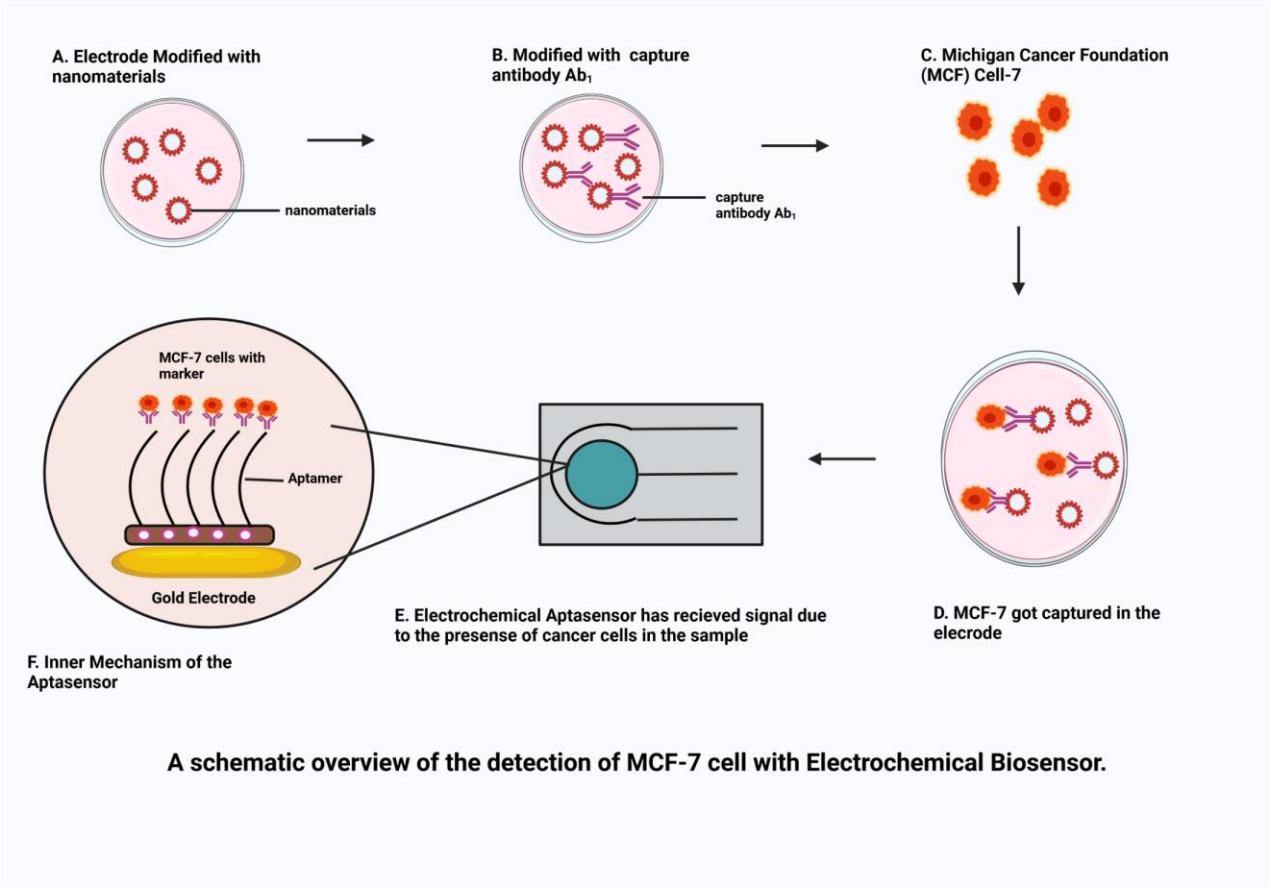

Figure 3: A schematic overview of detection of MCF-7 cell with Electrochemical Biosensor.

A team of scientist has devised a sandwich electrochemical biosensor based on a a polyadenine-aptamer functionalized AuNPs/graphene oxide hybrid and polyadenine-aptamer generated Au electrode to detect selective and label free MUC1 in MCF-7, [56]. The biosensor detected cells as low as 8 cells/mL under ideal experimental circumstances, with a LR of 10-105 cells per mL [56]. By concentrated in the characteristics of a polymer nanocomposite, a scientific team have developed an electrochemical apta-sensor to detect MUC1 . On a surface of fluorine tin oxide glass, a nanocomposite layer comprising AuNPs and graphene oxide doped PEDOT was formed [57]. With an apta-electrode reusability of 8 times, this method was capable to find MUC1 at concentrations as minimal as 0.31 fM [57].

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Table 4: The application of biosensor technology in the detection of Mucin 1 biomarker

Biosensor Transducer	Biomarker Type	Detection Limit(DL)	Linear Range(LR)	References
Electrochemical	Mucin 1	100 cells/mL;	10^2 - 10^7 cells/mL	54
Electrochemical	Mucin 1	100 cells;	10^2-10^5 cells/mL	55
Electrochemical	Mucin 1	0.031 fM;	3.13-31.25 nM	57
Electrochemical (voltammetry)	Mucin 1	8 cells/mL;	10 - 10^5 cells/mL	56

ERα and PR : To detect the biomarker ERα and PR , many studies has been performed to develop biosensors. Padmanabhan et al. are one of those who have created an immunobiosensor for detecting ERα by utilizing a transducer which was optical sensor based that can find the protein as minimal as fifty nano liters[58]. The whole biosensing device provided a visible radiation of green and red response from the detection of estrogen receptor alpha by the supplemental antibody employing a strong core photonic fiber of crystal in a reflection of arrangement which was a total internal [58].

Research was conducted to make a label-free apt sensor with higher signal gain observed by EIS technique. A research team Jime'nez et al. have used SELE to choose a progesterone aptamer [59]. The increased electron transfer resistance of an iron standard redox probe caused by the conformational alternation of the aptamer which was on the Au electrode upon attaching to PR was able to give a detection limit of 0.90 ng/mL and a linear range of progesterone from 10 to 60 ng/mL [59].

CEA: CEA is the Carcinoembryonic antigen. Numerous studies have been performed using biosensors to detect this biomarker. Peng et al. used the catalytic properties of some layer black phosphorus generated by onsite AuNP production against 4-nitrophenol, which was measured by colorimetric tests [60]. In the presence of the antibody, this catalytic activity was reversibly lowered, but it was revived when CEA was introduced. With the amount of 0.20 pg/mL and 1

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pg/mL 10 g/mL, respectively, the detection limit and linear detection range were found to be sufficient for sample analysis [60].

A study by Khang and his colleagues have created a chemiluminescence aptasensor that is all-in-one [61]. In this study, over thirty minutes were required for the competitive binding of hemin and carcinoembryonic antigen at room temperature, in which a dual DNA aptamer was utilized. The concentration of horseradish peroxidase (HRP)-mimicking G-quardruplex DNA zyme formed upon the binding interaction between hemin and the dual DNA was then determined by adding Amplex Red and H2O2 into the system to form resorufin, which was dependent on the concentration of HP-mimicking G-quardruplex DNA zyme formed upon the binding interaction between hemin and the dual DNA [61]. After adding 1,10- oxalyldiimidazole to the detecting device, a bright red light appeared, which faded as CEA concentrations increased [61].

Using AuNPs as carriers of HRP-labeled antiCEA detection antibody and magnetic microparticles as supporting substrates, a scientific team has developed a colorimetric enzyme immunoassay [62]. When compared to a CEA ELISA kit [62], the compound produced an optical signal with enhanced sensitivity. Wu et al. employed a sandwich immunoassay in which the secondary antibody allowed the long chain polymeric material to develop, resulting in a large number of sites for HRP binding [63]. The more secondary antibodies bound to the support (more CEA on the platform), the larger the electrochemical signal generated by the HRP-O-phenylenediamine-H2O2 system, which turned out to be a means to enhance the signal. A carbon electrode was printed on a paper-based microfluidic electrochemical immunodevice as the support [63].

Using fluorescence resonance energy transfer (FRET) between up-converting nanoparticles (UCPs) and palladium nanoparticles (PdNPs), Li et al. has created a biosensor [64]. Because the aptamer was linked to the UCPs, the near proximity of the PdNPs to the aptamer caused the UCPs' fluorescence to be quenched. When CEA was present, the aptamer preferentially interacted with CEA, resulting in conformational changes that decreased the aptamer's interaction with the PdNPs, allowing fluorescence signals to be recovered. With a linear range of 4100 pg/mL and a detection limit of 1.7 pg/mL, this technique enabled for ultrasensitive detection of CEA in diluted human serum [64].

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Table 5: The application of electrochemical and optical biosensors in the detection of CEA

Biosensor Technique	Biomarker	Linear Range(LR)	Detection Limit (DL)	References
Electrochemical	Carcinoembryonic Antigen (CEA)	-	0.01 ng/mL	63
Chemiluminescence	Carcinoembryonic Antigen (CEA)	0-200 ng/mL	0.58 ng/mL;	61
Colorimetric	Carcinoembryonic Antigen (CEA)	0.05 -50 ng/mL	48 pg/mL;	62
Colorimetric	Carcinoembryonic Antigen (CEA)	$1\text{-}10^4$ pg/mL	0.20 pg/mL;	60
Fluorescence	Carcinoembryonic Antigen (CEA)	4 -100 pg/mL	1.7 pg/mL;	64

miRNA21 and miRNA155: miRNA biomarkers 21 and 155 are two types of miRNA biomarkers that have been detected in several types of breast cancer. Kilic and his team.[65] has developed an electrochemical biosensor for total RNA cell lysate based on enzyme amplified mir21 biosensing. N-(dimethylamino)propyl-N0 -ethylcarbodiimide hydrochloride and N-hydroxysulfosuccinimide were used as coupling agents to detect Mir21 utilizing trap probes and/or cell residues covalently coupled to the pencil graphite electrode [65]. The new enzymatic detection technique was juxtaposed to the standard guanine oxidation-based assay in terms of DL and specificity [65]. With a range of detection of 1 g/mL, the biosensor approach was found to be sensitive [65].

Hong et al. used electrochemical technology to construct an ultrasensitive biosensor for the detection of cancer-associated circulating miRNA-21 [66]. A self-assembled DNA concatamer, which is a long DNA chain of repeated copies of the same DNA sequences linked end-to-end, was used to detect miRNA-21 in sophisticated biological materials, enzymes, or labels with a detection limit as low as 100 aM. Vargas et al. developed a sensitive amperometric magneto biosensor for quickly detecting microRNAs [67]. In this procedure, the target was directly hybridized with a particular biotinylated DNA probe placed on magnetic beads modified with streptavidin. The bacterial protein A was linked with an HRP homopolymer for signal amplification, and the label

was given by a certain DNARNA antibody [67]. Their single-step approach achieved a linear concentration range of 1.0 to 100.0 pM and a limit detection of 10 attomoles in a 25-L sample in under 30 minutes without any target miRNA amplification [67]. Raffiee-Pour et al. used an electrochemical transducer to detect miRNA-21 in a new way. In this study, methylene blue was used as a redox indicator, obviating the necessity for labels. In kinetic studies, methylene blue was found to be stronger and more stable with miRNA/DNA than with ss-DNA, with a detection limit of 84.3 fM [68].

By coupling a G-quadruplex structure with a 2-aminopurine probe, Li et al. produced a normal device that can find upregulated miRNA-21 from breast cancer cell lysate of human without the use of enzymes oe quenchers [69]. The biosensor featured two DNA hairpins, which significantly boosted the probe's fluorescence and allowed for a detection limit of 1.48 pM [69]. Using a modified electrode, Kangkamano et al. created a label-free electrochemical biosensor for miRNA-21 detection [70]. The concentrations of miRNA-21 were proportional to electrochemical signal in the 0.20106 fM range, with a DL of 0.20 fM [70]. The electrochemical signal was proportional to miRNA-21 concentrations in the detection range 0.20106 fM, with a detection limit of 0.20 fM, when the probe was modified with a pyrrolidinyl peptide nucleic acid/polypyrrole/silver nanofoam. Deng and his colleagues invented an electrochemical device fully focused on propylamine functionalized mesoporous silica nanoparticles and glucose release caused by a target [71]. With a DL of 19 pM [71], the whole method allowed for the elimination of time-consuming labeling and repeated washing operations. There have been a variety of studies that have been conducted to detect miRNA155.

Azimzadeh and his colleagues developed an electrochemical nano biosensor for miRNA 155 detection in plasma samples, stating that the high selectivity and sensitivity was due to the combination of a graphene oxide sheet on the surface of the GCE with thiolated probe functionalized gold nanorods [72]. The diagnostic range for the l signal is 2.0 fM to 8.0 pM, with a DL of 0.6 fM. They used a electrochemical approach to construct a biosensor that can detect attomolar levels of miRNA 155. In a serum backdrop, this biosensor can detect miRNA 155 concentrations as minimal as 1-10 aM, allowing for a lot of sample dilution. It also overcomes interferences, allowing it to be reused in consecutive readings with varied solutions while showing excellent selectivity for other proteins in physiological fluids and cancer cell extracts [72].

Hakimian et al. identified miRNA 155 using an optical technique, and were able to specify three basepair disorganization and DNA (genomic) from the target miRNA 155 [73]. The method entails using a probe that can form a connection with the negatively charged gold nanoparticles, allowing the target miR-155 to electrostatically adsorb onto the positively charged AuNPs surface [73]. After

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hybridization, an optical signal with a detection limit of 100 aM and a linear range of 100 aM to 100 fM could be detected [73].

Table 6: The application of biosensors in the detection of miRNA-21 and miRNA 155.

Biosensor Technique	Biomarker	Detection Limit	Linear Range	References
Electrochemical	miRNA 21	84.3 fM;	0.1 -500.0 pM	67
Electrochemical	miRNA 21	1.0 mg/mL;	-	65
Electrochemical	miRNA 21	100 aM;	100-10^5 aM	66
Electrochemical	miRNA 21	0.20 fM;	0.20-10^6 fM	70
Electrochemical	miRNA 21	19 pM;	50^{-5} x10^3 pM	71
Electrochemical (ampterometric)	miRNA 21	0.04 pM;	1.0-100.0 pM	68
Fluorescence	miRNA 21	1.48 pM	-	69
Colorimetric	miRNA 155	100 aM;	100-10^5 aM	73
Electrochemical	miRNA 155	5.7 aM;	10-10^9 aM	72
Electrochemical	miRNA 155	0.6 fM;	2.0 - 8x 10^3 fM	72

CA-15-3: The elevated level of this biomarkers is highly found in distinct types of cancers such as breast, ovary, liver etc. Scientist has performed several studies to detect these biomarkers by variety of biosensors. Zhu et al. used an optical technique to construct a label-free optofluidic ring resonator sensor that could detect CA 15-3 quickly [74]. In diluted human serum samples, the sensor was capable of detecting about 1 U/mL CA 15-3 in about 30 minutes [74].

Elakkiya et al. used optics as the transducer technology to construct a biosensor for CA 15-3 utilizing a cysteamine-capped cadmium sulfide QD surface [75]. In saline and serum samples loaded with antigens, the device was able to detect a very low concentration of 0.002 KU/L with a continuous reaction time of 15 minutes [75].

The first multiplexed electrochemical immunosensor for the simultaneous detection of CA 15-3 and HER2 was developed by Marques et al. [76]. The immunosensor was built on a personalized dual screen-printed carbon electrode within situ electrodeposited gold nanoparticles on the surfaces [76]. After that, each electrode was separately coated with a monoclonal antihuman CA 15-3 or antihuman HER2 antibody [76]. Voltametric analysis was used to identify antigen antibody interactions with a limit of the detection of 5.0 U/mL [76].

Graphene was employed by Ge et al., Li et al., and Akter et al. to create electrochemical immunosensors. Scientist has assessed that the enzyme was released from the liposome in the presence of CA-15-3, which led to the reduction of thionine with hydrogen peroxide as an electron mediator. Ge et al. employed a nano porous/graphene hybrid as platform, employing liposomes with the enzyme HRP encapsulated as labels [77]. Encapsulation proved to be an effective multiplication method which allows the detection limits to as low as 5 U/mL [77].

Li et al. [78,79] employed graphene in an electrochemical immunosensor, but in the form of N-doped graphene sheets. Great conductivity was added to the graphene-modified electrode, resulting in considerable electron transfer and high sensitivity without the need for labeling . The immunosensor has a detection limit of 0.012 U/mL and a linear performance in the 0.120 U/mL range [78].

Akter et al. used noncovalent functionalized graphene oxides as sensor probes and multiwalled carbon nanotubes supporting many ferritins as labels in another amplification method [79]. The improved bio electrocatalytic reduction of hydrogen peroxide mediated by hydroquinone at the functionalized graphene probe enabled the detection of CA 15-3 via an amide link between amine groups of secondary antibodies and ferritin and carboxylic acid groups of MWCNTs [79].

Molecular imprinting (MIP) methods were used by Ribeiro et al. to create an electrochemical biosensor with a synthetic receptor screen [80]. CA 15-3 was imprinted on a poly(toluidine blue) film in this method, and tests in buffer and artificial sera revealed preferential adsorption of CA 15-3 onto MIP film after 30 minutes of incubation [80]. The target protein concentration was shown to be linear from 0.10 to 100 U/mL in calibration plots, with a detection limit of 0.10 U/mL [80].

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Table 7: The application of biosensors in the detection of CA-15-3

Biosensor Technique	Biomarker	Detection Limit	Linear Range	References
Electrochemical	CA-15-3	0.012 U/mL;	0.1-20 U/mL	78
Electrochemical	CA-15-3	0.009 U/mL;	0.05-100 U/mL	80
Electrochemical	CA-15-3	5 x 10^{-6} U/mL;	2 x 10^{-5}-40 U/mL	77
Electrochemical	CA-15-3	0.10 U/mL;	0.10-100 U/mL	81
Optical	CA-15-3	1 unit/mL	-	74
Optical	CA-15-3	0.002 kU/L	-	75
Electrochemical (voltammetry)	CA-15-3	0.7 U/mL	1.2-3.7 U/mL	76

HER2: It is the most common detectable cancer biomarker in breast cancer diagnosis . Studies has been done to detect it with distinct type of biosensors. The studies related to the detection of this biomarker are briefly described below: On screen-printed electrodes (SPEs), A research team has created a sandwich-type immunoassay which was completely designed with nanobodies to diagnose another epitope of HER2 [82]. The identification of the antibody was labelled with HRP and the capture nanobody was mounted on the electrode which was working through carbon. It was observed that the signal of the transducer was produced by the p-quinone of HRP electroreduction and rendered at the screen-printed electrodes in the presence of hydroquinone and hydrogen peroxide[82].

A study conducted by Shen and his team has created a DNA self-multiplication device that can produce electric current and power electrochemical biosensing. To develop a sandwich like configuration, a HER2 aptamer was employed as a signal-generating reporter and also as a ligand for recognition as well [83]. With a detection range of 1100 pg/mL, the limit of detection was 0.047 pg/mL [83]. A study conducted by another bunch of researchers where they have created a colorimetric biosensor. The function of that device was to utilize a probe with antibodies of HER2 on liposomes which were packed with gold nanoclusters or BSA. The intrinsic peroxidase property

of these gold nanoclusters causes them to respond with 3,30,5,50-tetramethylbenzidine (TMB) in the presence of hydrogen peroxide which generally change the color of the solution [84]. This platform was able to identify HER2-positive cancer cells in serum of human and also in the tissues of breast cancer by upholding a detection limit of five cells [84].

Another research by Saeed et al. has covalently bonded an silver nanoparticles with a small complementary sequence for HER2 to a GCE generated by graphene oxide . In the presence of TMB and hydrogen peroxide, an extra DNA short sequence modified with HRP was able to hybridize with the free sequence of HER2, creating an electrochemical signal [85]. To capture HER2, A study has. employed a specific aptamer of HER2 as a ligand and some other to give a redox electric signal. The reaction between the phosphate moieties in the aptamer and molybdate [86] produced this current. Overall, the aptasensor's electrochemical current was proportional to HER2 concentrations in the range of 0.015 ng/mL [87]. Another research has created a biosensor purely based on organic-electrochemical transistor that can detect activity of electrochemical on gate electrodes up to 10-14 g/mL [88]. A capture specific polyclonal antiHER2 antibody was added to the gold gate electrode, and detection was facilitated by a secondary antibody linked to HRP. In the presence of HER2 and hydrogen peroxide, a current was generated [88].

Tabasi et al. created an ultrasensitive electrochemical aptasensor that binds aptamers using a graphene and chitosan layer as an electrode material [89]. The conformational changes caused by HER2 association with the electrochemical probe MB provides a greater sign, which was density dependent [89]. A research team has created a sensing device that works in the same way as a sandwich. The probe was made by immobilizing the antibody directly on the bare electrode surface using a nanocomposite of AuNPs capped with 2,5-bis(2-thienyl)-1Hpyrrole-1-(p-benzoic acid). A hydrazine AuNP aptamer bioconjugate with the hydrazine reductant attached to the AuNPs and silver that should be reduced for signal amplification was used for detection [90]. Another intriguing feature of this method is that the silver-stained target cells have a black hue that can be seen using a microscope, making it a straightforward and practical method for clinical cancer cell analysis [90].

Emami et al. created a label-free immunosensor for HER2 detection in actual samples [91]. AntiHER2 antibodies were conjugated to iron oxide nanoparticles, resulting in stable bioconjugates that were applied to the gold electrode surface [91]. Against an iron redox probe, the immunosensor was responsive to HER2 concentrations as low as 0.995 pg/mL and had a sensitivity of 5.921A 3 mL/ng [91]. Using an oxide zinc and graphene composite and an S6 aptamer, a team of researcher has created a photoelectrochemical biosensor for the identification of a HER2-positive cell line which was SK-Br-3 [93]. The high photoelectric signal of zinc oxide, the superior charge

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transportation and separation of graphene, and the specificity of the S6 aptamer to target Sk-Br-3 cells appeared to improve sensitivity and selectivity, making this approach a promising candidate for accurate cancer cell detection [92].

By making a carbon paste electrode from multiwall carbon nanotubes (MWCNTs), graphite powder, an ionic liquid, and paraffin, which were then electrode plated with AuNPs, a research team led by Arkan has produced a sensor for the diagnosis of HER2. [93]. Li et al. used an electrochemical immunosensor with an immobilized polycytosine DNA sequence in an AuNP matrix as well [94]. The immunosensor identified HER2 through a response between molybdate and polycytosine DNA phosphate backbone, which generated an electrochemical signal at the electrode's surface [94]. With a limit detection of 0.5 pg/mL and no cross reactivity with human IgG, human IgA, p53, CEA, or protein kinase, the biosensor demonstrated linear behavior from 1 pg/mL to 1 ng/mL [94]. Arya et al. developed a simple and sensitive HER2 biosensor using modified microelectrodes with a thiol terminated DNA aptamer which was interdigitated [95]. The use of interdigitated Au electrodes is the most significant variation from earlier methods [96]. When challenged with different serum proteins, the biosensor demonstrated high selectivity and a dynamic linear range of 1 pM to 100 nM [95].

By constructing a fully inkjet-printed electrochemical sensor, Carvajal et al. discovered a low-cost technique (around US$0.25). An inkjet printed gold working 8-electrode array, a counter electrode, and an inkjet-printed silver electrode chlorinated with bleach to make an Ag/AgCl quasireference electrode were all part of the device platform [96]. In a microfluidic device, a complete sandwich immunoassay was built + with labeling done using a streptavidin/HRP composite. The experiment took 15 minutes and the detection limit was 12 pg/mL [96].

Table 8: The application of biosensors in the detection of HER2

Biosensor Technique	Biomarker	Linear Range	Detection Limit	References
Electrochemical	HER2	1 pM -100 nM	1 pM;	94
Electrochemical	HER2	1 -1000 pg/mL	0.5 pg/mL;	93
Electrochemical	HER2	-	12 pg/mL	89
Electrochemical	HER2	1 ng/L - 10.0 µg/L	37 pg/L;	95

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Electrochemical	HER2	10^{-14} - 10^{-7}g/mL	-	87
Electrochemical	HER2	0.01 - 5 ng/mL	-	86
Electrochemical	HER2	1 -100 pg/mL	0.047 pg/mL;	83
Electrochemical (amperometric)	HER2	0.37 -10 nM	0.16 nM;	85
Electrochemical (amperometric)	HER2	1 -200 µg/mL	-	82
Electrochemical (voltammetry)	HER2	0.5 - 2 ng/mL	0.21 ng/mL;	88
Electrochemical (voltammetry)	HER2	10 ng/L - 10 µg/L	0.995 pg/L;	80
Electrochemical (EIS)	HER2	10 - 110 ng/mL	7.4 ng/mL;	92
Photoelectrochemical	HER2	10^2-10^6 cells/mL	58 cells/mL;	91
Colorimetric	HER2	-	5 Sk-Br-3 cells	84

Detection of Ovarian Cancer Biomarkers with Biosensors Technology :

Cancer of different kinds is one of the leading reasons of death in women over the age of 50, with a fifteen percentage of death rate that rises to thirty six percent in developed nations, making it a global health problem [96]. Ovarian cancer, is used to define any malignancies that develop or locate tumors in the ovaries or fallopian tubes of women. It is one of the most severe cancers found in female patients [97].

Despite being less frequent than malignancies such as breast cancer, ovarian cancer has the highest fatality-to-case ratio of all gynecological cancers, making it a particularly critical concern for postmenopausal women. The death rate for women diagnosed with late-stage ovarian cancer is extremely high. As a result, detecting and diagnosing the disease as early as feasible in its progression is critical. The achievement of this goal necessitates the screening of a large number of women at a clinically relevant age using biomarkers for disease present in blood or serum. For the

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automatic detection of such species, biosensor detection is an appealing approach. The sole biomarker frequently tested for in clinical use is cancer antigen 125, which is regarded a poor biomarker for the disease out of numerous that have been identified in individuals with ovarian cancer. There are distinct varieties of ovarian cancer biomarkers which can be detected through molecular diagnostics such as CA-125 , CA-125 with ApoA-I, transferrin and TTR ,OVA 1 Panel ,leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor ,and CA-125 ,TTR, Hb, ApoAI, TF ,HE4,HE4 with CA-125 ,Mesothelin ,Osteopontin ,HSP-27, HSP-60, Calreticulin, Vimentin , Fibrinogen- γ ,miRNAs ,HSP-10 , and LPA 1.A number of studies has applied the biosensor technology to develop devices which can efficiently detect ovarian cancer biomarkers. Among such researches, some of the studies are described below:

Be31-2: Urinary anti-apoptotic protein B-cell (Be3l-2) is a potential biomarker in the detection of ovarian cancer cells. In the year of 2012, Onen et al., developed an ultrasonic MEMS-based biosensor by using a microelectronic device to detect the biomarker of ovarian cancer. The design, manufacturing, and surface functionalization of antibodies for the marker were disclosed in this study, resulting in an experimental sensitivity of sub ng/mL detection [98]. The sensor uses ST-quartz surface functionalized shear horizontal (SH) surface acoustic wave technology to quantify the change of mass loading caused by protein adhesion to the interval path. A couple of microfabricated interdigital transducers (IDTs) separated by a well-constructed delay path created and received SH-SAWs. The surface chemistry was chosen to avoid fouling difficulties caused by organisms found in urine. It was suggested that the arrangement would work best in a point-of-care setting [99].

HER4*:* Yuan et al., described a biosensor on a localized surface plasmon resonance for the detection of the biomarker human epididymis secretory protein 4 (HE4) in an earlier paper [100]. The probe in this case was a HE4 antibody species that was coupled to a silver nano-chip using normal EDC-NHS chemistry. The device was incubated on the functionalized LSPR chip for 40 minutes with varying concentrations of standard HE4 (1 pM to 0.1 M), followed by a thorough rinse with phosphate-buffered solution containing 0.05 percent Tween-20 to dissolve the nonspecific binding.

An ultraviolet-visible spectroscope with a charge-coupled device detector was used to monitor and record the peak wavelength of the LSPR extinction spectrum (max) excited by the silver nanoparticles for each experiment. Following incubation in 500 pM HE4, the LSPR wavelength shifted to +14.48 nm, with a λmax of 645.45 nm, indicating that HE4 in a buffer solution was successfully detected by the LSPR biosensor [101]. The method's limit of detection was claimed to be 4 pM, and it performed well in comparison to a standard ELISA assay. Because of the

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ubiquitous non-specific adsorption issue, there was some concern regarding the sustainability of a concentration calibration curve when serum was present [101].

Various efforts have been made to build electrochemical-type biosensors for biomarkers, which is predictable. The development of an electrochemical impedance spectroscopic approach for the detection of HE4 and CA125 by Whited et al., is an example of this. The biosensor was required the usage of an SD card formatted device with micron-scale interdigitate electrodes (IDEs). In this example, the HE4 probe was a protein-enzyme conjugated label. Although the sensor was used to assess the molecules at serum type quantities, it was unclear whether the device was used directly on serum or blood samples carrying the markers in this study [101].

A nano biosensor based on a double-gate field effect transistor (DGFET) is a second electrochemistry example. The benefits of this device were lauded in this paper through numerous plots of signal vs HE4 concentration, but there was no mention of biological fluid tests or even the use of a selective probe for the marker [102].

HSP-10: Chen et al. investigated the interaction of HSP10, a with several aptamers using an acoustic wave biosensor in their study[103]. Rather than developing an ovarian cancer biosensor, the researchers wanted to look into the nature of this connection. For acoustic tests at 940 MHz, the hexa-histidine-tagged protein was bonded to the device (quartz) surface using nickel-NTAL chemistry. Surprisingly, when the DNA aptamer was bound to the surface-immobilized protein, the signal was substantially lower than when the protein was not present, resulting in significantly bigger frequency shifts. The rigidification of the monolayer as a result of the interaction between probe and ligand was blamed for the lesser shift in frequency. This rigidification is countered by mass loading effects, resulting in a reduced total frequency shift when these two components are balanced. The bulk layer does not rigidify without the binding contact, hence mass loading is the key contributor to the signal [103].

LPA: A research conducted by De La Franier created a prototype biosensor for LPA based on its great promise as a biomarker for ovarian cancer compared to CA125 and HE4, but it is not yet ready for clinical usage [104] . The dual protein system of gelsolin and actin is used in this assay. Fluorescently labeled actin is released into solution in the presence of LPA and may be quantified. At the moment, this test only works in serum and has a low detection limit for LPA. The goal is to obtain a measurable LPA cut-off level of 1.3 μM for ovarian cancer.

***HE-4* with *CA-125*:** Williams and his colleagues recently announced the development of a non-invasive ovarian cancer biomarker detection system based on an optical nano sensor implant [9].

Both HE4 and CA125 are marginal indicators for the early-stage identification of ovarian cancer, according to their findings. As a result, the case was made that detecting these markers close to the site of disease, such as the fallopian tube, ovary, uterine cavity, or peritoneal cavity, where marker concentrations are higher, would be extremely beneficial. SSWCNTs were chosen in this research because they exhibit electrical and optical properties that are ideal for in vivo signal transduction [105]. Near-infrared (NIR) bandgap photoluminescence produced by semiconducting carbon nanotubes has a wavelength range of 800 to 1600 nm and can penetrate live tissues to a distance of centimeters. In practice, a HE4 antibody was linked to a nano-probe tip using a step-by-step approach that included ssDNA, standard EDC-NHS chemistry, and the antibody. The sensor was implanted in animals for photo luminescent HE4 measurement after extensive ex-vivo evaluation. Finally, the authors state that an implantable device might be used in patients with risk factors to predict illness development, recurrence, or evaluate therapy response in the future. It needs to be seen whether this approach could be used to screen a population on a big basis [105].

The diagnosis of Lung Cancer Biomarkers with the application of Biosensor technology:
Lung Cancer is the deadliest among all kind of cancer. In the year of 2017, lung cancer became the most common cancer in the world, with an approximate number of 1.76 million deaths and around 2.09 million new cases .Smoking, chemical exposure, radiation, diesel exhaust, and air pollution are all key risk factors for lung cancer. However, passive smoke or cigarette smoke causes nearly 80% of fatalities, making it the main cause of lung cancer [106-108].

According to reports, the death rate of lung cancer has decreased by forty-eight percent in males and twenty three percent in women between 1990 and 2016, owing to advances in early identification and screening procedures. Patients with early detection of lung cancer had a higher survival rate as a result of this [109]. Primal diagnosis is a measurement that can be used to detect cancer at an early phase when it is more treatable. Screening for precancerous tissues and identifying signs before cancer advances to an advanced stage are among the approaches [109].Early identification improves the prognosis of cancers where aberrant cells may be resect-ed with less difficulty than others, such as cervical, prostate, brain, skin cancer and breast cancer. When lung cancer is diagnosed early on, the chances of survival are usually great. Cancer spreads throughout a large area in the latter stages, lowering survival rates.

To diagnosis malignant cells present in the lungs, a variety of imaging and laboratory tests are used, including X-Ray, CT-Scan , Cytology, Ultrasound, MRI and Positron Emission Tomography (PET). Mass Spectrometry, Magnetic Induced Tomography, Breath-Test, Optical and Electrochemical, Piezoelectric biosensors are some of the non-invasive techniques now used to

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detect lung cancer. The optimal sample area, footprint, limit of detection, figure of merit and effective indices are all taken into consideration when designing these sensors. On malignant cell culture and a breath test, detection approaches are used. They can detect malignant features without putting the patient at risk, even if the procedure is done several times. Extraction of tissues or hazardous radiations, that were previously employed, are no longer required [110]. There are several types of biomarkers of Lung Cancers. The types are genetic, epigenetic, proteomic, metabolic . The detectable biomarkers are HER-2, CYFRA 21-1, CEA, SCC, CEACAM, FHIT , HP,EPCAM, ProGRP, SAA, HAS, TERT, CFL, CTNNB1,TMS, MUC1, P53, EGFR, POT1, TERT-2, cfDNA, cfniRNA etc.

To detect distinct variety of biomarkers , biosensors such as electrochemical , mass based and optical are being employed . In the below table 9, the studies related to biosensor application in the detection of lung cancers are enlisted :

Table 9: The application of biosensors in the detection of lung cancer biomarkers.

Names of the Biosensors	**Detected Biomarkers**	**Transducer and Ligand**	**Detection Limit (DL)and Linear Range(LR)**	**References**
Electrochemical	Vascular endothelial growth factor (VEGF165)	Voltametric and DNA Aptasensor	DL: 0.5pM LR: 1 to 150pM	111
	Vascular endothelial growth factor (VEGF165)	Impedimetric, DNA Aptamer	DL: 1.0 pg mL-1 LR:10.0 to 300.0 pg mL-1	112
	Epidermal Growth Receptor Factor (EGFR)	Amperometric, DNA probe	-	113

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	miR-21	Voltametric, 2D stem loop DNA structure combined with 3D DNA origami	DL: 10p; LR: 100pM to 1uM	114
	mir-126	Voltametric, DNA probe	DL: 0.1 fM LR: -	115
	Carcinoembryonic antigen (CEA)	Voltametric, Anti CEA antibody	DL:1 fg/ml	115
	Carcinoembryonic antigen (CEA)	Impedimetric , Anti CEA antibody	DL: 0.006ng/L^{-1}	116
	Neuron-specific enolase (NSE)	Voltametric , Anti NSE antibody	DL:0.05 ng mL−1 LR:0.1 to 2000 ng mL−1	117
	Epidermal Growth Receptor Factor (EGFR)	Amperometric, DNA probe	DL: 0.167 nM LR: 0.5 to 500NM	118
Optical Biosensors	Cytokeratine 17 protein (CK17)	Surface Plasmon Resonance, Antibody	DL: 10^{-10} g/mL LR:-	119
	Epidermal Growth Receptor Factor (EGFR), Carcinoembryonic antigen (CEA)	Surface Plasmon Resonance, Anti CEA and Anti GFR antibodies	-	120

	Amyloid A1	Localized SPR (LSPR), Antibody	DL: 100ag/mL^{-1} LR:-	121
	Carcinoembryonic antigen (CEA)	Fluorescence Based Detection Techniques (FRET), DNA aptamer	DL: 1.7 pg mL^{-1} LR: 4 to 100 pg mL^{-1}	122
	Carcinoembryonic antigen (CEA)	Chemiluminescence (CL), Antibody	DL: 20 pg mL^{-1} LR: 100 pg mL-1 to 1000 ng mL^{-1}	123
	Vascular endothelial growth factor	Chemiluminescence (CL), Antibody	DL: 60 pg mL^{-1}	124,125

The detection of Prostate Cancer Biomarker with the application of Biosensors:

It is often seen that in males, Prostate cancer (PCa) is the most frequent ones. The specific antigen of prostrate has been a well-known prostate cancer associated protein biomarker since the early 1990s. PSA testing, on the other hand, has been demonstrated to be lacking in sensitivity and specificity when used to successfully detect, observe disease progression, and/or treat PCa patients. PSA was among the first cancer biomarkers to be discovered and brought into regular pathological usage for prostate cancer screening and diagnosis. PSA levels that are higher than normal have been linked to this cancer in studies. Generally , 4.0 ng/mL of PSA level is considered normal. According to Smith's research, almost thirty percent of men with prostate specific antigen level between 4.1 and 9.9 ng/mL had prostate cancer [126]. Additionally in prostate cancer, increased PSA levels can signal benign prostatic hyperplasia, prostatitis (prostate inflammation), or smaller tumors that aren't lethal. As a result, the levels of prostate cancer specific antigen are not necessarily suggestive of malignant tumors, which has sparked debate regarding the efficacy of regular screening for prostate cancer. Small tumors found by screening prostrate specific antigens can develop so slow that decease from the tumor is impracticable to achieve within a man's lifetime. Treatment for these slow-growing tumors is often expensive, and it frequently includes life-altering surgery that are not always indispensable. Research on around seven hundred men who were infected with this cancer has gone through either simple observation or radical prostatectomy . Later it was observed that the prostatectomy has decreased the death rate, morbidity, the chances of

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spreading of the cancer, and local progression more than watchful waiting which implies that any treatment is preferable to normal observation [127]. Despite the controversy surrounding PSA screening, it is possible that receiving needless treatment for a benign illness is less detrimental to a patient than untreated for a cancerous tumor. Some other problem with the prostate-specific antigen examination is that it frequently produces errors, and many men with elevated levels of prostate-specific antigen do not have this cancer.

Multiplexing, or the simultaneous diagnosis of numerous prostate cancer-associated protein biomarkers alongside prostrate specific antigens, could be one improvement. The detection of such protein biomarker which are generally multiplexed by using conventional methods like the ELISA might show an elevated levels in the needed volume of samples, the complex conditions in the analytical procedures, and an increase in the expense of the test. Companion diagnostic equipment, like biosensors, that are transportable and less expensive and have multiplexing capabilities, could help to overcome these restrictions. The FDA has approved the utilization of a prostrate specific imaging examination in conjunction with a digital rectal examination (DRE) in 1994 [128]. Due to the sheer specificity and sensitivity of prostrate specific antigens and/or digital rectal examination , one important study method have been conducted to identify a section of prostate cancer protein biomarkers at the same time, a technique known as multiplexing [129-135]. PCa biomarkers can be presented in body samples, such as serum, urine and prostatic tissue. Metabolomics, circulating tumor DNA (ctDNA), microRNAs, DNA methylation, circulating tumor cells (CTCs) and volatile organic compounds (VOCs) are some of the other indicators that could be investigated [136-139]. When compared to ELISA, some biosensor devices coupled with microfluidic systems have showed numerous benefits, including the ability to obtain data quickly, with fewer steps and lower costs [140].

There are several Prostrate Cancer Protein Biomarkers which are generally detected in diagnostic process (Table 10).

Table 10: The distinct types of Prostate Cancer Biomarkers

Types of Prostate Cancer Biomarkers
Chromogranin-A(CgA)
Alpha- Methylacyl-CoA Racemase(AMACR)
Early Prostate Cell Antigen (EPCA)-1
Golgi Membrane protein (GOLM)-1

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Cluster of Differentiation(CD)-14
EPCA-2
GF-Binding Protein-3 (IGFBP-3)
Human Kallikrein 2 (hK2)
Interleukin-6 (IL-6) and Receptor (IL-6R)
Insulin-like Growth Factor-1 (IGF-1)
Prostatic Acid Phosphatase (PAP)
Prostate Stem Cell Antigen (PSCA)
Platelet Factor-4 (PF-4)
Prostate-Specific Antigen (PSA)
Prostate-Specific Membrane Antigen (PSMA)
Vascular Endothelial Growth Factor (VEGF)
Testosterone
Transforming Growth Factor- ß1 (TGF-ß1)
Urokinase Plasminogen Activator (uPA) and Receptor (uPAR)

The application of electrochemical and optical biosensors technology in the detection method of prostate cancer biomarkers has done significant changes for which prostate cancer is now easily detectable and curable due to early detection. In the following tables 11 and 12 , there are enlisted studies regarding the detection of PCa biomarkers with the help of biosensors.

Table 11 : The application of electrochemical biosensor in the detection of Prostate Cancer Biomarkers.

Name of Method	**Sensor Surface Modification with Ligands**	**Detectable Biomarkers**	**Detection Limit (DL) and Linear Range (LR)**	**References**

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Amperometry	Poly(diallyl dimethylammonium chloride)/Glutathione/Gold nanoparticles/Capture antibody	CD14(Cluster of differentiation-14)	DL:130 pg/mL LR:0.13–32.5 ng/mL	141
		VEGF(Vascular endothelial growth factor.)	DL: 90 pg/mL, LR: 0.09–23.8 ng/mL	
		PSA(Prostate-Specific Antigen)	DL: 140 pg/mL,LR: 0.14–34.2 ng/mL	
		ERG(Erythroblast transforma-tion specific related gene,)	DL: 15 pg/mL,LR: 0.015–3.9 ng/mL	
		IGF-1	DL: 13 pg/mL,LR: 0.013–3.4 ng/mL	
		PEDF(Pigment epithelium-derived factor)	DL: 90 pg/mL,LR: 0.09–11.2 ng/mL	
		Golgi membrane protein-1	DL: 15 pg/mL, LR: 0.015–1.95 ng/mL	
		IGFBP-3(Insulin-like Growth Factor binding protein-3)	DL: 150 pg/mL,LR: 0.15–38.7 ng/mL	

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Cyclic Voltammetry,	capture antibody Ab[1]/magnetic beads MBs/	Prostate-specific membrane antigen (PSMA)	DL: 0.8 ng/mL, LR:0.8–400 ng/mL	142
		Prostate-Specific Antigen (PSA)	DL:0.1 ng/mL,LR:0.1–10 ng/mL	
		Interleukin-6,(IL-6)	DL:0.005 ng/mL,LR:1000 pg/mL	
Differential Pulse Voltammetry	SAM(self-assembly mono-layer) MPA (mercaptopropionic acid), Ab[1]=capture antibody	PSMA(Prostate-specific membrane antigen)	DL:0.05–2 pg/mL ,LR:0.15 pg/mL– 15 ng/mL *	143
		Prostate-Specific Antigen (PSA)	DL:0.05–2 pg/mL ,LR:2 pg/mL– 200 ng/mL *	
		Interleukin-6(IL-6)	DL:0.05–2 pg/mL , LR:0.05 pg/mL– 5 ng/mL *	
		PF-4(Platelet factor-4)	DL:0.05–2 pg/mL ,LR:0.1 pg/mL– 10 pg/mL *	

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Square Wave Voltammetry,	Graphene oxide/Gold nanoparticles/Capture antibody	tPSA(Total PSA)	DL:0.2 ng/mL	144
		fPSA (Free PSA)	DL:0.07 ng/mL	
Electrical Impedance Spectroscopy	Self-assembly mono-layer(11-mercaptoundecanoic acid -2-mercaptoethanol,)/Capture Antiody	fPSA (Free PSA)	DL:1 ng/mL	145
		tPSA(Total PSA)	DL:L1 ng/mL	
Electrical Impedance Spectroscopy	SAM(self-assembly mono-layer)AUT(11-amino-1-undecanothiol)/6-mercapto-1-hexanol/AuNPs(Gold nanoparticles)/SAM (Self-assembly mono-layer)Apt (DNA ap-tamer)MCH (6-mercapto-1-hexanol)	PSA glycans	DL:0.26 ng/mL,LR:0.26–62.5 ng/mL *	146
		PSA	DL:0.64 ng/mL,LR:0.64–62.5 ng/mL *	
Electrical Impedance Spectroscopy	SAM(self-assembly mono-layer)MUA (11-mercaptoundecanoic acid)-MCH (6-mercapto-1-hexanol)/Ab^1(capture antibody)	PSA glycans	DL:down to 4 a.m. (~0.13 fg/mL),LR:4 a.m. to 40 nM	147
		PSA	DL:4 aM, LR:4 a.m. to 40 nM	
Differential Pulse Voltammetry,		PSA (Prostate-Specific Antigen)	DL:1 ng/mL	148
		VEGF(Vascular endothelial growth factor)	DL:50 pg/mL	

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Amperometry	GSH (Glutathione), AuNPs(Gold nanoparticles). Ab^1(Capture Antibody)	IL-6	DL:0.30 pg/mL	149
		PSA	DL:0.23 pg/mL,LR:1–40 ng/mL	
Amperometry	GSH (Glutathione), AuNPs(Gold nanoparticles). Ab^1(Capture Antibody)	PSA	DL:1 ng/mL,LR:1–40 ng/mL	150
		IL-6	DL:0.03 ng/mL,LR:50–500 pg/mL	
		PSMA	DL:10 ng/mL,LR:10–250 ng/mL	
		PF-4	DL:1 ng/mL,LR:1–40 ng/mL	
Amperometry	ERGO(electrochemically reduced graphene oxide)/Ab^1	PSMA	DL:4.8 fg/mL,LR:9.8 fg/mL–10 pg/mL *	151
		PSA	DL:15 fg/mL,LR:61 fg/mL–3.9 pg/mL *	

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Table 12 : The application of optical biosensors in the detection of Prostate Cancer Biomarkers.

Names of the biosensors	Sensor Surface Modication	Detectable Biosensors	Linear Range (LR)	Detection Limit (DL)	References
SERS (Surface-enhanced Raman scattering)	Ab1 (capture antibody)	PSA (Prostrate Specific Antigen)	LR:1 pg/mL–10 µg/mL	DL:0.37 pg/mL	152
		AFP (α-1-fetoprotein)	LR:10 pg/mL–1 µg/mL	DL:0.26 pg/mL,	
		CEA (Carcinoembryonic antigen)	LR:10 pg/mL–1 µg/mL	DL:0.43 pg/mL	
SERS (Surface-enhanced Raman scattering)	SiC/AgNP (silver nanoparticles)/Ab1 (capture antibody)	PSMA (Prostate-specific membrane antigen)	LR:1.05 fg/mL–113.4 ng/mL	DL:1.05 fg/mL,	153
		PSA (Prostrate Specific Antigen)	LR:0.46 fg/mL–478.93 ng/mL	DL:0.46 fg/mL,	
		hK2 (Human kallikrein)	,LR: 0.67 fg/mL–466.23	DL:0.67 fg/mL	

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			ng/mL		
SERS (Surface-enhanced Raman scattering)	Ab1 (capture antibody)	PSA (Prostrate Specific Antigen)	-		154
		AFP (α-1-fetoprotein)	-		
		CEA (Carcinoembryonic antigen)	-		
ECL (Electrochemiluminescence)	SWNCT (single-wall carbon nanotube)/Ab1 (capture antibody)	IGF-1 (Insulin-like Growth Factor-1)	LR:0.5 pg/mL–10 ng/mL	DL:110 –500 fg/mL	155
		PSMA (Prostate-specific membrane antigen)			
		PSA (Prostrate Specific Antigen)			
		PF-4 (Platelet Factor-4)			
		GOLM-1 (Golgi membrane protein-1)			
		VEGF-D (Vascular endothelial growth factor)			

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		IGFBP-3 (Insulin-like Growth Factor binding protein-3)			
		CD-14 (Cluster of differentiation-14)			
ECL (Electrochemiluminescence)	SWNCT (single-wall carbon nanotube)/Ab1 (capture antibody)	PSMA (Prostate-specific membrane antigen)	LR:100 fg/mL–10 ng/mL *	DL:100 fg/mL	156
		PSA (Prostate Specific Antigen)	LR:100 fg/mL–1 ng/mL *	DL:50 fg/mL	
		PF-4 (Platelet Factor-4)	LR:100 fg/mL–5 ng/mL *	DL:50 fg/mL	
		IL-6 (Interleakin 6)	LR:100 fg/mL–5 ng/mL *	DL:10 fg/mL	
ECL (Electrochemiluminesce	SWNCT (single-wall carbon nanotube)/Ab1	PF-4 (Platelet Factor-4)	LR:500 fg/mL–10	DL:420 fg/mL	157

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nce)	(capture antibody)		ng/mL *		
		PSMA (Prostate-specific membrane antigen)	LR:500 fg/mL–10 ng/mL	DL:535 fg/mL	
		PSA (Prostate Specific Antigen)	LR:500 fg/mL–10 ng/mL *	DL:300 fg/mL,	
ECL (Electrochemiluminescence)	SWNCT (single-wall carbon nanotube)/Ab1 (capture antibody)	PSA (Prostate Specific Antigen)	LR:100 fg/mL	DL:100 fg/mL	158
		IL-6 (Interleukin 6)	LR:0.5 fg/mL–10 fg/mL (0.5 fg/mL–1 ng/mL *)	DL:10 fg/mL	
ECL (Electrochemiluminescence)	SWNCT (single-wall carbon nanotube)/Ab1 (capture antibody)	PSA (Prostate Specific Antigen)	LR:1 pg/mL–10 ng/mL *	DL:1 pg/mL	159
		IL-6 (Interleukin 6)	LR:0.1 pg/mL–2	DL:0.25	

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			ng/mL *	pg/mL	
CL(Chemiluminescence)	Ab1 (monoclonal tPSA capture antibody)	fPSA (free Prostate Specific Antigen)	-	DL:0.03 ng/mL	158
		tPSA (Prostate Specific Antigen)	-	DL:0.05 ng/mL	
CL(Chemiluminescence)	GOPTS (3-Glycidyloxypropyl) trimethoxysi-lane)/Apt	fPSA (free Prostate Specific Antigen)	-	DL:0.03 ng/mL,	158
		tPSA (Prostate Specific Antigen)	-	DL:0.05 ng/mL	
CL(Chemiluminescence)	Ab1(Capture Antibody)	PSA (Prostate Specific Antigen)	LR:0.5 pg/mL–5ng/mL *	DL:0.5 pg mL−1,	158
		PF-4 (Platelet Factor-4)	,LR:0.5 pg/mL–10 ng/mL *	DL:0.5 pg mL−1	
Fluorescence	Ab1 (monoclonal tPSA capture antibody)	cPSA (complexed Prostrate Specific Antigen)	-	DL:0.08 7 ng/mL	159
		fPSA(free Prostate Specific Antigen)	-	DL:0.00 9 ng/mL,	

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The detection of Colorectal Cancer by Biosensors technology:

Colon Cancer is 3rd most frequent malignancy and the fourth major cause of tumorigenesis-related death in the world [160]. The generality of colon or colorectal patients are detected at metastasized stage, meaning the aberrant cells have spread and established new tumors around other parts of body, resulting in a high mortality rate. Patients with advanced CRC have a 5-year survival rate of approximately 5–10%, while those with the earliest stage had a 5-year survival rate of 90 percent [161]. As a result, early detection of CRC will lower the disease's related mortality, allowing for more intervention and therapeutic options. Patients with primary level of colorectal cancer have no evident symptoms (e.g., abdominal pain or intestinal bleeding), and confirmation of the diagnosis might take 7–10 years or even decades [162]. This procedure allows for the diagnosis of CRC at a primary stage. There a variety of approaches have been developed for diagnosing CRC. Colonoscopy is an efficient method for this cancer screening because it can clearly locate gastrointestinal abnormalities, resect malignant lesions, and halt bleeding [163-165]. People, on the other hand, are sometimes apprehensive about having a colonoscopy because of the intrusiveness of the procedure and the need for bowel preparation.

Furthermore, during a colonoscopy procedure, there is a danger of bleeding, perforation, or even death [166]. To diagnose polyps, CT colonography is considered as best diagnostic method as it has auxiliary imaging that uses a less intrusive methodology and an 8.8 mSv radiation dosage [167]. CT colonography, on the other hand, has limitations due to its lack of selectivity and capacity to detect small cancers. The hemoglobin concentration in human feces is quantitatively measured using noninvasive detection methods such as the antibody-based fecal immunochemical test (FIT) and immune-based fecal occult blood test (FOBTS) [168,169]. These approaches don't require any bowel preparation. The results generated by these approaches, on the other hand, has deficiency in specificity and are linked to false positivity in clinical testing. CRC biomarkers can be detected quantitatively using electrochemical biosensors and optical biosensors. Early screening, diagnosis through CT colonography, therapeutic observation, cancer monitoring, prognosis, and focused therapy all benefit from the discovery of CRC biomarkers [10].

There are several types of biomarkers of colorectal cancers which can be very helpful for the diagnosis and prognosis (Table 13)

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Table 13: The different types of Colorectal Cancer Biomarkers.

Biomarkers of Colorectal Cancer
carcinoembryonic antigen (CEA)
carbohydrate antigen 19-9 (CA19-9
CA11-19,
interleukin-8 (IL-8),
interleukin-6 (IL-6)
etinol-bind- ing protein 4 (RBP4)
heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1)
epidermal growth factor receptor (EGFR)
tumor protein 53 (p53)
thrombo- spondin (THBS)

The application of electrochemical and optical biosensors in the detection of colorectal cancer has shown significant outcomes. In the following table 14 and 15 , the studies with their information are listed:

Table 14:Electrochemical Biosensor Application in the CRC biomarker detection

Technique	**Used Electrode**	**Detected Biomarkers**	**Detection Limit and Linear Range**	**References**
Voltammetry	ITO- indium tin oxide.	IL-6	6 fg/mL	170-173
Voltammetry		IL-6	3.2 fg/mL	
Voltammetry Impedometry		IL-8	90 pg/mL	

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Voltammetry Impedometry		IL-8	72.73 ± 0.18 pg/mL	
Impedometry	PCE: plastic chip electrode	RBP4:retinol binding protein 4,	DL:0.1 pg/mL,LR:0.1~1,000 pg/mL	174
Photoelectrochemical	FTO: fluorine-doped tin oxide	CEA: Carcinoembryonic antigen	DL:5.2 pg/mL,LR:0.02~40 ng/mL	175
Voltammetry	SPCE: Screen printed carbon electrode,	CA 19-9: carbohydrate antigen 19-9	DL:0.07 U/mL,LR:0.01~40 U/mL	176-181
Voltammetry		p53	DL:5.0 fg/mL,LR:1.0~1,000 pg/mL	
Voltammetry		VEGF	DL:210 pg/mL,LR:0.0001~100 ng/mL	
Voltammetry Impedometry		CEA: Carcinoembryonic antigen	DL:0.10, 0.30 pg/mL,LR:0.001~100 ng/mL	
Amperometry		CEA: Carcinoembryonic antigen	DL:210 pg/mL,LR:1~5,000 ng/mL	
Capacitance		CA19-9-carbohydrate antigen 19-9	DL:0.12 U/mL,LR:0.3~100 U/mL	

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Table 15: Optical Biosensor Application in the CRC biomarker detection

Technique	Configuration of Biosensors	Detected Biomarkers	Detection Limit and Linear Range	References
SERS: Surface-enhanced Raman scattering	Gold nano-particles/Fe3O4 NPs/Ti3C2Tx MXenes/anti-carcinoembryonic antigen Ab2/CEA/ anti-carcinoembryonic antigen with capture antibody 1/MoS2 nanoflowers@Gold nano-particles/glass slide	CEA: carcinoembryonic antigen,	DL:0.033 pg/mL,LR:0.0001~ 100 ng/mL	182
LFIA: lateral flow immunoassay,	EuNPs-anti-Interleukin 6 (capture antibody 2Interleukin 6/anti-Interleukin 6 (capture antibody 1)/NC membrane	IL-6	DL:0.37 pg/mL,LR:2~500 pg/mL	183-186
	Epidermal Growth Factor Receptor/Silver Nanoparticles biotinylated epidermal growth receptor factor aptamer/streptavidin/NC membrane	EGFR	DL:9.8 nM.LR:0~50 nM	
	Gold Nanoparticles /anti-carcinoembryonic antigen with capture antibody 2/carcinoembryonic antigen /anti-carcinoembryonic antigen with capture antibody 1/protein G/NC membrane	CEA	DL:0.35 ng/mL,LR:2~50 ng/mL	

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	anti-CA19-9 capture antibody 1/CA19-9/CNTs-Fe3O4/anti-CA19-9 capture NTIBODY2/NC membrane	CA19-9	DL:1.75 U/mL,LR:	
SPR: surface plasmon resonance	Gold Nanoparticles/streptavidin/biotin-anti-carcinoembryonic antigen with capture antibody 2/carcinoembryonic antigen/anti-carcinoembryonic antigen capture antibody 1/Gold coated glass chip	CEA	DL:17.8 pg/mL,	187
	hnRNP A1/anti-hnRNP A/DNA aptamer/Gold chip	hnRNP A1	DL:0.22 nM,LR:0.1~10 nM	

The utilization of biosensor technology in the detection of Liver Cancer Biomarker:

Liver Cancer is the world's seventh most frequent malignancy, with a significant fatality rate [188]. In the medical line , the term Hepatocellular cancer (HCC) is used for Liver Cancer. HCC is a distinct malignancy because it usually grows in the context of degenerative liver disease, particularly cirrhosis, and is associated with the risk of liver failure, which contributes to its low 5-year survival rates of 18%–20%. [189]. In Asia, endemic hepatitis B (HBV) infection is responsible for more than half of all HCC-related deaths. Despite the availability of direct acting antiviral treatments, the incidence of HCC is increasing in many western nations due to the rising frequency of , alcoholic and nonalcoholic-related fatty liver disease, and HCV-related comorbidities [190-192]. Overall mortality is strongly linked to the phase of this cancer diagnosis. Curative therapy, including as surgical process, ablative therapies, and transplantation of liver, are available to early-stage patients, whereas late-stage patients are typically only eligible for palliative systemic therapies with low response rates. As a result, patients with primary level of HCC have a five-year survival rate of more than 70%, while those with advanced HCC have a 5-year survival rate of fewer than 5%. [193-194]. Unfortunately, most patients are detected late due to a lack of risk-based strategies, inadequate surveillance, and a lack of risk-based surveillance [195]. A biomarker could be utilized as a potential target for a diagnosis approach to detect such cancer early. The biomarker AFP, or

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Alpha-fetoprotein, can be used to diagnose liver cancer early. It is known to be a functional glycoprotein with multipurpose. AFP is a part of the albuminoid gene family, which includes the AFP molecule, alpha-albumin, vitamin D binding (Gc) protein, albumin, and the AFP-gene-associated protein (ARG) [196]. During the development of fetus, the liver and yolk sac create the most abundant plasma protein. Because of AFP's biological activity in lipoprotein and fatty acid uptake by monocytes, hepatocytes, and tumorigenic cells, it has been related to tumorigenesis in breast cancer, lymphoma cells and hepatocellular carcinoma.[197]. Other biological effects of the AFP molecule include suppressing the proliferation of uterine cells which are estrogen induced and influencing ovarian function [198]. In healthy humans, the quantity of this biomarker is five to eight ng/mL, but high levels of AFP have been found in various tumors in mice and humans, including ovarian tumors, testicular tumors, gastric tumors, pulmonary carcinomas, pancreatic tumors, gallbladder cancers, and Barrett's adenocarcinoma. Furthermore, AFP levels are commonly excessively increased in liver carcinomas [197]. Due to the inability of mature hepatocytes to make AFP, the large quantity of AFP in serum of fetal eventually reduces to a minimal amount of AFP in the blood after birth. Cancer cells (particularly liver cancer cells) can manufacture it after being converted [199].

To detect AFP in the early stage of liver cancer, researchers have conducted several studies by applying electrochemical (aptasensor, Immunosensor Label free Sensor or ILS and MIP based sensors) and optical biosensor. In the following table 16, the data of such studies are enlisted below:

Table 16: The application of electrochemical biosensor in the detection of AFP in liver cancer

Biosensor Type	Technique	Configuration	Linear Range	Detection Limit	References
Aptasensors	DPV	Au/ hairpin-structured DNA-MB	50 pg/mL - 10 ng/mL	8.76 pg/mL	200
Aptasensors	DPV	Au electrode /zwitterionic peptide/ Aptamer	10.0 fg/mL-100.0 pg/mL	3.1 fg/mL	201
Aptasensor	DPV	Development of	0.00005	2.0 fg/mL	202

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s		immunocomplex between Ab1 and DNA primer/Ab2/ molybdenum disulfide (MoS2) microboxs/AuNPs/ followed by HCR and catalytic activity of HRP	-75 ng/mL		
Aptasensors	DPV	Au electrode/ MB- oligo-DNA /thiolated aptamer/ -tagged anti-AFP	2.0 pg/mL-20.0 ng/mL	1 pg/mL	203
ILS	DPV	Formation of immnocomplex between MWCNTs/AuNPs/HRP/Ab2 and GCE/ AuNPs/3-mercaptopropyl trimethoxysilane/Ab1	0.01- 50 ng/mL	3 pg/mL	204
ILS	DPV	Development of immunocomplex using Ab2/glucoamylase/AuNPs and Ab1 leading to transition of glucose from starch and detection on electrodes (SPCEs) made with carbons (screen printed) by adding glucose oxidase (GOD)	0.05 - 100 ng/mL	0.02 ng/mL	205
ILS	DPV	GCE/Hep/ PGA/PPy/anti-AFP	0.1-100 ng/mL	0.099 ng/mL	206

ILS	DPV	anti-AFP/GCE/CS/Au /p-nitrophenyl oxycarbonyl group-terminated hyperbranched polyester (HBPE-NO2)	0.1 -120 ng/mL	0.055 ng/mL	207
ILS	DPV	GCE/ Fe3O4 NPs /PAMAM denderimer/ PB/ anti-AFP	0.02 -10 ng/ mL	50 pg/mL	208
ILS	DPV	poly(sodium 4-styrene sulfonate) (PSS)-doped PANI/ GCE/anti-AFP	0.01-1000	3.7 fg /mL	209
ILS	DPV	GCE/ poly aniline (PANI)/ AuNPs /PEG/anti-AFP/	0.01 pg/mL-1.0 ng/mL	0.007pg/mL	210
ILS	DPV	AuNPs/anti-AFP/GCE/ poly dopamine (PDA) / gallium nitride (GaN) nanowires array	0.01-100 ng/ml	0.003 ng/mL	211
ILS	Square wave voltammetry (SWV)	Formation of immunocomplex between GCE/ Ab1 and IL/rGO/Au/ diallyldimethylammonium chloride / PB/Ab2 nonocomposite /ionic liquid (IL) - functionalized rGO/ / followed by catalytic activity of H2O2	0.01–100 ng/mL	4.6 pg/mL	212
ILS	Square wave	anti-AFP /GCE/Pd	0.01 -	4 pg/mL	213

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	voltammetry (SWV)	nanoplates	75.0 ng/mL		
ILS	Electrochemical impedance spectroscopy (EIS)	screen-printing electrode (SPE) generated by CuS nanoparticle-decorated GO/ gold nanowires (GNWs)-functionalized graphene sheet (GO)/ /anti-AFP	0.001-10 ng/mL	0.5 pg/mL	214
ILS	Electrochemical impedance spectroscopy (EIS)	anti-AFP /GCE/ PEG/AuNPs/ poly 3,4-ethylenedioxythiophene (PEDOT)	0.002 - 10 fg/mL	0.0003 fg/mL	215
ILS	differential pulse anodic stripping voltammetry (DPASV).	Development of of immunocomplex between Ab2 and Ab1 /metal-organic frameworks (MOFs)/ in presence of AFP and detection of Pb(II) and Cd(II) in MOFs using GCE/PANI/Ab1	0.3 pg/mL-3 ng/mL	0.1 pg/mL	216
ILS	Amperometry	Creation of immunocomplex between HRP /AuNPs/Ab2 and Fe3O4/Au NPs/Ab1 in presence of AFP observed by trapping of immunocomplex on magnetic glassy carbon	20 ng/mL-100 ng/mL	0.64 ng/mL	217

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		electrode (MGCE) leading to catalytic activity reduction of H2O2 with hydroquinone			
ILS	CV	GCE/AuNPs/PDA/PB/GO/ anti-AFP	0.01 - 80.0 ng/mL	0.007 ng/mL	218
ILS	CV	GCE/Ag and EMT zeolite nanoparticles/anti-AFP	1.0–100 ng/mL	30 pg/mL	219
MIP-based sensors	DPV	GCE/CS/ glutaraldehyde (GA)/MIP	8.0 × 10-4 -10 µg/ mL	9.6 × 10-5 µg/ mL	220
MIP-based sensors	CV	Nano sensor biofuel cells (BFCs) composed of creation	1 ng/mL-	12.8 ng/mL	221

Table 17: The application of optical biosensor in the detection of AFP in liver cancer

Biosensor Technology	**Technique**	**Detection Limit**	**Linear Range**	**References**
Electrochemiluminescence	Label-free sensors	6.2 pg/mL	0.05-20.0 ng/mL	222
Electrochemiluminescence	Label-free sensors	0.0005 ng/mL	0.001- 5.0 ng/mL	223
Electrochemiluminescence	Label-free sensors	0.1 pg/mL	1.0×104 - 10.0 ng/mL and 10.0-320.0 ng/mL	224

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Electrochemiluminescence	Label-free sensors	0.09 pg/mL	0.1 pg/mL - 160	225
Electrochemiluminescence	Label-free sensors	0.003 µg/L	0.005 - 100 µg/L	226
Electrochemiluminescence	Label-free sensors	10 fg/mL	50 fg/mL- 100 pg/mL	227
Electrochemiluminescence	Label-free sensors	0.05 pg/mL	0.00005 - 1.0 ng/ml	228
Electrochemiluminescence	Label-free sensors	0.33 fg/mL	1 fg/mL -80 ng/mL	229
Electrochemiluminescence	Label-free sensors	0.5 pg/mL	3 pg/mL- 50 ng/mL	230
Electrochemiluminescence	Label-free sensors	0.031 ng/mL	0.04 -500 ng/mL	231
Colorimetric	-Non-enzymatic sensors - AuNPs-based sensors with catalytic activity	39pg/mL	1ng/mL- 10µg/mL	232
Colorimetric	-Non-enzymatic sensors - AuNPs-based sensors with aggregation capability	33.45 pg/mL	50-100 pg/mL	233
Colorimetric	-Non-enzymatic sensors - AuNPs-based	30 pg/ mL	-	234

	sensors with aggregation capability			
Colorimetric	-Non-enzymatic sensors -AuNPs-free sensors	7 pg/mL	0.05 -12 ng/mL	235
Colorimetric	Enzymatic sensors	10 pg/mL	-	236
Colorimetric	Enzymatic sensors	1.95 pg/mL	0.005-1 ng/mL	237
Colorimetric	Enzymatic sensors	78 pg/mL	0.10 -50 ng/mL	238
Colorimetric	- AuNPs-free sensors -Non-enzymatic sensors	0.5 ng/mL	1.0-100 ng/mL	239
Fluorescence	Immunosensor	0.16 ng/mL	0.18-11.44 ng/mL	240
Fluorescence	Immunosensor	1 pg/mL	1 pg/mL-1 μg/mL	241
Fluorescence	Immunosensor	4 pg/mL	20 ng/mL-2 pg/mL	242
Fluorescence	Aptasensor	6.631 ng/mL	10.0-100.0 ng/mL	243
Fluorescence	Aptasensor	0.16 ng/mL	0.5-120 ng/mL	244

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Localized surface plasmon resonance	Non-array nano gold sensors	0.85 (PBS)	5 -200 ng/mL	245
Localized surface plasmon resonance	Non-array nano gold sensors	100 pg/mL	1 ng/mL-1 μg/mL	246
Localized surface plasmon resonance	Non-array nano gold sensors	0.1 ng/mL	-	247
Localized surface plasmon resonance	Au sensor (array nano)	25 ng/ml	-	248
Localized surface plasmon resonance	Au sensor (array nano)	1 fg/mL	10 fg/mL-10 ng/mL	249
Localized surface plasmon resonance	Au sensor (array nano)	24 ng/mL	20-200 ng/mL	250
Localized surface plasmon resonance	Au sensor (array nano)	15 ng/mL	-	251
Photoelectric sensor	Label-free biosensor	8 pg/mL	0.05-200 ng/mL	252
Photoelectric sensor	Label-free biosensor	5 pg/mL	0.01-200 ng/mL	253
Photoelectric sensor	Label-free biosensor	5.0 pg/mL	0.01-1000 ng/mL	254
Photoelectric sensor	Label-free biosensor	0.54 pg/mL	1 pg/mL - 100 ng/mL	255
Photoelectric sensor	Label-free biosensor	0.03 pg/mL	160 ng/mL - 0.1 pg/mL	256
Photoelectric sensor	Label-free biosensor	0.01	0.1 - 500	257

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		ng/ml	ng/m	
SERs	Surface-enhanced Raman spectroscopy tags-based sensors	1.86 fg/mL	2 fg/mL-0.8 g/mL	258
SERs	Surface-enhanced Raman spectroscopy tags-based sensors	3 (PBS) and 17 ng/mL	50- 500 ng/mL	259

Conclusion:

Biomarkers for cancer are a key predictor of the disease progression. In the field of medicine, biomarkers are not only used in the diagnose and monitor process of a disease, but also to predict therapeutic outcomes. POC cancer diagnosis is one of the main aims of biosensor technology. Point-of-care testing (POCT), or on-site disease examination, is an area where biosensors could have a big influence, allowing patients and doctors to acquire findings quickly and conveniently. POCT provides for quicker diagnosis and has the potential to save a lot of money. However, multitarget detection of many biomarkers is required to progress biosensors toward POC devices. Furthermore, if the future goal of nanotechnology is to bring biosensor services to the patient's bedside, the POCT and multi-biosensors should always observe the laboratory's reliability and accuracy. The article is fully centered on the analytical data of the implementation of various biosensor technology in the diagnosis process of cancer biomarkers. In this article, we have seen that the application of electrochemical and optical biosensor is most used in the detection of the biomarkers. The future advancements in the nanomaterial technology will bring significant benefits in the medical field. Nanomaterials, particularly quantum dots, are among the most powerful areas of nanotechnology on biosensor development because they are able to facilitate the detection process and locating cancerous cells, and also can deliver medicine to cancer cells with pinpoint accuracy and enable the development of best reliable imaging systems that can detect cancer at a primary stage. Nanotechnology will undoubtedly change cancer diagnosis and treatment in the next 5–10 years, according to experts which will make us capable to diagnose cancer earlier and bring improvement in its imaging, help in the diagnosis and prognosis, and advance drug administration while subsiding the side effects as a result of integrating nanomaterials and biosensors. Because cancer occurs at the nanoscopic level, it also requires that the process of treating this disease takes place at the nanoscopic level as well. Despite the many hurdles presented by cancer's complexity and diversity in the healthcare section, this device has the ability to give fast-paced and most

accurate results while yet remaining cost effective.

Declarations

1. **Conflict of Interest:** None.
2. **Informed Consent:** N/A
3. **Compliance with ethical standards:** N/A
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