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Biosensors in Cancer Research: A New Frontier in Screening, Diagnosis and Treatment Management

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ABSTRACT

Cancer is a type of genetic-related disease that some cells become unnormal and form cancer clusters or tumours and it is one of the main causes of death for humans. While qualified treatment and adequate survivorship care in the early stages of cancer can improve survival rates and reduce side effects, most of the early cancer symptoms or signs are not obvious and specific enough to be observed and recognize. Therefore, reliable, cost-effective, and powerful technologies to detect the disease are needed. Cancer biomarkers are substances such as nucleic acids, enzymes, and metabolites, present in cancer clusters, tumours, or serum. While biosensors provide a quick, accurate, sensitive, uncomplicated, and economical method of diagnosing a particular cancer biomarker and is important to cancer detection and treatment, especially early diagnosis. Biosensors could be classified into three types: mass-based, electrochemical, or optical biosensors. With the development of science and technology and continuous research, more biosensors are designed for advanced technology, such as nanotechnology. The new and novel biosensors provide a powerful way for cancer detection. The objective of this research is to discuss the novel biosensors designed in recent years for screening, diagnosis and treatment management of cancers.

Keywords: *Cancer; Biosensors; AI; Biomarkers*

1. INTRODUCTION

Cancer is a multifaceted and multistage disease characterized by a wide range of genetic and epigenetic alterations that disrupt normal cellular processes. These alterations interfere with cellular signaling pathways, leading to the trans- formation of normal cells into malignant tumor causing cells. Under normal circumstances, human cells divide to create new cells as needed, while old or damaged cells undergo programmed cell death and are replaced by healthy ones [1]. However, cancer disrupts this orderly process; old or injured cells survive, and new abnormal cells are produced. These abnormal cells divide uncontrollably, potentially forming tumors and invading neighboring tissues[2,3]. Cancer manifests in various

forms, including breast, skin, lung, colon, prostate, and lymphoma, with each type presenting distinct symptoms, diagnostic challenges, and treatment options[4]. Both environmental and genetic factors contribute to cancer development, with known risk factors including radiation, chemical exposure, tobacco use, alcohol consumption, and immune dysfunction. Additionally, infections caused by certain bacteria and viruses, such as Helicobacter pylori and human papilloma virus, can lead to stomach and cervical cancers, respectively. Globally, cancer poses a vast and multifaceted challenge. According to the World Health Organization, it is one of the leading causes of death worldwide, with millions of new cases diagnosed annually [5]. (Figure-1).

Figure-1: Progression from Normal Cells to cancer Cells and its impact on health [Sana Noreena, et al . 2025].

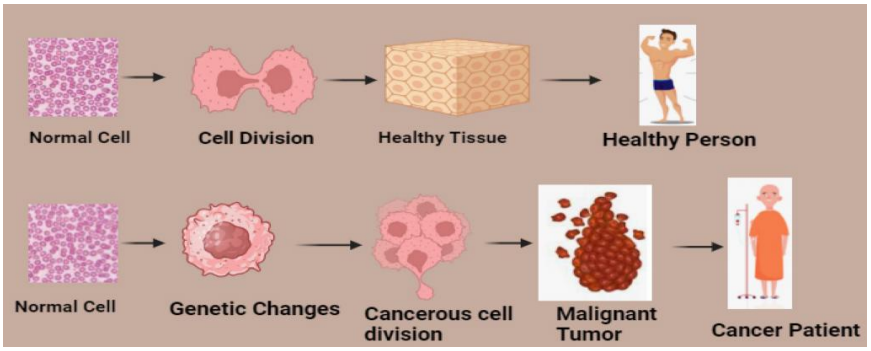
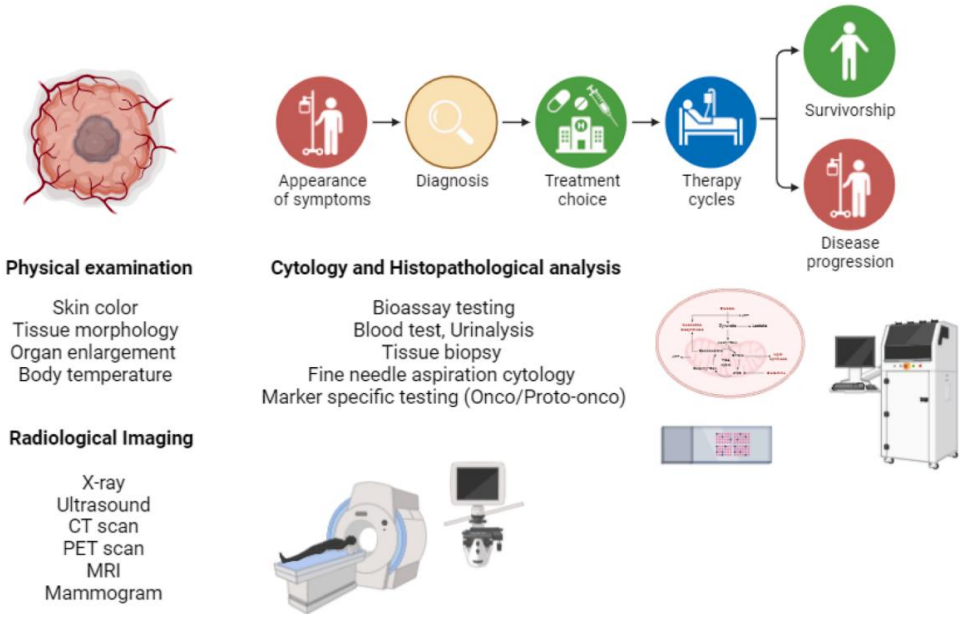


Figure-1, illustrating that the upper pathway illustrates the normal process of cell division, where healthy cells divide to form tissues that maintain proper bodily functions, ensuring the overall health of an individual. The lower pathway demonstrates the development of cancer, starting with genetic changes in normal cells. These alterations lead to uncontrolled and abnormal cell division, forming a malignant tumor. As the tumor progresses, it disrupts normal bodily functions, ultimately manifesting in the condition of a cancer patient requiring medical intervention. This figure highlights the stark contrast between normal cellular processes and cancerous transformations, emphasizing the importance of early detection and intervention in cancer care.

History of Cancer Therapy:

Cancer diagnosis and treatment represent a critical frontier in modern medicine. The journey from detecting the existence of cancerous cells or abnormal cellular pathway to provide effective therapies is a complex and rapidly evolving process [6]. Over the years, a myriad of diagnostic techniques and treatment modalities have been developed, ranging from traditional approaches like surgery and chemotherapy to cutting-edge methods like targeted therapies and immunotherapy [6–9].

Figure-2: Conventional approches for the diagnostic and screening of cancer.



2. ADVANCED THERAPEUTIC MODALITIES

Biomarkers and Biosensors:

A reliable, cost-effective, powerful cancer detection method is in significant demand for diagnosis and treatment.

A biomarker is a medical sign that indicates a reaction between possible hazards and an organism, and it involves chemical, biological, or biological substances, structures, and processes [10]. For cancer biomarkers, it is the substances like DNA, mRNA, enzymes, metabolites, transcription factors, and cell surface receptors that present in cancer clusters, tumours, or serum. Specific types of cancer biomarkers allow for the early identification of cancers such as oral regions, pancreatic and pancreatic. Alpha-fetoprotein (AFP) is a biomarker of hepatocellular carcinoma, and breast cancer cells can be used as biomarkers for the identification of breast cancer directly. Detection of these cancer biomarkers provides a solution for the requirement to prognosis and diagnose a specific cancer and monitor the recurrence. In the field of biomarker detection, technology has advanced greatly, and various biomarker detection techniques utilizing highly specific biomarkers for recognition have been developed. Biosensor provides a quick, accurate, sensitive, uncomplicated, and economical method of diagnosing a particular cancer biomarker.

Biosensors are analytical devices that combine a biological component, like a protein, enzyme, or cell, with a transducer to detect specific biochemical reactions and produce a measurable signal. This fusion of biological specificity with analytical sensitivity allows biosensors to detect and quantify a wide range of compounds, from simple ions to complex molecules and cells[11]. Biosensors advanced research at a new level. Biosensing is the absence of set techniques for producing an accessible detection signal of interaction between biological molecules. Biosensors detect these molecular interactions[12].

Figure-3: Mechanism and Interactions among the bioreceptors, biomarkers and Biosensors:

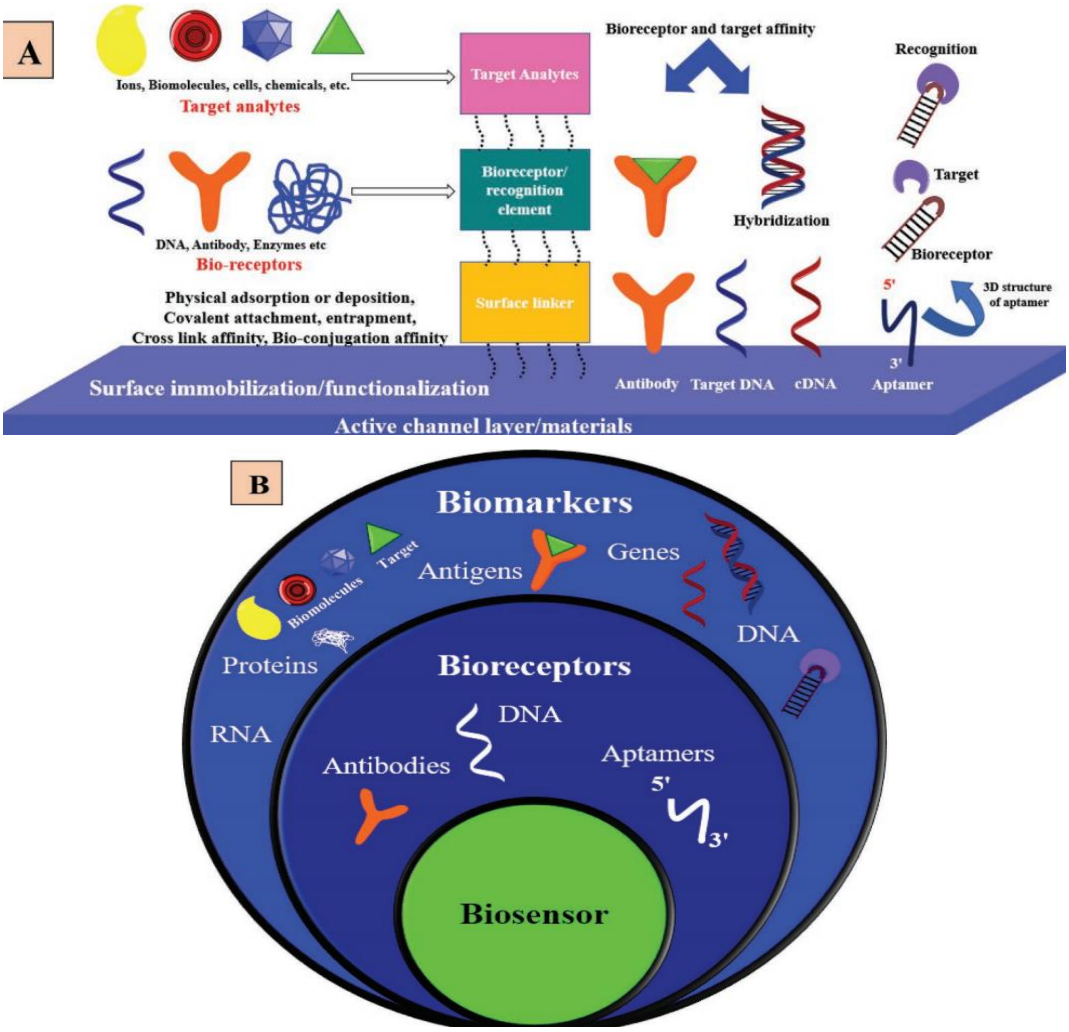


Figure-3 A) , illustrating the mechanism and process of interactions between the bioreceptors and biomarkers. B) Biosensor with different bioreceptor and biomarkers

Classification and Mode of Action of biosensors:

Many classification techniques have been developed for biosensors; however, the most widely applied scheme is based on two factors: signal transduction and the biorecognition component (Figs 4 & 5).

Figure-4: Schematic representation of a biosensor[Iqbal et al. Cancer Cell International (2022) 22:354].

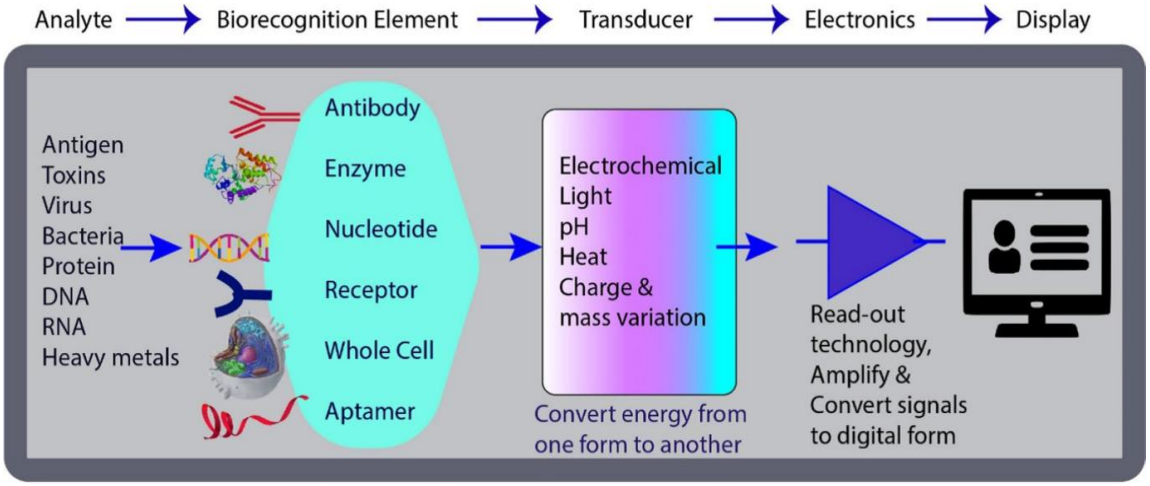


Figure-5:. Biosensor components and classification

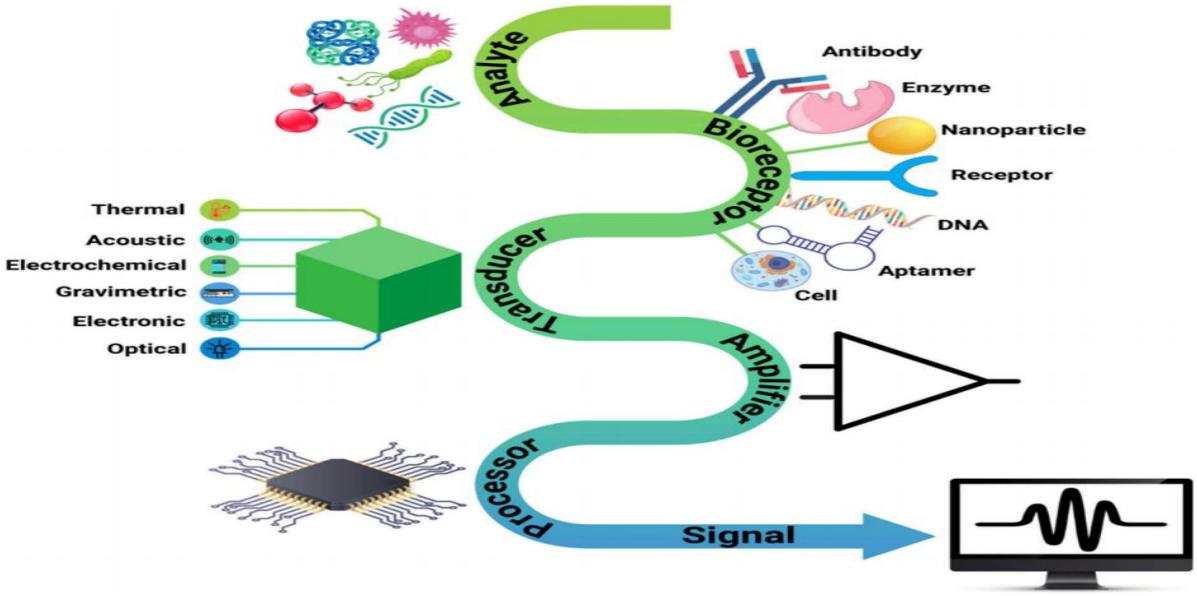


Figure-4 & 5, demostrated that a biosensor is an analytical device with a transducer that reads out the data, and a biomarker identification component that uses certain biomolecules as biorecognition components, and a converter. Based on the types of biocomponents used, biosensors can be sorted into DNA and enzyme antibodies. According to the types of transducers, there are three types of biosensors: mass-based, electrochemical, and optical biosensors.

3. BIOSENSOR COMPONENTS AND CLASSIFICATION

Biosensors are designed to detect specific biological analytes by converting biological entities such as peptides, proteins, DNA, and RNA into electrical signals that can be detected and analyzed [13,14]. They work by detecting biomarkers, which are biological molecules or substances that indicate the presence of disease. In the case of cancer, these biomarkers can be peptides, proteins, genetic material DNA or RNA, metabolites, or other molecules that cancer cells either overexpress or uniquely produce [15]. The primary component of a biosensor is typically a bioreceptor that recognizes and binds specifically to the biomarker. The receptor components include antibodies, nucleic acids (such as aptamers), peptides, enzymes, and other molecular recognition elements. The second step is the transducer, which converts the biological interaction between the biomarker and the bioreceptor into a measurable signal, which can be electrical, optical, or mechanical [16]. The third step is the signal processor, which processes the data and converts it into useful diagnostic information. Several biosensors have recently been developed and used to detect cancer in the past few years [17]. Based on the types of biocomponents used, biosensors can be sorted into DNA and enzyme antibodies. According to the types of transducers, there are three types of biosensors: mass-based, electrochemical, and optical biosensors.

Classification of Biosensors in Details in Cancer Research: [17-21]

Biosensors are broadly classified based on their biological recognition element and signal transduction mechanism.

- Based on Biological Recognition Elements:
  - ❖ Enzyme-based biosensors
  - ❖ Antibody-based (Immunosensors)
  - ❖ Aptamer-based biosensors
  - ❖ Nucleic acid (DNA/RNA)-based biosensors
  - ❖ Cell and tissue-based biosensors
- Based on Transduction Mechanism
  - ❖ Electrochemical biosensors
  - ❖ Optical biosensors
  - ❖ Piezoelectric biosensors
  - ❖ Thermal biosensors

- ❖ Magnetic biosensors
- Types and Mechanisms of Biosensors in Cancer Detection
- ❖ Electrochemical Biosensors

These sensors detect cancer biomarkers by monitoring electrical signals generated

- ➢ during redox reactions.

Applications:

- ➢ Detection of PSA (Prostate Specific Antigen)
- ➢ HER2 in breast cancer
- ➢ miRNAs in colorectal cancer
- Electrochemical Biosensors

These sensors detect cancer biomarkers by monitoring electrical signals generated.

- ➢ during redox reactions.

Applications:

- ➢ Detection of PSA (Prostate Specific Antigen)
- ➢ HER2 in breast cancer
- ➢ miRNAs in colorectal cancer
- Piezoelectric Biosensors

Measure mass changes on sensor surfaces due to biomolecule interaction using acoustic

- ➢ wave detection.

Applications:

- ➢ Label-free detection of proteins
- ➢ Analysis of cancer cell adhesion
- Nanomaterial-based Biosensors

Incorporate nanoparticles (AuNPs, CNTs, graphene) for enhanced sensitivity and multiplexing.

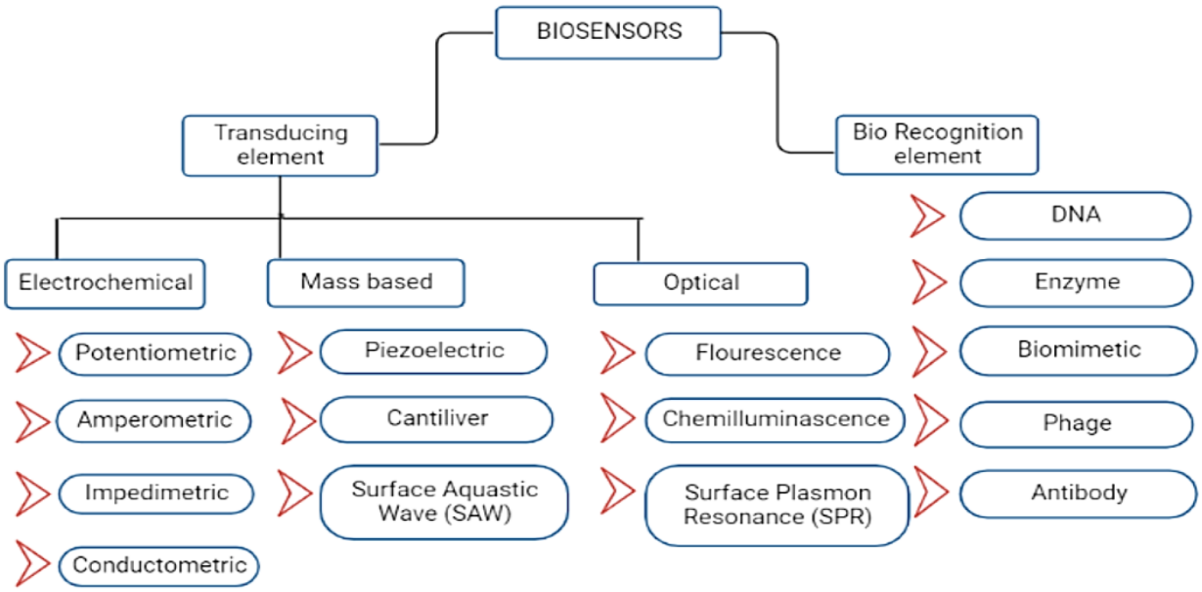
Applications:

- ➢ Early detection of p53 gene mutation
- ➢ Monitoring circulating tumor DNA (ctDNA)

Recent Advances in Biosensing Technologies:

- Clinical Applications:
- ➢ Early Diagnosis: Detection of specific miRNAs (e.g., miR-155, miR-21)
- ➢ Therapy Monitoring: Quantification of drug response biomarkers
- ➢ Prognosis: Analysis of metastatic potential via CTC monitoring
- ➢ Point-of-care (POC): Portable biosensor devices for rapid cancer screening
- Future Prospects
- ➢ Integration with Artificial Intelligence (AI) for data interpretation
- ➢ Wearable biosensors for real-time cancer monitoring
- ➢ Lab-on-a-chip microfluidic biosensors
- ➢ Personalized medicine via patient-specific biomarker panels

Figure-6: Types of biosensors for cancers [Xueyan Chen, 2024]



- Detection of cancer by using different types of biosensors:

❖ Conventional & Advanced Modalities:

➢ Enzyme-linked Immunosorbent assay (ELISA)

The ELISA is an analysis method that quantifies the target proteins in biological samples, such as antibodies, antigens, or glycoproteins. The technique provides a rapid, easy-preformed, and costefficient method to detect a specific cancer biomarker [21-25]. Uses are delineated below.

❖ Oral squamous cell carcinoma (OSCC)

It is more desirable to detect oral cancer as soon as possible to maximize treatment efficacy and lower death and morbidity rates. EGFR, p53, and Ki67 are currently accessible and integrated in their ability to diagnose OSCC. The targets of immune checkpoint blockade therapy are PD-L1, B7-H6, and HLA-E. These six substances could be used as the biomarkers of the OSCC in the early stage. An innovative ELISA is applied to detect the six biomarkers in the cytobrush biopsies samples of patients. The Femtohunter® which is an automated ELISA developer equipment, and the Stark Oral Screening® IVD test are used to collect and analyze samples. It produces a patient report and provides the biomarkers' analytical information in less than 60 minutes [26-29].

❖ Cervical cancer

A sandwich ELISA is designed to screen cervical dysplasia and cancer in an affordable way with higher sensitivity. P16 could be a biomarker for HPV in cervical cancer detection because one downstream effect of high-risk HPV infection is p16 overexpression [30]. The sandwich ELISA is designed that 133A6G5 and 151A7B9 are capture antibodies, and biotinylated 155E11G3 and 155D11G10 are detect antibodies. ELISA plate reader records the absorbance at 492 nm. This ELISA has higher detection limits and can detect p16 mouse monoclonal antibodies with a sensitivity of up to 2 pg [31-33].

➢ Surface plasmon resonance (SPR) biosensors:

SPR is an optical sensor technology that evaluates molecules, for example, antibodies, viruses, and nucleic acids, which bind to a metal surface by detecting changes in the localized refractive index. Compared to traditional cancer detection techniques, SPR biosensors have a number of benefits, like the capacity to immediately identify cancer in situ, with greater sensitivity, and without the need for labels. The used specimens could be clear or colorful like blood, urine, saliva, or plasma since the turbidity of the material does not affect its sensing potential [34-38].

❖ Breast cancer cell:

Conventional prism-based SPR sensing has constraints including huge design and limited analysis throughput for detecting the cancerous cells. However, the Photonic Crystal Fiber (PCF)-based SPR biosensors could overcome the limits. A PCF-based SPR biosensor is designed based on a PCF structured as a spiral with a hexagonal lattice and specific dimensions. The refractive index is determined using the Sellmeier Equation, and the dielectric constant of gold is calculated using the Drude Lorentz Model. The effective range of the sensor is 1.36 to 1.401 for refractive index. With a resolution of 2.33×10−4, for

breast cancer cell diagnostic, the PCF-based biosensor demonstrated a high sensitivity for the refractive index [39-41].

❖ Cancerous cells

A highly sensitive SPR biosensor was designed by incorporating a graphene-layered structure using FEM-based numerical analysis and the attenuated total reflection (ATR) method, and it demonstrated improved sensitivity for detecting various types of cancer cells. The sensor exhibited high sensitivity in detecting skin (basal) cancer cells (210 deg/RIU), cervical (HeLa) cancer cells (245.83 deg/RIU), adrenal gland (PC12) cancer cells (264.285 deg/RIU), blood (Jurkat) cancer cells (285.71 deg/RIU), and breast (MCF-7) cancer cells (292.86 deg/RIU) and breast (MDA-MB-231) cancer cells (278.57 deg/RIU). Moreover, the measured signal-to-noise ratio is 3.84, the figure of merits is 48.02 RIU−1 , and detection accuracy is 0.263 deg−1 [42,43]

➢ Surface-enhanced Raman spectroscopy (SERS)

SERS is a surface-sensitive method that increases molecular Raman scattering by specific nanostructured materials. Sensitive and multimodal SERS-based sensors are very helpful in analyzing biomolecular targets with minimal chemical complexity and abundance. The targets include exosomes, circulating tumor cells (CTCs), tumor-derived materials, circulating nucleic acids, and proteins[44-46].

❖ Breast cancer

The SERS spectra were acquired by adding urine to the silver nanoparticles and activating the colloid with Ca(NO3)2. With PCA-LDA, discrimination of the breast cancer patients from the control group using 81% sensitivity, 95% specificity, and 88% accuracy [47-53].

❖ Cancer-related biomarkers in blood

A label-free SERS biosensor using silver nanoparticles (AgNPs) as substrates is designed for cancer detection. Tests were performed on blood samples obtained from 30 healthy people, 30 patients with various cancers, and 15 patients with various chronic illnesses. The serum samples from the cancer patients had a larger standard deviation. Two methods were applied to analyze the data. The 95% accuracy rate, 90% sensitivity, and 93% specificity were obtained in the PCA-DA-assisted separation of the cancer group from the healthy group. PLS-DA showed a 95% accuracy rate, 90% sensitivity, and 100% specificity [54-59].

➢ Colorimetric biosensors

Colorimetric assay is a method of detecting the spectral absorbance of a chemical substance at a certain wavelength using a colorimeter (spectrophotometer) to quantify the quantity of the compound in a solution. Selectivity and sensitivity in colorimetric cancer biomarker detection have been increased through the introduction of nanomaterials with unique physical and chemical characteristics. The affordability, ease of use, and practicality of colorimetric techniques for real-time detection of the naked eye have sparked an increasing interest[60-65].

❖ Ovarian cancer

A colorimetric biosensor using citrate-modified gold nanoparticles was developed for the naked eye detection of the ovarian cancer biomarker PDGF. PDGF, representing platelet-derived growth factor, could be generated and kept in platelet granules throughout the clotting process. To identify PDGF, gold nanoparticles were combined with a PDGF-specific aptamer, and alterations in color and absorbance resulting from aggregation were observed. The PDGF detection signal ranged linear from 0.01 to 10 μg/ml with a detection limit of 0.01 μg/ml under optimal conditions [66-69].

❖ Malignant tumors

A colorimetric method for identifying cancer biomarkers that combines pH sensing with enzyme enrichment has been developed. Tests are conducted on human PDGF-BB, a protein that is frequently overexpressed in malignant tumors. The target was captured by immunomagnetic beads, and signal amplification through multi-branched rolling circle amplification, and signal conversion using glucose oxidase. The change in pH caused by the oxidation of glucose is detected using the pH indicator bromocresol purple. The concentration of human PDGF-BB and pH variations had a positive log-linear relationship, according to the pH-based colorimetric approach. With a 0.94 pM detection limit, the detection range was linear and ranged from 1 pM to 25 pM [70-76].

➢ Electrochemical biosensors

The electrochemical biosensor is a diagnostic instrument that works by converting biological processes such as the interaction between an enzyme and a substrate or an antigen and an antibody to electrical signals like the voltage, current, and impedance [77-81].

❖ Trypsin for pancreatic cancer

An electrochemical peptide sensor was proposed with an original electroanalytical technique for the assessment of trypsin.

A labeled short synthetic peptide sequence was immobilized onto magnetic beads and then digested with trypsin. The modified magnetic beads are incubated with a labeled fluorescein Fab fragment antibody. The MBs are magnetically trapped on the surface of a screen-printed carbon electrode. Amperometric detection is then carried out utilizing the hydroquinone (HQ)/HRP/H2O2 combination. The results showed the limit of quantification is 23 nM and the limit of detection is 7 nM [82-87].

❖ Carcinoembryonic antigen (CEA)

Cervical, gastric, pancreatic, and colorectal carcinomas can all be clinically identified and treated with the tumor marker CEA. Electrochemical immunosensors could detect a single protein. However, the primary challenge in the design of electrochemical immunosensors is creating a sensing platform with outstanding conductivity, high operational stability, exceptional biocompatibility, and a large active surface area. Currently, the nanocomposites' great conductivity, substantial surface area, and low toxicity make them suitable materials for the development of electrochemical immunosensors. A new electrochemical immunosensor was developed using CNTs-COOH/rGO/Ag@BSA nanocomposites to detect CEA.The detection limit of CEA is 1×10−4 ng·mL−1 and it has been assessed with concentrations ranging from 0.0001 to 50 ng·mL−1 [88-90].

➢ Fluorescence biosensors

Fluorescent biosensors are optical devices based on the fluorescence phenomenon to detect noninvasively the biomolecules present in biological samples, for example, proteins, glucose, or nucleic acids. The fluorescence phenomenon is triggered by the absorption of electromagnetic radiation by fluorophores or fluorescently labeled molecules. There are numerous benefits to using fluorescence biosensors to detect cancer biomarkers, including quick reaction times and visual identification [91-100].

❖ Hepatocellular carcinoma (HCC)

Serological protein alpha-fetoprotein (AFP) is the tumor biomarker of HCC while current techniques for AFP analysis have limitations like low sensitivity. A fluorescent aptasensor is designed for sensitive detection of the AFP using sandwich-structured QDs-AFPAuNPs and the Förster resonance energy transfer (FRET) method. With a detection limit of 0.4 ng·mL−1, the FRET-based biosensor designed for AFP detection demonstrated a linear detection range of 0.5 to 45 ng·mL−1 [101-110].

❖ CEA for cancer recurrence

A paper-based FRET biosensor is fabricated for the detection of multiple cancer biomarkers with high sensitivity. The paper-based biosensor demonstrated good stability, repeatability, and anti-interference properties. With a low detection limit of 0.89 ng/mL for CEA, the device demonstrated a linear connection between the FITC520/Tm480 signal and the concentration of the CEA in the range of 0-100 ng/mL [111-116].

Table 1: Biosensors were Used to Detect Biomarkers in Different Cancers [117-139]

Cancer Type	Biosensor Type	Biomarker Detected	Detection Mechanism	Detection Limit
Breast Cancer	Optical (SPR)	HER2	Antibody-HER2 interaction	50 pg/mL
Prostate Cancer	Electrochemical	PSA	Enzyme-linked reaction	0.1 ng/mL
Lung Cancer	Aptamer-based Electrochemical	miRNA-21	Hybridization	0.3 fM

Colorectal Cancer	DNA Biosensor	KRAS mutation	DNA hybridization	1 pM
Liver Cancer	Nanomaterial (Graphene)	AFP	Field-effect transistor (FET)	5 pg/mL
Pancreatic Cancer	Colorimetric (Gold NP)	CA 19-9	Antigen-antibody color shift	1.5 U/mL
Ovarian Cancer	Piezoelectric	CA-125	Mass change measurement	0.2 U/mL
Leukemia	Optical (Fluorescence)	BCR-ABL fusion gene	Fluorescent DNA probe	10 copies/reaction

Figurer-7: Detection of various Ovarian Cancer biomarkers recognized by recognition receptors (Bioreceptors-Biosensores)[129]

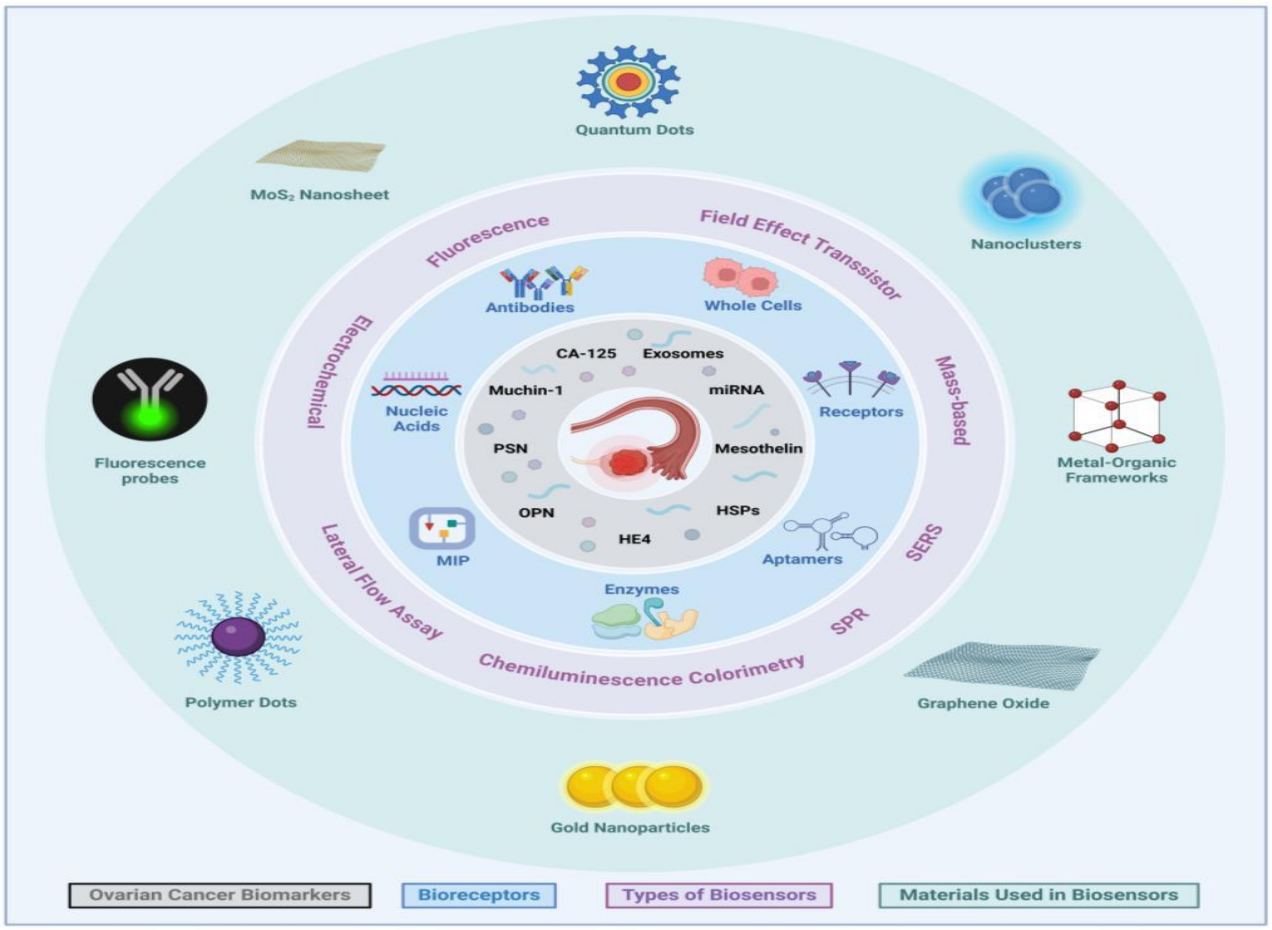


Figure-7: illustrating the ovarian cancer biomarkers detection using various recognition elements and sensing materials used for sensor development.

Table 2: Biosensor Technologies in Cancer Detection [129-142]

Biosensor Type	Recognition Element	Transducer	Cancer Application	Strengths
Colorimetric	Gold nanoparticles	Visible color change	Pancreatic, Prostate	Simple, visual detection
Electrochemical	Aptamer, Antibody	Current, Voltage	Lung, Prostate, Colorectal	High sensitivity, low cost
Optical (SPR/Fluorescent)	Antibody, DNA	Light reflection/emission	Breast, Leukemia, Ovarian	Real-time, label-free
Piezoelectric	Antibody, Whole cells	Mass change	Ovarian, Colorectal	Label-free, reusable sensor surface
Nanomaterial-based	Aptamer, DNA	Electronic, Optical	Liver, Pancreatic, Breast	High specificity, miniaturized

4. INTRODUCTION TO ADVANCED BIOSENSORS:

The electrochemical biosensors: The most widely used in cancer diagnostics. These sensors detect current, voltage, or impedance changes caused by the interaction between the target biomarker and the sensor surface. They offer high sensitivity, simplicity, and low cost, making them suitable for point-of-care diagnostics [47,48]. Electrochemical sensors can detect cancer-specific proteins such as prostate-specific antigen (PSA) or CA-125 in blood or urine.

- Electrical & electrochemical:

In general, the biosensors indicate the presence of variability in pH and ionic levels of the cell and pathological samples simply by color change indicators. At cellular level, the potential gradient depicted in the extracellular and intracellular environments provides indications to track the metabolic abnormalities and cell functioning [15]. These physiological anomalies including cellular functioning, membrane permeability of the transcript and gene expression products ionic strength of the cancerous tissues as a biomarker measured by electrochemical biosensors. The electrochemical biosensors detect potential or current generated by the interaction between the analyte cancer marker molecule and sensor electrode for their detections including conductometric biosensors, potentiometric, amperometric, and impedance sensors [25-31].

Innovative nanotechnological approaches utilize carbon nanotubes (CNT)-based biosensors, which offer high translational potential for detecting biomolecules or metabolites. For instance, enzyme-linked CNT nanoelectrode ensembles (NEEs) designed to detect specific molecules like glucose based on redox reactions catalyzed by oxidase enzymes [81]. These biosensors can efficiently diagnose the minor amounts of glucose in pathological samples such as sweat, and saliva accompanied by other metabolites like fatty acids, cholesterol, alcohol, lactate, and acetylcholine [96].

A field-effect transistor (FET)-based biosensor: is one type of electrical biosensor that attracted much attention in the past decade, owing to its suitability for devices used for point-of-care diagnostics, as well as in other fields such as, e.g., monitoring of environmental pollution, food quality, and pharmaceuticals. FET devices directly translate the analyte-receptor interaction into electrical signals. Thus, the binding of analytes to receptors can be detected by tracking changes in the electrical conductivity or resistance of the FET channel. The basis for this is a transformation of the receptor molecule (oxidation/reduction or other types of conversion), triggered by the binding of the analyte. This transformation causes a change in the current and threshold voltage of the FET biosensor device.[42–45]

Table-3: List of some of the reported electrochemical biosensors with their performance to detect cancerous biomarkers: [131-143]

Biomarker Targeted	Details of electrodes	Method	Limit of Detection	Linear Range
CEA	anti-CEA/PEDOT/Ag@BSA/rGO/CNTs-COOH/Au		1×10^{-4} ng/mL	0.002–50 ng/mL
	Ab1/rGO-AuNPs/GCE		5.3 pg/mL	50–650 pg/mL
	Anti-CEA/MWCNTs/GNPs/HNF/CPE	EIS	0.09 ng/mL	0.4–125 ng/mL
	SPCE/GNP-MnO2/ Fe_3O_4@Au-anti-CEA	LSV EIS	0.10 pg/mL, 0.30 pg/mL	0.001–100 ng/mL
PSA	Ab_2- QD(CdTe:Ni)/Fe_3O_4@ TMU-10		0.45 pg mL^{-1}	1 pg/mL–100 ng/mL
	GCE/CdS/p53-Ab1 p53-Ab2-tGO-AuNPs		3 pg/mL	0.005–10 ng/mL
	Nafion-rGO-CHO-MPGE/$[Fe(CN)_6]^{3-/4-}$	DPV	1.6 pg mL^{-1}	5 pg/mL–90 ng mL
	Aptamer/IDE/$[Fe(CN)_6]^{3-/4-}$ Label free		0.51 ng mL^{-1}	0.5 ng/mL–5000 ng/mL
	COOH-AgPtPd-NH_2-rGO/$[Fe(CN)_6]^{3-/4-}$	DPV	4 fg mL^{-1}	4 fg/mL–300 ng/mL
CYFRA21-1	GCE/rGO/PPy/AgNPs/ssDNA		2.14 fM	
	ssDNA-modified prob		1.0×10^{-14} M	10 fM–100 nM
	BSA/Ab1/GA/3D-G @Au/GCE	DPV	100 pg/mL	0.25–800 ng/mL
AFP	Isoorientin/anti-AFP modified GCE	DPV	0.0002 ng/mL	0.001–10 ng/mL
	Au-APTESMCS/$[Fe(CN)_6]^{3-}$	DPV	0.13 pg mL^{-1}	0.4 pg/mL–100 ng/mL
	Ab_2 label/AFP/BSA/Ab1/D-Au NPs/GCE	Amperometry	6.7 fg/mL	20 fg/mL–100 ng/mL
NSE	GCE/Au@MOFs/Ab1/BSA/NSE/MnO_2 UNs/Au@Pd^Pt NCs-Ab_2	DPV	4.7 fg/mL	10 fg/mL–100 ng/mL
CA15-3	Dye labeled DNA probe		0.0039 U/mL	0.01–1 U/mL
	CoS_2-GR-AuNPs/Ab/SPE	DPV	0.03 µ/mL	0.1–150 u/mL
BRCA1	Self-assembled ferrocenecored poly (amidoamine) dendrimers		0.38 nM	1.3–20 nM
CA 125	Ab/CysA-AuNPs/Ag-DPA-GQDs/GCE	DPV	0.001 U/mL	0.001–400 U/mL
CD59	Anti-CD59/GrONPs/PG	CV	1 fg/mL	1 fg/mL–10 ng/mL
EpCAM	Anti-EpCAM/rGO@TiO2/ITO	DPV	0.0065 ng/mL	0.01–60 ng/mL
MEG3	Primer probes		0.25 fM	1 fM–100 pM
UBE2C	Ab/GCE-PANI/$[Fe(CN)_6]^{3-/4-}$		7.907 pg mL^{-1}	500 pg/mL –5 mg/mL
LAG-3	SiO_2-Ab2/LAG-3/BSA/bio-Ab1/streptavidin/rGO-SnO_2/HNMs/AuPt/GCE	Amperometry	1.1 pg/mL	0.01 ng/mL–1 µg/mL
MUC1 **CA15-3** **HER2**	Screen-printed carbon electrode /PEI-AuNPs		0.21 U mL^{-1} 0.53 ng mL^{-1} 0.50 ng mL^{-1}	
IgG	GCE/G2Fc/Ab		2.0 ng/mL	5.0–50 ng/mL
EGFR exon 21	ssDNA λ-exo-modified prob		120 nM	0.1 µM–3 µM
	PPD-GR-AuNPs/Ab/SPE	DPV	0.3 ng/mL	1–1000 ng/mL
miRNA-141 **miRNA-21**	Dual signal-labeled hairpin-structured DNA (dhDNA)-based probes		0.89 fM 1.24 fM	2.0 to 10^5 fM
miR-21	FTO/SWCNTs/den-Au/prob		0.01 fM L^{-1}	01 fM/L–1 µM/L

- Light-Based Optical Biosensors: These are used to detect the biomarker and sensor surface interaction [49]. These sensors are particularly sensitive and can detect low concentrations of biomarkers, such as those using surface plasmon resonance and fluorescence-based techniques. Optical biosensors can offer high accuracy and real-time detection, which is essential in monitoring cancer progression.
- Immunosensors: A subset of biosensors that rely on the specific binding between antibodies and antigens (biomarkers). These sensors are commonly used to detect proteins, tumour antigens, and other biomarkers that are highly specific to different types of cancer. Immunosensors provide a reliable method for cancer biomarker detection in blood and tissue samples with high specificity and sensitivity but are limited to known antigens and possible cross-reactivity [50].

Surface Plasmon Resonance (SPR) biosensors: Detected the changes in refractive index on a sensor surface [51]. Hossain et al. (2020) developed a graphene-coated fiber optic SPR biosensor that detects point mutations in the BRCA1 and BRCA2 genes for breast cancer detection [52]. The SPR biosensor is also used to detect the carbohydrate antigen CA 15-3, commonly used in breast cancer diagnosis, in a simplified and automated manner [73,84].

- Microfluid chip-based biosensors: These are developed of a customized microenvironment that accurately regulates and controls microfluidic flow in microchannels, boosting detection sensitivity, which is the most significant benefit of microfluidics above conventional techniques [55,56]. Piezoelectric biosensors: rely on a piezoelectric material that

generates an electrical signal when stressed by the binding of cancer biomarkers. The change in frequency correlates with the concentration of the target biomarker.

- Photoelectrochemical (PEC) biosensor: A MoS2@Ti3C2 nanohybrid was developed for the ultrasensitive detection of miRNAs. The incorporation of Ti3C2, which exhibits excellent electron transfer properties, significantly enhances the photocurrent response of the PEC biosensor. Furthermore, the electrodeposition of Au nanoparticles onto the MoS2@Ti3C2 nanohybrid surface further amplifies the photocurrent. The biosensor's detection capability was evaluated using miR-92a-3p, an exosomal miRNA associated with colorectal cancer [57-59].

Table-4 List of Biosensors/ Biomarkers for cancer and their clinical relevance in diagnosis and prognosis.[122-143]

Biosensor type	Biomarker	Cancer type	Clinical relevance
Amperometric magneto-immunosensor	ErbB2 protein	Breast cancer	Quantification of biomakerin serum and cell, cell lysates with LOD 26 pg mL^{-1}
AuNPs-Surface plasmon resonance immunosensor	ErbB2	Breast cancer	LOD 80 pg mL^{-1} i.e., higher sensitivity for cell lystae
anti-miRNA-155 coated electrochemical biosensor with Au-screen printed electrode (Au-SPE)	miRNA-155	breast cancer	low detection limit (LOD) of 5.7 aM in serum samples, point-of-care (POC) diagnosis for multi-panel biomarker CA-15.3
electrochemical DNA biosensor	epidermal growth factor receptor (EGFR) exon21 L858R	lung cancer	high sensitivity (0.0188 mA/μM), LOD 120 nM, long-term stability 21 days
Electrochemical immunosensor	p53	Tumor	LOD of 3 fg/mL in serum samples, reasonable sensitivity, excellent selectivity and long-term stability
surface plasmon resonance (SPR) Optical-immunobiosensor	EGFR andprogrammed death-ligand 1 (PD-L1)	nonsmall cell lung cancer (NSCLC)	nanoplasmonic exosome having sensitivity of 9.258 × 10^3 %/RIU and resolution of 8.311 × 10^{-6} RIU, user-friendly
anchor-like DNA (alDNA) electrochemical sensor	KRAS gene	non-small-cell lung cancer (NSCLC) as well as colorectal cancer, pancreatic cancer and breast cancer	detection accuracy LOD 0.1 pM to 10 nM for t-DNA and from 100 pM to 10 nM for Mutated-DNA in serum sample
interdigitated electrode biosensors	prostate-specific antigen (PSA)	Prostate cancer	Potential portable of Au interdigitated triple-microelectrodes LOD ≤0.51 ng/ml, excellent sensitivity of 2.710 kΩ/log.
Aptamer-based electrochemical biosensor	Aptamer	non-small cell lung cancer, non-specific cervical cancer	Labelled free composite nanofiber (polyacrylonitrile (PAN) and polypyrrole (PPy) polymers)-modified disposable pencil graphite electrodes (PGEs), LOD 1.2 × 10^3 cells/mL
polyethyleneimine (PEI)-Ag NPs electrochemical biosensor	microRNAs (miRNAs)	Serum and body fluid of breast cancer	LOD 20 zmol
TiO_2-Ag quartz crystal microbalance (QCM) biosensor	MicroRNA-21 (miR-21)	malignant tumor	LOD of 0.87 pM in serum samples
Localized SPR (LSPR) Optical biosensor	prostate-specific antigen (PSA)	Prostrate cancer	antibody conjugated-gold nanoparticle (GNP) having LOD 0.2 ng mL^{-1}, and calibration sensitivity of 43.75 nm/(ng mL^{-1}) in serum sample
electrochemical immune-biosensor	PSA	Prostate cancer	AuPt metallic nanoparticle and manganese dioxide (MnO_2)-functionalized covalent organic frameworks (AuPt@MnO_2@COF) having LOD 16.7 fg/ml, excellent selectivity, repeatability, and stability
Ag_3PO_4 NPs@MoS_2 nanosheet-based electrochemiluminescence (ECL)	KRAS gene	colorectal cancer tumor and tumor-adjacent tissues	(LOD) of 0.2 fM
Au-on-Ag heterostructure and DNA tetrahedral framework (DTF) Optical Biosensor	exosomal miRNAs	non-small cell lung cancer (NSCLC)	LOD 1.68 fM, antifouling capability, multiplex exosomal miRNAs detection, reduces nonspecific adsorption
Electrochemiluminescence resonance energy transfer (ECL-RET) biosensors	double-stranded circulating tumor DNA (ctDNA)	non-small-cell lung cancer	LOD 0.0023fM for circulating tumor DNA in blood plasma or noninvasive biopsies
electrochemical biosensor (multi-walled carbon nanotube (Au NCs/MWCNT-NH_2)-decorated screen-printed carbon electrode (SPCE)	Long non-coding RNAs (lncRNAs)	non-small cell lung cancer	Cost-effective material for rapid screening and diagnosis, LOD 42.8 fM
Electrochemical immunosensor	p53	breast cancer cell (MCF7 lysates)	Low cost nano-cellulosic interdigitated diagnosis and prognosis of p53 LOD 0.16 U_{cell} mL^{-1}
Graphene oxide-DNA nanohybrid biosensor	Mutated ssDNA	Lung cancer	Rapid and cost-effective detection 100 pmol
Photonic crystal fiber (PCF) SPR optical biosensor	Cell receptor	Breast, cervical and basal carcinoma	high optical sensitivity of 6214.28, 3800, and 5008.33 nm/RIU, for quasi-transverse magnetic (TM), and 6000 nm/RIU, 4400 nm/RIU, and 5333.3 nm/RIU,
SiO2 Optical sensor	Carcinoma cell	Cervical skin cancer, blood, breast (type 1, type 2), and adrenal gland cancer	spiral shaped photonic crystal fiber structure maximum sensitivity of −289 *RIU*−1
Electrochemical immune-biosensor	carcinoembryonic antigen (CEA)	colorectal cancer	graphene oxide nanocomposite having LOD 0.3 pg/mL, RSD (4.49 %–5.04 %) and recovery (90.00 %–99.98 %).
electrochemiluminescence	microRNA	breast cancer cell	enzyme-free DNA amplification circuits signal from luminophore, LOD 2.03aM for miRNA2, 80.4aM for miR 105

Table-5: Comprehensive study on breast cancer detection using biosensors: [91-98]]

Name of biosensor	Biosensor specification	Analyte	Performance	Linear range
FET biosensor [91]	Transducer rGO-Encapsulated SiO_2 NPs	HER2	The detection limit is 1 pM Mobility is 3 $cm^2V^{-1}s^{-1}$	1 pM to 1 μM
Electrochemical [92]	Hemin/miR/DNA-Au/probe/AuNPs/Au electrode	miR-21	Detection limit is 6 fM	0.01–500 pM
Electrochemical [93]	Two auxiliary probes that self-assemble to form 1D DNA concatemers	miRNA 21	LOD is 100 aM	100–10^5 aM
Electrochemical [94]	P19 captured dual aptamer complex on SPCE	miR-205	Detection limit is 0.6 nM	2–10 nM
Electrochemical (EIS) [95]	Aptamer on a gold electrode and iron redox probe readings	Progesterone (PR)	LOD is 0.90 ng/mL Response time: 40 min	10–60 ng/mL
Electrochemi-cal [96]	Anti-miR probe/GNR/GO/GCE	miR-155	Detection limit is 0.6 fM	2.0 fM to 8.0 pM
Electrochemi-cal [86]	Immobilization of anti-miRNA-155 on Au-SPE	miRNA 155	LOD is 5.7 aM	10–10^9 aM
Sandwich electrochemi-cal biosensor [13]	polydA-aptamer-modified gold electrode polydA-aptamer functionalized gold nanoparticles/graphene oxide hybrid	MCF-7 cells	The detection limit of 8 cells/mL (3σ/slope)	10–10^5 cells/mL
FET biosensor [97]	Transducer G-graphene/PBASE	DNA	Detection limit is 100 fM Mobility is 64 $cm^2V^{-1}s^{-1}$	100 fM to 1 nM
FET biosensor [98]	Transducer rGO/SA	BRCA1	Detection limit is 0.2 nM	0.2–75 nM

- DNA biosensors:

These biosensors detect specific sequences of DNA, often related to oncogenes or tumor suppressor genes that might indicate a predisposition to certain cancers or confirm the presence of a cancerous mutation. A DNA biosensor typically has a probe – a short sequence of DNA that can hybridize (bind) to a target sequence. When the target sequence is pre- sent, binding occurs, leading to a measurable electrochemical change. The stability, specificity, and inexpensive cost of these biosensors make them alternatives to antibodies. DNA- aptamers-based biosensors can bind bacteria, viruses, proteins, hormones, analytes, tiny molecules, and ions with high specificity and affinity.[33,35]

- Protein biosensors:

Protein biosensors use cell membrane protein receptors. These receptors allow metabotropic (enzyme secretion) or ionotropic receptors to transduce the binding signal across the membrane.33 Many cancers produce specific proteins or cause alterations in protein levels that can be indicative of the disease. Protein biosensors can detect these proteins at very low concentrations. They often use antibodies or apta- mers as the biological component, as these molecules can bind to specific proteins with high affinity

- Cell-based biosensors

Cell-based microbial biosensors detect chemical composition, toxicity, carcinogenicity, and mutagenicity in real time and cost-effectively using prokaryotic or eukaryotic cells.[36] Cell-based microbial biosensors use prokaryotic or eukaryotic cells to detect chemical composition, toxicity, carcinogenicity, and mutagenicity in real time and cost- effective.37 Instead of detecting molecules, these biosensors detect changes in living cells that might be indicative of cancer. Certain electrochemical changes might occur on the surface of cancerous cells, different from healthy cells. Cell-based biosensors can detect these changes.38 They are particularly valuable in assessing the overall health of a cell population, understanding cancer cell behaviors, or evaluating how cells respond to potential treatments as mentioned

Tasble-6: Different Biosensors Technology Used In Cancer:[4-50].

Biosensors	Functions	References
Electrochemical biosensors	• Electrochemical biosensors are mostly used to detect glucose levels, DNA-binding medicines, and hybridized DNA.They combine electrical and biological detection methods. • These sensors work through an electrochemical interaction between the target analyte and the working electrode surface. When the analyte reacts with the working electrode, current, impedance, and potential are measured. • Based on how they monitor electricity, electrochemical biosensors fall into three categories: (1) conducti-metric, (2) amperometric, (3) potentiometric. Electrochemistry is better than optical approaches because analyzers may use turbid samples and the equipment is cheaper. • Electrochemical methods are less selective and sensitive than optical approaches.	4 39 40
Multiplexed immune checkpoint biosensor (MICB)	• Highly particular and discriminatory • Small sample volumes are required for multiplex biosensors to diagnose the condition and identify several immunological checkpoints immediately. • These sensors, the analyte tends to take longer to bind with the cell surface without the use of nanofluidic mixing. • MICB has capability to evaluate 28 samples in less than two hours.	41 42

	• MICB was evaluated for its capacity to detect soluble PD-1, PD-L1, and LAG-3 in liquid biopsies utilizing immune checkpoint concentrations in diluted human serum. Fortified samples had a concentration equal to the prognostic cut-off, which may differ from the cancer detection threshold, whereas immune checkpoint samples showed a different signal response.	
Exosome Biosensor	• Exosomes are essential for surface biomarker-mediated intercellular communication. For instance, exosomal proteins are essential for drug resistance, uniqueness, and the growth of cancer. • This biosensor achieved optical resolution by means of laser beams. The positioning of the two laser beams, in essence, allowed SPR to interact with the exosomal proteins on the sensor's surface. • • The two photodetectors measured exosomal proteins by magnifying the original and reflection beams, using the other beam as a reference. • Researchers evaluated biomarker specificity and sensitivity in serum samples from lung cancer patients using this biosensor.	42 43
Surface plasmon resonance (SPR) biosensor	• When it depends on identifying PD-L1 in serum samples, including one from a patient with Stage III lung cancer, the SPR biosensor is incredibly precise and efficient. • Evanescent field-based optical sensors, built with a thin gold layer, are effective for sensing. Photodetector array sensors find reflection minima in analyte flow across a gold-immobilized interactant. Through immunoreactions, SPR has identified illness microorganisms.	44 4 45
Optical biosensor	• . A transducer system integrated with a biorecognition element makes up an optical biosensor, which is a small analytical instrument. An optical signal that optical biosensors produce is directly proportional to the analyte's concentration. • Biological and chemical compounds can be detected in real time, label-free, and with great sensitivity, specificity, and economy using optical biosensors. High specificity, sensitivity, compact size, and cost-effectiveness are some of the benefits.	46,47
Piezoelectric Sensors	• These sensors respond rapidly and with highly effective sensitivity. • A piezoelectric (PZ) sensor may detect minute changes in biorecognition element mass, frequency, or other quantitative attributes by attaching molecules to antibodies. • The PZ sensor was developed to identify biomarkers for cervical cancer in concentration ranges of 50 to 1200 ng mL−1. Its analysis time was quite short. • The marker can be found at concentrations 100 million times lower with a PZ sensor. • In order to convey the biomarker's existence, piezoelectric sensors require an adjustment in the sensor. • PZ sensors are a dependable choice for efficient cancer detection since they are durable and sensitive to minuscule biomarker concentrations.	48 49 50

➢ Optical biosensor:

Optical biosensors are commonly used in clinical diagnostics, offering the advantage of continuous monitoring of biochemical reactions. These sensors can detect both labeled and unlabeled analytes, as well as the products of analyte-receptor interactions in real-time. They employ various optical spectroscopy techniques, including absorption, fluorescence, luminescence, Raman, refraction, and scattering spectroscopy, to achieve continuous equivalent detection [49]. Wide range of optical biosensors based on the analyte characteristics, sensitivity, therefore in novel approaches to enhance the detection efficiency or sensitivity, immobilization recombinant antibodies or antibody fragments immobilized carbon nanotubes (CNTs) designed [92]. Vertically aligned single-wall carbon nanotube (SWNT) forests have been utilized for the amperometric enzyme-linked immunodetection of human serum albumin, significantly improving the limit of detection (as low as 1 nM) and sensitivity by facilitating efficient electron exchange between nanotubes and enzymes attached to their tips [32]. Similar, CNT-based immunosensors have also been used to detect antigens such as alpha-fetoprotein, gonadotropin, interleukin, and various other biomarkers [92].

➢ Immunobiosensor with Graphene-Based:

Recent advancements have witnessed the emergence of conventional and wearable immunosensors, with graphene-based immunosensors showcasing significant promise in the field of biosensing for a wide

➢ Nucleic acid-based biosensors:

Nucleic acid integral strands are utilized in the synthesis of nucleic acid-based biosensors for the natural acknowledgment component. For example, twofold abandoned DNA (dsDNA) is formed by the limiting reaction between two single-strand DNA (ssDNA) chains [85]. The successions that are integral to a perceived objective nucleic corrosive grouping can be produced, followed, and in the long run immobilized on the sensor. Kang et al. fostered a glucose oxidase/graphene/chitosan nanocomposite for glucose detection by enormous catalyst stacking (1.12 3 1029 mol/cm2) with maximum strength and compound move- ment [47]. Biosensors can specifically recognize glucose with a discov- ery breaking point of 0.02 mM and a high responsiveness (37.93 µA/mM/cm2) [26]. This improved presentation was ascribed to the enormous high conductivity and surface-to-volume proportion of graphene, which could additionally upgrade the chemical ingestion and advances the electron move between the redox compounds and the outer layers of the cathodes. Wu et al. a delicate biosensor was accomplished for the location of glucose, which could distinguish the centralization of glucose down to 0.6 µM [108]. The nanocomposite film that contained glucose oxidase, Pt, useful graphene sheets, and chitosan eliminated the ascorbic corrosive and uric corrosive interfering signals. By integrating with different chemicals, graphene buildings can likewise be utilized to recognize an expansive scope of biomolecules through enzymatic electrochemical responses (like H2O2, and cholesterol).

5. TYPES OF BIOMATERIALS USED FOR BIOSENSORS:

There are various types of biomaterials that can be used in the design of biosensors, such as synthetic or bio-synthetic polymers with surface-functionalized receptors that interact with the analyte, such as proteins, nucleic acids, signaling molecules, or hormones[76-79].

Enzyme-labeled probes are common biosensors used as conventional detector with poor analysis outcome. Novel materials are being utilized in cancer theranostics to improve biosensors' physicochemical, optical, piezoelectric, and electrochemical properties. Hence, to improve the diagnosis efficiency at multiple parameters, biosensors are categorized into a number of groups based on their unique competences for recog- nition and signal transduction of cancer biomarkers [80,82].

Nano-conjugated hybrid materials based transducing platform for sensing minuscule amounts cancer specific biomolecule in the micro- environment or within the body.

- Nano-polymers and Nano-polymers based Biosensors in Cancer Reseaech:

Nanotechnology have a wide range of applications in cancer theranotics either modify the delivery agent, drug formulation and increasing the sensing effecting of the biosensors (Fig. 4). It is also possible to deliver drugs directly by covalently linking or encapsulating beneficial substances without further modification of the polymer surface [93]. A thorough investigation of synthetic and natural polymer-based carriers has been conducted due to their benefits for prolonging blood circulation, improving drug delivery, and preventing metabolic clearance [76]. Furthermore, the degradation of polymers based on physiological parameters such as pH and temperature can be used in the delivery of medications by polymer carriers by altering physiologic parameters such as pH.

- Natural Polymer Based Biosensors: [115].

Biosensors require functional materials to detect specific biological analytes. However, these materials may not always maintain the necessary biocompatibility for proper biorecognition.

Chitosan: Chitosan (Cs) is a natural polysaccharide that has been exploited for a broad range of biomedical applications,67,68 including drug delivery,69 gene delivery,70 and biosensors.71 Cs is characterized by high permeability and mechanical strength, biocompatibility, cost-effectiveness, pHdependent solubility, nontoxicity, availability, good adhesion, and easy chemical modification. The linear chain of chitosan contains reactive amino and hydroxyl groups that confer excellent mass transfer properties, beneficial hydrodynamic properties for enzyme immobilization, and a unique filmforming ability.72

Cellulose: Cellulose is a well-known natural biopolymer composed of glucose residues linked by β-(1 → 4) glycosidic linkages.86,87 It exhibits considerable potential as a sustainable sensing material due to its excellent biocompatibility, strong mechanical strength, high degradation efficiency, and regeneration capabilities.[115]

Table-7. Cellulose-Based Biosensors for Cancer Detection

type	target	ligand/bioreceptor	detection technique	LOD	linear range	disease
electrochemical	lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1)	biotinylated antibody of LYVE-1	CV, EIS, SWV, and DPV	0.312 pg/mL	20–320 pg/mL 0.625–10 pg/mL	different types of cancers
colorimetric	osteopontin (OPN)	OPN aptamer	dye for color development	5 ng/mL	5–1000 ng/mL	different types of cancers

Table-8. Gelatin-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/ bioreceptor	detection technique	LOD	linear range	disease
stimuli responsive	MiRNA-let-7a	gelatin	strand displacement amplification and CRISPR/Cas12a	6.28 pM	10 pM to 10 nM	breast cancer
fluorometric and colorimetric	matrix metalloproteinase-9	gelatin	fluorescence resonance energy transfer (FRET) and surface plasmon resonance (SPR)	fluorometrically: 0.25 ng/mL calorimetrically: 2 ng/mL	fluorometrically: 1–200 ng/mL calorimetrically: 10–100 ng/mL	different types of cancer

Table 9:. Alginate-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/bioreceptor	detection technique	LOD	linear range	disease
optical	alpha-fetoprotein (AFP)	AFP antibody	fluorescence intensity	0.1 ng/mL	1–250 ng/mL	liver cancer
optical	HER2 protein	anti-HER2 monoclonal IgG antibody	fluorescence intensity	HER2 protein: 0.004 ng/mL	HER2 protein: 0–10 ng/mL	breast cancer
	CA125 protein	anti-CA125 monoclonal IgG antibody		CA125 protein: 0.005 U/mL	CA125 protein: 0–10 U/mL	
surface plasmon resonance (SPR)	prostate specific antigen (PSA)	PSA antibody	SPR imaging	PSA: 29 pg	-	prostate cancer
	β-2-microglobulin (B2M)	B2M antibody		B2M: 58 pg		

Table-10. Polypyrrole-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/bioreceptor	detection technique	LOD	linear range	disease
electrochemical	tryptophan (Trp)	pencil graphite electrode modified with overoxidized polypyrrole/ deposited carbon dot film	square wave voltammetry (SWV)	0.003 μmol/L	0.01–0.09 and 0.50–9.00 μmol/L	breast cancer
geno-sensors	PML/RARα gene	APLB/M7 oligonucleotide sequences	cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS)	0.214 pM/0.677 pM	1.0–100 pM	leukemia
electrochemical	BCR/ABL fusion gene	DNA probe	CV and EIS	1.34 fM	138.80 aM to 13.88 pM	leukemia
electrochemical	HPV L1 sequence and p53	DNA probe	CV and EIS	0.11–0.61 pg/μL	0.001–100 pg/μL	cervical cancer
electrochemical	calreticulin (CLAR)	anti-CALR antibodies	CV and EIS	10.4 fg/mL	0.025–75 pg/mL	breast cancer

Table-11. Polyaniline-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/ bioreceptor	detection technique	LOD	linear range	disease
electrochemical	mucin 1 (MUC1)	anti MUC1	electrochemical impedance spectroscopy (EIS)	3.23 pg/mL	1–100 pg/mL and 1–100 ng/mL	different types of cancer
electrochemical	carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP)	CEA antibody and AFP antibody	chronoamperometry (CA) and cyclic voltammetry (CV)	80, 30 pg/mL	1–50 ng/mL	different types of cancer
electrochemical	aminopeptidase N (APN)	specific aptamer	DPV and CV	24.25 pg/mL	0.1–10000 ng/mL	different types of cancer
electrochemical	AFP	AFP antibody	EIS and CV	2 pg/mL	0.25–40 ng/mL	liver cancer
electrochemical	μDNA-224	single-stranded DNA	EIS	9.77 pmol/L	1 pmol/L to 1 μmol/L	colon cancer
electrochemical	AFP	AFP antibody	CA and CV	4.7 pg/mL	0.01–1 ng/mL and 1–10 ng/mL	liver cancer

Table-12. Polyethylene Glycol-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/ bioreceptor	detection technique	LOD	linear range	disease
electrochemical	ERBB2	RBCM-PP	electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV)	0.21 ng/mL	1×10^{-2} to 10 ng/mL	breast cancer
electrochemiluminescence	MUC1	DNA probe	electrochemiluminescence (ECL)	100 fg/mL to 10 ng/mL	16.5 fg/mL	breast cancer
photoelectrochemical	folate receptor (FR) on MDA-MB-231 cells	folic acid	photoelectrochemical	20 to 2.0×10^6 cells/mL	15 cells/mL	different types of cancer
nanowire	miRNA-21	DNA probe	field effect transistors (FETs)	10 aM to 10 pM	1 fM	different types of cancer
electrochemical	HER2	HER2 aptamer	EIS and differential pulse voltammetry (DPV)	0.01–15.0 ng/mL	1.52 ng/mL	breast cancer

Table-13. Nafion-Based Biosensors for Cancer Detection

type of biosensor	target	ligand/bioreceptor	detection technique	LOD	linear range	disease
electrochemical	prostate specific antigen (PSA)	PSA aptamer	Electrochemical impedance spectroscopy (EIS)	0.0306 ng/mL	0.05—50 ng/mL	prostate cancer
electrochemical	zinc ions	encoded redox amino acid	DPV	0.129 nM	5−50 nM	bladder cancer
electrochemical	CYFRA 21-1	antibodies	SWV	0.03 pg/mL	0.5 to 5.0 × 10^4 pg/mL	nonsmall cell lung cancer
electrochemical	exosomes	epidermal growth factor receptor (EGFR) antibody	SWV and CV	2.67 × 10^4 exosomes/mL	5 × 10^4−5 × 10^9 exosomes/mL	lung cancer
aptameric	IFN-γ	aptamer probes	-	740 fM	0.015−250 nM	different types of diseases including cancer

Table-14: MIP-Based Biosensors for Cancer Detection

type of sensor	analyte	composite materials (ligand-MIP)	detection technique	application	LOD
electrochemical	STEAP1[a]	C-SPE-pyrrole-2-carboxylic acid[b]	SWV[c]	early diagnosis of prostate cancer	-
electrochemical	Her-2[d]	LSG-AuNS-PEDOT[e]	SWV	point-of-care device to detect HER2	0.43 ng/mL.
electrochemical	AFP[f]	FTO-Ppy[g]	CV, EIS[h]	detection of AFP in serum samples	3.3 pg/mL
electrochemical	PSA[i]	AuE-poly(toluidine blue)[j]	DPV[k]	sensitive detection of PSA	1 μg/L
electrochemical	Myo[l] and PSA	AuSPE-poly(*N*,*N*′methylenebisacrylamide-acrylamide)	EIS	detection of PSA and Myo in human serum and urine samples	0.83 ng/mL and 5.4 pg/mL
electrochemical	CA-125[m]	AuSPE-Ppy	SWV	CA-125 detection in artificial serum samples	0.01 U/mL
electrochemical	PSA	AuSPE-Ppy	DPV	detection of prostate cancer	2.0 pg/mL
electrochemical	CA15-3[n]	AuSPE-poly(toluidine blue)	DPV	detection of breast cancer	0.10 U/mL
electrochemical	AFP	GCE-PDA P[o]	DPV	detection of AFP in human serum sample	0.8138 pg/mL

Note: STEAP: six-transmembrane epithelial antigens of the prostate. b C-SPE: screen-printed electrode. c SWV: square wave voltammetry. d Her-2:human epidermal growth factor receptor 2. e LSG: laser scribed graphene; AuNS: gold nanostructures. f AFP: alpha-fetoprotein. g FTO: fluorine tin oxide. H CV: cyclic voltammetry; EIS: electrochemical impedance spectroscopy. i PSA: prostate specific antigen. j Gold electrode. k DPV: differential pulse voltammetry. l Myo: myoglobin. mCA-125: carbohydrate antigen 125. n CA15-3: cancer antigen 15-3. o GCE: glassy carbon electrode.

- Hydrogels based Biosensor for Cancer:

Since the first hydrogel was synthesized in 1960, a number of synthetic polymers and natural polymers have been pervasively used to produce hydrogels .Hydrogels are functional biomaterials that have been in high demand for synthesis, production, and applications in the past few decades. Hydrogels are generally made from synthetic polymers such as poly(2-hydroxyethyl methacrylate) (PHEMA), polyethylene glycol (PEG), polyacrylamide (PAM), and poly(vinyl alcohol) (PVA), or natural polymers such as alginate, chitin, cellulose, and chitosan. Hydrogels are threedimensional and cross-linked networks of hydrophilic polymers that have properties similar to biological tissues. They can be combined with various biosensors to achieve high sensitivity, specificity, and stability.

Figure-8:Hydrogel-based biosensors [143]..

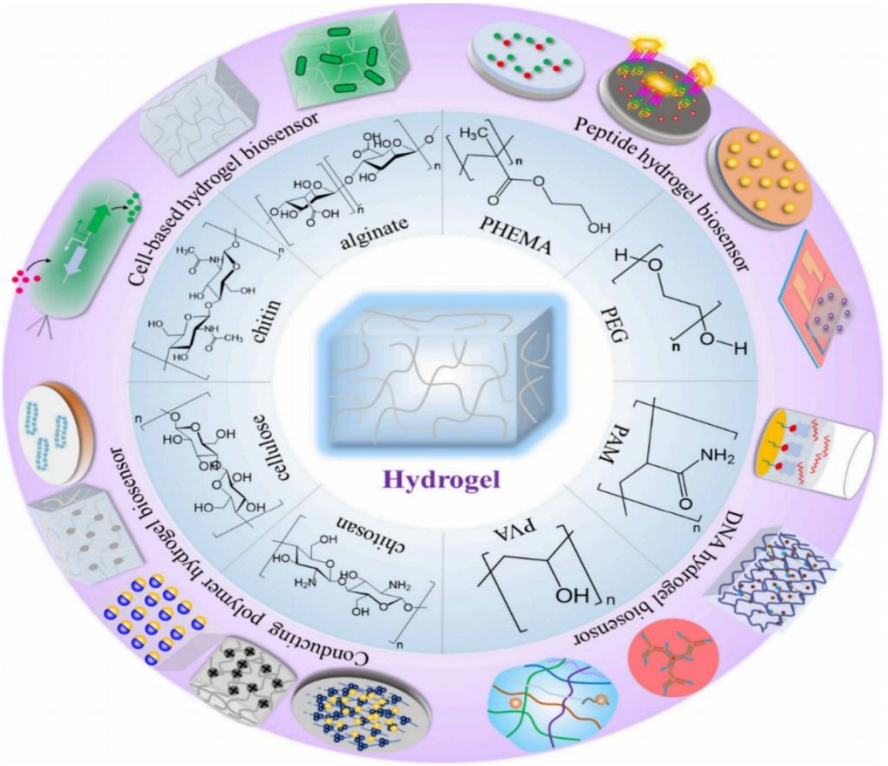


Figure-9:Hydrogel-based biosensor for cancer biomarkers detection

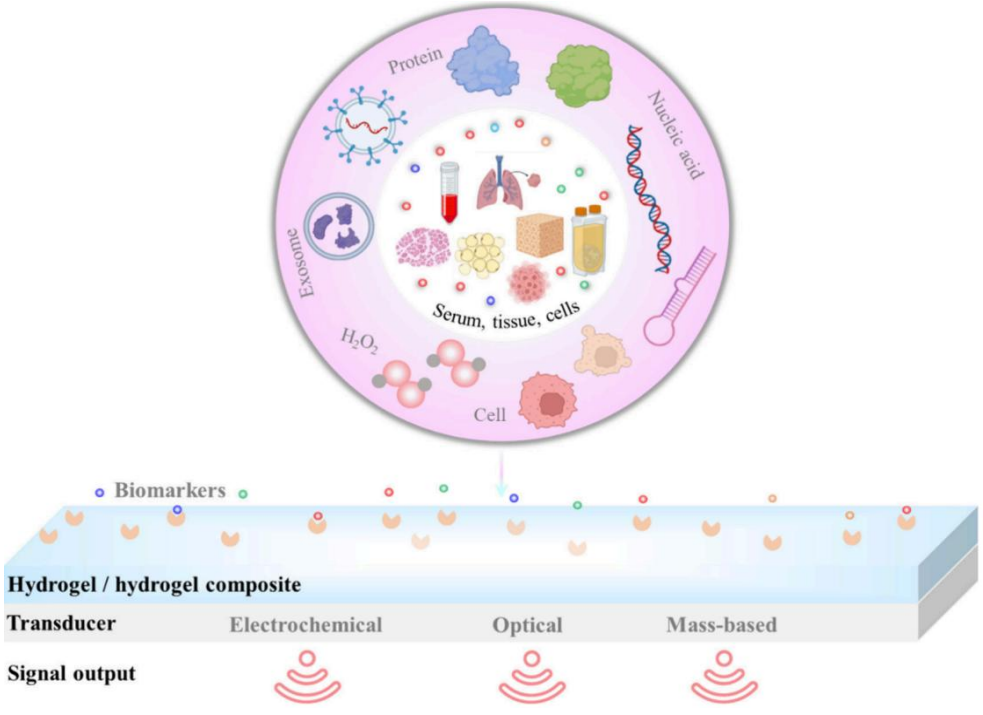


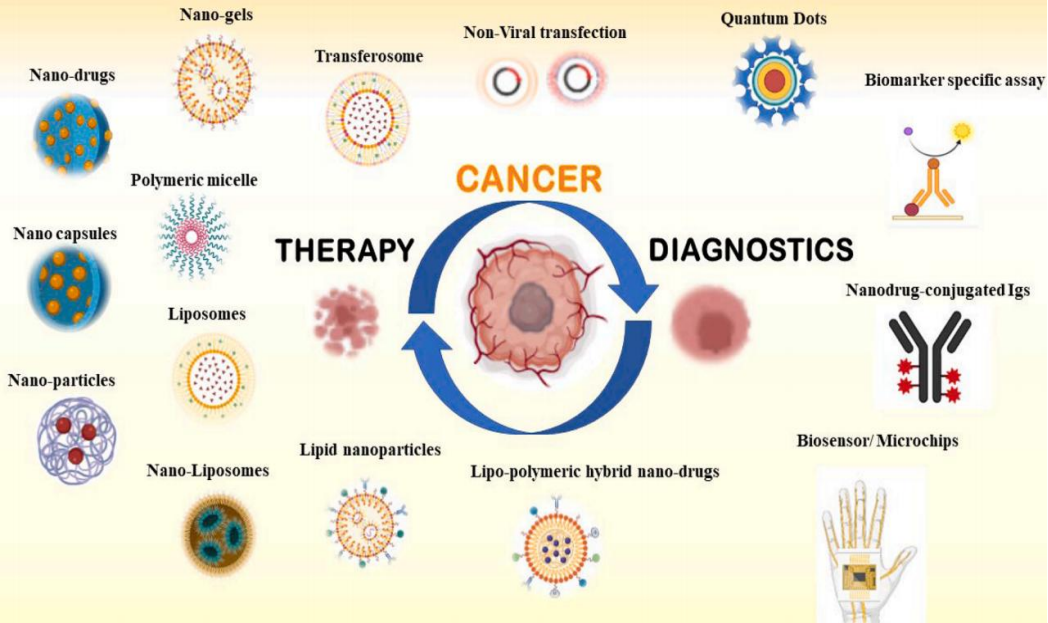
Figure-9, Illustrating that the human samples (e.g., serum, tissue fluid, cells) are collected and the analytes containing the target biomolecules are extracted. The biomarkers will interact with the bioprobes immobilized on the hydrogel matrix. For signal detection, the affinity interaction will be converted into a measurable signal, such as an electrochemical, optical, or massbased signal.

Besides all those, nanotechnology plays a key role in enhancing the sensitivity and specificity of biosensors. Nanomaterials such as gold nanoparticles, quantum dots, and carbon nanotubes are being integrated into cancer biosensors to improve

sensitivity with small amounts of cancer biomarkers [67-69]. These materials enhance the surface area available for biomarker binding, increase sensitivity, and enable highly targeted detection, which is crucial for early cancer diagnosis.

- Nanobiosensors: can combine multiple types of signals (e.g., electrical, optical, and electrochemical) to provide more comprehensive diagnostic information. Quantum dot-based nano-biosensors are nanoscale devices designed for cancer detection and research. These sensors work by identifying blood-borne biomarkers, including cancer-associated proteins, circulating tumor cells, circulating tumor DNA, and exosomes released by tumours [70-73]. The integration of nanotechnology into biosensors represents a cutting-edge approach that is revolutionizing cancer diagnostics [74,75].

Figure-10. Role of nanotechology in cancer diagnostics and therapy



- Applications of biosensors in cancer diagnosis:

Early-stage cancer detection and screening: Biosensors, with their ability to identify biomarkers at very low concentrations, offer a promising avenue for cancer detection before symptoms appear. Liquid biopsy, an emerging non-invasive method using blood-based biosensors, can detect circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), and other cancer-associated biomarkers [30]. This offers a convenient alternative to traditional tissue biopsies and can be used for routine screening of cancers such as lung, breast, colorectal, and prostate cancer. Biosensors can also detect volatile organic compounds released by tumours in a patient's breath, a non-invasive method being explored for early lung cancer detection. Biosensors are also being developed for screening purposes in high-risk populations. Biosensors that detect prostate-specific antigen (PSA) levels in blood samples can be used to screen for prostate cancer. Similarly, those detecting CA-125 in blood or urine are used to monitor ovarian cancer, offering hope for early detection and improved outcomes [31].

- Monitoring Cancer Progression: After diagnosis, biosensors play a crucial role in monitoring cancer progression and, importantly, in assessing the effectiveness of treatment. The real-time tracking of biomarkers allows clinicians to observe changes in the tumour, identify metastasis, and evaluate responses to treatment [32]. Given the altered glucose metabolism in many cancer cells, a prime example is the use of glucose-based biosensors to monitor the metabolic activity of cancer cells. This continuous monitoring provides reassurance about the effectiveness of the treatment, giving hope to both patients and healthcare professionals [33].
- Personalized Treatment: The landscape of cancer treatment is evolving towards personalized therapy, with biosensors leading the way. These state-of-the-art tools aid in treatment decisions based on an individual's unique cancer profile [34]. By identifying and interpreting biomarkers such as mutations in the EGFR or KRAS genes, biosensors help clinicians select the most appropriate treatment plan. This increases the likelihood of success and significantly reduces the risk of unnecessary side effects, enhancing the patient's treatment experience and quality of life [3,35].
- Molecular Diagnostics and Biomarker Detection: Biosensors, designed to detect cancer biomarkers, offer a non-invasive and patient-friendly approach to diagnostics. Cancer cells release unique biomarkers that differ from those of healthy cells. These biomarkers, which can include proteins, are the key to early detection. Specific proteins like HER2, PSA (Prostate-Specific Antigen), and CA-125, each associated with a different type of cancer, can be detected by biosensors. Genetic mutations, such as those in the KRAS or TP53 genes, are unmistakable signs of certain cancers and

can be pinpointed by DNA biosensors. Even the small vesicles called exosomes, released by cancer cells and containing nucleic acids and proteins, can be detected by biosensors, offering a noninvasive method to monitor cancer progression [10,36].

- Monitoring Tumor Microenvironment: The tumour microenvironment (TME) plays a crucial role in cancer progression and therapy response [37]. Biosensors can be used to detect TME signals, such as (i) pH levels: tumor tissues often have a lower pH than normal tissues. The pH-sensitive biosensors can help monitor these changes and provide insight into tumour behaviour. (ii) Oxygen and glucose levels: tumor cells often exhibit altered metabolic activity, which can be tracked using biosensors that measure oxygen and glucose consumption in the TME. (iii) Matrix metalloproteinases (MMPs): these enzymes are involved in the degradation of the extracellular matrix and are often upregulated in cancer. Biosensors can detect the presence of MMPs in biological fluids [38].

Table-15: Describes the types of biosensors and their principle and applications. [77-131]

Category	Principle	Application
Electrochemical Biosensors	Measure electrical signals	Glucose monitoring, pathogen detection
Optical Biosensors	Light absorbance	Biomoelcues, DNA, protein interactions detection
Surface Plasmon Resonance	Detects changes in refractive index	Biomolecular interaction analysis.
Piezoelectric Biosensors	Detect mass changes via oscillation frequency shifts	Clinical diagnostics
Fluorescence-Based Biosensors	Use fluorophores	Cell imaging, tracking biological molecules
Microfluidic Biosensors	Miniaturized systems	Point-of-care diagnostics
Quantum Dot-Based Biosensors	semiconductor nanoparticles	Images and bio assay
Enzymatic Biosensors	Catalyze reactions	Different biomolecule detection
Photonic Biosensors	Photonic crystals	Biomolecule sensing
ELISA	Enzyme-labelled antibodies for colorimetric detection	Disease diagnostics, biomarker quantification

Figure-11: Wide range of biosensor applications and opertive mechanics.

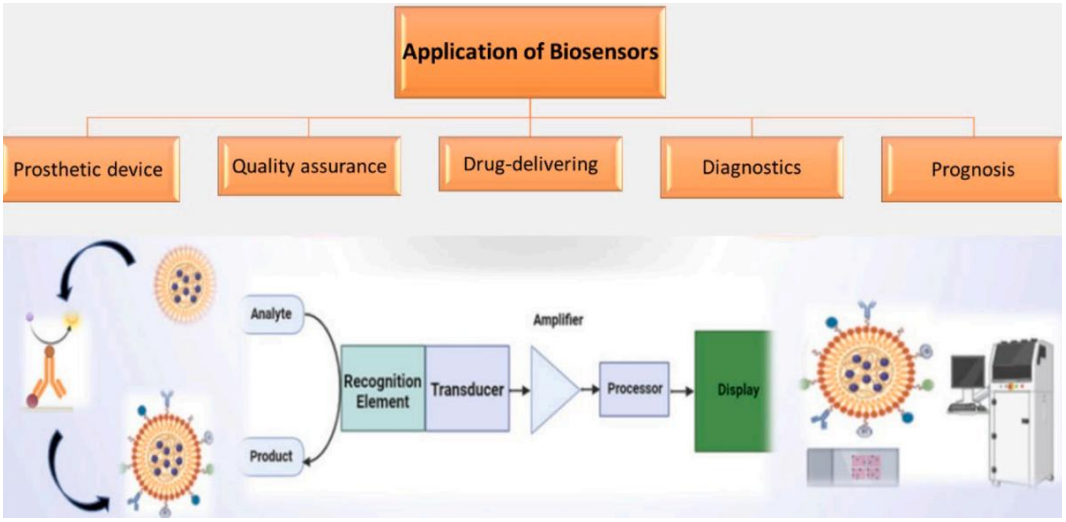


Table-16: Compative analysis of traditional vs advance approaches in clinical biosensors:[33-78]

Characteristics	Traditional biosensors	Advance Biosensors	Commercialized
Mechanism	Analyte, biomolecules, microfluidics enzyme linked, pH sensors . Less adaptable to automation, requiring manual intervention.	Molecular/omics level detection through electrochemical, optical, immunoassays, nanomaterials sensing. Easily integrated with IoT, AI, and lab-on-a-chip systems for smart diagnostics.	Cobas EGFR Mutation Test (Roche)
Biomarkers	Emerging biomarkers (microRNA, exosomes, novel protein signatures) present in tissue biopsy, blood etc.	Established cancer biomarkers (e.g., PSA, CA-125, CTCs, cfDNA) I pathological samples (blood, urine etc.)	FoundationOne Liquid CDx (Foundation Medicine)
Accuracy	Poor sensitivity, lack validation and variability in outcomes	Highly selective, specific and sensitive for particular marker in clinical samples (e.g., antibodies, enzymes, DNA probes).	OncoBEAM (Sysmex Inostics) Biocept CTC Test
Real-Time Monitoring	Time consuming, requires sample preparation and analysis leading to delays.	High throughout, rapid diagnosis, Multiplexing Ability	FoundationOne CDx (~10 days)
Cost	High costs due for translation to clinical use	Cost-effective, due to miniaturization and reagent efficiency.	Guardant360 (~$3500 per test)
Portability/Durability	Complex operation, Lab-based or portable prototypes, robust and stable under standardized lab conditions.	User-friendly, suitable for point-of-care diagnostics (PoC) and specific storage parameters	Cepheid GeneXpert
Regulatory Approval & Standardization	Standardized protocols ensuring reproducibility and reliability. Under trials phase with limited clinical validation	Emerging FDA approved technology for clinical trials, limited regulatory frameworks in some areas.	Guardant360 (Guardant Health), Epi proColon (Epigenomics)

The above tables and figures are illustrating that the biosensors are rapidly advancing cancer detection by providing fast, non-invasive testing, early detection, real-time monitoring, personalized treatment and cost-effective diagnostic solutions. The role of biosensors in personalized treatment is significant, as they provide a powerful and sensitive means of identifying cancers at early stages and tracking disease progression. Nanotechnology, advanced NGS sequence technology, AI, bioinformatics and molecular biology biosensor techniques are becoming increasingly accurate and accessible, making them a crucial tool in the fight against cancer. While challenges remain regarding sensitivity, standardization, and regulatory approval, the potential of biosensors to overcome these barriers in the coming years is promising and instils hope and optimism. With advances in nanotechnology, AI, and biomarker discovery, cancer biosensors are becoming more sensitive, accurate, and user-friendly, making them a critical tool in modern oncology. [140-144]

- Future perspectives and emerging AI trends in oncology:

advancements in big data analytics, AI, and customized treatments, the healthcare industry is poised for dramatic changes in the near future. These developments have enormous potential to optimize healthcare delivery, and improve patient care and health outcomes. AI-driven innovations are poised to transform diagnosis and treatment, with algorithms already enhancing medical imaging, predicting disease progression, and personalizing care. AI has demonstrated superior early detection capabilities, particularly in cancer, and is expected to further improve diagnostic precision and individualized treatment as it evolves.

Figure-12: Eight-point conceptual framework for translational AI in oncology[141]

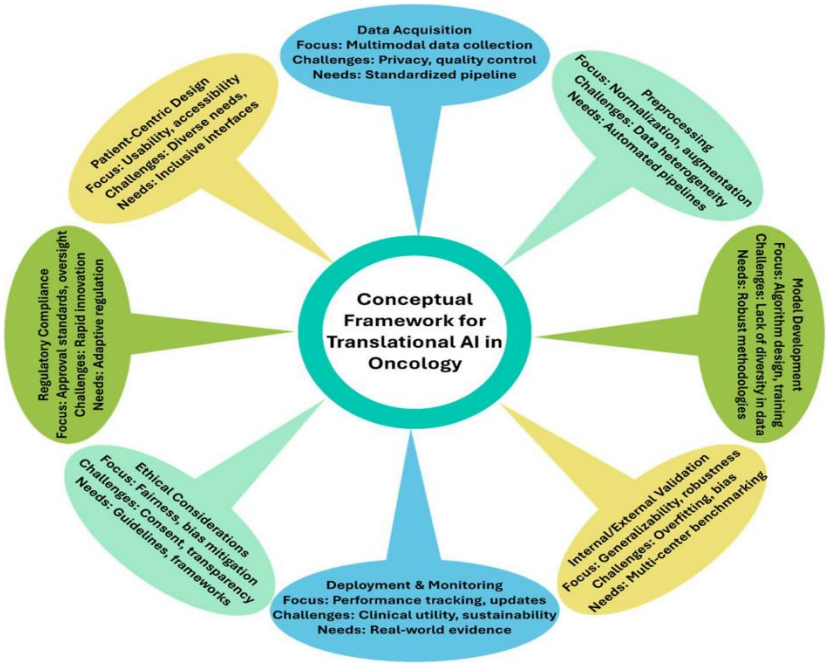


Figure-12, illustrating the framework which delineated eight critical areas required for effective AI deployment in cancer therapy: Data Acquisition, Preprocessing, Model Development, Internal/External Validation, Deployment & Monitoring, Ethical Considerations, Regulatory Compliance, and Patient-Centric Design. Each one is defined by its prime purpose, primary challenges, and strategic needs. All these dependent factors make up an end-to-end handbook for AI development toward safe, ethical, and equitable clinical release in oncology

Figure-13: Whole slide images from different cancer tissues are processed using diverse AI models [141]

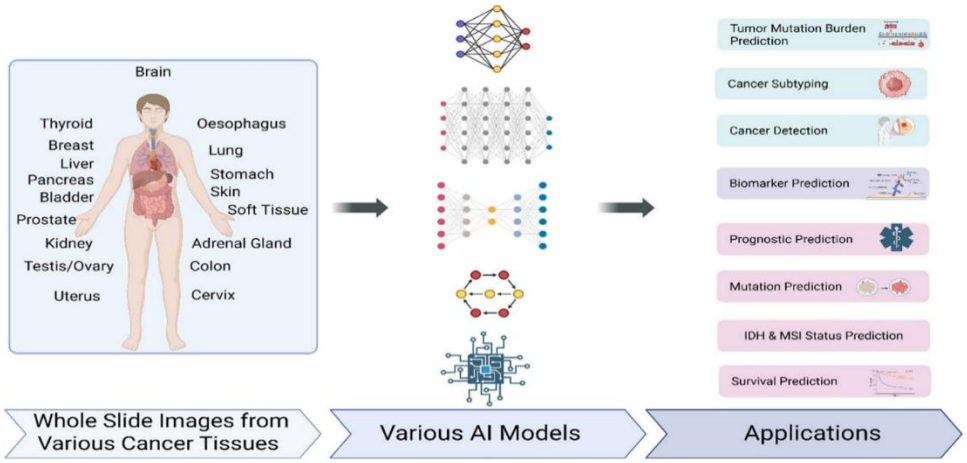


Figure-13, Illustrating the diverse AI models and key applications like cancer detection, subtyping, mutation and biomarker prediction, prognostic evaluation, and survival forecasting, advancing precision oncology through deep learning insights

- AI-Powered liquid biopsies and early cancer detection:

The identification and examination of liquid biopsy biomarkers, such as circulating tumor cells (CTCs) and circulating tumor DNA (ct)DNA, have made tremendous strides in the last 10 years. Their clinical utility in early cancer detection, disease monitoring, and therapy response evaluations have earned them acclaim (Fig. 5). The advent of liquid biopsies is beneficial since it provides a quick, real-time monitoring method that is minimally invasive and may be an alternative to conventional tissue biopsies. In environments with limited resources, the optimal liquid biopsy platform should correctly reflect the molecular heterogeneity of the patient's illness in addition to extracting more CTCs or ctDNA from a small sample volume [122].In liquid biopsies, small amounts of biofluids are collected to analyze components produced by cancer cells. Rich supplies of cancer biomarkers can be found in blood, saliva, urine, and cerebrospinal fluid. These biomarkers can exist in free form or be linked to other fluidsecreted structures. Liquid biopsies may make it easier to conduct dynamic studies of molecular or cellular biomarkers. Accurate early-stage diagnosis and prognosis, tracking the course of the disease, evaluating the effectiveness of certain treatments, and determining therapeutic goals for drug development are all made possible by liquid biopsies [123].

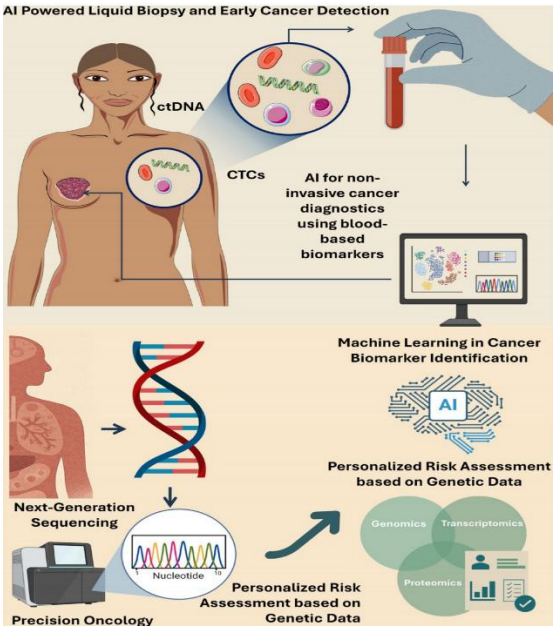
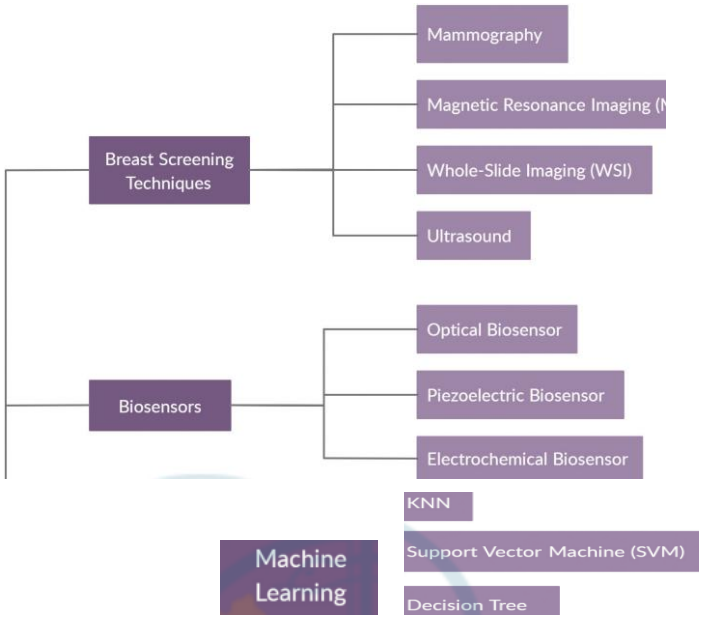


Figure-14: AI-powered liquid biopsy and genomic technologies for early cancer detection and personalized oncology. It highlights the use of circulating biomarkers (ctDNA, CTCs), next-generation sequencing, and AI/ML models to identify cancer biomarkers and assess individual risk using multi-omics data for precision treatment planning

A study compared the detection of different types of analytes such as HER2, miRNA 21, miRNA 155, MCF-7 cells, DNA, BRCA1, BRCA2, human tears, and saliva by using different types of biosensors including FET, electrochemical, and sandwich electrochemical, among others. The result of which was analysed on the basis of detection limit, linear ranges, and response time. Different studies and related articles were reviewed and analysed systematically, and those published from 2010 to 2021 were considered. Biosensors and ML both have the potential to detect breast cancer quickly and effectively [Figure-15]

Figure-15: Technologies used for breast cancer detection. (BIOSENSORS & AI-ML)[109]



6. CONCLUSION

Biosensors have developed significantly in recent years. Various technology developments, like nanotechnology, enhance the advance of biosensors. The nanotechnology has been used to design biosensors with higher selectivity and sensitivity. For example, a surface-enhanced Raman spectroscopy biosensor using silver nanoparticles and a colorimetric biosensor using gold nanoparticles. Varieties of novel and advanced biosensors have been designed to detect specific cancer biomarkers. Various biosensors are able to identify the same cancer. For breast cancer, the crystal fiber-based SPR biosensors could detect breast cancer cells with a high sensitivity of -289 RIU-1 for the refractive index, and the SERS biosensors could also diagnose breast cancer with 81% sensitivity. Moreover, a biosensor can also detect multiple cancers at the same time. A FEM-based surface plasmon resonance can detect various cancers using blood with a high accuracy rate, sensitivity, and specificity. A paper-based FRET biosensor can detect multiple cancer biomarkers with good sensitivity and high anti-interference, stability, and reproducibility. In the future, as science and technology continue to advance, an increasing number of easy-to-operate, highly sensitive, highly selective, miniaturized, multi-purpose, high-throughput, and efficient biosensors will be used to diagnose cancer biomarkers and applied to cancer diagnosis and treatment, especially early diagnosis. This review also highlighted the groundbreaking potential of AI with biosensor to revolutionize cancer care by making diagnostics, treatments, and patient management more precise, efficient, and personalized. With advances in nanotechnology, AI, and biomarker discovery, cancer biosensors are becoming more sensitive, accurate, and user-friendly, making them a critical tool in modern oncology.

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