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Review

Advancements in nanosensors for cancer detection

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Abstract: "Faster diagnosis, better outcomes: Biosensors pave the way for a brighter future for cancer patients". As one of the top causes of death worldwide, cancer must be addressed with the help of innovative treatments and state-of-the-art diagnostic techniques. Due to stress, poor lifestyle choices, and environmental factors, cancer incidence is worryingly on the rise in India, especially among the younger generation. In India, 1 in 5 persons may receive a cancer diagnosis by 2025, potentially impacting 1.57 million people, even though 30–50% of cancers are preventable. Even though standard screening techniques are frequently too costly and impracticable for everyday use, early detection is vital. Alternatives that show promise include emerging biosensor technologies, which give quick, accurate, and customized diagnostic results. Due to its capacity to quickly and automatically identify biological changes, ultra-sensitive biosensing systems utilizing single chips have revolutionized cancer detection. Since they are more effective than conventional techniques, point-of-care (PoC) biosensors—such as innovative nano-sensing devices for exosomal micro-RNA analysis—are becoming increasingly popular. Developing sophisticated diagnostic instruments like bio-computers and resonant mirrors is made easier by these biosensors, which combine analytes, receptors, and electrical sensors to detect cancer biomarkers in biological samples. The accuracy and usability of detection are further improved by advancements in wearable technologies, microfluidics, and electrochemical and graphene-based sensors. BrCyS-Q and NanoLiposomes provide improved photodynamic treatment and targeted medication delivery, respectively. Improved patient outcomes and early intervention are anticipated using the i-Genbox, a colorimetric sensor based on LAMP technology, and DNA-SWCNT-based sensors that further improve biomarker identification for gynecologic tumors.

Keywords: nano-sensors; cancer detection; biomarker detection; label-free detection; ultra-sensitive detection

Abbreviations: ABC-BPNN: Artificial Bee Colony-Based Backpropagation Neural Network; AI: Artificial Intelligence; ALD: Albumin; ALL-IDB: Acute Lymphoblastic Leukemia Image Database; ANN: Artificial Neural Network; ASH: American Society of Hematology; AuNPs: Gold Nanoparticles; BHCG: Beta Human Chorionic Gonadotropin; BCE: Before the Common Era; CA 125: Cancer Antigen 125; CA 19−9: Carbohydrate Antigen 19-9; CD63: Cluster of Differentiation 63 (a protein commonly found on exosomes); CEA - Carcinoembryonic Antigen; cfDNA : Cell-Free DNA; CNN: Convolutional Neural Network; CTC: Circulating Tumor Cells; CTCs: Circulating Tumor Cells; CRC: Colorectal Cancer; DNA: Deoxyribonucleic Acid; DNA-SWCNT: DNA-Single-Walled Carbon Nanotube; DBT: Digital Breast Tomosynthesis; DM: Digital Mammography; DOST: Discrete Orthogonal Stockwell Transform; ELISA: Enzyme-Linked Immunosorbent Assay; EPR: Enhanced Permeability and Retention; FDAZ: Food and Drug Administration; FACS: Fluorescence-Activated Cell Sorting; FICTION: Fluorescence Immunophenotyping and Interphase Cytogenetics as a Tool for Investigation of Neoplasms; FISH: Fluorescence in Situ Hybridization; HIA: Histological Image Analysis; HE4: Human Epididymis Protein 4; HPV: Human Papillomavirus; HPLC: High-Performance Liquid Chromatography; IoMT: Internet of Medical Things; IR: Infrared; KNN: K-Nearest Neighbors; LC: Lung Cancer; LDA : Linear Discriminant Analysis; L-MISC: Lung-Metastasis Initiating Stem Cells; LAMP: Loop-Mediated Isothermal Amplification; MACS: Magnetic-Activated Cell Sorting; MIM: Metal Insulator Metal; MISCs: Metastasis-Initiating Stem Cells; miRNA: MicroRNA; miRNAs: MicroRNAs; MM: Multiple Myeloma; MDR: Multidrug Resistance; NCD: Non-Communicable Diseases; NGs : Next-Generation Sequencing; NK Cells: Natural Killer Cells; NIR: Near-Infrared; NPs: Nanoparticles; PET: Positron Emission Tomography; PCA: Principal Component Analysis; PSA: Prostate-Specific Antigen; PS: Phosphoserine; PDT: Photodynamic Therapy; RNA: Ribonucleic Acid; RGO/AuNPs: Reduced Graphene Oxide/Gold Nanoparticles; ResNet-34: Residual Convolutional Neural Network with 34 layers; RF: Random Forest; ROS: Reactive Oxygen Species; SERS: Surface-Enhanced Raman Spectroscopy; SVM: Support Vector Machine; SWCNT: Single-Walled Carbon Nanotube; TEX: Tumor-Derived Exosomes; TEXs: Tumor-Derived Exosomes; U/ml: Units per Milliliter; VOCs: Volatile Organic Compounds; WBCs: White Blood Cells; X-rays: X-radiation (a form of electromagnetic radiation); YKL-40: Chitinase-3-like Protein 1

1. Introduction

Cancer cases are on the rise in India, especially among the youth. The country is facing a dire cancer epidemic. Some suggested causes include stress, environmental variables, and bad habits. It is noteworthy that although 30–50% of cancers are preventable, incidence rates are rising [1]. According to Jyotsana Govil of the Indian Cancer Society, 1 in 5 persons would experience cancer at some point in their lifetime. Globally, there were 20 million new cases of cancer and 9.7 million deaths in 2022. India's cancer burden is expected to reach 15.7 lakh cases by 2025, according to the Indian Council of Medical Research (ICMR), which will have a major negative influence on younger generations [2]. Early detection is essential because cancer is the primary cause of death worldwide. Conventional

screenings are expensive and not suitable for regular use.

With their great sensitivity and quick reaction, biosensor-based diagnostics present a potent substitute. With the promise of more individualized care and improved results, we focus on recent developments in electrochemical approaches for identifying cancer biosensors. To diagnose cancer accurately and quickly while minimizing errors and delays, data science must be integrated with genomic and proteomic data [3]. The significance of biosensors in cancer care has increased due to developments in molecular-targeted medicines and genomic profiling [4]. Therapeutic choices and clinical staging are guided by predictive and prognostic biosensor assays, notwithstanding the considerable obstacles to their clinical application. We cover the different stages in developing, validating, and implementing biosensors. We also identify important cancer cases, regulatory considerations, and potential future developments in big data analysis and precision medicine. New developments in nanotechnology have produced point-of-care diagnostic tools that lower mortality and enhance patient outcomes. Innovations like immuno-biochips for exosomal RNA detection and electrochemical biosensors hold promise for better cancer diagnosis [5]. Further investigation has enhanced cooperation between industry and academics and simplified rules to transform cancer diagnostics in India, facilitating prompt identification and better patient results [6].

In this review, we carefully examine a range of macromolecules present in biological samples, including DNA, RNA, exosomes, antigens, antibodies, and tiny molecules, to obtain a better understanding of the identification of cancer nanosensors. A worse prognosis and fewer treatment options may result from the low sensitivity, invasiveness, and delayed identification of traditional cancer detection techniques like imaging and tissue biopsy. On the other hand, the increasing corpus of research in the domains of molecular biology and biosensing technologies presents an opportunity to transform the paradigms of cancer treatment and detection. By utilizing this profound knowledge, we can greatly improve therapeutic approaches and diagnostic precision, which will eventually increase patient survival rates. This research initiative centers on these remarkable advancements in nanosensor technology, addressing the pressing need for more precise, sensitive, and non-invasive detection techniques. With their exceptional sensitivity and specificity, modern nanosensors produce outstanding results, especially when detecting malignancies in their initial stages (stages 0−1), thereby improving the survival rates chances close to 100% [7].

The use of nanosensors in cancer diagnosis has grown, particularly in conjunction with low-dose CT scans for the identification of lung cancer and the tracking of treatment [8]. For example, nanosensors are crucial to the treatment of several forms of lung cancer, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and general lung cancer [9]. The well-known epithelial marker cytokeratin 19 (CK19) is frequently used in clinical practice for tumor diagnosis, prognosis, and treatment [10]. Furthermore, as a non-invasive nanosensor for early cancer detection, extracellular vesicles like exosomes—which transport proteins and nucleic acids—have demonstrated remarkable promises. Exosomes have the potential to serve as helpful markers in diagnostic assays by mirroring the molecular state of the parent cells [11]. Due to their low cost, ease of use, and quick response time, colorimetric nanosensors are becoming quite popular in biosensing applications. Growing gold nanoparticles (AuNPs) on sporopollenin microcapsules (SP), a naturally occurring biopolymer generated from pollen, results in a unique nanosensor. Label-free exosome detection is made easier by functionalizing the SP-AuNP complex with CD63 aptamers [12,13]. The thermal infrared (IR) measurement, which takes advantage of the electromagnetic radiation qualities of IR released by heated objects, including the human body, is becoming a non-invasive and affordable

method for the detection of skin cancer [14,15]. This technique highlights the technological sophistication and usefulness of medical diagnostics by covering wavelengths from 800 nanometers to a few hundred micrometers. The convergence of these developments in nanosensor technology holds immense potential to transform the landscape of cancer diagnostics, enabling sooner identification and more efficacious interventions.

The development of nanosensor technology has also advanced to a higher level than that of first-generation cancer nanomedicines, which sought to enhance the accumulation of nanotherapeutics within solid tumors and decrease off-target effects through tissue-specific targeting. Using cell-specific targeting mechanisms, the second generation of cancer nanosensors aims to internalize tumor cells selectively and efficiently. The usual method for targeting tumor cells is to functionalize nanosensors with targeting moieties, which include small chemicals, peptides, carbohydrates, nucleic acid aptamers, and antibodies and their fragments. These moieties facilitate the conjugated nanosensors' cellular absorption by selectively binding to tumor-specific antigens or receptors on the plasma membrane. Additionally, there has been widespread interest in developing a promising biomimetic targeting method. A source cell's homotypic or heterotypic sticky characteristics can be transferred to nanosensors by coating nanoparticles (NPs) with plasma membranes produced from cancer cells, blood cells, or stem cells. The nanosensors' ability to target tumor cells precisely and effectively is improved by this method. For nanosensors to be as effective as possible in diagnosing and treating diseases while preventing multidrug resistance (MDR), they must be precisely delivered to their sites of action, usually inside organelles like the nucleus, mitochondria, and lysosomes. Organelle-targeted nanosensors, sometimes known as the third wave of nanosensors, are a state-of-the-art development in the field. To achieve greater sensitivity and specificity in cancer detection and therapy, these nanosensors are engineered to traverse precisely inside the cellular environment, focusing on certain organelles. This deliberate development in nanosensor technology is expected to significantly advance the continuing battle against cancer by improving the effectiveness of cancer diagnosis and treatment.

2. Cancer

Cancer's unchecked cell proliferation and potential for systemic metastasis make it the second most common cause of death globally and a serious health concern. While partially effective, traditional medicines such as chemotherapy and radiation therapy target both healthy and malignant cells indiscriminately. Human cells normally divide and grow in a controlled cycle, but age or injury can throw this cycle off during cancer, which can develop in any body part [16,17]. As cells age or incur damage, they undergo programmed cell death, enabling new cells to assume their functions. However, this regulated cycle can malfunction, leading to the proliferation of abnormal or damaged cells when it is inappropriate. These aberrant cells may aggregate to form tumors, which manifest as abnormal tissue masses. Tumors can exhibit cancerous or non-cancerous (benign) characteristics [18].

Approximately 5,000 years ago, in ancient Egypt, breast cancer was treated with cauterization instruments. Hippocrates, who used terminology like "karkinos" and "carcinoma" to characterize tumors, connected cancer to an overabundance of black bile in 460 BCE. Later, the Roman physician Celsus translated the phrase "cancer" into Latin [19,20]. Giovanni Morgagni's work on autopsies in 1761 contributed to our growing knowledge of cancer. Eventually, in 1775, Percival Pott connected chimney sweeps to testicular cancer, so establishing a connection between environmental causes and cancer [19,20]. These days, a third of cancer fatalities are linked to risk factors such as obesity, alcoholism, smoking,

poor food, and inactivity. About 30% of cancer incidences in low-income nations are brought on by infections like HPV and hepatitis [21]. The black bile idea of cancer was superseded by the lymph theory following the 17th-century discovery of the lymphatic system. Johannes Mueller recognized cancer as a biological phenomenon in 1838, and Karl Thiersch demonstrated how cancer progressed through the growth of malignant cells in 1860 [22,23]. Radiation therapy was developed by Wilhelm Konrad Roentgen's 1895 discovery of X-rays, which transformed cancer diagnostics [24]. Tumors, or neoplasms, are caused by a dysregulation of cell division. While some tumors are benign, malignant tumors cause great harm because they quickly spread and infect crucial organs [25,26]. The suffix "-oma" is frequently used in tumor classification to denote the origin of tissue or cell type [27].

Though conventional diagnostic techniques like biopsies and imaging have limitations that frequently result in late-stage diagnoses, early detection is essential for effective cancer care. This emphasizes how novel diagnostic strategies are required. Using the intricate network of secretory proteins in the bloodstream, advanced proteomic technologies may be able to detect diseases early and provide a better prognosis [28]. PSA, or prostate-specific antigen, is a good example of this change and offers important information about prostate cancer in its early stages [29]. Detecting early tumor markers in the blood, however, is very difficult because of their low quantities and the interference of common serum proteins such as albumin, which makes detection more difficult [30]. Sensitivity, expense, and complexity are issues with traditional techniques like high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assay (ELISA) [31]. For the detection and monitoring of cancer, nanotechnology offers a possible option by improving biosensor capabilities with remarkable sensitivity. Microcantilever biosensors are at the forefront of this innovation wave, utilizing sophisticated transduction mechanisms to translate molecular interactions into mechanical stress, thus enabling more accurate and focused cancer diagnoses [31].

3. Cancer detection

Cancer detection is a precise scientific endeavor focused on identifying cellular aberrations marked by unrestrained proliferation, invasion of adjacent tissues, and the potential for metastasis. This early detection is pivotal in oncology, as recognizing malignant transformations at an incipient stage greatly enhances therapeutic effectiveness and patient survival rates. Conventional diagnostic modalities, such as imaging and biopsies, while critical, often lack the sensitivity to detect early molecular alterations indicative of malignancy. Nanosensors—exquisitely engineered devices operating at the nanoscale—are at the forefront of revolutionizing cancer diagnostics. The first nanosensor, created in 1999 at the Georgia Institute of Technology using carbon nanotubes, set a precedent in molecular diagnostics by demonstrating how nanoscale interactions could be detected with unparalleled precision [32]. Unlike traditional diagnostic tools, nanosensors can discern minute physical or chemical fluctuations that correspond to early pathological transformations at the cellular and molecular levels. By detecting subtle structural or molecular shifts, these sensors can reveal budding oncogenic activity with exceptional sensitivity and specificity, often preceding visible tumor development on conventional imaging. [33].

3.1. Cancer detection techniques

Innovations fall into four major categories: Imaging modalities (like mammograms, CT scans,

and MRI scans) that offer detailed views of internal organs; biopsy procedures (like sigmoidoscopy for examination of the lower intestine and liquid biopsies for identification of cancer cells in bodily fluids); molecular and genetic techniques (like next-generation sequencing, or NGS, for cancer genetic analysis and fluorescence in situ hybridization for targeted DNA sequence identification); and proteomics, which studies protein networks within cells to find unique biomarkers linked to different cancer types [34−36]. For a transparent understanding of various detection methods, we have enclosed data in Table 1 with relevant theory below:

Table 1. Overview of available techniques for cancer detection.

SL. No	Type	Cancer Detection Techniques	Cancer Types	Key Components	Detection Limit / Wavelength	Year
1	Imaging Modalities	Magnetic Resonance Imaging (MRI)	Breast, lung, Gynecological Cancers (e.g., ovarian cancer, cervical cancer)	Strong magnets, radio waves, computer processing	High-resolution (submillimeter), radio frequencies	1980
2	Imaging Modalities	Digital Breast Tomosynthesis (DBT)	Breast cancer	X-rays, computer reconstruction	1 mm slices, low-energy X-rays	2011
3	Imaging Modalities	Sigmoidoscopy	Colorectal cancer	Flexible scope, air insufflation	Visible light (endoscopic view)	1960s
4	Biopsy Procedures	Liquid Biopsy	Non-small cell lung cancer, Colorectal cancer	Circulating tumor cells (CTCs), cell-free DNA	Detection of rare mutations (single-digit copies)	2014
5	Biopsy Procedures	Image-guided Biopsy	Bone cancer, prostate cancer	Imaging modalities (e.g., ultrasound, MRI)	Precise tissue targeting (millimeter scale)	1980s
6	Molecular and Genetic Approaches	Next-generation Sequencing (NGS)	Various cancers	Whole genome or gene panel sequencing	High throughput (millions of reads per run)	2005
7	Molecular and Genetic Approaches	Fluorescence In Situ Hybridization (FISH)	Multiple myeloma, others	Fluorescent probes	Specific DNA sequence identification (micrometer scale)	1980s
8	Proteomics and Cancer Biomarkers	Enzyme-linked Immunosorbent Assay (ELISA)	Gastrointestinal cancers, hepatocellular carcinoma, gestational trophoblastic diseases	Antigen-antibody binding	Optical density measurement (nanometer scale)	1971
9	Proteomics and Cancer Biomarkers	Mass Spectrometry (MS)	Multiple Myeloma, Leukemia, and various	Molecular profiling	Mass-to-charge ratio (atomic mass units)	2006

3.1.1. Imaging modalities

a. Magnetic Resonance Imaging (MRI): The non-invasive method known as Magnetic Resonance Imaging (MRI) produces finely detailed cross-sectional images of the body's internal components using powerful magnets in place of radiation [37]. MRI is helpful for spotting subtleties in soft tissues because it captures slices of the tissues from several angles, resulting in high-resolution images. This engineering aids in guiding treatment decisions, creating 3D images, and evaluating treatment efficiency by detecting cancer spread to nearby tissues or lymph nodes. Using multi-parametric MRI with gadolinium contrast reduces superfluous biopsies and identifies high-risk prostate cancer. Dynamic contrast-enhanced MRI enhances sensitivity in detecting invasive, high-grade tumors over mammography. Liu et al. informed the development of zwitterionic gadolinium (III) (Gd(III))-complexed dendrimer-entrapped gold nanoparticles (AuNP-DEN), functionalized with an arginine-glycine-aspartic acid (RGD) peptide, for enhanced dual-mode computed tomography (CT) and magnetic resonance (MR) imaging of lung cancer metastases. Given that 25–50% of clinical MRI scans utilize contrast agents (CAs), the study aimed to address the need for improved diagnostic tools [38]. The synthesized nanoparticles, with a core size of 2.7 nm and a surface potential of 7.6 ± 0.9 mV, demonstrated excellent X-ray attenuation properties, high longitudinal relaxivity (r_1) of 13.17 s^{-1} mM^{-1}, good cytocompatibility, and specific targeting to αvβ3 integrin-expressing cancer cells [38]. Hu et al. developed PFTQ-PEG-Gd-NPs, a water-soluble gadolinium-based theragnostic compound for tri-modal imaging (photoacoustic (PA), MR second near-infrared (NIR-II), and tumor photothermal therapy (PTT)). These nanoparticles exhibited significant cytotoxicity against 4T1 cells, with MTT assay results showing dose-dependent cell viability reduction. The PFTQ-PEG-Gd-NPs enhanced imaging contrast and induced tumor cell death via PTT, making them promising for cancer detection and therapy [39]. Gadolinium-based contrast agents (Gd-CAs) are widely used in MRI for tumor imaging with minimal adverse effects, as they lack iodine. Clinical studies demonstrate their dose-dependent enhancement of T1 and T2 images, confirming their dual contrast capabilities. To evaluate the PFTQ-PEG-Gd NPs, 4T1 cells were cultured in DMEM medium with varying nanoparticle concentrations, and cell viability was assessed using MTT assay. Tumor models were created by subcutaneously injecting 4T1 cells (~ 1×10^6) into mice, enabling tumors to reach ~80 mm^3 over 4–6 weeks. Neoplastic mice were administered PFTQ-PEG-Gd NPs (150 μL, 1 mg mL^{-1}), anesthetized, and placed in a dark chamber at 38 °C [39]. Tumor imaging was performed using the Vevo LAZR photoacoustic imaging (PAI) system, which showed effective accumulation of PFTQ-PEG-Gd NPs in tumor tissues, providing enhanced contrast and precise cancer detection [40].

b. Digital Breast Tomosynthesis (DBT): Digital Breast Tomosynthesis (DBT) is a mammography technology that uses numerous X-ray images taken at different angles to generate thin slices of breast tissue, roughly one millimeter thick. Compared to conventional 2D digital mammography (DM), this technique gives radiologists a better level of sensitivity and specificity when examining these slices for indications of breast cancer [41]. DBT, or 3D mammography, creates a thorough 3D image from a sequence of 2D images, which lowers false positive rates and improves cancer diagnosis, especially in dense breast tissue [42]. Slab viewing with changeable thickness can speed up the process while more thoroughly covering the full breast volume, even though DBT takes a longer interpretation time. DBT, which received FDA approval in 2011, has the potential to

overtake breast imaging standards. It is considered safe even if its radiation dose is less than three times that of a typical mammography. While there is a minor increase in radiation exposure, new tomo-synthesis systems can provide 2D images from 3D data equivalent to traditional mammograms. [43]. Lee et al. employed digital breast tomosynthesis (DBT) and full-field digital mammography (FFDM) in conjunction with transfer learning for breast cancer mass classification, demonstrating that transfer learning improved classification performance for both modalities. Their method achieved an AUC of 0.91 ± 0.03. The study focused on tumors ≤ 2 cm and > 2 cm, marking the critical transition between T1 and T2 stages in the TNM staging system, a distinction that is clinically significant as it often impacts treatment strategies and prognosis. The dataset was sourced from Soroka University Medical Center in southern Israel, with ethical approval from the local Institutional Review Board (IRB) (SOR0280-21). It included DBT images from female patients over 18 years, covering all breast density categories (A–D). Lesion sizes were confirmed through ultrasound imaging within six months post-DBT. Additionally, the model's performance was assessed by patient age (under and over 50) and breast density, reflecting the inverse correlation between age and mammographic density [44]. Housammi et al. conducted a systematic review and meta-analysis comparing digital breast tomosynthesis (DBT) with digital mammography (DM) for breast cancer (BC) screening. The evaluation, which is confined to screening and diagnostic outcomes, revealed that digital breast tomosynthesis (DBT) in conjunction with diagnostic modalities (DM) augmented the cancer detection rate (CDR), exhibiting a relative risk (RR) of 1.29 (95% CI 1.16–1.43). Moreover, a rapid synthesis of eight investigations juxtaposing DBT plus DM to DM alone indicated a statistically significant elevation in incremental cancer detection per 1,000 screenings: 3.9 (95% CI 2.7–5.1) within the homogeneous cohort and 1.4 (95% CI 0.9–2.0) across disparate participant groups. These findings rig the enhanced acuities into the virtue of DBT in bolstering breast cancer identification, particularly within populations characterized by dense glandular tissue. [45].

c. Sigmoidoscopy: A sigmoidoscopy examines the rectum and sigmoid colon, the lower part of the large intestine. This procedure screens for colorectal cancer and abnormalities like polyps, which can develop into cancer over time [46]. Atkin et al investigated causes of bowel issues such as bleeding or changes in bowel habits. During the procedure, a flexible sigmoidoscope with a viewing lens and tissue removal tool is inserted through the anus, and air is pumped into the colon to improve visibility. Abnormal growths can be biopsied or removed, and preparation involves clearing stool from the lower colon without extensive measures or sedation. Polyps are often removed directly, helping to reduce colorectal cancer risk [47]. A study by Otto et al. showed that sigmoidoscopy reduced the risk of colon cancer (Odds Ratio [OR] 0.56 [0.46–0.67]) and rectal cancer (OR 0.61 [0.49–0.75]). A population-based case-control study with 1,048 colon cancer patients also confirmed protective effects, especially in women (OR 0.53 [0.33–0.77]). Colonoscopy was more effective, showing significant reductions in CRC incidence, with ORs ranging from 0.23 [0.19–0.27] in Germany to 0.70 [0.57–0.87] in Canada. Large cohort studies further demonstrated a decrease in CRC mortality with colonoscopy, including an Ontario study (OR 0.69 [0.63–0.74]) and a Manitoba study showing a 29% reduction. Additionally, screening led to earlier cancer detection, improving survival rates [48].

3.1.2. Biopsy procedures

a. Liquid biopsy: Liquid biopsy is a novel, less invasive technique for cancer monitoring and detection that finds circulating tumor cells (CTCs) or cell-free DNA (cfDNA) in body fluids, including blood [49]. Liquid biopsy is a less invasive option for cancer diagnosis, prognosis, and therapy than standard biopsies, which involve the extraction of tissue using needles or surgery. We examine CTCs (circulating tumor cells) and cfDNA (cell-free DNA), two essential components of liquid biopsy. Although difficult to separate from healthy cells, CTCs (circulating tumor cells) are malignant cells that have broken free from a tumor and entered the bloodstream. Their presence shows signs of advanced cancer recurrence [50]. DNA fragments from tumor cells are among the DNA fragments that make up cfDNA (cell-free DNA) in blood. Valued insights into the features of cancer can be gained via cfDNA (cell-free DNA) mutation analysis [49]. NK cell DNA changes are identified as indicators for colorectal cancer (CRC) using Raman spectroscopy. Through machine learning approaches, a diagnostic model was created to accurately differentiate between individuals with CRC and healthy controls based on the methylation profiles of NK cells from CRC patients. This diagnostic workflow for CRC, depicted in Figure 1, integrates advanced molecular and spectroscopic techniques for precise detection and monitoring. The process begins with the localization of malignant lesions or polyps in the colon through endoscopic imaging or colonoscopy, enabling targeted analysis. A liquid biopsy, the minimally invasive diagnostic method, is then performed by collecting peripheral blood samples. These samples are analyzed to isolate key biomarkers, including CTCs, circulating tumor DNA (ctDNA), exosomes, and non-coding RNAs (ncRNAs), which are indicative of CRC onset and progression. The biomarkers undergo evaluation using Surface-Enhanced Raman Spectroscopy (SERS), a technique that significantly enhances vibrational signals to detect cancer-specific molecular alterations. A nano-sensor, as illustrated in the figure, targets epigenetic modifications, specifically aberrant DNA methylation in Natural Killer (NK) cells exposed to CRC [51]. Methylation, involving the addition of methyl groups to DNA, induces changes in vibrational energy levels, creating unique Raman spectral signatures. The Raman spectra depicted in the figure distinguish between CRC-affected and healthy samples. The red spectrum corresponds to hypermethylated DNA from CRC-affected samples, exhibiting characteristic shifts in Raman intensity, while the blue spectrum represents unmethylated DNA from healthy controls. These spectral differences reflect the aberrant methylation profiles that are hallmarks of CRC. An indirect SERS-based detection method for circulating tumor cells (CTCs) was developed by Paloro et al., integrating microfluidics with silver nanostructure SERS tags functionalized with Raman-active molecules and affinity biomolecules. This approach enabled the sensitive identification of tumor cells among non-tumor cells through distinct Raman signatures. In colorectal cancer (CRC), SERS was applied to 430 metastatic patients, using immunomagnetic separation to isolate CTCs pre-treatment and during therapy. Results showed that unfavorable CTC profiles before treatment correlated with poorer progression-free survival, demonstrating their prognostic value [52]. Earlier, Sha et al. (2008) combined EpCAM-conjugated magnetic beads with HER2-functionalized SERS tags to detect breast cancer cells (SKBR3), achieving a limit of detection (LOD) of 50 cells/mL. This method was later validated for head and neck cancer, detecting CTCs at concentrations as low as 5 cells/mL without additional sample processing. In 2016,

SERS further advanced by detecting CTCs at an LOD of 1 cell/mL, eliminating the need for enrichment steps, and showcasing its high sensitivity and versatility for cancer diagnostics.

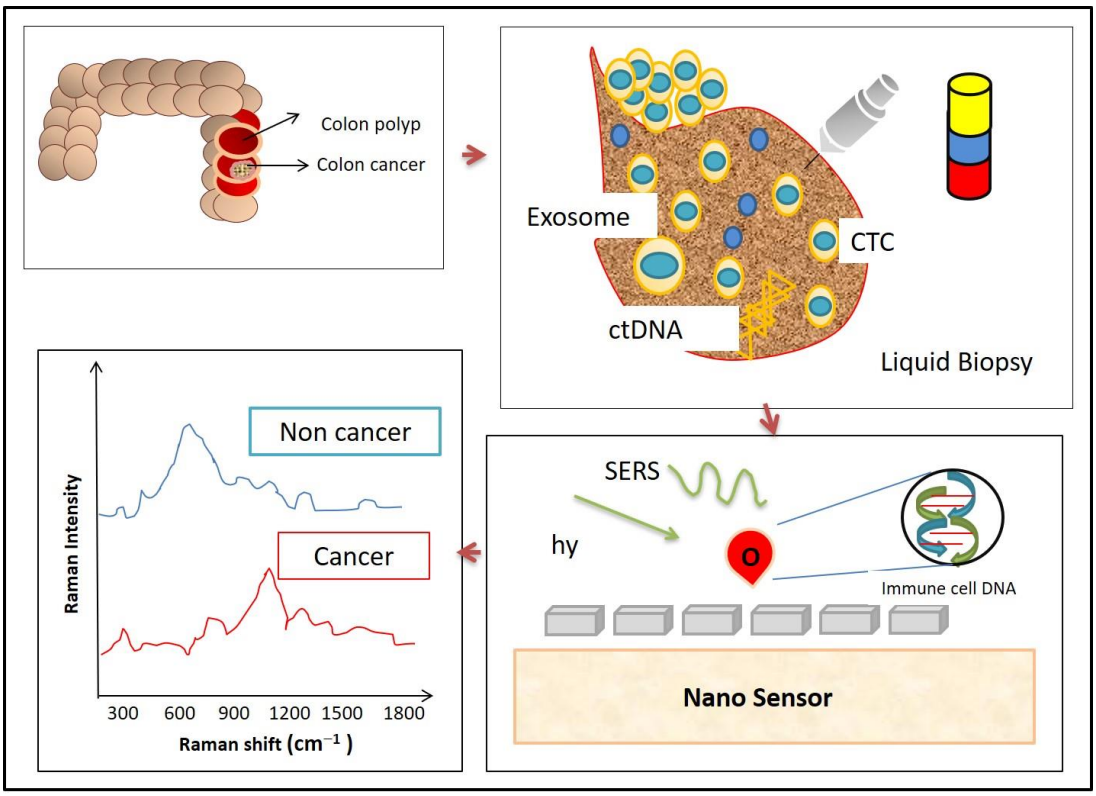

Figure 1. DNA Signatures on tumor-associated sodium potassium cells.

b. Image-guided biopsy: The importance of tissue samples for precise diagnosis and differentiation of benign abnormalities from cancers is highlighted by recent developments in breast imaging. Percutaneous biopsies enable customized treatment plans based on imaging results and tumor characteristics and offer conclusive histological confirmation, avoiding needless operations and their risks and expenses. Technical alternatives include vacuum-assisted biopsy (VAB), core needle biopsy (CNB), and fine-needle sampling (FNS). Image-guided techniques, such as CNB and VAB, have been shown to have higher sensitivity and specificity than non-imaging-guided biopsies [53]. Comparing CNB to open surgical biopsy, fewer risks and problems are involved. Validating a navigation grid for image-guided interventions has shown measurable gains in precision, reduced radiation exposure, and shorter procedural times, though randomized trials are scarce. Fischer et al. demonstrated improved accuracy, fewer needle inspections, and reduced targeting time using electromagnetic (EM) navigation over conventional CT-guided biopsies [54]. Ciliberti et al. highlighted personalized imaging and biopsy techniques based on lesion characteristics, anatomical location, and molecular study requirements. FNAC samples were prepared with Diff-Quik and Papanicolaou staining, while core needle biopsies underwent formalin fixation, paraffin embedding, and immunohistochemical analysis (e.g., S-100, MART-1) when necessary [55]. Pathologists classified lesions as metastatic, suspicious, or inconclusive. Among 600 biopsies on 460 patients (41.3% women, 58.7% men), the mean interval from

melanoma diagnosis to biopsy was 40.7 months (SD 48.9), with a median follow-up of 3.7 years (IQR 1.5–7.7). Sensitivity and NPV were lower for CT-guided biopsies, sub-centimeter lesions, and lymph nodes in the inguinal or iliac regions. Vilana et al. reported 99% sensitivity for metastases > 10 mm, compared to 94.6% for lesions < 10 mm, underscoring challenges with smaller targets [56].

3.1.3. Molecular and genetic approaches

a. Next-generation Sequencing (NGS): Next-generation sequencing (NGS), which provides a thorough and quick method of examining genomic data, has changed cancer detection methodology. Unlike conventional techniques, NGS can quickly and accurately sequence a whole genome or individual gene panels, giving physicians a comprehensive understanding of the genetic composition of cancers [57]. The primary objective of cancer genomic profiling tests is to guide treatment strategies rather than serve as diagnostic tools. However, in a global study of 5,749 patients with soft tissue sarcomas, genomic profiling facilitated diagnostic refinements by identifying fusion genes in 2% of cases and enhancing histological classification in another 2% [58]. In Japan's TOP-GEAR project, the NCC Oncopanel test detected MDM2 amplification in 2 of 187 cases, contributing to the identification of dedifferentiated liposarcomas. A prospective cohort study in 42 patients with post-treatment-resistant gastrointestinal cancers demonstrated that cfDNA analysis detected resistance-related genetic alterations in 76% of cases, surpassing tissue biopsy, which identified such mutations in only 48% of matched samples. Remarkably, cfDNA uncovered resistance mechanisms in 87% of cases, highlighting its diagnostic sensitivity over tissue-based methods [59]. NGS-based ctDNA assays are increasingly recognized for their diagnostic potential, particularly in detecting acquired resistance-associated genomic aberrations. By enabling minimally invasive, repeatable testing, cfDNA assays reduce the physical burden of tissue biopsies and improve detection rates, as evidenced in cases like osimertinib resistance in EGFR T790M-positive non-small-cell lung cancer [59]. This in-depth analysis of genetic data improves patient care overall, diagnosis, and therapy planning. Millions of DNA fragments can be sequenced through NGS, making it possible to analyze enormous volumes of genetic data effectively. Moreover, NGS enables focused sequencing of genes linked to specific malignancies, providing a quick and affordable screening choice. With comprehensive genetic data from next-generation sequencing (NGS), physicians may practice personalized medicine by customizing treatment regimens to the specific genetic makeup of each patient's cancer [60]. This approach maximizes efficacy while reducing side effects.
b. Fluorescence in Situ Hybridization (FISH): When it comes to gene mapping, oncogene detection, and the identification of specific DNA sequences that are aberrant in malignancies, fluorescence in situ hybridization (FISH) is a highly dependable method [61]. FISH is essential for risk stratification in multiple myeloma (MM), detecting high-risk markers that influence therapeutic options and prognosis, such as t (4; 14), t (14; 16), deletion 17p, t (14; 20), and gain 1q. By resolving the difficulties of cytogenetic testing, techniques including fluorescence-activated cell sorting (FACS), magnetic-activated cell sorting (MACS), and FICTION can improve the accuracy of FISH analysis [62]. These developments highlight the importance of FISH in enhancing therapy regimens and enhancing prognoses for MM and other malignancies.

3.1.4. Proteomics and cancer biomarkers

For proteins, proteomics resembles a fingerprint scanner. It examines the enormous protein network found in tissues and cells. Since cancer alters these protein networks, this information is important for cancer research. Certain proteins, either by themselves or in altered amounts, are known as cancer biomarkers. Proteomics facilitates the identification of these distinct protein fingerprints linked to various cancer types [63]. Through the examination of these protein patterns, researchers may be able to create novel tests: Early cancer detection is important, even before symptoms arise; keep track of a patient's reaction to medication; and determine who is most likely to develop cancer.

a. Enzyme-linked Immunosorbent Assay (ELISA): When it comes to finding cancer protein biomarkers in clinical diagnostics, the enzyme-linked immunosorbent test (ELISA) is the gold standard [64]. A solid surface containing a cancer-specific antigen is immobilized in ELISA, to which antibodies from the sample can attach to it. When a secondary enzyme-linked antibody correlates the quantity of antigen with a detectable signal, ELISA is a useful tool for identifying cancer. Raised levels of the fat-storage protein perilipin-2 have been associated with renal cell carcinoma (RCC) in recent research. By identifying perilipin-2 in urine samples, which may reveal the existence of RCC early on, ELISA is utilized for non-invasive cancer screening [65]. Additionally, perilipin-2 levels can be tracked over time by serial ELISA testing, which helps to assess treatment response. In 2010, Rissin, Walt, and colleagues revolutionized digital ELISA using optical fiber etching to create uniform microarrays, improving the limit of detection (LOD) compared to traditional ELISAs. They used antibody-conjugated magnetic beads and microarrays to detect prostate-specific antigen (PSA) with attomolar sensitivity. The PSA sample was diluted to achieve a Poisson distribution, where approximately one PSA molecule was present per ten beads [66]. Immunocomplexes were formed by labeling bead-captured PSA with biotinylated antibodies and streptavidin-β-galactosidase. Beads were then transferred to microarrays with thousands of 4.5 μm diameter wells, each holding a single bead. Fluorescent signals were generated upon substrate conversion, enabling detection. The commercial Simoa® analyzer developed by Walt et al. transferred only ~5% of magnetic beads, leading to Poisson noise and measurement uncertainty. To overcome this, the team improved digital ELISA using bead drop casting on microscope slides, which increased sampling efficiency to 40–50%. This approach, combined with rolling circle amplification, improved the LOD by 3 to 25 times for interleukins and showed superior sensitivity for detecting Brachyury in chordoma and chondrosarcoma patients compared to the commercial platform [67]. Liu and colleagues advanced digital ELISA further with droplet digital ExoELISA, which enabled low-LOD detection of patient samples. This method combined magnetic bead isolation of CD63+ extracellular vesicles (EVs) from breast cancer patient sera with β-galactosidase-conjugated anti-glypican-1 (GPC1) antibodies. Immunocomplexes and substrate were encapsulated in droplets, and fluorescent signals were generated upon incubation. The ExoELISA demonstrated a 5–7-fold increase in CD63+/GPC1+ EV levels in breast cancer sera, showing its diagnostic potential [68]. Example include: A marker called carcinoembryonic antigen (CEA) is a specific tumor, such as colorectal cancer [69]; CA 19−9: Used to track and identify gastrointestinal and pancreatic malignancies [70]; and CA 125 and CA 15−3: Increased levels could be a sign of ovarian and breast cancer, respectively [71].
b. Mass Spectrometry (MS): To examine molecular components in tissues or bodily fluids for biomarker research, mass spectrometry (MS)-based clinical proteomics uses profound-edge

technologies. Clinical proteomics, which directly measures proteins—which are essential for comprehending cancer progression and finding biomarkers—more precisely depicts human disease dynamics than data from cancer cell lines or animal models. A subclass of MS-based methods called expression proteomics measures the amount of protein in organelles, biofluids, and cellular compartments. It picks up on post-translational changes like phosphorylation, which are important for signaling and the development of cancer [72]. Novel mass spectrometry methods profile clinical specimens, exposing different protein patterns between tumor and normal tissue, which are essential for detecting discrete tumor signatures and comprehending protein-level genetic effects. Petricoin et al. (2002) employed surface-enhanced laser desorption-ionization time-of-flight mass spectrometry (SELDI-TOF MS) for ovarian cancer detection, identifying blood-based protein biomarkers. This proteomic approach has extended to lung cancer diagnostics, showing protein markers as a superior diagnostic tool over genomic analysis [73]. In clinical trials, Lilley et al. (2004) used two-dimensional gel electrophoresis and mass spectrometry on lung cancer tissues, uncovering novel biomarkers for early detection [74]. Chen et al. (2002) identified nine enzyme proteins elevated in lung adenocarcinoma (ADC) using MALDI MS. In a clinical validation, Chen et al. (2019) found PGK1 to be a survival predictor in stage I lung ADC using proteomics and tissue microarrays, confirmed in clinical trials with 117 ADC and squamous cell carcinoma (SCC) tissues [75,76].

Example: A blood test called EarlyCDT examines a patient's immune system to determine whether or not they have an early-stage malignancy. It assesses a patient's immune response using a sophisticated biosignature and may be able to identify up to 15 different malignancies, even if it does not use MS [77].

3.2. Role of sensors

Biomedical sensors are indispensable constituents of biomedical systems. They function solely as detectors and with transducers, converting intricate biological signals into digital outputs for refined computational analysis. Contrary to conventional sensors that merely measure physical parameters, biomedical sensors act as the crucial interface between living organisms and digital systems, thus enabling the seamless assimilation of biological processes with supreme technological structure. In the context of cancer detection, these sensors are crucial in identifying biomarkers, monitoring tumor progression, and assisting in the early diagnosis of various cancer types. Sensors can be classified into three principal categories: physical, chemical, and biosensors. Physical sensors, such as piezoelectric, temperature, photoelectric, and acoustic sensors, quantify physical phenomena, which can be tapped to monitor changes associated with tumor growth. Chemical sensors, including humidity sensors, electrodes, and optical gas sensors, detect specific chemical variables, such as the presence of tumor-specific metabolites or volatile organic compounds, which can serve as biomarkers for cancer. Biosensors, which synergize both physical and chemical sensing modalities, include devices like gravimetric, pyroelectric, and optical photoelectric sensors, facilitating cancer detection through the identification of specific biomarkers or cellular changes. Upon detecting a change in the input variable, the sensor generates a corresponding output signal, which may be optical, electrical, or in some other format. This signal is subsequently received by a microcontroller or microprocessor, which processes the data further. In cancer diagnostics, this processed data can be used to quantify tumor markers, detect early signs of cancer, or track the efficacy of treatments. Sensors are vital components of

measurement systems, typically positioned at the outset of the system's block diagram. They interface directly with the measured variables to produce reliable, accurate output data, forming the foundation for subsequent processing and analysis in cancer detection and monitoring [78].

Envision a small gadget that can conveniently and rapidly identify cancer in its early stages. Biosensors have great promise for the diagnosis of cancer. In the body, biosensors function like detectives, with some parts being vital (Figure 2 (a)):

a. Target: The culprit—cancer cells or specific molecules associated with cancer (analyte).
b. Recognition Unit: Like a detective's fingerprint scanner, this biorecognition element (often a protein or antibody) identifies the target molecule.
c. Signal Converter: Similar to a fingerprint match triggering an alarm, the transducer converts the molecular recognition into a measurable signal (electrical, optical, etc.).
d. Signal Processor: The electronics unit acts as the detective's team analyzing the alarm, amplifying the signal, and converting it into a digital format for easy interpretation.
e. Results Display: Finally, the display presents the findings—a visual image, graph, or table—indicating the presence and level of the cancer marker.

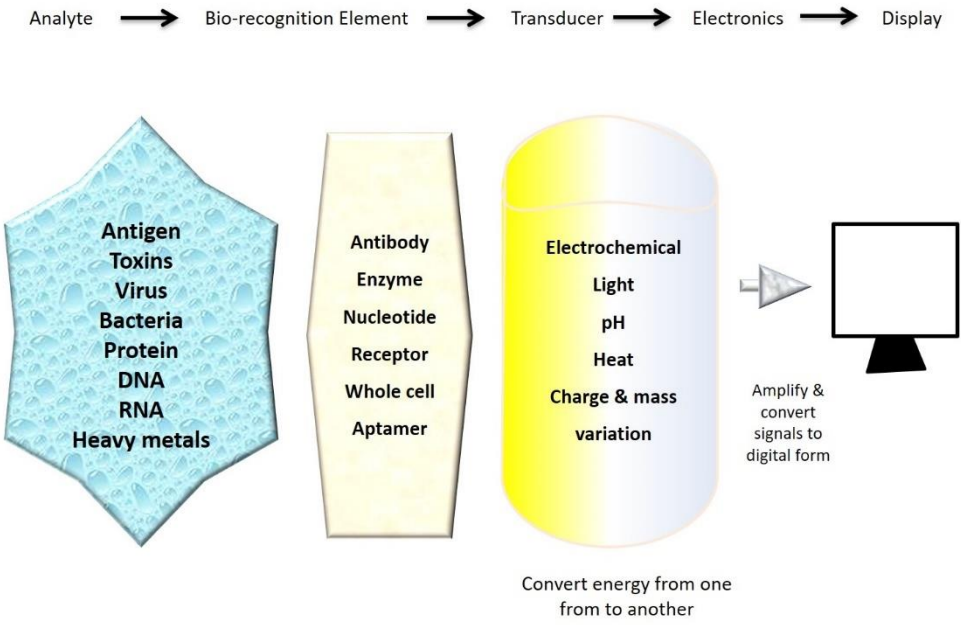

Figure 2 (a). Working of biosensors.

As Figure 2(a) illustrates, biosensors work through a multi-step process involving a biorecognition element, a transducer, and electronic output.

Together, these enable the detection and quantification of specific analytes. The glucose biosensor case study offers a comprehensive understanding of the process. The glucose biosensor utilizes glucose oxidase (GOx) as the biorecognition element, which selectively binds glucose, catalyzing its oxidation to produce hydrogen peroxide (H_2O_2) and gluconic acid. Immobilized on an electrode, GOx interacts with glucose in the sample. The transducer, electrochemical in nature, detects the current generated when hydrogen peroxide is oxidized at the electrode surface. The

current intensity correlates directly with glucose concentration, providing a quantitative measurement. The electrode, typically platinum, gold, or carbon, serves as the interface between the biorecognition element and the electronic system. The electronic system amplifies and processes the signal, converting it into a readable output on a digital display, indicating glucose concentration in mg/dL or m.mol/L [79]. Alerts may be included for abnormal glucose levels, assisting in patient management.

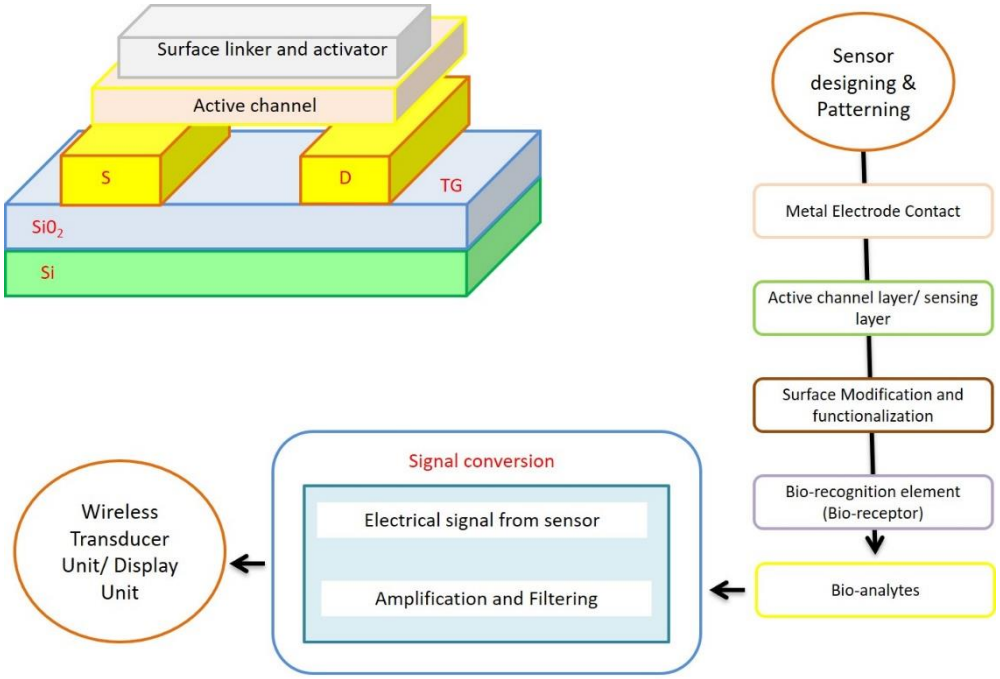

Figure 2 (b). A biosensor based on Field-Effect Transistor (FET).

An FET biosensor can be up to 20 times cheaper than the traditional ELISA (Enzyme-Linked Immunosorbent Assay), as demonstrated by Sungkyung et al., who used paper and multi-walled carbon nanotubes as the substrate. The sensor surface was functionalized with a prostate-specific antigen (PSA) antibody, and the binding levels of PSA and its antigens were indirectly detected by measuring resistance changes. The sensor's sensitivity and detection range make it ideal for early-stage detection and diagnosis of prostate cancer, with a detection limit of > 4 ng/mL of PSA [80]. In another study, Ding et al. developed a dual-aptamer decorated graphene FET nanosensor for specific detection of hepatocellular carcinoma (HCC)-derived microvesicles. For target-specific binding and detection of HepG2 microvesicles (HepG2-MVs), both epithelial cell adhesion molecule (AptEpCAM) and sulfhydrylated HepG2 cell-specific TLS11a aptamer (AptTLS11a) were attached to gold nanoparticles (AuNP) via Au−S interactions. The fabricated sensor exhibited a broad linear output, ranging from 6×10^5 to 6×10^9 particles/mL, with exceptional sensitivity of 84 particles/μL for detecting HepG2-MVs [81]. The diagram illustrates the working of an optical biosensor, where biorecognition elements such as antibodies, nucleic acids, or enzymes are immobilized on a surface, typically a waveguide or fiber-optic sensor. The bioreceptors are crucial in target selectivity and specificity, as they bind to the target analyte of interest while discriminating against coexisting

molecules or substances in complex biological samples, as depicted in Figure 2(b). The selectivity, specificity, and sensitivity of the sensor are also influenced by the Debye screening length, which depends on the size of the bioreceptors used. When the analyte binds to the biorecognition element, it induces measurable changes in optical properties such as absorption, reflection, or fluorescence. These changes are detected using methods like Surface Plasmon Resonance (SPR) or fluorescence-based optical biosensors [81]. In SPR, light is directed at a metal surface, where it interacts with the surface-bound recognition element. The binding of the target analyte alters the refractive index, changing the reflection angle, which correlates with the concentration of the analyte. In fluorescence-based biosensors, fluorescent tags attached to the recognition element emit light upon analyte binding, and the intensity of the emitted light is proportional to the analyte concentration. The changes in optical properties are then converted into an electrical signal by a photodetector. This signal is processed, amplified, and displayed on an output screen, providing real-time, non-invasive detection of the analyte's concentration. Optical biosensors are crucial in cancer diagnostics, where they detect biomarkers such as human epidermal growth factor receptor 2 (HER2) or tumor protein p53 (TP53) in blood or tissue. These biomarkers are indicative of cancers such as breast cancer, lung cancer, and prostate cancer, facilitating early diagnosis and monitoring the efficacy of treatments.

Cancer alters normal cell activity at the molecular level, producing unique biomarker traces, as seen in Table 1. These biomarkers can be found by biosensors, providing information about the kind and prevalence of cancer. An outline of the biomarkers that biosensors target is provided below:

a. Protein biomarkers

The workhorses of cells and proteins are vital to many different biological functions. Cancer can change the function or synthesis of proteins. It is possible to develop biosensors to identify particular proteins linked to cancer. As an early warning sign for the illness, a biosensor may, for example, target a protein that is overexpressed in specific tumors.

b. DNA markers

Our DNA's genetic code controls how our cells operate. It is recognized that certain malignancies are associated with mutations in particular genes. These mutations can be accurately detected by biosensors that are tailored for them. Biosensors can detect genetic changes that could point to the existence of cancer or susceptibility to it by examining DNA samples.

c. VOC markers

A complex variety of volatile organic chemicals (VOCs) indicative of the body's metabolic activities can be found in our breath. These metabolic pathways can be altered by cancer, which can modify the VOC profile. Breath analysis biosensors may be able to identify these distinct VOC signatures linked to particular cancer types [82]. This provides a non-invasive screening method for the early identification of cancer.

Advantages of sensors in the cancer-killing world:

a. Early Detection: Early-stage malignancies may go undetected by conventional approaches like biopsies and imaging. Because biosensors are so sensitive, they can identify the smallest amounts of particular cancer biomarkers (DNA mutations, proteins, etc.) in samples such as breath or blood. This enables early diagnosis when the benefits of treatment are greatest.
b. Faster Results: The start of treatment may be delayed by days or weeks for traditional procedures. However, biosensors can yield data in minutes to hours, enabling prompt and better-informed treatment decisions.

c. Accessibility: Conventional procedures frequently call for spaces like hospitals and specific equipment. Clinics and even homes can use biosensors because of their potential for downsizing and point-of-care testing. Patients can now be more easily accessed, particularly in environments with limited resources.
d. Techniques that are Non-invasive or Minimally Invasive: Biopsies and some imaging methods
e. might cause discomfort or be intrusive for patients. Biosensors can often assess bodily fluids such as breath or blood, obviating the necessity for such operations. As a result, the procedure is more patient-friendly.
f. The potential of biosensor technology lies in its ability to identify the precise mutations or indicators linked to a patient's cancer, thus contributing to the development of tailored medication. For better results, this can direct individualized treatment programs.
g. Wearable biosensor advancements present the possibility of constant monitoring of cancer biomarkers once they are inside the human body. This makes rapid intervention possible and enables early diagnosis of recurrence.

4. Nanosensors

A length of about one nanometer (nm), or one billionth of a meter (0.000000001 m or 10^{-9} meters), is what is meant by "nano" in terms of nanosensor operation. When particle behavior and attributes are detected at the nanoscale, nanosensors are instruments that can transport data and information to the macroscopic level, where it can be employed and studied. Utilizing nanosensors, one may monitor physical factors like temperature at the nanoscale or identify chemical or mechanical information like the existence of chemical species and nanoparticles. Based on their composition and intended use, nanosensors can be categorized. Two types of nanosensors exist based on their structural differences: Optical and electrochemical nanosensors. They are classified as chemical, biosensors, electrometer, and deployable based on their applications and usage. Nanosensors, minuscule sensors measuring below 100 nanometers, offer groundbreaking applications in medicine, healthcare, and beyond. Their potential applications span from wearables to aerospace and defense industries [83]. Compared to traditional methods, nanosensors promise greater precision, speed, and cost-effectiveness in measurements. Nanosensors, microscopic powerhouses in the fight against cancer, hold immense promise for early detection. Unlike traditional methods that often miss the disease until symptoms appear, nanosensors have the potential to identify cancer biomarkers at their earliest stages, even before symptoms arise. This revolutionary capability could fundamentally transform cancer diagnostics by enabling interventions at a critical window when treatment success rates are highest. Nobel physicist Richard P. Feynman predicted that nanotechnology would transform industries such as biotechnology and medicine and might pave the way for nanorobots that can do complex molecular jobs [84]. This includes potential uses for nanodevices in cancer treatment, where they might be used to detect and target cancer cells with previously unheard-of levels of precision. Feynman's visionary insight underscores the revolutionary potential of nanotechnology in improving diagnosis, therapy, and the development of tiny tools specifically designed to fight cancer at the molecular level. Nanorobots can identify and eradicate illnesses in the body thanks to the development of minute sensors and actuators, which are essential to IT infrastructure [85]. By moving the focus from treatment to prevention, these gadgets hold great medical potential. In contrast to conventional chemotherapy, which impacts both malignant and healthy cells, tailored medication delivery made

possible by nanotechnology lowers toxicity and enhances treatment results.

Working principle: Nanosensors are sensitive instruments for cancer detection because they function at the single-molecule level. They are made up of a transducer, detector, and sensing layer. The sensing layer binds to cancer biomarkers and changes its physicochemical properties in response to biomarkers. After detecting the change, the transducer transforms it into an optical or electrical signal. Early identification of the development or progression of cancer is made possible by this signal, which shows the existence of the biomarker even at low concentrations [86].

Features: 1 Conceptualization and design: To find minute levels of cancer biomarkers in blood, breath, or other samples, scientists created nanosensors with extraordinary sensitivity and selectivity. To identify a biomarker in blood samples at low concentrations while maintaining high sensitivity, a team might, for example, create a nanosensor that selectively targets a protein linked to breast cancer.

2. Selection of nanomaterials: Selecting the right nanomaterials is essential. Specific sensors may employ gold nanoparticles due to their capacity to attach to proteins particular to cancer, whereas other sensors may make use of carbon nanotubes due to their remarkable electrical characteristics.

a. Gold nanoparticles: Gold nanoparticles are a popular option because of their biocompatibility and ease of binding to biomolecules. Businesses like Nanodiagnostics Solutions are developing nanosensors by functionalizing gold nanoparticles with antibodies specific to cancer indicators. In biological materials, these sensors can draw in and identify these markers [87].
b. Carbon nanotubes: These nanostructures are cylindrical and have special electrical characteristics. Businesses such as NanoIntegris are developing nanosensors the conductivity of the carbon nanotube surface is changed when a cancer biomarker binds to it. The presence of the change in conductivity can then be determined electrically [88].

3. Sensing mechanism: Mechanisms specific to the intended biomarker are given priority in the design. When a protein attaches itself to the surface of a sensor, for example, the sensor may use an electrical sensing mechanism to detect changes in conductivity. Electrical Sensing, as previously indicated, several cancer-detection nanosensors rely on electrical signals. Businesses such as Roche Diagnostics are investigating electrical biosensors, in which the conductivity of the material is changed when a cancer biomarker attaches to the sensor's surface [89]. Electronic measurement of this change in conductivity yields a signal suitable for detection. The following types of biosensors and their respective sensing mechanisms are designed to detect a high range of biological analytes:

a. Fluorescence-Based Biosensors (Quantum Dot-Based Biosensors)
   Mechanism: Fluorescence-based biosensors use optical sensing to detect changes in fluorescence intensity when quantum dots (QDs) interact with target analytes. For example, nitrogen-doped carbon quantum dots (N-CQDs) detect acetylcholine (Ach) by fluorescence quenching that occurs due to the enzymatic hydrolysis of Ach by acetylcholinesterase (AchE). The change in fluorescence intensity is then measured to determine the analyte concentration [90].
b. Localized Surface Plasmon Resonance (LSPR) Biosensors
   Mechanism: LSPR-based biosensors use optical sensing by leveraging the interaction between incident light and metal nanoparticles (e.g., silver nanoparticles, AgNPs, or copper oxide nanoparticles, CuO-NPs). This interaction induces a shift in the resonance signal based on the refractive index change when an analyte binds to the surface [91]. This shift in resonance is detected optically and used to measure the concentration of the target analyte.
c. Surface Plasmon Resonance (SPR) Biosensors
   Mechanism: SPR biosensors employ optical sensing to detect refractive index changes at a metal

surface when an analyte binds to immobilized recognition elements (e.g., antibodies or nucleic acids). The binding event alters the angle of light reflection, which is measured optically. This change in reflection angle correlates with the analyte concentration, providing a quantitative measure of the target substance [92].

d. Field-Effect Transistor (FET) Biosensors

Mechanism: FET biosensors utilize electrical sensing to detect changes in the electrical characteristics of a transistor when biological interactions occur at the sensor surface. For example, graphene FET-based biosensors detect viral proteins by monitoring the changes in channel current and gate capacitance as biological molecules immobilize on the sensor surface. The current shift corresponds to the presence and concentration of the target analyte [81].

e. GNP-based biosensor:

Mechanism: The 5-nm GNP-based biosensor employs electrical sensing via resistive changes to detect cancer biomarkers. The biosensor is composed of gold nanoparticles (GNPs) functionalized with different organic molecules (e.g., dodecanethiol, hexanethiol, etc.). These functionalized GNPs are deposited onto inter-digitated gold electrodes on a silicon wafer. When cancer biomarkers, such as those associated with lung, colon, breast, and prostate cancers, interact with the functionalized GNPs, the binding event induces changes in the resistance of the biosensor. The interaction alters the electrical properties, such as resistance or conductance, of the GNPs and the underlying sensor surface. The magnitude of this resistance change is directly related to the presence and concentration of specific cancer biomarkers.

4. Fabrication techniques: Excellent performance requires high precision. Nanosensors with the precise dimensions, form, and functionality required for the effective collection and identification of cancer biomarkers are produced thanks to processes like electron beam lithography. The fabrication techniques for the miscellaneous biosensors are as follows:

a. Fluorescence-Based Biosensors (Quantum Dot-Based Biosensors): The fiber surface is functionalized with nitrogen-doped carbon quantum dots (N-CQDs) and acetylcholinesterase (AchE). The enzyme AchE hydrolyzes acetylcholine (Ach), producing acetic acid, which quenches the fluorescence of N-CQDs. The fiber-optic platform is integrated into a fluorescence detection system to measure the change in fluorescence intensity, indicating the presence of acetylcholine [90].

b. Localized Surface Plasmon Resonance (LSPR) Biosensors: Fibers are coated with metal nanoparticles like silver nanoparticles (AgNPs) and copper oxide nanoparticles (CuO-NPs) to enhance the Localized Surface Plasmon Resonance (LSPR) effect. The Mach-Zehnder interferometer (MZI) configuration with single-mode fiber-multimode fiber-single-mode fiber (SMF-MMF-SMF) structure is used. Nanoparticles such as AgNPs and CuO-NPs are deposited on the fiber surface to create sensitive probes with optimized nanoparticle combinations like Probe-1 (CuO) and Probe-2 (AgNPs/CuO) [91].

c. Surface Plasmon Resonance (SPR) Biosensors: The fiber surface is coated with a thin layer of silver, which is modified with self-assembled monolayers (SAMs) of varying chain lengths. The SAMs immobilize recognition elements, like anti-NS1 antibodies. This modification enables the detection of the dengue virus NS1 antigen through changes in the refractive index, which are measured by shifts in the reflection angle [92].

d. Field-Effect Transistor (FET) Biosensors: A high-quality single graphene layer is deposited onto a commercially available biosensor chip. The graphene is functionalized to detect specific

molecules, such as Zika virus proteins or the COVID-19 spike protein. The sensor's channel current and gate capacitance are monitored to detect shifts caused by the immobilization of the biological target [80].

e. 5-nm GNP-Based Resistive Biosensor for Cancer Detection: Monolayer-capped 5 nm gold nanoparticles (GNPs) are synthesized using a modified two-phase method. These GNPs are functionalized with organic molecules such as dodecanethiol and hexanethiol. Circular inter-digitated gold electrodes are fabricated on silicon wafers using an electron-beam evaporator. The GNPs are dispersed in toluene, sonicated, and drop-cast onto the electrodes. After drying under nitrogen (N_2) and baking at 50 °C in a vacuum oven, the GNPs bond strongly to the electrodes. The 14 GNP sensors are integrated into a custom PTFE circuit board, forming a nanosensor array for detecting multiple cancer biomarkers.

5. Surface functionalization: Special "recognition elements" are placed on the nanosensor's surface to ensure they interact with the intended cancer biomarker. These may be DNA sequences complementary to particular mutations linked to cancer or antibodies made to attach to the target protein.

a. DNA Probes: Short, single-stranded DNA sequences can target specific cancer-associated mutations. By attaching these DNA probes to the nanosensor surface, scientists create a sensor that can detect the presence of these mutations in a patient's DNA sample. Companies like Illumina are making advancements in DNA probe technology for nanosensor design.

b. Antibodies: Highly particular molecules that the immune system makes that can cling to the surface of a nanosensor. By exclusively identifying and attaching to the intended cancer biomarker, these antibodies function as tiny grappling hooks. Businesses such as Merck KGaA have nanosensors with antibody functionalities for cancer detection.

6. Signal transduction and readout: A detectable signal is produced when a cancer biomarker interacts with the sensor and causes changes. To make the presence of the biomarker easy this may entail converting electrical or optical changes into a readable output.

7. Testing and optimization: Thorough testing using recognized cancer cells or biomarkers is essential. Scientists assess the sensor's response speed, sensitivity, and capacity to discern between healthy and malignant cells. They improve the design in light of these findings to detect cancer with the greatest efficiency and accuracy.

4.1. Advancements in cancer detection technology

Recent developments in nanotechnology are bringing about a revolution in cancer diagnosis. The early identification and better patient outcomes are made possible by these tiny sensors' high sensitivity and specificity in identifying cancer biomarkers as shown in Tables 2 and Table 3.

Table 2. Advancements in sensors for cancer detection.

Name	Sensor Type	Biomarker Target	Description	Working Principle	Features	Ranges/Wavelengths	Cancer Types Detected	Year
Cancer Antigen 125	Gold Nanoparticle Sensor	CA 125	Detects ovarian cancer biomarker CA 125 using phosphoserine-imprinted nanosensors with metal-chelating monomers.	Uses molecular imprinting of phosphoserine (PS) to create specific cavities for CA 125 binding. Detection involves fluorescence changes upon CA 125 binding.	Dual functionality with inherent fluorescence, template mimicry using phosphoserine, high sensitivity with low detection limits.	Fluorescence	Ovarian cancer	2016
Plasmonic Nanosensor	Plasmonic Nanosensor	CEA, CA 19-9	Utilizes photonics and nanotechnology for label-free biomarker detection using surface plasmon resonance (SPR).	Operates on Metal-Insulator-Metal (MIM) design with triple Fano resonances at specific wavelengths. Offers high sensitivity and improved Figure of Merit (FOM).	Label-free detection, high sensitivity with triple Fano resonances, improved FOM (46.18 RIU^{-1}).	SPR resonance	Colorectal cancer Pancreatic cancer Ovarian cancer	2018

Continued on next page

Name	Sensor Type	Biomarker Target	Description	Working Principle	Features	Ranges/ Wavelengths	Cancer Types Detected	Year
CancerDot	LSPR Nanosensor	Cancer Biomarkers (Proteins, DNA, RNA)	Employs localized surface plasmon resonance (LSPR) in gold nanorods to detect cancer biomarkers with high sensitivity and specificity.	Gold nanorods resonate with incident light based on biomarker presence, causing a wavelength shift in LSPR.	High sensitivity for single-molecule detection, enhanced signal amplification, specificity with reduced non-specific binding, non-invasive testing suitable for point-of-care.	LSPR	Prostate Cancer	2015
QDots	Fluorescenc-based Nanosensor	EGFR, HER2	Uses semiconductor quantum dots to detect cancer biomarkers via fluorescence shifts upon biomarker interaction.	Quantum dots emit light at specific wavelengths upon biomarker binding, indicating their presence and concentration.	Enhanced signal strength, high specificity targeted binding, the capacity to detect single molecules, and a wide range of applications in imaging, flow cytometry, and biosensors	Fluorescence	Colorectal cancer	2013
MagSense	Magnetic Nanosensor	PSA, AFP	Identifies cancer biomarkers using biocompatible magnetic nanoparticles that bind to specific targets for magnetic detection.	Magnetic nanoparticles coated with biorecognition molecules selectively bind to cancer biomarkers. Magnetic detection measures alterations in magnetic fields due to bound nanoparticles.	Low detection limits, minimal sample requirement, compatible with optical detection techniques, utilizes magnetic characteristics for detection.	Magnetic field	Various cancer types	2017

Continued on next page

Name	Sensor Type	Biomarker Target	Description	Working Principle	Features	Ranges/ Wavelengths	Cancer Types Detected	Year
ExoSense	Exosomal Nanosensor	Exosomes	Detects cancer-related exosomes using functionalized nanoparticles for non-invasive diagnostics.	Functionalized nanoparticles bind to exosomes carrying cancer-related biomarkers, detecting changes in light absorption (LSPR) or fluorescence.	Specific targeting with ligands or antibodies, quantitative analysis of exosome concentration, non-invasive testing with low sample requirement.	Light absorption	Various cancer types	2016
NanoFlare	Hybrid Nanosensor	mRNA Sequences (e.g. KRAS)	Gold nanoparticles functionalized with DNA strands that fluoresce upon binding to cancer-specific mRNA, enabling sensitive detection of cancer cells.	DNA recognition sequences on gold nanoparticles bind to cancer mRNA, altering fluorescence upon binding and indicating cancer presence.	High sensitivity to mRNA detection, specificity with DNA-mRNA complementarity, quantitative analysis of cancer biomarkers.	Fluorescence	Various cancer types	2014
L-MISC	SERS Nanosensor	MISCs	Uses ultrashort laser ablation to create nanostructured surfaces for detecting metastatic signatures in lung cancer using Raman spectroscopy.	Laser ablation creates nanostructured surfaces that enhance Raman signals for detecting metastasis-initiating stem cells (MISCs).	High sensitivity with SERS functionality, nanoarchitecture for single-cell analysis, non-invasive diagnostic potential using small blood samples.	Enhanced Raman signals	Lung cancer, metastatic signatures	2019

Continued on next page

Name	Sensor Type	Biomarker Target	Description	Working Principle	Features	Ranges/ Wavelengths	Cancer Types Detected	Year
DrugSense	Electrochemical Nanosensor	Drug Concentration	Measures drug concentrations in blood using electrode-modified nanoparticles, applicable for monitoring cancer treatments.	Nanoparticles modify electrodes to bind to specific cancer biomarkers, altering electrical characteristics upon binding and indicating drug presence.	Wide detection range from nanomolar to micromolar concentrations, auxiliary optical detection, and signal amplification for enhanced sensitivity.	Electrochemical	Various cancer type	2015
NanoLiposomes	Liposomal Nanosensor	Therapeutic Drugs	Delivers therapeutic drugs encapsulated in liposomes to cancer sites, offering controlled release and improved efficacy.	Liposomal encapsulation of drugs enables controlled release at tumor sites based on environmental stimuli like pH or external factors.	Tumor microenvironment interaction, biomimicry with liposomal structure, enhanced drug delivery with minimized side effects.	Controlled release	Breast, lung and ovarian cancer.	2012
BrCyS-Q	Near-Infrared Photosensitizer	Breast Cancer Cells	Activatable photosensitizer targeting breast cancer cells, fluorescing upon activation with NIR light in tumor microenvironment .	When exposed to NIR light, BrCyS-Q preferentially activates under tumor microenvironment circumstances (low pH, high biothiol levels), creating ROS and fluorescence for cancer therapy and detection	NIR wavelengths for biological specificity, tunable activation for accurate imaging and therapy, and enhanced safety profile with targeted activation	Near-Infrared	Breast cancer	2020

4.1.1. CA 125 detecting nanosensors

Type: Carbon nanotube nanosensor**.** Tissues and biological fluids, such as blood, ascites, uterine lavage, cervical smears, and urine, are analyzed using multi-platform omics technologies, such as proteomic and metabolomic mass spectrometry and genomic and transcriptome sequencing. Machine learning algorithms with multi-omics techniques facilitate the rapid identification of biomarkers for early diagnosis of ovarian cancer (OC) and advance our understanding of the disease [93]. One such biomarker is the glycoprotein CA 125, produced by organs such as the fallopian tubes, cervix, and uterus. Levels of CA 125 exceeding 35 U/ml are deemed excessively high. CA 125 can enter the bloodstream when these tissues are injured or irritated, as in the case of ovarian cancer. Interpreting CA 125 values, however, is challenging because non-cancerous diseases such as endometriosis, menstruation, liver disease, and pregnancy can cause increased levels. The rise in CA 125 levels is not caused by more than half of ovarian tumors in the early stages. Cancer Antigen 125 (CA 125) is a glycoprotein biomarker frequently used to diagnose ovarian cancer. Its levels indicate the progression or regression of the disease [94]. Sibel Büyüktiryaki et al.'s nanosensors, which employ an imprinting technique with Methacryloyl Antipyrine Terbium (III) and Methacryloyl Antipyrine Europium (III) as metal-chelating agents, are examples of advances in detection technologies [95]. Using phosphorine (PS) as a template, iron oxide nanoparticles (Fe_3O_4) and carbon nanotubes (CNT) imprinted with PS were used to build the nanosensor, which binds to CA 125 exclusively. The PS-imprinted CNT nanosensor demonstrated a detection limit of 0.49 U mL^{-1} for CA 125 and 1.77×10^{-10} M for PS. Human serum samples spiked with varying quantities of CA 125 in pH 7.4 phosphate-buffered saline (PBS) were used to assess its clinical viability [95].

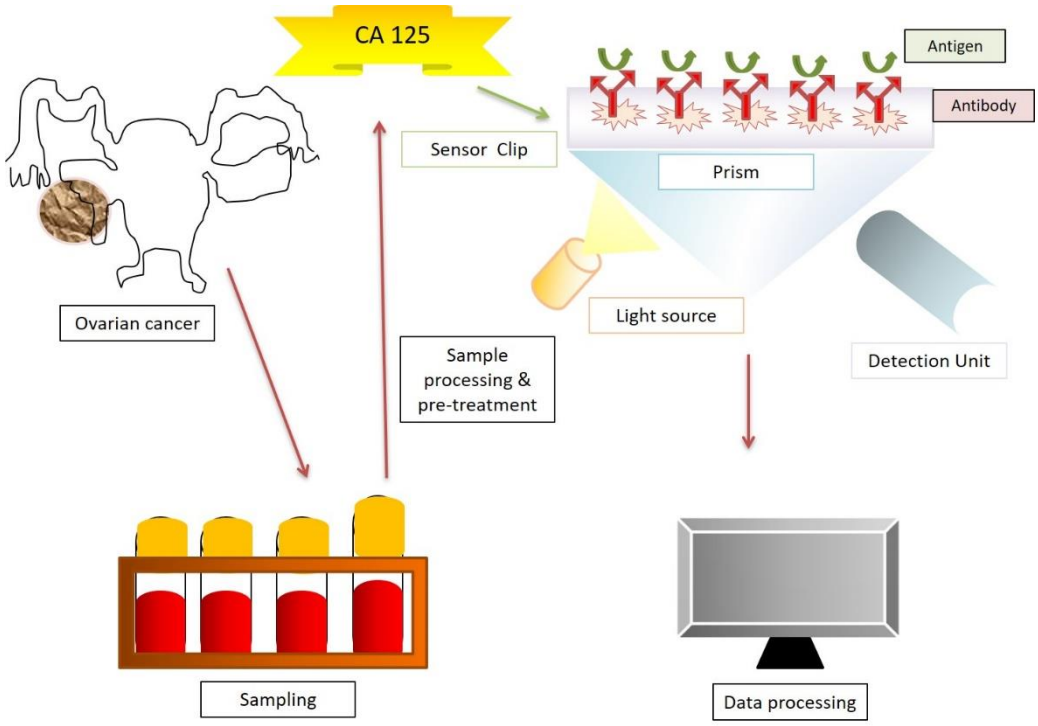

Figure 3 (a). CA 125 in surface PR bio-sensing.

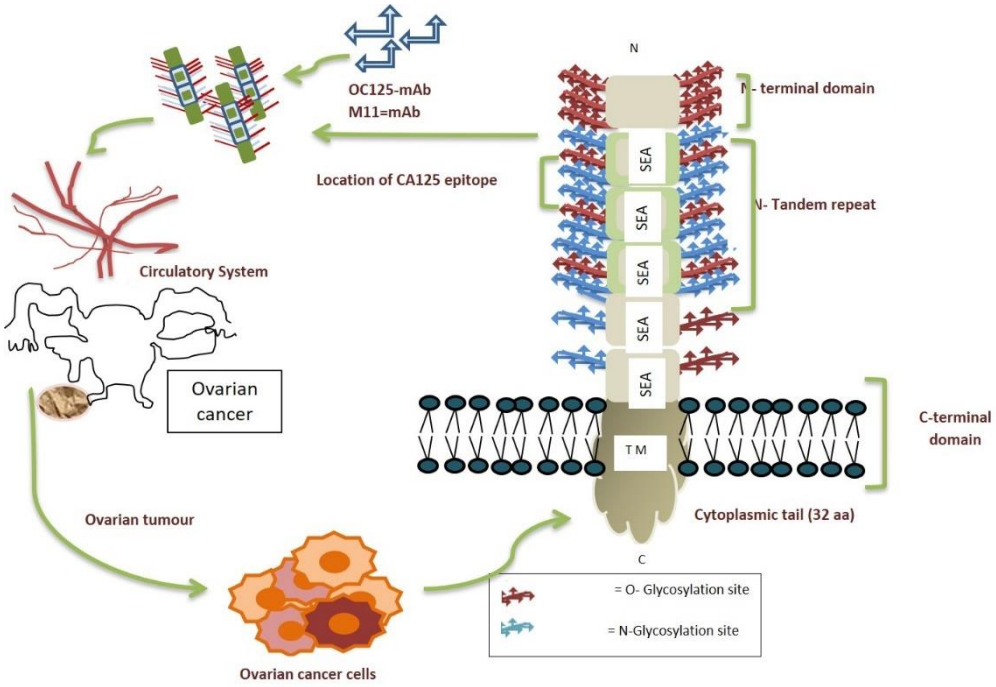

Figure 3(b). MUC16 (CA125): structure and its oncogenic role in ovarian cancer.

Working principle: Surface Plasmon Resonance (SPR) biosensing platforms utilizing molecular imprinting have been applied for cancer biomarker detection, such as CA125. In sensor design, phosphoserine (PS) acts as a template, with metal-chelating monomers like europium (III) and methacryloyl antipyrine terbium (III) binding to PS via metal coordination. This mixture undergoes polymerization, creating imprinted cavities that closely resemble CA125's structure. These cavities selectively bind CA125, enabling precise detection through fluorescence-based measurements [96]. The binding affinity is quantified using Langmuir adsorption isotherms, ensuring accurate sensitivity SPR sensors have been validated against clinical samples and used in preclinical experiments for cancer marker detection. Springer and Homola developed an SPR biosensor for carcinoembryonic antigen (CEA), a biomarker for colon cancer, improving its limit of detection (LOD) from 8 ng/mL for clinical use. A fluidic SPR method was also used to develop a sensor for detecting CA125 in serum samples, employing 11-mercaptoundecanoic acid coupling to a gold surface and anti-CA125 antibody attachment via the EDS/NHS technique. These SPR-based methods are effective for accurate cancer marker detection. Figure 3(a) illustrates the process of CA125 detection via the SPR biosensing platform. When a sample containing CA125 is introduced, the CA125 molecules bind to the imprinted cavities on the nanosensor. This binding induces fluorescence changes in the metal-chelating monomers, producing a measurable signal. Elevated levels of CA125 (> 35 U/mL) are associated with 82% of ovarian cancer cases but can also be elevated in other cancers and benign conditions. The monoclonal antibody OC125 is used for antigen detection, although human anti-mouse antibodies may cause false readings. The cut-off for abnormal levels is typically 35 U/mL, with higher levels correlating with poorer prognosis and normalization after treatment indicating improved survival. CA125, a glycoprotein expressed on MUC16, is found in various tissues, including cervical mucus, amniotic fluid, and the chorionic membrane of the fetus. It is also present in human milk, respiratory epithelial

cells, and bronchial mucus. Studies by Kabawat et al. demonstrated the reactivity of the OC125 monoclonal antibody with fetal and adult tissues, including those derived from coelomic and Mullerian epithelia, such as the endocervix, endometrium, pleura, pericardium, peritoneum, mammary glands, sweat glands, intestines, lungs, and kidneys [97]. Furthermore, CA125 is expressed in adenocarcinomas of the endocervix, endometrium, mesotheliomas, and fallopian tubes. Though CA125 is initially present during embryonic ovarian development, its expression diminishes and is reactivated in ovarian neoplasms. Elevated CA125 levels are frequently seen in peritoneal and pleural fluids due to their production by coelomic epithelium-derived tissues. Its extracellular fragment is cleaved and shed by ovarian cancer cells, making it detectable in serum, peritoneal, and amniotic fluids. In Figure 3(b), the structure of MUC16 (CA125) is depicted, highlighting its role as a nanosensor for ovarian cancer detection. MUC16 consists of cytoplasmic, transmembrane, and extracellular domains with O- and N-glycosylation sites. Its peptide chain, 22,152 amino acids long, includes a tandem repeat region with over 60 repeats of 156 amino acids, which harbor the CA125 epitope. This epitope, cleaved by ovarian cancer cells, is detectable in serum and peritoneal fluids. The nanosensor detects CA125 by binding to these epitopes, producing measurable fluorescence, and enabling early detection of ovarian cancer. Additionally, antibodies like oregovomab and abagovomab, which target MUC16's tandem repeats, are used therapeutically to reduce cancer recurrence, linking diagnostic and therapeutic approaches in ovarian cancer management.

Features:

a. Dual Functionality: The chosen monomers, methacryloyl antipyrine terbium (III) and europium (III), might possess inherent fluorescent properties. If their fluorescence changes upon CA 125 binding, it offers a potential built-in detection method without the need for additional techniques like Langmuir adsorption isotherms used in this study.
b. Template Mimicry: Using phosphoserine, a part of the CA 125 structure, as the template molecule ensures a high degree of complementarity between the imprinted cavities and the target molecule. This enhances the binding affinity and detection sensitivity.

4.1.2. Plasmonic nanosensor

Plasmon nanosensors combine photonics and nanotechnology to detect biomolecules with great sensitivity and specificity. They are a cutting-edge biosensing technology. It uses plasmonics principles to provide label-free biomarker analysis and identification, especially in cancer diagnostics. These sensors improve the capability of surface plasmon resonance (SPR) and microwave transmission to detect cancer early on by employing nanostructured materials and nano-antenna-based designs.

Working principle: An inventive Metal Insulator Metal (MIM) design with a panda ring configuration powers the plasmonic nanosensor for multi-Fano resonance cancer cell detection. This sensor uses plasmonics to integrate photonics and electronics at the nanoscale, offering label-free detection benefits crucial for delicate biological applications. High sensitivity to changes in refractive index is made possible by its triple Fano resonances at particular wavelengths (0.949 μm, 1.728 μm, and 2.103 μm). This is essential for identifying minute fluctuations in biological samples that may indicate the presence of malignant cells [98]. The fabrication complexity of the sensor, which includes the usage of a square slit, is meticulously thought out to maximize performance measures like the figure of merit, which reaches an impressive 46.18 RIU^{-1}. This plasmonic sensor exhibits promise in

the different cancer cell types (e.g., Jurkat, PC-12, MDA-MB-231, MCF-7, and Basal Cell) in the context of cancer detection. Its sensitive and exact detection abilities could lead to advancements in early diagnosis and personalized medicine [99].

Features:

a. Label-free Detection: Unlike traditional methods that require attaching labels to target molecules, this sensor can directly detect changes in the refractive index caused by the presence of cancer cells. This eliminates the need for complex labeling procedures and reduces the risk of damaging biological samples.
b. High Sensitivity: The triple Fano resonances at specific wavelengths enable the sensor to detect minute fluctuations in the refractive index of a sample. This high sensitivity is crucial for identifying even small changes that might indicate the presence of cancer cells at an early stage.
c. Improved Figure of Merit (FOM): **T**he FOM shows the sensor's sensitivity compared to its spectral linewidth. This sensor achieves an impressive FOM of 46.18 RIU^{-1}, indicating a good balance between sensitivity and selectivity [98].

4.1.3. CancerDot

Type: LSPR Nanosensor. With a high degree of sensitivity and specificity, CancerDot is a sophisticated nanosensor that uses the concepts of Localized Surface Plasmon Resonance (LSPR) to identify cancer biomarkers. One kind of nanoparticle designed especially for use in cancer diagnosis and detection is called a cancer nanodot. Usually, these nanodots are made of luminescent or fluorescent materials, which light up when exposed to a particular wavelength. Long-wavelength surface plasmon resonance (LSPR) occurs when conduction electrons on the surface of metallic nanoparticles resonate with incident light at specific wavelengths, greatly enhancing the electromagnetic field at the nanoparticle surface. Because of their exceptional capacity to vary the resonance wavelength based on their aspect ratio (length vs. width), gold nanorods are especially well-suited for LSPR applications [99]. Researchers can now create gold nanorods that resonate with particular light colors because of this.

Working principle: Because of their significant surface plasmon resonance, which improves their optical qualities for cancer detection, gold nanorods are essential to CancerDots. By functionalizing these nanorods to target particular cancer biomarkers, it is possible to image and localize cancer cells. They enhance contrast in imaging modalities such as fluorescence and photoacoustic imaging, and they can be employed in photothermal therapy, which uses near-infrared light exposure to kill cancer cells. Furthermore, multiplexed detection is supported by gold nanorods, enabling the simultaneous identification of several cancer biomarkers. The gold nanorods in CancerDot can be functionalized with substances that attach to particular cancer biomarkers. The resonance of the gold nanorods can change depending on how light interacts with the CancerDot and if the biomarker is present. This shift indicates malignancy and can be evaluated to identify the biomarker's presence.

Features:

a. High sensitivity:

- Single-Molecule Detection: CancerDot can identify biomolecules at the single-molecule level, which is essential for identifying cancer in its early stages.

- Enhanced Signal: Low amounts of cancer biomarkers can be identified thanks to the substantial amplification of the detection signal caused by the powerful electromagnetic field enhancement brought about by LSPR [100].

b. Specificity:

- Targeted Binding: To specifically attach to cancer biomarkers, such as proteins, DNA, or RNA linked to cancer cells, the surface of CancerDot nanoparticles is functionalized with certain ligands or antibodies.
- Reduced Non-Specific Binding: The functionalization procedure makes sure that non-specific interactions are kept to a minimum, which improves the sensor's accuracy.

c. Non-invasive testing:

- Low Sample Requirement: The testing procedure is less intrusive and more patient-friendly because it only requires a tiny sample volume, such as a drop of blood or a biopsy extract, for analysis.
- Point-of-Care Use: CancerDot is suited for point-of-care diagnostics, enabling on-site testing and quick findings thanks to its mobility and user-friendliness [100].

4.1.4. Quantum dots (QDots)

Type: Fluorescence-based Nanosensor. To fully understand the patient's cancer kind and stage and to anticipate the best course of treatment, high sensitivity, specificity, and multiplexing of measures can be achieved with the development of nanoscale sensors. Additionally, genetic analysis can also be performed. Promising techniques for medical imaging platforms are emerging, including nanoparticles like QDs and superparamagnetic iron oxide. QDs are semiconductor nanocrystalline structures with excellent fluorescence and minimal photobleaching, with sizes ranging from 2 to 10 nm (Figure 4) [101]. The top-down methodologies for quantum dot synthesis are outlined in the following figure. The methods essentially entail breaking down a bulk material component piece by step. Moreover, focused ion beam, lithography, and etching processes are examples of top-down approaches. The semiconductor QDots are sophisticated nanosensors that use fluorescence shifts to identify cancer linked to specific chemicals. Due to their unique optical properties resulting from quantum confinement effects, QDs are semiconductor particles at the nanoscale that are particularly useful for biomedical imaging and diagnostics [101]. These are microscopic optically distinct semiconductor particles. Because of their ability to modulate fluorescence emission due to their small size, they are useful for biological imaging and diagnostics.

Figure 4 shows how top-down nanofabrication methods, including lithography and ion implantation, are used to create innovative QD biosensors for detecting cell-free microRNAs (miRNAs) in lung cancer. Lithography is the first step in the process, when a resist layer is patterned on a silicon (Si) wafer coated in silica (SiO_2) using a concentrated electron or X-ray beam. To construct the nanoscale structures necessary for the biosensor to function, the exposed resist is dissolved, enabling the etching of the silica layer underneath. The residual resist is then removed, and the underlying silicon is etched. Ion implantation creates an implanted layer concurrently by introducing certain ions into a matrix material. Annealing the material after implantation stabilizes and integrates the inserted nanoclusters into the matrix. The sensitivity and specificity of the QD biosensor in identifying miRNAs linked to lung cancer depend on this. Following a final treatment with hydrofluoric acid (HF) and a platinum (Pt) catalyst, the wafer is left with an etched silicon surface that has free-standing silicon quantum dots (FS

Si QDs).

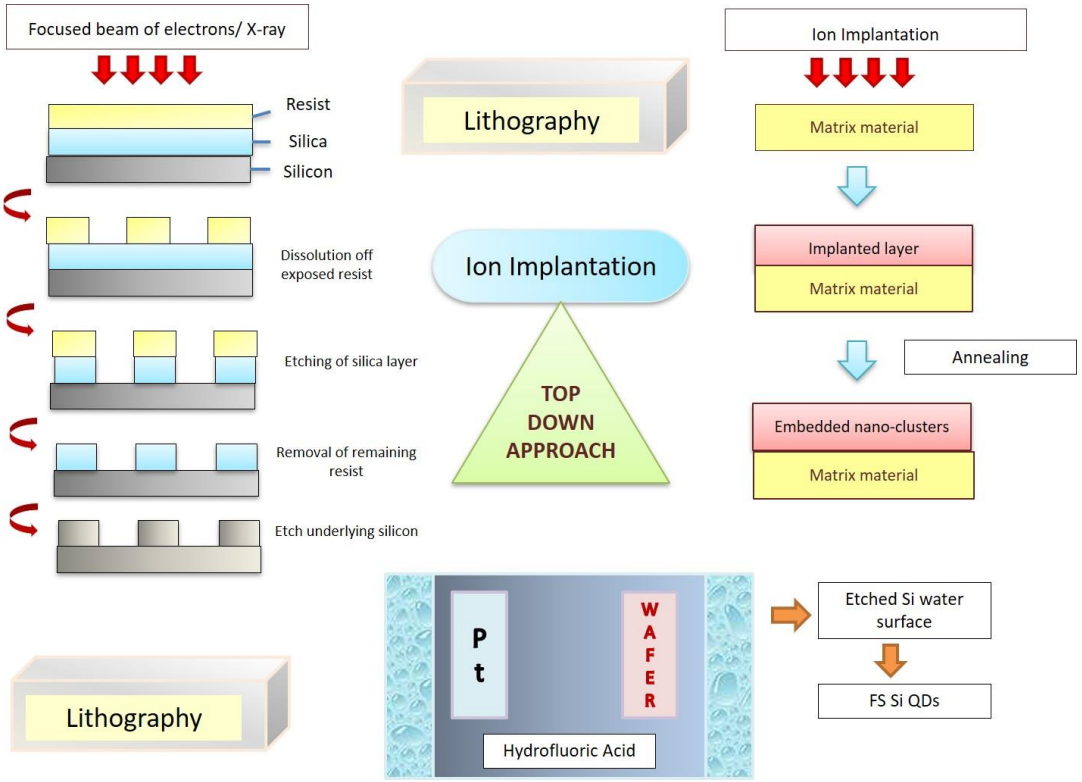

Figure 4. Sensing cell-free miRNAs in lung cancer with novel quantum dot biosensors.

Working principle:

a. Designer QDs: To target cancer biomarkers, scientists create QDs with certain characteristics. These characteristics consist of:

- The wavelength of light emitted by a QD can be varied by changing the QD material's size and composition in the semiconductor crystals. With this, they may create QDs that, upon interaction with the target biomarker, glow at a particular color.
- The QD surface is frequently modified by chemicals (antibodies, peptides) that have the unique ability to identify and connect to proteins linked to cancer or other compounds present on the surface of cancer cells or circulating tumor cells.

b. Interaction with biomarker: When QDs are introduced into a sample (blood, tissue), the modified QDs can interact with their target biomarkers. If the biomarker is present, the binding molecules on the QD surface will attach to the biomarker on the cancer cell.

c. Fluorescence change: Once the QD binds to the biomarker, its optical properties change. This typically involves variation in fluorescence intensity or wavelength. For example, the QD might become brighter or emit light at a slightly different color.

d. Detection: The change in fluorescence is then measured using specialized equipment like a fluorescence microscope or a fluorescence reader. The presence and amount of the biomarker can be determined by analyzing the fluorescence signal.

Features:

a. Enhanced signal strength: The brightness of QDots' fluorescence is significantly higher than that of traditional dyes, improving the sensitivity of detection methods
b. Single-molecule detection: QDots can detect individual cancer-related molecules, which is crucial for early-stage cancer diagnosis. Their high fluorescence intensity enables biomarkers at low concentrations.
c. Targeted binding: QDots can be functionalized with specific molecules (e.g., antibodies, peptides) that bind selectively to cancer biomarkers. This specificity ensures that only the cancer-related molecules are detected, reducing false positives.
d. Broad range of uses: QDots can be employed in various diagnostic platforms, including imaging, flow cytometry, and biosensors. This versatility enhances their utility across cancer detection methods.

Examples:

a. Through Fluorescence In Situ Hybridization (FISH), genetic defects linked to cancer can be identified in cells by labeling DNA or RNA sequences with QDots.
b. Immunohistochemistry (IHC): To stain cancer tissues and produce finely detailed pictures of protein expression patterns in malignancies, QDots conjugated with antibodies are utilized [82].
c. Flow Cytometry: QDots are used to identify and measure cancer cells in blood samples, which helps in blood cancer detection and tracking.

4.1.5. Magneto-nanosensor

A magneto-nanosensor (MNS) is a diagnostic device that uses magnetoresistance (MR) phenomena for detecting cancer biomarkers with high sensitivity. It employs magnetic nanoparticles as labels, which bind to specific biomolecules. The sensor surface is coated with immobilized probes that capture target analytes. When an analyte with magnetic labels interacts with the sensor, an external magnetic field induces resistance changes, correlating with the analyte concentration [102]. The three major types of MR sensors are:

a. Anisotropic Magnetoresistance (AMR): Resistivity changes with the angle between magnetization and current direction.
b. Giant Magnetoresistance (GMR): Resistance changes significantly under a biased magnetic field.
c. Tunnel Magnetoresistance (TMR): Tunneling resistance varies based on the alignment of ferromagnetic layers, offering the highest sensitivity among MR sensors. TMR biosensors are particularly effective in cancer detection due to their high sensitivity and broad application potential.

Working principle:

a. Nanoparticle design: The process of making magnetic nanoparticles from a safe and biocompatible material is called Magneto-nanosensor. Following conjugation, these nanoparticles are joined to biorecognition molecules, which can selectively bind and target cancer biomarkers.
b. Biomarker targeting: Depending on the application, Magneto-nanosensor nanoparticles may enter the body by injection or other means and pass through the circulation to potentially reach target regions. The nanoparticles' biorecognition molecules will bind to cancer biomarkers on cancer cells or in the surrounding environment.

c. Magnetic detection: The magnetic characteristics of the nanoparticles are essential to Magneto-nanosensor. Using low-strength, safe magnetic fields, external magnetic fields are applied to the body. Specific scanners can identify these magnetic fields.

d. Signal analysis: By examining the alterations in the applied magnetic field brought about by the collected nanoparticles, it is possible to infer the existence and location of the magnetic nanoparticles. A higher magnetic signal in a specific area may indicate the presence of cancer cells or biomarkers since the nanoparticles are coupled with biorecognition molecules that target cancer biomarkers.

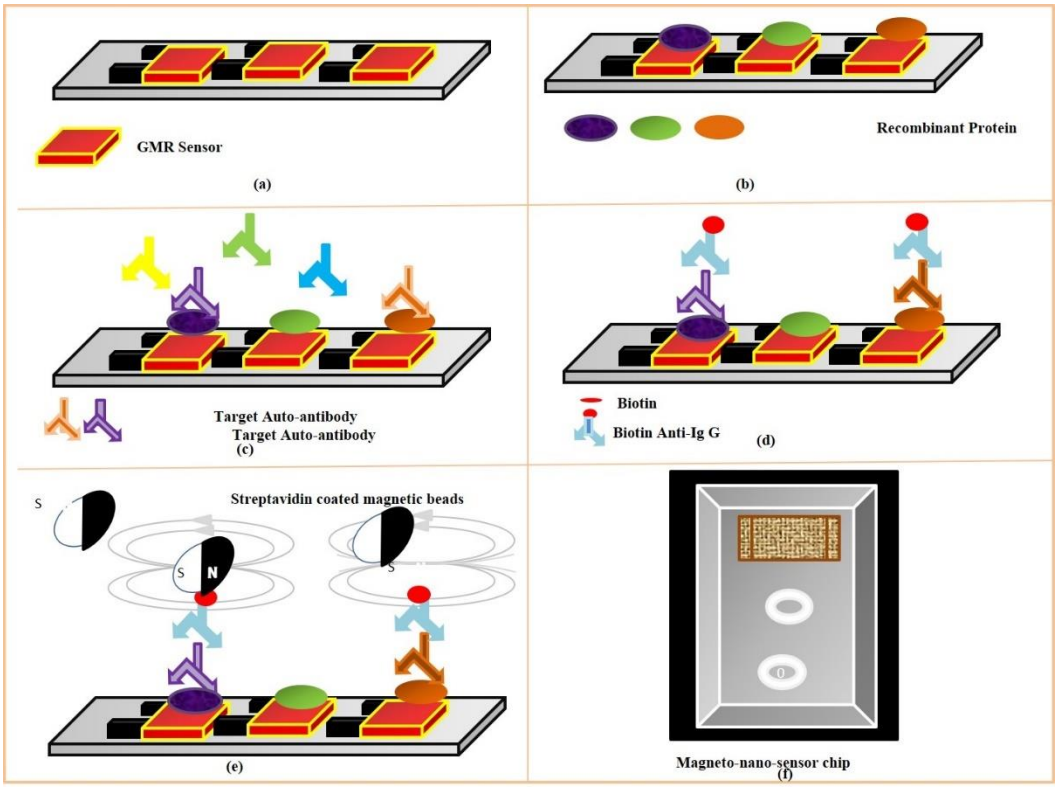

Figure 5. Multiplexed magnetic nano-sensor (MNS) immunoassay for high-sensitivity cancer biomarker detection.

The diagram (Figure 5) demonstrates a multiplexed magnetic nanosensor (MNS)-based immunoassay, a progressed platform for the ultrasensitive detection of autoantibody and protein biomarkers critical in cancer diagnostics. The MNS chip (Figure 5a), a miniaturized 10 × 12 mm device containing 80 nanoscale GMR (giant magnetoresistance) sensors, leverages the GMR effect to transduce biomolecular interactions into quantifiable electrical signals, offering exceptional sensitivity and specificity [102]. In this workflow, distinct recombinant proteins (Figure 5b) with a precise affinity for their target autoantibodies are immobilized on the nanosensor's surface, creating highly selective biofunctionalized regions. Subsequently, patient serum samples are applied to the sensor array (Figure 5c), enabling the specific binding of target autoantibodies to their respective capture proteins. Following stringent washing steps to remove non-specifically bound components (Figure 5d), biotinylated anti-human IgG antibodies are introduced, serving as detection probes that bind exclusively to the captured autoantibodies. The system is then augmented with streptavidin-functionalized magnetic

nanoparticles (Figure 5e), which interact with the biotinylated antibodies to induce a measurable shift in the resistance of the MNS, facilitating highly sensitive quantification of the target analytes. The final image (Figure 5f) showcases the compact and scrupulously engineered 10 × 12 mm MNS chip, underscoring its potential as a transformative tool for portable, point-of-care diagnostic applications. This innovative approach assimilates nanotechnology with biosensing to achieve high-throughput and precise biomarker detection, representing a significant advancement in clinical diagnostics.

Features:

a. Low detection limits**:** Able to find cancer biomarkers at low quantities, which enables the identification of malignancies in their early stages. Based on the test design and biomarker, the detection limits can vary from femtomolar ($10^{\wedge -15M}$) to attomolar ($10^{\wedge -18M}$) values [103].
b. Minimal sample requirement: This makes the testing process less intrusive by working well with small amounts of biological samples like blood, urine, or saliva.
c. Wavelength: Magnetic nanosensors, such as Magneto-nanosensor, can be used with optical detection techniques, even though they largely rely on magnetic characteristics rather than optical characteristics like wavelength. For example, depending on the fluorescent markers employed, typical excitation/emission wavelengths, if integrated with fluorescence or other optical markers, could range from 450 nm (blue) to 800 nm (near-infrared) [103].
d. Size and Composition: Magnetic nanoparticles are typically composed of iron oxide (Fe_3O_4 or γ-Fe_2O_3) and have sizes ranging from 10 to 100 nanometers, optimized for maximum magnetic response and biocompatibility [104]. Fe_3O_4 is a Magnetite (a mixed iron oxide with both Fe^{2+} and Fe^{3+} ions), and γ-Fe_2O_3 or Gamma-Fe_2O_3 (also known as Maghemite), is an iron oxide with Fe^{3+} ions

4.1.6. ExoSense

Type: Exosomal Nanosensor. Exosomes are tiny, membrane-bound sacs secreted by bodily cells, including cancer cells. The ExoSense uses functionalized nanoparticles for specific binding of these nanoparticles to attach themselves to exosomes that carry signatures linked to malignancy. ExoSense facilitates non-invasive cancer diagnostics by identifying these exosomes [105].

Working principle: Non-invasive cancer detection is made possible by ExoSense, an exosomal nanosensor that works based on functionalized nanoparticles to identify exosomes associated with cancer. From a physical standpoint, the nanosensor makes better use of the high surface area-to-volume ratio of nanoparticles to improve contact with the surface proteins of exosomes. Chemical coatings of certain ligands or antibodies that preferentially attach to target molecules on the surface of exosomes are applied to these nanoparticles. The functionalized nanoparticles aid in a particular binding response with the exosomes in a buffer solution during sample collection and processing, which entails separating exosomes from physiological fluids like blood or urine. Optical methods like fluorescence or Localized Surface Plasmon Resonance (LSPR) are used to identify the contact. When LSPR and fluorescence-based technologies interact with exosomes, the light spectrum absorbed by the nanoparticles shifts due to the shift in binding [106]. The QDs or dye-labeled nanoparticles exhibit different emissions following engagement. Using combined physics and chemistry principles, this optical signal change is quantitatively examined to assess the existence and concentration of exosomes connected to cancer. The results yield important diagnostic insights.

Features:

a. Targeting with specificity: Functionalized nanoparticles attach themselves to exosomes that are specific to cancer, such as those that contain biomarkers like miRNAs or proteins that show the course of the malignancy. For instance, exoSense can identify exosomes that contain miR-21, a recognized biomarker for several malignancies, including lung and breast cancer [107].
b. Quantitative analysis: Offers numerical values for exosome concentration, providing information on the course of the illness and the effectiveness of treatment. As an illustration, ExoSense can measure the amounts of CD63-positive exosomes, which are linked to the development and spread of tumors [108].

4.1.7. NanoFlare

Type: Hybrid nanosensor. Gold nanoparticles functionalized with particular DNA strands are used as hybrid nanosensors known as NanoFlares. The unique messenger RNA (mRNA) sequences linked to cancer cells complement these DNA strands. When a NanoFlare comes into contact with its target mRNA, it sets off a special light-based reaction that may indicate the existence of malignancy [109].

Working principle: NanoFlares are innovative nanosensors designed to detect cancer cells by leveraging the unique properties of gold nanoparticles and DNA sequences. At their core, NanoFlares consist of gold nanoparticles that provide a stable platform for attaching molecules and enhancing detection signals. Attached to these nanoparticles are short DNA strands known as recognition sequences, specifically tailored to complement mRNA sequences found in cancer cells. Additionally, NanoFlares incorporate reporter flares—DNA strands with fluorescent molecules attached—that act as signal generators. In operation, NanoFlares are introduced into biological samples like blood or tissue, where their DNA recognition sequences bind to complementary mRNA targets present in cancer cells. This binding triggers a structural change that brings the reporter flares into proximity to the gold nanoparticle core. Normally, the gold nanoparticles quench the fluorescence of the reporter flares through a light-quenching effect. However, when the DNA binding occurs, the reporter flares are shielded from this quenching effect, enabling their fluorescent molecules to emit light. This emitted light generates a detectable fluorescence signal, whose intensity correlates with the presence and concentration of cancer cells expressing the targeted mRNA [110].

NanoFlares operate at the nanoscale, utilizing principles from physics—such as light quenching by gold nanoparticles—and chemistry—specific DNA-mRNA recognition—to achieve sensitive and specific detection of cancer biomarkers. The emitted fluorescence typically falls within visible wavelengths, enabling measurement using specialized equipment designed for fluorescence detection in biological samples.

Features:

a. High sensitivity: NanoFlares are highly sensitive to target mRNA sequences in cancer cells. For instance, researchers have developed NanoFlares that specifically detect overexpressed mRNA in breast cancer cells. These NanoFlares can identify even small amounts of cancer-related mRNA, enabling early detection and monitoring of the disease progression [110].
b. Specificity: The DNA recognition sequences on NanoFlares are tailored to bind only to the targeted mRNA sequences in cancer cells. This specificity ensures that NanoFlares accurately distinguish cancerous cells from healthy ones. For example, in studies focusing on prostate cancer, NanoFlares have been engineered to target specific mRNA biomarkers associated with this type of cancer, enhancing diagnostic accuracy.

c. Quantitative analysis: The fluorescence emitted by NanoFlares correlates directly with the concentration of target mRNA, enabling precise quantitative analysis of cancer biomarkers. For instance, NanoFlares have been used to quantitatively measure mRNA levels associated with aggressive forms of pancreatic cancer, guiding clinicians in making informed treatment decisions [110].

4.1.8. L-MISC nanosensor

An L-MISC (Lung-Metastasis Initiating Stem Cells) nanosensor with SERS (Surface-Enhanced Raman Spectroscopy) functionality was created to identify trace amounts of metastatic signatures in patient blood samples. To create a distinct metastatic profile exclusive to lung cancer, this nanosensor focuses on recognizing cancer stem cell-enriched heterogeneous populations in primary and metastatic lung cancer cells. Significant variations in the molecular profiles of original cancer cells, metastatic cancer cells, and healthy cells have been found using multivariate statistical analysis. With its single-cell sensitivity, the L-MISC nanosensor enables the high sensitivity and specificity label-free detection of metastasis-initiating stem cells (MISCs) [111]. This diagnostic approach shows promise for accurate and minimally invasive cancer diagnosis with as little as 5 μl of blood needed to detect metastatic lung cancer using a robust machine learning algorithm.

Working principle: An ultrashort femtosecond laser ablation approach is used to produce the L-MISC nanosensor. This technique includes hitting the silicon (Si) surface with a high-intensity laser pulse. The Si substrate becomes an ionized process, and an expanding plume of Si^{2+} ions, electrons, and neutral atoms forms in the ambient environment. Rapid condensation at the plume-air interface causes entities to self-assemble into a layered structure on the substrate surface [112]. Si wafers with (100) orientation are utilized in the manufacture of the L-MISC nanosensor, and they are first cleaned by ultrasonically sonicating them in distilled water and acetone. These substrates are mounted on an XYZ mounting stage so that they are perpendicular to the incident laser beam [112]. EZCAD software is used to manage the ablation pattern. The great sensitivity of this nanosensor, which is made possible by the nanostructured surface produced by laser ablation, is one of its primary characteristics for cancer detection. The interaction space for ensnaring cancer cells or biomarkers from biological samples is maximized by this surface layout [113].

Features:

a. For high sensitivity and Raman signal enhancement, the silicon-based L-MISC nanosensor uses ultrashort pulsed laser ablation. This is essential for identifying metastasis-initiating stem cells (MISCs) in peripheral blood in trace quantities [111].
b. Its nanoarchitecture optimizes surface area for effective single-cell analysis and cell capture. The nanosensor demonstrated its potential as a quick and non-invasive diagnostic tool by correctly differentiating between primary and metastatic lung cancer in initial trials using patient samples. Early detection enables prompt management before symptomatic relapses, which may enhance treatment success.

4.1.9. DrugSense

Type: Electrochemical nanosensor. Using electrode-modified nanoparticles, DrugSense is an innovative electrochemical nanosensor that measures the concentration of medicinal medications in a patient's circulation directly. Compared to conventional blood draws and lab analysis, this

cutting-edge technology provides a quicker and more practical option. It is essential to customize medicine for precise monitoring and modifying drug dosages, assuring the best possible therapeutic outcomes while reducing adverse effects [114].

Working principle: In principle, DrugSense can be modified to detect cancer by focusing on particular biomarkers linked to cancerous cells or activity. To make this alteration, the sensor's electrode is changed utilizing nanoparticles that show a strong affinity for miRNAs, cancer-specific proteins, or circulating tumor cells (CTCs). To facilitate the binding of the target biomarkers to the electrode surface nanoparticles, a small amount of the patient's blood is injected into the sensor. By providing a little electrical signal and examining the ensuing current, the binding modifies the electrode's electrical characteristics, which are then measured [115]. Indicators of the biomarker's presence and perhaps malignancy include a notable shift in current from the baseline (Figure 4).

Features:

a. Broad range of detection: The nanosensor's wide detection range—from extremely low (nanomolar) to high (micromolar) drug concentrations—guarantees its efficacy over the usual therapeutic range in cancer therapies.
b. Auxiliary optical detection: To supplement electrochemical data, this technology works in the visible to near-infrared (400-800 nm) range when combined with optical components.
c. Large range of detection: Picomolar to Millimolar: Capable of detecting a wide range of drug concentrations, from extremely low (picomolar) to high (millimolar) levels, it can address varied drug classes and phases of cancer treatment.
d. Signal amplification: Increases sensitivity to detect even minuscule amounts of cancer biomarkers and medications by multiplying the electrochemical signals by redox-active components in the nanoparticles.

4.1.10. Nano-Liposomes

Type: Liposomal nanosensor. Therapeutic medications are contained within nanoscale liposomes by nano-liposomes, a liposomal nanosensor that enables accurate drug monitoring and controlled release. Nano-liposomes made up of tiny spheres of fatty molecules (lipids) act as a clever drug delivery system that maximizes medication distribution while reducing adverse effects, hence improving the efficacy of cancer treatment. To further enhance therapeutic results, some Nano-Liposomes can be made to track the drug's release and location [116].

Working principle: To prevent early breakdown and maintain stability in the bloodstream until they reach the target site, therapeutic medicines are encapsulated within the lipid bilayer or aqueous core of nano-liposomes. The liposomal membrane is safe for the body and lowers the possibility of negative immunological reactions because it is made of biocompatible and biodegradable lipids. Because tumor tissue has poor lymphatic drainage and leaky vasculature, it can accumulate passively. This is made possible by the Enhanced Permeability and Retention (EPR) effect, which enhances the nanoliposomes. Moreover, ligands like peptides, antibodies, or tiny molecules that bind selectively to receptors overexpressed on cancer cells can change the liposome surface to achieve active targeting. Due to the liposomal structure, medication release can be regulated and sustained, resulting in longer-lasting therapeutic levels and fewer dose intervals. Moreover, nano-Liposomes can be designed to release drugs in response to internal stimuli, such as pH variations in the tumor microenvironment, or external stimuli, such as light, ultrasound, or temperature. This ensures the release of the drug

primarily at the tumor site, increasing efficacy and reducing systemic side effects [117].
Features:

a. Tumor microenvironment interaction: By engineering NanoLiposomes to detect and react to factors in the tumor microenvironment, such as low oxygen levels or high enzyme activity, which point to malignant growths, it is possible to detect and treat situations there.
b. Biomimicry: Nanoliposomes mimic natural structures like cell membranes. This enables them to interact with the body familiarly, reducing the risk of immune rejection.
c. Enhanced delivery: The lipid bilayer of the nanoliposome protects the imaging agent from degradation in the bloodstream. This enables efficient delivery to the target site and ensures a strong signal for detection.

4.1.11. BrCyS-Q

BrCyS-Q is a novel near-infrared activated photosensitizer intended for the diagnosis and management of breast cancer. The biological marker NAD(P)H: quinone oxidoreductase 1 targets breast cancer cells selectively [118]. Photodynamic treatment (PDT) produces reactive oxygen species (ROS) and fluoresces this photosensitizer when exposed to near-infrared light. BrCyS-Q, in contrast to conventional PDT agents, selectively activates in the tumor microenvironment, which is defined by low pH, elevated biothiol levels, reactive oxygen species, or overexpressed enzymes. Its activation technique improves its efficacy and safety profile, making it a viable method for the detection and management of clinical breast cancer.

Working principle: BrCyS-Q works based on an activatable mechanism that improves the system's capacity for both diagnostic and treatment. Because of the phenol etherification-induced suppression of intramolecular charge transfer, BrCyS-Q first shows modest NIR fluorescence emission. Its slower intersystem crossing (ISC) rate is the cause of its poorer singlet oxygen ($^1O_2$) production. When NQO-1 recognizes and reduces the quinone group in BrCyS-Q, a series of elimination processes inside the molecule convert it into BrCyS-OH. BrCyS-OH produces a larger yield of $^1O_2$ and emits intense NIR fluorescence due to this transition. With the photophysical characteristics of BrCyS-OH and BrCyS-Q, NIR PDT is efficient and tunable, enabling accurate imaging and the targeted destruction of breast cancer cells [119].
Features:

a. BrCyS-Q's biological applicability is improved by NIR wavelengths greater safety in tumor tissues, decreased light attenuation, and deeper tissue penetration.
b. In addition to streamlining the therapeutic and diagnostic procedures, the dual-function activatable PS enables accurate tumor localization via fluorescence imaging.
c. It targets NAD(P)H: quinone oxidoreductase 1 (NQO-1), commonly referred to as DT-diaphorase, an enzyme that is overexpressed in a variety of cancer cells, including breast cancer cells [118].
d. NQO-1 is a good biological target for photodynamic treatment (PDT) and fluorescence imaging because it catalyzes a two-electron reduction process with NADH or NADPH.

Table 3. Development and advancement in cancer detection.

Authors	Year	Title	Journal	Volume	Pages
Melicow et al	1975	Percivall Pott (1713–1788) 200th Anniversary of First Report of Occupation-Induced Cancer of Scrotum in Chimney Sweepers (1775)	Urology	6(6)	745–749
Anumula et al	1989	Quantitative determination of kinins released by trypsin using enzyme-linked immunosorbent assay (ELISA) and identification by high-performance liquid chromatography (HPLC)	Biochemical Pharmacology	38(15)	2421–2427
Gadducci et al	1994	Combined Use of CA 125 and CA 15-3 in Patients with Endometrial Carcinoma	Gynecologic Oncology	54(3)	292–297
Somatostatin analogue scintigraphy in patients with small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC)	1994	Somatostatin analogue scintigraphy in patients with small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC)	Lung Cancer	11	65
Hoppenrath et al	2006	Silent Waves: Theory and Practice of Lymph Drainage Therapy, ed 2	Physical Therapy	86(1)	146–147
Spangler et al.	2011	Detection and Classification of Calcifications on Digital Breast Tomosynthesis and 2D Digital Mammography: A Comparison	American Journal of Roentgenology	196(2)	320–324

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Authors	Year	Title	Journal	Volume	Pages
Seddon et al	2013	Mid-infrared (IR) – A hot topic: The potential for using mid-IR light for non-invasive early detection of skin cancer in vivo	Physica Status Solidi (B)	250(5)	1020–1027
Javery et al	2013	FDG PET or PET/CT in patients with pancreatic cancer: when does it add to diagnostic CT or MRI?	Clinical Imaging	37(2)	295–301
Gao et al	2014	Serum Cytokeratin 19 Fragment, CK19-2G2, as a Newly Identified Biomarker for Lung Cancer	PLoS ONE	9(7)	e101979
Park et al	2014	A regeneratable, label-free, localized surface plasmon resonance (LSPR) aptasensor for the detection of ochratoxin A	Biosensors & Bioelectronics	59	321–327
Brenner et al	2014	Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies	BMJ	348(apr09 1)	g2467
Piagnerelli, et al	2015	Clinical value and impact on prognosis of peri-operative CA 19-9 serum levels in stage I and II adenocarcinoma of the pancreas	Tumor Biology	37(2)	1959–1966

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Authors	Year	Title	Journal	Volume	Pages
Raverot et al	2016	Establishment of revised diagnostic cut-offs for adrenal laboratory investigation using the new Roche Diagnostics Elecsys® Cortisol II assay	Annales D'endocrinologie	77(5)	620–622
Hirsch et al	2016	Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis	BJOG	123(11)	1761–1768
Radtke et al	2016	Multiparametric Magnetic Resonance Imaging (MRI) and MRI–Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen	European Urology	70(5)	846–853
Wang et al	2018	Novel exosome proteins as potential biomarkers for early detection of lung cancer	Journal of Cancer Diagnosis	03	N/A
Bernardi et.al	2020	Effect of implementing digital breast tomosynthesis (DBT) instead of mammography on population screening outcomes including interval cancer rates: Results of the Trento DBT pilot evaluation	Breast	50	135–140

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Authors	Year	Title	Journal	Volume	Pages
Thomsen et al	2021	Human papillomavirus (HPV) testing for cervical cancer screening in a middle-income country: comment on a large real-world implementation study in China	BMC Medicine	19(1)	N/A
Ozkan-Ariksoysal et al	2022	Current Perspectives in Graphene Oxide-Based Electrochemical Biosensors for Cancer Diagnostics	Biosensors	12(8)	607
Xiao et al	2022	Multi-omics approaches for biomarker discovery in early ovarian cancer diagnosis	EBioMedicine	79	104001
Kaur et al	2022	Nanocomposites of Carbon Quantum Dots and Graphene Quantum Dots: Environmental Applications as Sensors	Chemosensors	10(9)	367
Cheng et al	2023	Asymmetrically split DNAzyme-based colorimetric and electrochemical dual-modal biosensor for detection of breast cancer exosomal surface proteins	Biosensors and Bioelectronics	238	115552
Tutanov et al	2023	Emerging connections between GPI-anchored proteins and their extracellular carriers in colorectal cancer	Extracellular Vesicles and Circulating Nucleic Acids	4(2)	195–217

Continued on next page

Authors	Year	Title	Journal	Volume	Pages
Borah et al	2023	SP-AuNP@Tollens' complex as a highly sensitive plasmonic nanosensor for detection of formaldehyde and benzaldehyde in preserved food products	Food Chemistry	399	133975
Tobita et al	2023	Single Cycle Selection of CD63-targeting Aptamers Using a Microscale Electrophoretic Filtration Device	BUNSEKI KAGAKU	72(3)	111–116
Chung et al	2023	Harnessing liquid biopsies: Exosomes and ctDNA as minimally invasive biomarkers for precision cancer medicine	The Journal of Liquid Biopsy	2	100126

4.2. Technological modernization in cancer detection

Over the years, significant advancements in cancer detection have reshaped how we diagnose and monitor this disease. In 1971, the development of the Enzyme-linked Immunosorbent Assay (ELISA) marked a breakthrough, enabling the detection of gastrointestinal cancer biomarkers like CEA and CA 19−9. The 1980s saw the introduction of Magnetic Resonance Imaging (MRI), providing a non-invasive method for detecting breast, lung, and gynecological cancers. Furthermore, Fluorescence In Situ Hybridization (FISH) emerged to detect genetic abnormalities in cancers like multiple myeloma. During the time 1977, image-guided biopsies using ultrasound and MRI also improved biopsy precision. In 2005, Next-generation sequencing (NGS) came into play, enabling comprehensive genetic profiling across cancers. This was followed by the use of Mass Spectrometry (MS) in 2006 to analyze molecular profiles and find cancer biomarkers in blood. The introduction of Digital Breast Tomosynthesis (DBT) in 1987, which provided 3D images for breast cancer detection, was another step forward [120]. By 2013, QDots were developed to detect cancer biomarkers through fluorescence, and the NanoFlare molecular diagnostic tool emerged in 2014, offering a fresh way to identify cancer markers. Liquid biopsy also gained prominence that same year, using circulating tumor cells and cell-free DNA to detect mutations in non-small cell lung and colorectal cancers. In 2015, CancerDot, a nanosensor for prostate cancer detection, was introduced, followed by the CA 125 gold nanoparticle sensor in 1981, which was used to detect ovarian cancer biomarkers. The same year, ExoSense, a rostrum for analyzing cancer through exosomes, was developed, while MagSense, a magnetic resonance-based detection platform, offered early cancer detection. In 2018, plasmonic nanosensors using surface plasmon resonance (SPR) were introduced to detect biomarkers

like CEA and CA 19−9. Fast forward to 2023, when MIT's Bhatia Laboratory unveiled a nanoparticle-based urine test to detect cancer through biomarkers, offering a non-invasive approach for early diagnosis. That same year, Queen Mary University of London introduced a terahertz biosensor for skin cancer detection, utilizing terahertz radiation for high-sensitivity and early detection. These advancements have been packed with cancer diagnostics, bringing us closer to non-invasive, precise, and early-stage detection methods. The timeline of such is depicted in Figure 6.

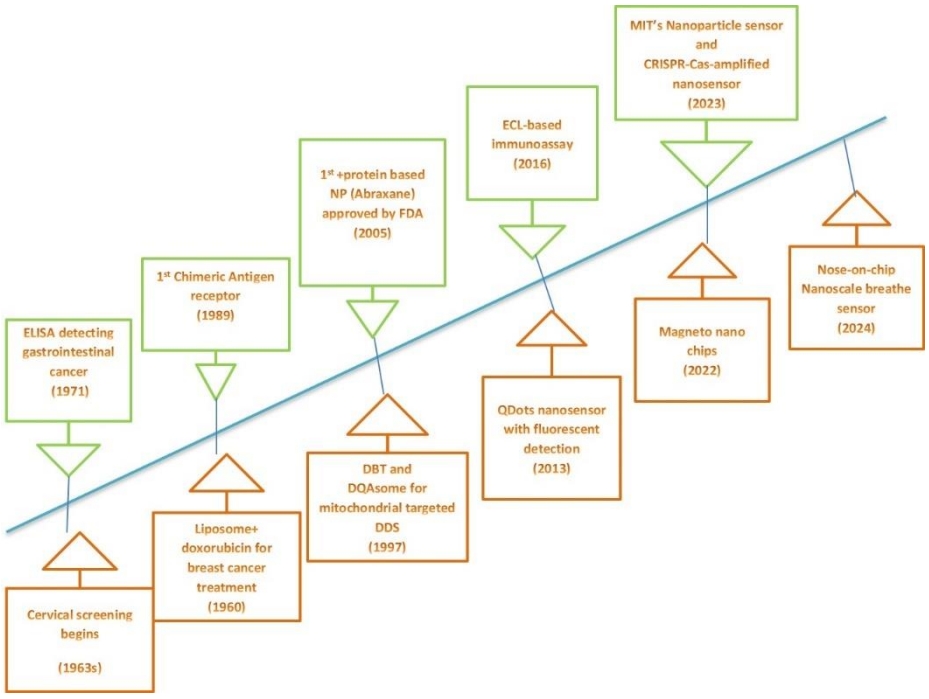

Figure 6. Historical array of progress in cancer detection.

4.2.1. Breast cancer detection using machine learning

Breast cancer risk is elevated by some gene mutations, including those in the Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) genes. These genetic anomalies can lead to a sharp increase in the risk of breast cancer. Moreover, benign lesions such as fibroadenomas may exhibit contrast enhancement on T1-weighted Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) in a manner akin to malignant lesions; in T2-weighted images, on the other hand, they often have lesser signal strength. Because of these similarities, differentiating between benign and malignant tumors can be difficult, requiring sophisticated imaging methods [121]. The goal of this is to create a deep learning-based model that can effectively identify breast cancer in digital mammograms with different densities. The removal of low-variance features, univariate feature selection, and recursive feature elimination are the three separate feature selection modules included in the suggested model. It improves detection using mediolateral and craniocaudal views of mammography. A subclass of machine learning called Convolutional Neural Networks (CNNs) is used to identify and classify invasive ductal carcinoma in images of breast cancer. These algorithms have proven to be highly accurate; in some trials, they achieved an accuracy rate of almost 88%. This is verified by contrasting its output with cutting-edge techniques for diagnosing breast cancer using histological image analysis

(HIA). With a 10-fold cross-validation approach, they evaluated classification algorithms on eight different NCD datasets [122]. The precision of the analysis was studied utilizing the area under the curve (AUC). Relevant characteristics and noisy data were problems in the non-communicable disease (NCD) datasets. The considerable robustness was shown by algorithms like Neural Networks (NN), Support Vector Machines (SVM), and K-nearest neighbors (KNN). To improve precision and eliminate superfluous elements, novel pre-processing methods were suggested. Artificial intelligence (AI) and convolutional neural networks (CNNs) may greatly enhance low-contrast features, minimize noise, eliminate artifacts, and optimize picture registration to improve medical image quality. By helping with picture segmentation and region of interest (ROI) recognition, these technologies enable accurate diagnosis and study of lesions or anatomical features. To enhance image quality, AI algorithms can modify the contrast, brightness, and intensity levels of images. They can do this with contrast-limited adaptive histogram equalization (CLAHE) [123]. CNNs can recognize and remove common artifacts from images, guaranteeing proper interpretation. AI algorithms also improve image alignment, while segmentation and ROI identification help with accurate area diagnosis and analysis. Super-resolution imaging is another application for CNNs that enhances image quality and resolution over the original acquisition. AI-driven super-resolution methods produce high-resolution images from low-resolution inputs using deep learning models, offering more detail and diagnostic data.

4.2.2. i-Genbox

An integrated gene box (i-Genbox) with a LAMP chip is part of a smartphone-based colorimetric sensor platform that has been created. Seven reaction chambers on this platform can estimate how many copies of nucleic acids are present in test materials. Furthermore, a technique that uses Phenol red as a pH-sensitive readout exhibits a favorable reaction by changing color from pink to yellow. It has been shown that monocytogenes, in which the complementary target DNA sequence stays red and the non-complementary target DNA sequence changes from red to purple, may be detected using this LAMP-based colorimetric approach [124].

4.2.3. Leukemia cancer detection

Leukemia is a disorder associated with white blood cells (WBCs) that can damage the bone marrow, blood, or both. Early-stage leukemia detection that is prompt, secure, and reliable is essential to the disease's cure and patients' survival. Acute and chronic leukemia are the two main types of leukemia, depending on advances. Both myeloid and lymphoid forms can be subdivided into each other. A system based on the Internet of Medical Things (IoMT) is presented in this study to improve leukemia identification in a safe and timely manner. Clinical devices are connected to network resources in the proposed IoMT system via cloud computing [125].

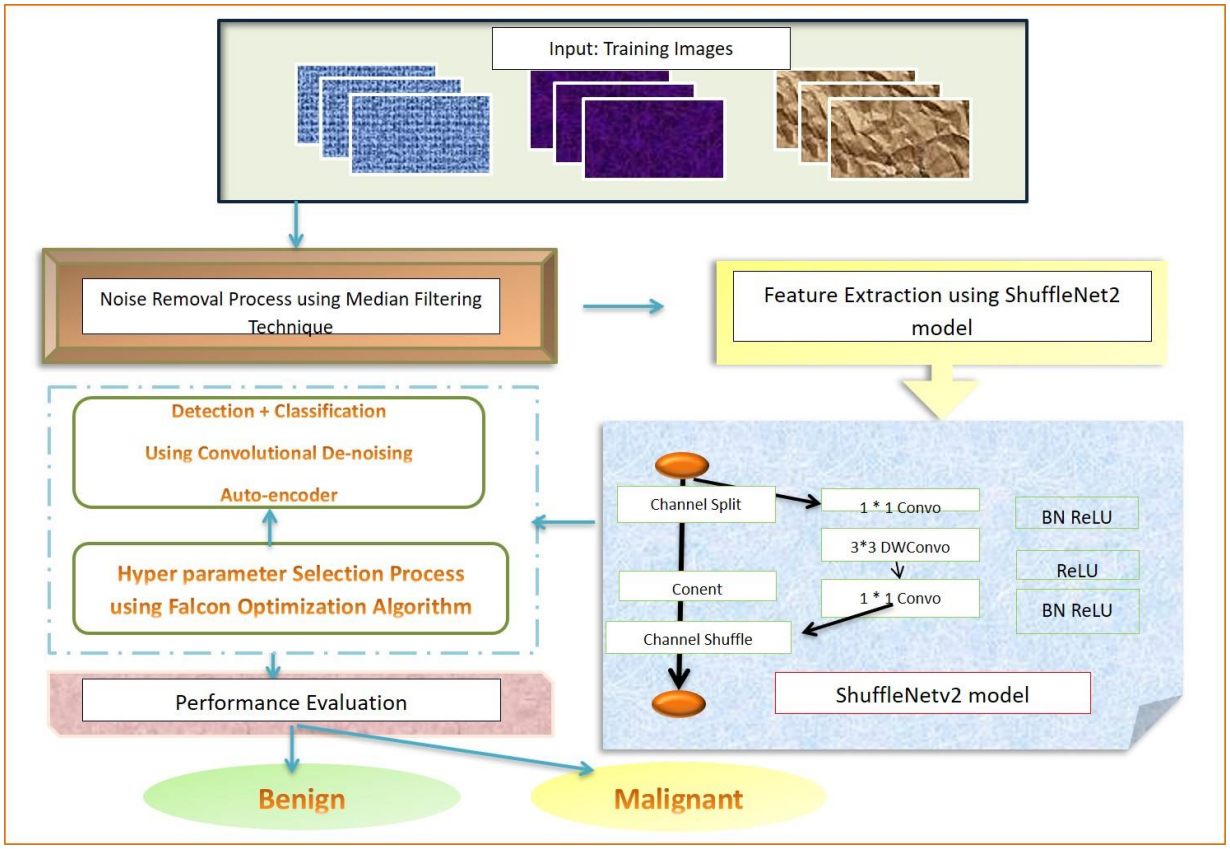

Figure 7. Automated leukemia detection and classification with deep learning and IoMT.

Patients and medical personnel can save time and effort using the system to coordinate leukemia testing, diagnosis, and treatment in real-time. In addition, patients in pandemics like COVID-19 can also benefit from the framework described to address their critical condition issues Figure 7 illustrates how advanced machine learning and deep learning techniques are employed for accurate leukemia detection and classification of subtypes. It begins with blood smear images sourced from publicly available datasets like ALL-IDB (Acute Lymphoblastic Leukemia Image Database) and ASH (American Society of Hematology) image library, uploaded via an Internet of Things (IoT)-enabled microscope to a leukemia cloud for analysis. Noise in the images is removed using Median Filtering (MF), preserving vital details essential for accurate processing. Feature extraction is performed using ShuffleNetV2, known for its efficiency in handling large datasets. For leukemia subtype classification, the framework employs Residual Convolutional Neural Network (ResNet-34) and Dense Convolutional Neural Network (DenseNet-121), which outperform traditional machine learning methods in identifying subtypes like CML (Chronic Myeloid Leukemia), ALL (Acute Lymphoblastic Leukemia), CLL (Chronic Lymphocytic Leukemia), and healthy samples [126,127]. The integration of deep transfer learning techniques enhances the detection capabilities, utilizing models like Convolutional Denoising Autoencoder (CDAE) to reconstruct clean features for precise classification. Hyperparameter tuning with the Falcon Optimization Algorithm (FOA) ensures robustness and adaptability. Relative studies show the framework's superiority, with methods like Random Forest achieving 94.3% accuracy for White Blood Cell (WBC) cancer detection, K-Nearest Neighbor (KNN) with 92.8% for ALL detection, and Support Vector Machines (SVM) reaching 95% accuracy using unsharp masking,

fuzzy clustering, and feature extraction methods [127,128]. Feature extraction using Principal Component Analysis (PCA) combined with the Artificial Bee Colony-Back Propagation Neural Network (ABC-BPNN) yields an accuracy of 98.72%. Furthermore, Discrete Orthogonal Stockwell Transform (DOST) aids in successful segmentation and classification [129,130]. The system concludes with output classification into benign or malignant conditions or further subtype classification, using robust feature extraction and classification techniques. By transposing these progressed models and IoMT (Internet of Medical Things) capabilities, the shell sets a benchmark for accurate and automated leukemia diagnosis [125,126,131].

5. Conclusion and future scope

There is great potential for the detection of gynecologic cancer in the future with the DNA-SWCNT-based photoluminescent sensor array. This method detects biomarkers HE4, CA-125, and YKL-40 in patient fluids and laboratory samples by analyzing the optical responses of DNA-SWCNT combinations using machine learning (ML) models. When these protein analytes are present, the sensor detects noticeable variations in the fluorescence peak position and intensity. Accurate biomarker categorization and concentration prediction are made possible by machine learning (ML) algorithms including support vector machine (SVM), random forest (RF), and artificial neural network (ANN). The system achieved approximately 0.95 F1 scores in lab samples from uterine lavage samples, 91% classification success for YKL-40, and 100% classification success for HE4 and CA-125 from cancer patient samples [132]. Color changes in response to the incidence of an optical signal on the test subject are used in the promising field of colorimetric cancer diagnosis using nanomaterials. There are three methods for detection: Intensity-based optical detectors, the human eye, and basic cameras. Diverse bioassays, including nanoparticles, silicon-nitride thin films, and loop-mediated isothermal amplification (LAMP), have been utilized to recognize and identify cancer-related specimens through color alterations. Green I, hydroxynaphthol blue (HNB), or propidium iodide, the LAMP bioassay dramatically multiplies DNA using DNA polymerase, resulting in color changes that are visible to the unaided eye. HNB remains blue for positive reactions and turns purple for negative ones, while propidium iodide turns orange for negative and pink for positive ones. SYBR Green I transform from orange to green. Because of sample carry-over or cross-contamination, LAMP might produce false positive results even with its great sensitivity. Real-time LAMP detection by turbidity, fluorescence resonance energy transfer, and quenching probe competition assays can be used to lessen these problems [133].

The miR-150 holds significant potential as a key biomarker and therapeutic target for future advancements in the detection and treatment of colorectal, gastric, acute myeloid leukemia, and lung cancer (LC) [134]. MiR-21 and other TEX microRNAs exosomal biomarkers for the quick and precise diagnosis of lung cancer (LC). Ion-exchange nanomembranes in microfluidic biochips enable TEXs to have a chemical affinity for the biochip surface. Emerging technologies seek to use microfluidic and electrochemical biosensing devices to directly identify TEXs from bodily fluids, in contrast to many current clinical microdevices that necessitate RNA, DNA, or protein extraction methods [135]. A nanosensor to identify circulating tumor DNA (ctDNA) is a recent discovery in cancer nanosensors. Cancer cells produce tiny DNA fragments called ctDNA into the bloodstream, which can be used in a non-invasive manner to track the development of the disease and how well a treatment is working. An Australian team of researchers at the Universities of Queensland and New South Wales has created a

graphene oxide-based nanosensor to identify low levels of ctDNA [136]. This nanosensor can identify ctDNA mutations linked to different types of cancer and is incredibly sensitive and selective. For the graphene oxide nanosensor to function, particular DNA sequences found in ctDNA must be captured and detected. It is a promising tool for early cancer detection and surveillance because of its high surface area and electrical characteristics, which enable the exact detection of biomarkers at low concentrations. Further, the detection of programmed cell death protein 1 (PD-1) and its ligand (PD-L1) has been made possible by recent advances in biosensing technologies, which have transformed cancer diagnosis and treatment. These technologies employ different transduction techniques, including electrochemical, optical, and piezoelectric sensors, along with biological recognition elements. To detect PD-L1 concentrations in cancer cell lysates and breast tumor tissues, for instance, a flow-photometric microfluidic technology with picomolar sensitivity has been created. For multiplexed biomarker detection, the device uses magnetic beads-attached nanoyeast single-chain variable segments and antibodies conjugated with fluorescent dyes. Cancers, including melanoma, hepatocellular carcinoma, and non-small cell lung cancers, are easier to diagnose and treat thanks to these advancements [137].

6. Limitations and challenges

The limitation and challenges that could be elaborated are that the use of nanomaterials in medicine is fraught with dangers, such as non-targeted dispersion that reduces signal-to-noise ratios in imaging, intricate production procedures, diminished photostability, lower biocompatibility, and possible systemic toxicity. Additionally, body fluids, including blood, may contain trace amounts of TEXs, which may cause difficulty in their detection. For detection, methods for concentrating and enriching TEXs from samples must be developed. The deep learning models such as DenseNet-121 and ResNet-34 are highly complex and often “black boxes”. This lack of interpretability can hinder understanding how decisions are made, affecting trust and adoption in clinical settings. Even though they seem promising, the cost-effectiveness of using cutting-edge technologies for leukemia detection, such as IoT-based systems and deep learning models, needs to be carefully considered, especially when compared to more conventional diagnostic techniques. Further, the CA-125 levels are not always significantly altered by early-stage ovarian cancer, which could result in missed diagnosis.

Use of Generative-AI toolstools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors report no conflict of interest in preparation of the manuscript.

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Author contributions

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