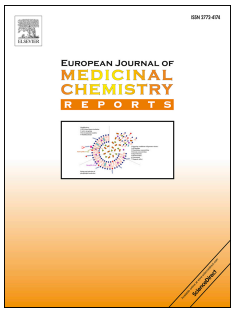

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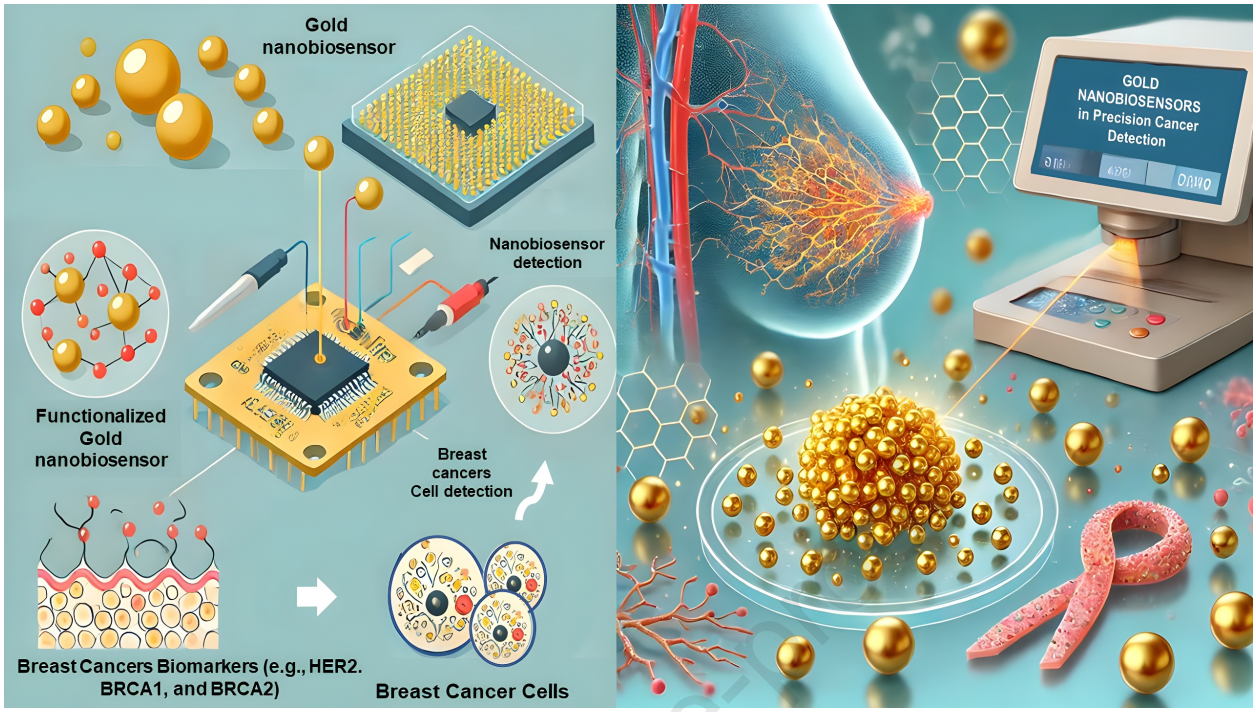

Gold Nanobiosensors: Pioneering Breakthroughs in Precision Breast Cancer Detection

Soheil Sadr[1], Ashkan Hajjafari[2], Abbas Rahdar[3*], Sadanand Pandey[4*], Parian Poorjafari Jafroodi[5], Narges Lotfalizadeh[1], Mahdi Soroushianfar[1], Shahla Salimpour Kavasebi[6], Zelal Kharaba[7], Sonia Fathi-karkan [8, 9], Hassan Borji[1*]

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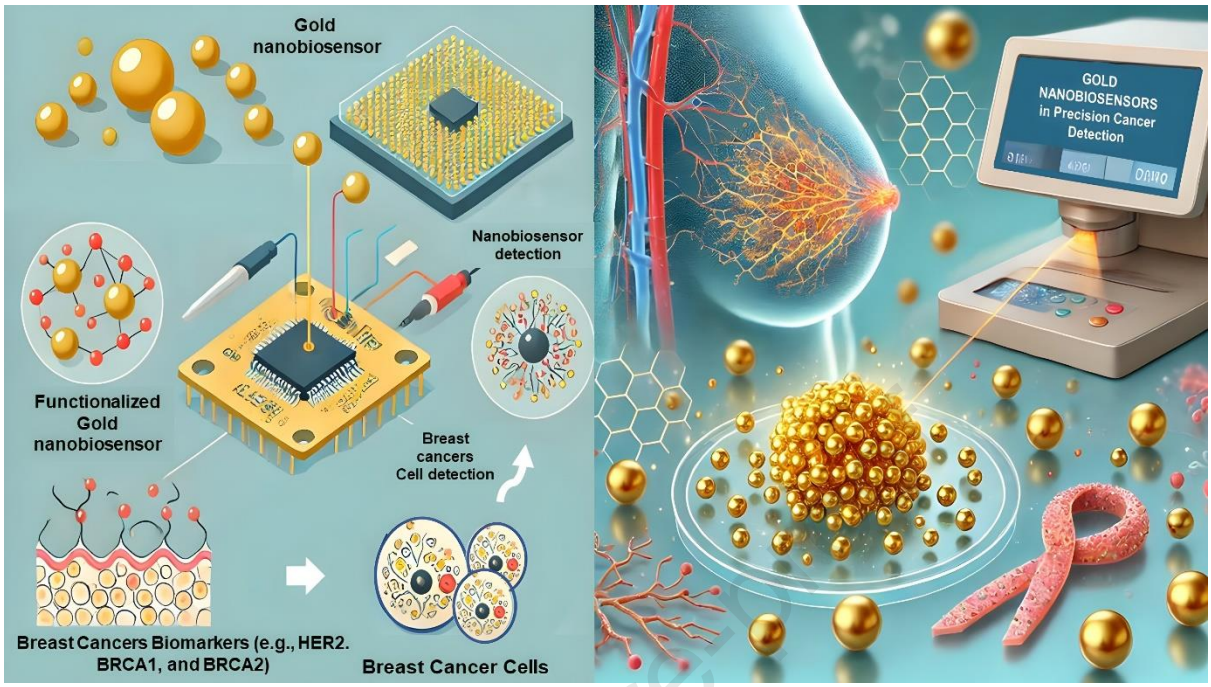
Abstract

Breast cancer is still one of the major health concerns of today's world. In light of such a scenario, regular improvement in the detection technique is crucial to meet better early diagnosis and treatment outcomes. This present work places much emphasis on gold nanobiosensors, which might be of utmost use in improving breast cancer diagnosis by the excellent sensitivity and specificity they offer for the identification of cancer-related biomarkers. These sensors take advantage of the unique optical and electric properties that gold nanoparticles have, enabling them to achieve an accurate molecular level of detection. Gold nanobiosensors have been significantly developed through innovations like signal amplification and surface functionalization, integrated with the use of advanced imaging techniques. Efforts have been done to enhance their biocompatibility, stability, and scalability for clinical applications. The integration of gold nanobiosensors with emerging technologies, including microfluidics and machine learning, opens new perspectives for personalized diagnostics and point-of-care testing in resource-constrained settings. However, further challenges lie ahead: to enhance manufacturing techniques, to conduct large-scale clinical trials, and to overcome limitations in regulations before widespread clinical applications. Continuous studies and technological advances indicate that gold nanobiosensors have the potential to significantly improve early diagnosis of breast cancer, reducing mortality rates and enhancing the care of patients.

Keywords: Breast cancer; Cancer; Nanobiosensors; Nanotechnology, Biomarkers; Diagnosis

Graphical abstract



1. Introduction

Breast cancer stands out as a global health concern and one of the most widespread malignancies (1-3). Breast cancer presents a significant challenge to the healthcare community, with over two million new cases annually, resulting in over 620,000 deaths each year (4, 5). Comprehensive prevention, detection, and treatment strategies are essential (6, 7). Early detection is critical to mitigating breast cancer's effects (8). A timely diagnosis enhances treatment prospects and contributes to a favorable prognosis (9). Despite notable advancements in medical technology, the intricacies of detecting breast cancer at its incipient stages persist (10-12). These challenges are marked by limited accessibility to screening facilities, inadequate awareness, and inherent limitations of existing diagnostic methodologies.

Nanotechnology, with its unique capabilities at the nanoscale, has emerged as a powerful force in cancer diagnosis and treatment (13). A unique approach to breast cancer is nanotechnology, aimed at detecting it early and optimizing treatment options (14, 15). Nanoparticles and nanomaterials facilitate targeted drug delivery and enable highly sensitive imaging techniques, enhancing intervention precision (16). Nanotechnology's impact on breast cancer diagnostics lies in nanobiosensors (17). Combining nanotechnology with biosensor principles, these nanoscale devices detect breast cancer biomarkers with unprecedented sensitivity and specificity (18). Nanobiosensors can identify cancer-related aberrations at a minute scale by observing molecular structures (19).

Nanotechnology integration into breast cancer diagnostics represents a significant shift with broad implications (20-22). Nanobiosensors can redefine the diagnostic landscape, providing early and precise detection (23). Gold nanobiosensors have received special attention as advanced and sensitive tools in diagnosing and managing breast cancer (24, 25). These sensors use the nanoscale properties of gold particles, such as high surface area to volume and surface

modification capability, to detect cancer-related biomolecules (26, 27). Using this technology, biomarkers associated with breast cancer can be detected at very low concentrations, which allows for an earlier and more accurate diagnosis of the disease (28, 29). Moreover, gold nanobiosensors provide the possibility of monitoring disease progression and evaluating the effectiveness of different treatments, which leads to improved management and treatment outcomes for breast cancer patients (30, 31).

The current review aims to usher in an era where early intervention becomes a powerful tool for saving lives. It also advances the global fight against breast cancer. As research in this pioneering domain continues, nanotechnology could be leveraged for enhanced breast cancer diagnostics with gold nanobiosensors. This sets the stage for significant advancements in clinical practice.

2. Limitations of Current Screening Methods

Many factors influence early breast cancer detection, from screening procedures to access to healthcare resources (32). In addition, socioeconomic factors affect the timely diagnosis of breast cancer (33, 34). It is crucial to have a comprehensive understanding to overcome barriers and enhance early detection rates (35, 36). Current screening methods for breast cancer, primarily mammography, are limited in their ability to detect cancer at its earliest stages (37, 38). Although widely used and considered the gold standard, mammography may produce false positives or negatives (39). Furthermore, dense breast tissue, which is common in many women, reduces the sensitivity of mammography. There has been growing recognition of the need for supplemental screening modalities in recent years. This is particularly true for individuals with dense breast tissue or those at high risk. Furthermore, integrating adjunctive techniques, such as ultrasound or MRI, is difficult (40). This is because they are costly, difficult

to standardize, and not widely available. The overuse of these advanced imaging modalities may strain healthcare resources and contribute to economic inequality in access to breast cancer screenings.

As an advanced scientific field, nanotechnology has found wide applications in medicine, especially in cancer diagnosis and treatment (41-43). In this field, nanobiosensors have become very sensitive tools for detecting biological molecules due to their unique nanoscale characteristics (44). Gold nanobiosensors play an important role in breast cancer diagnosis, especially due to their special electronic and chemical properties, high surface-to-volume ratio, and surface modification capability. These sensors can detect cancer-related biomarkers at very low concentrations, which enables early and more accurate diagnosis of the disease (45-47). With early diagnosis, the possibility of more effective treatment interventions and improving patient treatment results increases (48-50).

Old diagnostic methods such as mammography and biopsy usually have limitations such as low sensitivity in the early stages of the disease, the inability to accurately identify specific biomarkers and the need for invasive sampling. Gold nanobiosensors overcome these challenges by providing high accuracy, high sensitivity, and non-invasiveness in detecting biomarkers (51, 52). These sensors can react with very small changes in the level of biomarkers and provide accurate information about the disease state (53). In addition, the ability to modify the surface of gold nanobiosensors allows multiple and simultaneous detection of several biomarkers, which increases the accuracy and speed of diagnosis and thus improves the management and monitoring of breast cancer patients (54).

3. Biomarkers in Breast Cancer Detection

The complex and heterogeneous nature of breast cancer, coupled with its several genetic subtypes, demands a profound understanding of various biomarkers. These biomarkers, being increasingly and routinely adopted for clinical use, are very critical in the identification, classification, and management of breast cancer. Biomarkers are quantifiable chemicals or cellular changes which can be utilized in the identification, classification, and monitoring of disease processes. Consequently, as a result of such development in diagnostics of breast cancer, a number of biomarkers were incorporated into the clinical diagnostic strategies, presenting increasingly precise and personalized diagnostic options (55, 56).

3.1. Human Epidermal Growth Factor Receptor 2 (HER2)

HER2 is a receptor tyrosine kinase of the epidermal growth factor receptor family that controls the growth and proliferation of cells. Its overexpression or gene amplification occurs in approximately 20-30% of human breast cancers and can be associated with a worse prognosis (57, 58). HER2 status is crucial for the administration of targeted medicines, which include trastuzumab (Herceptin) and pertuzumab; these have proved quite effective against HER2-positive breast cancer (59-62). Gold nanobiosensors, developed to detect HER2 accurately with higher sensitivity, offer promising advancements in the real-time detection of HER2 levels in patients, thus enhancing early detection and effectiveness of treatment (63).

3.2. Estrogen Receptor and Progesterone Receptor

Progesterone Receptor (PR) and Estrogen Receptor (ER) status have become critical in subtyping breast cancers and the choice of treatment (64, 65). Generally, cancers that are positive for estrogen receptor and/or progesterone receptor have a better response to the endocrine treatments such as tamoxifen or aromatase inhibitors (66, 67). Gold nanobiosensors also have higher sensitivity with respect to the levels of ER and PR compared to traditional techniques; thus, they allow for more precise determination of the status of hormone receptors and help clinicians optimize the treatment of hormones (68, 69).

3.3. Ki-67

Ki-67 is a proliferation marker that represents the growth fraction of neoplastic cells. High levels of Ki-67 expression are associated with more aggressive types of tumors and higher recurrence rates (70). Clinical applications include assessment of tumor aggressiveness and the basis for adjuvant treatment decisions. Gold nanobiosensors have been developed to detect Ki-67 at lower levels, allowing monitoring of changes in tumor growth over the course of therapy (71-73).

3.4. BRCA1 and BRCA2 mutations

Several genes are responsible for repairing DNA, including BRCA1 and BRCA2 (74). Cancers of the breast, ovary, and other organs are more likely to develop when one of these genes is mutated (75, 76). Through genetic testing, individuals with BRCA1/2 mutations potentially have an increased cancer risk, as well as the possibility of receiving targeted therapy using PARP inhibitors (77-79).

3.5. Mutations in BRCA1 and BRCA2

Mutations in the BRCA1 and BRCA2 genes significantly increase the risk for carcinomas of the breast and ovaries (80). Clinical use of genetic testing to identify such individuals at increased risk, especially those that will benefit from treatment with PARP inhibitors, is extremely widespread. Gold nanobiosensors make for more sensitive and more accurate detection of BRCA1/2 mutations and may, in the future, simplify genetic testing and speed up the identification of mutant carriers (81).

3.6. TP53 mutation

TP53 is a cell-cycle regulatory gene whose mutations have been associated with the more aggressive subtypes of breast cancers and linked to poor prognosis. TP53-mutant cancers have developed resistance against certain medicines that may influence the treatment modalities (82-84). Recently, the development of gold nanobiosensors that can detect TP53 mutations opens

up new directions in real-time evaluation of TP53 status and its implications on therapy response (85, 86).

3.7. Cyclin D1

Cyclin D1 is a cell cycle-regulating protein. Overexpression of cyclin D1 has frequently been found in hormone receptor-positive breast tumors (87, 88). The status of cyclin D1 expression might give important prognostic information and support the therapeutic decisions especially in endocrine therapy (89, 90). Gold nanobiosensors can give more power to this cyclin D1 detection and, thus, further enhance the diagnostic accuracy of molecular diagnostics (91).

3.8. Epidermal Growth Factor Receptor (EGFR)

EGFR is a member of the epidermal growth factor receptor family that plays an important role in cell proliferation (92, 93). The overexpression of EGFR is usually found in TNBC, generally devoid of the expressions of ER, PR, and HER2. This subtype of cancer often shows more aggressive behavior and is more resistant to treatment (94, 95). Medications targeting EGFR are under study for TNBC, and gold nanobiosensors provide a very sensitive method of assessing the level of EGFR to optimize available options for this challenging subtype (96-98).

3.9. CA 15-3 and CA 27.29

CA 15-3 and CA 27.29 are blood biomarkers that reflect the extent of disease in breast cancer, especially in metastatic disease (99-101). The higher levels indicate that the disease is highly advanced or recurrence has taken place. Clinicians use these biomarkers for appropriate treatment selection and assessment of the overall response of patients. It is expected that gold nanobiosensors could bring a change in the diagnostics of CA 15-3 and CA 27.29 by improving sensitivity and allowing early detection of metastasis or recurrence (102, 103).

3.10. Phosphatase and Tensin Homolog PTEN

PTEN is a tumor suppressor gene that regulates cellular growth and division. Loss of PTEN function is associated with aggressive features of breast cancer and poor prognosis (104-106).

Gold nanobiosensors enhance the sensitivity of PTEN abnormality detection that may enable the selection of patients for targeted therapy and improve prognostic accuracy (107-110).

3.11. MicroRNA

miRNAs are small, non-coding RNA molecules with role in the regulation of genes. The dysregulation of some miRNAs, such as miR-21 and miR-155, has been implicated in the development and progression of breast cancer (111, 112). miRNA expression profiling is increasingly being utilized as a non-invasive diagnostic and prognostic tool. Gold nanobiosensors have enormous potential for miRNA detection at low levels and hence provide a successful platform for early detection of breast cancer and follow-up on the disease process (113-115).

3.12. Vascular Endothelial Growth Factor (VEGF)

VEGF is an important angiogenic factor that plays a significant role in tumor proliferation and metastasis. It mediates the formation of new blood vessels (116). VEGF expression analysis may support the use of anti-angiogenic drugs in the treatment of breast cancer. The sensitivity of detection of VEGF levels has been enhanced by Gold nanobiosensors, hence permitting personalized anti-angiogenic treatments (117, 118).

3.13. MammaPrint and Oncotype DX

MammaPrint and Oncotype DX are genetic tests that determine the likelihood of recurrence of the breast cancer (119, 120). These tests help the clinician to decide on the use of adjuvant chemotherapy based on the genetic profile of the tumor. Gold nanobiosensors can further improve genomic tests by offering rapid and more sensitive assessment of the genetic makeup of the tumor which can assist in making better therapeutic decisions (121-123).

3.14. Carbonic Anhydrase IX (CAIX)

CAIX is a transmembrane protein associated with hypoxia within the tumor microenvironment. High levels of CAIX expression in tumors correlate with increased aggressiveness and/or

resistance to specific therapies (124). The level of CAIX, as determined by gold nanobiosensors may indicate the resilience of a tumor toward hypoxia thus allowing for therapeutic interventions that need to be invoked (125, 126).

3.15. $p16^{INK4a}$

$P16^{INK4a}$ is the inhibitor of cyclin-dependent kinases that regulate the cell cycle. Aberrant expression of $P16^{INK4a}$ may indicate abnormalities in the cell cycle, manifesting aggressive features of the tumor (127, 128). Gold nanobiosensors enhance the detection of levels of $P16^{INK4a}$, enabling more accurate decisions on prognostic and therapeutic options (129).

3.16. PAM50

PAM50 gene signature classifies a breast tumour into the following molecular subtypes: luminal A, luminal B, HER2-enriched, basal-like and normal-like. The classification yields critical information concerning the prognosis and formulation of the method of treatment. Gold nanobiosensors can enhance the accuracy of molecular profiling using the PAM50 and hence increase the accuracy of the classification of breast cancer to enable personalized therapy approaches (130, 131).

3.17. Nipple Aspirate Fluid (NAF)

NAF represents a complex mixture of proteins and genetic material that are secreted by ductal epithelium lining the breast. Testing of the NAF is lately becoming a promising non-invasive biomarker for an early diagnosis of breast cancer (132). Gold nanobiosensors amplify the sensitivity in the trace of biomarkers in the NAF; hence, may be utilized as a complementary diagnostic tool to the traditional techniques of screening (133).

3.18. Human Epididymis Protein 4 (HE4)

Conventional biomarker for ovarian cancer, HE4 has now also been identified as a biomarker for breast cancer, particularly in postmenopausal women. It is believed that higher levels of HE4 might contribute to a risk in the development of breast cancer (134). Gold nanobiosensors

could contribute to the development of early detection strategies that classify patients into different groups based on the levels of HE4 and thereby increase diagnostic accuracy (135).

3.19. GATA Binding Protein 3 (GATA3)

GATA3 is a transcription factor associated with the luminal subtypes of breast cancer (136). It is related to hormone receptor status and has predictive value. Gold nanobiosensors are capable of detecting the expression of GATA3, hence improving molecular subtyping to support treatments (137).

3.20. HOX transcript antisense RNA

HOTAIR is a long non-coding RNA associated with metastasis in breast cancer. Overexpression of HOTAIR means poorer prognosis and more aggressive tumor behavior (138). Gold nanobiosensors enable measurement of the levels of HOTAIR and are important for insights into the management of metastatic disease, thus altering treatment modalities (**Figure 1**) (139, 140).

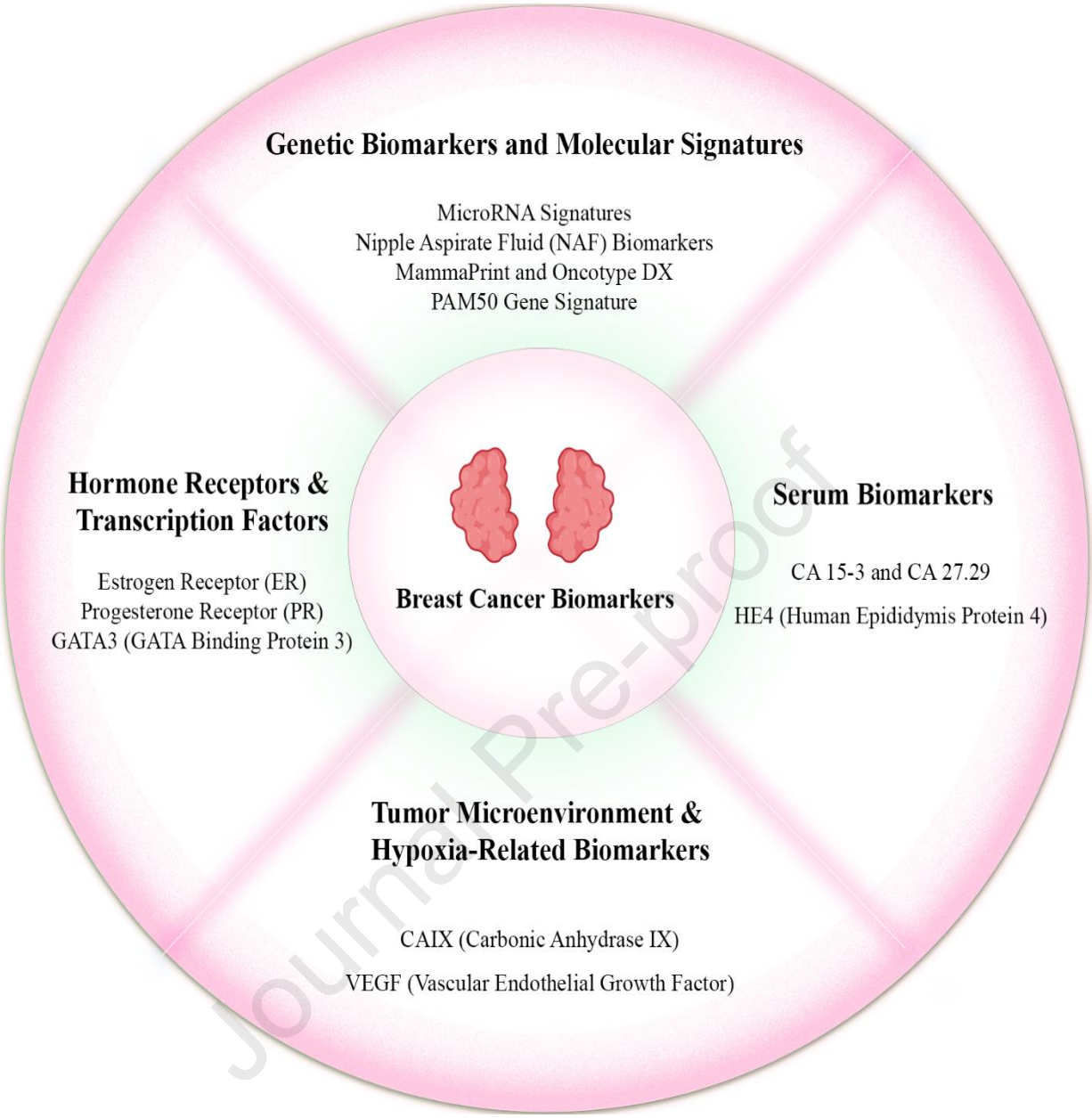


Figure 1: Breast cancer biomarkers

The interplay among these markers is critical to understanding the biology of breast cancer and thus to providing personalized therapy. Most HER2-positive cancers have high Ki-67 expression, indicative of rapid cellular proliferation and, therefore, a more aggressive disease phenotype. Often, tumors that are positive for ER tend to have an absence of the HER2 overexpression, thereby resulting in distinct clinical behaviors compared to malignant diseases with overexpression of HER2. BRCA1 mutations were also associated with TNBC defined by

the absence of ER, PR, and HER2, thus making treatment notoriously difficult. It can be designed that the multiplexed detection with the gold nanobiosensors is accomplished, thereby the measurement of numerous biomarkers in parallel may be allowed with more detailed insight into the molecular tumor profile.

4. Gold nanobiosensors

The major of breast cancer treatment is being revolutionized with a novel nano biosensor technique called nano biosensors, suggesting new sensitivity and accuracy that detects biomarkers related to the disorder. Mixing biosensing and nanotechnology enables nanobiosensors to make small tools able to detect cellular and molecular changes related to breast cancer. Gold nanoparticles are excellent nanobiosensors for their distinctive electronic and optical features. AuNPs via functionalized surface chemistry can be explored by analyzing the interaction between quantifying optical properties and target biomarkers. AuNP-biosensors can detect breast cancer nucleic acids and antigens. Therefore, specificity can be increased by modifying detection procedures.

A nanocomposite material, including nanostructured polyaniline and gold nanoparticle-grafted graphene, showed more than 90% efficacy in detecting label-free breast cancer cells in whole blood without needing cell staining and sample preparation (30). A recent study has also developed a very sensitive electrochemical biosensor to detect multiple miRNAs by enhancing silver-gold nanoparticles with tagged metal ions, paired with a reduction graphene oxide/poly(2-aminobenzylamine)/gold nanoparticle electrode (141). This electrode is designed to enhance porous, hollow silver-gold nanoparticles with metal ions. This advanced electrochemical system shows great stability, selectivity, and sensitivity.

A gold platinum bimetallic nanoparticle (AuPtBNPs)/3-aminopropyltriethoxy silane (APTS) nanocomposite containing a Fluorine-doped Tin Oxide (FTO) coating was also developed for the detection of miRNA-21 using hybridization using an electrochemical biosensor for the

detection of miRNA-21 detected using a gold platinum bimetallic nanoparticle (AuPtBNPs)/3-aminoprop (142). The biosensor in serum samples showed great performance.

A new electrochemical DNA (E-DNA) biosensing method for the detection of the breast cancer susceptibility gene (BRCA-1) was synthesized by means of a gold nanoparticles-reduced graphene oxide (AuNPs-GO) covered with a layer of molecularly imprinted polymers (MIPs) and improved glass carbon electrode (GCE) (143). Signal magnification was accomplished via SiO_2@Ag NPs as a tracing tag, and the biosensor showed a broad linear limit (10 fM - 100 nM), a low detection range of 2.53 fM, reproducibility, excellent selectivity, feasibility, and stability in serum analysis. In addition, bioconjugated gold nanorods (GNR@Pd SSs—Apt—HRP) were studied to create a DNA tetrahedron biosensor for HER2 (144). DNA tetrahedrons considerably enhanced the detection potential towards HER2 compared with ss-DNA-based aptamers. Moreover, gold nanoparticles were utilized to make a plasmonic nanobiosensor for early cancer discovery, indicating bright results in nanoantenna-based wireless communication, microwave transmission, and surface plasmonic resonance. This provides a flexible system for tumor diagnosis.

Scientists planned an optical sensor for the early discovery of HER2-positive breast cancer via direct interaction of trastuzumab (Herceptin) with surface-mediated AuNPs using Localized Surface Plasmon Resonance (LSPR) (145). The AuNPs were designed with negatively charged citrate ions, showing improved direct-surface interactions with HER antibody; mixing with AgNPs, the sensor shows improved sensitivity and specify with a linear detection limit and a fast action time of less than 1 minute, which shows its strength for early breast cancer diagnostic.

Sensory interfaces were prepared through the modification of a glassy carbon electrode with highly cross-linked PEG film containing amine groups, followed by the self-assembly of gold nanoparticles and the immobilization of BRCA1 complementary single-strand 19-mer

oligonucleotides. The sensor verified great sensitivity with a broad linear range (50.0 fM-1.0 nM) with a low detection limit (1.72 fM), showing its capability for breast cancer treatment used in the clinical investigation of BRCA1 in the serum samples (146). Additionally, a label-free electrochemical immunosensor for CEA detection was developed using a three-dimensional (3D) gold nanoparticle/prussian blue-poly(3,4-ethylenedioxythiophene) (AuNPs/PB-PEDOT) nanocomposite (147). Therefore, nanocomposite with a hierarchical and 3D porous nanostructure helped as both 3D matrices and electron mediators in the immunosensor, showing a linear reaction to CEA concentrations 0.05-40 ng/mL, with a low detection range of 0.01 ng/mL, with excellent selectivity, repeatability and stability for possible use for real sample analysis.

A composite made of graphene oxide, chitosan, and gold has been investigated as an electrochemical aptasensor that can detect breast cancer cells (MCF-7) without requiring ultrasensitive aptasensor labels (26). Additionally, a nanosensor array was introduced using gradually functionalized gas chromatography-mass spectrometry (GC-MS) gold nanoparticles to differentiate between breath volatile organic compounds (VOCs) related to healthy states and lung, colorectal, breast, and prostate cancers. The nanosensor array successfully differentiated between healthy and cancerous breath and classified breath designs for cancer forms, suggesting the possibility of a non-invasive and cheap diagnostic device for cancer discovery.

Graphene oxide (GO) sheets and thiolated probe-functionalized gold nanorods (GNRs) have been combined to develop an electrochemical nanobiosensor to detect plasma miR-155, a circulating miRNA associated with cancer (25). Detection limits of 0.6 fM were achieved with the nanobiosensor based on miR-155 concentrations of 2.0 fM to 8.0 pM. Besides showing excellent storage ability, the sensor demonstrated high specificity and distinguished between closely related targets. An efficient electrochemical immunoassay for CEA has also been

developed by combining a magnetic nanocore with electroactive poly(o-phenylenediamine) (PPD) and a silver metallic shell. Using nanogold-patterned graphene oxide nanoscale (AuNP-GO) as the secondary antibody, the immunocomposites showed great electrochemical reactions, allowing the CEA sensitive detection down to 1.0 pg/mL with good precision in clinical serum specimens (148). Moreover, a nanocomposite of Au nanoparticles with a GO-based organic molecule (GO) was developed, as well as an Ionic Liquid (IL) to improve a biosensor that can detect CD44 (149). The GO was displayed for its oxygen-containing functionality to enable the immobilization of antibodies. At the same time, the AuNPs improved the performance of the biosensors by growing the effective surface area and facilitating charge transfer.

In a recent study, researchers developed an electrochemical biosensor to detect cancer antigen 15-3 and miRNA-21 simultaneously (150). This was achieved by modifying a screen-printed carbon electrode (SPCE) using a nanocomposite made of GO, poly(3-aminobenzylamine), molybdenum selenide (MoSe2), and AuNPs. Moreover, a biosensor for analyzing MUC1 by using a combination of gold platinum bimetallic nanoparticles (Au-PtBNPs) and carboxylated graphene oxides (CGO) was developed to modify the surface of a Fluorine-doped Tin Oxide electrode (FTO) (151). Including Au-PtBNPs enhanced the electrode's conductivity, resulting in a biosensor that exhibited excellent discrimination of the MUC1 biomarker. According to a previous study, a nanocomposite based on hierarchical flower-like gold, poly(n-butyl acrylate), and MXene was developed as an innovative electrochemical biosensor (AuHFGNs/PnBA-MXene) (152). This biosensor was activated by highly specific antisense single-stranded DNA and showed promise for detecting miRNA-122, a breast cancer biomarker. When tested on breast cancer miRNAs obtained from actual serum samples, the biosensor achieved 100% specificity and sensitivity, outperforming RT-qPCR in terms of specificity, sensitivity, and

detection limit. These results highlight the potential of this biosensor for clinical diagnostic applications.

In another study, two different DNA (ERBB2c and CD24c) modified AuNPs and GO loaded on glassy carbon electrodes prepared by electrochemical detection of HER2 for early detection of breast cancer (153). Detection limits of 0.16 nM and 0.23 nM were observed with a sensitivity of 219 nA/nM and 378 nA/nM for CD24 and ERBB2, respectively.

Furthermore, a method was presented for electrochemical determination of the breast cancer biomarker HER2 (154). A GCE was modified with densely packed AuNPs placed on a composite consisting of electrochemically reduced graphene oxide and single-walled carbon nanotubes (ErGO-SWCNTs). This method showed a low limit of detection of 50 $fg \cdot mL^{-1}$ and an analytical range of 0.1 $pg \cdot mL^{-1}$ to 1 $ng \cdot mL^{-1}$.

In another study, a sandwich-type sensitive voltammetric immunosensor for HER2 detection was conducted (155). The electrochemical immunosensor was developed based on gold nanoparticles decorated copper-organic framework (AuNPs/Cu-MOF) and quaternary chalcogenide with platinum-doped graphitic carbon nitride (g-C_3N_4). This immunosensor demonstrated high sensitivity with a detection limit of 3.00 fg mL−1.

Moreover, another study was conducted to fabricate a sandwich–type electrochemical aptasensor for the simultaneous determination of CEA and cancer antigen 15–3 (CA 15–3) (156). Gold nanoparticles three–dimensional graphene hydrogel (AuNPs/3DGH) nanocomposite used as a biosensing substrate. CEA and CA 15–3 aptamers linked to AuNPs/redox probe/graphene nanocomposite were used as biosensing probes. The detection limits of CEA and CA 15–3 was 11.2 pg mL^{-1} and 11.2×10^{-2} U mL^{-1}, respectively.

An enhanced signal method using gold nanoclusters encapsulated in mesoporous silica nanoparticles (MSNs) has been devised for the early and accurate detection of breast cancer cells. The use of MSNs for enzyme immobilization and gold nanoclusters as a peroxidase

mimic improves sensitivity. HER2 antibodies that are target-specific also improve selectivity. This biosensor design has potential uses in clinical diagnostics and bioanalysis (157).

In another study, researchers developed an electrochemical biosensor for HER2 based on a gold nanoparticle-aptamer bioconjugate (AuNP@HER2 aptamer) and explored the interaction between HER2 and DNA aptamer using computational methods (158). For this study, the limit of detection, the linear range of HER2, precision, and accuracy were 1.52 ng mL^{-1}, 0.01 to 15.0 ng mL^{-1}, 0.1298, and 94.06%, respectively.

An electrochemical immunosensor was constructed for the detection of human epidermal growth factor receptor 2 (HER2) and its overexpressing breast cancer cells. The sensor probe was immobilized onto AuNPs, while a hydrazine-AuNP-aptamer bioconjugate was used for the selective reduction of silver ions. This sensor showed discrimination between HER2-positive and HER2-negative breast cancer cells, presenting an ultrasensitive detection method (159). In addition another electrochemical cytosensor with high sensitivity and specificity was designed so that CTCs can be detected with the use of reduced graphene oxide/gold nanoparticle composites (rGO/AuNPs composites) as the support material and copper oxide (CuO) nanozymes as the catalyst (160). The cytosensor effectively recognized the specific mucin 1 protein (MUC-1) overexpressed on MCF-7 cell membranes through surface interaction with MUC-1 aptamer. Another study investigated an electrochemical DNA biosensor utilizing zinc oxide nanowires (ZnONWs) on gold surfaces to detect the BRCA1 gene (161). The biosensor exhibited a detection limit of 3.32 μM and could detect BRCA1 within a concentration range of 10.0 to 100.0 μM. This demonstrated the potential of ZnONWs/Au platforms for biosensor development, offering a promising technique for detecting genes associated with breast cancer, such as BRCA2 and p53, in more complex array formats (**Figure 2**) (**Table 1**). A separate research created an electrochemical DNA sensor for the precise detection of BRCA1, a biomarker essential for the early identification and treatment

of breast cancer. The sensor employs a DNA tetrahedral-structured probe (TSP) and poly-adenine (polyA) mediated gold nanoparticles (AuNPs). The sensor attained a minimal detection limit of 0.1 fM, with prospective applications in the early clinical diagnosis of breast cancer (162).

Figure 2. GNR@Pd SSs—Apt—HRP and HER2 detection. A) illustrates the schematic representation of a DNA nanostructured biosensor developed for the sensitive analysis of HER2**.** B) To enhance specificity and efficiency in HER2 detection, the clean Au electrode surface was decorated with DNA tetrahedron through the formation of an Au-S bond. Following HER2 capture, the synthesized GNR@Pd SSs—Apt—HRP were attached to HER2 via the strong affinity of the HB5 aptamer.

Table 1. The present table summarizes the current studies regarding AuNP-biosensors detecting breast cancer nucleic acids and antigens.

Method	Result	Author Names
Electrochemical biosensor for miRNA detection using silver-gold nanoparticles enhanced with metal ions and graphene oxide/poly(2-aminobenzylamine)/gold nanoparticle electrode.	The system shows great stability, selectivity, and sensitivity.	Pimalai D et al. (2021)(141)
AuPtBNPs/APTS nanocomposite with FTO coating for miRNA-21 detection through hybridization using an electrochemical biosensor.	The biosensor showed great performance in serum samples.	Bharti, A., et al. (2020)(142)
E-DNA biosensing for BRCA-1 detection using AuNPs-GO covered with MIPs and improved GCE, with SiO2@Ag NPs as a tag.	The biosensor showed a broad linear limit (10 fM - 100 nM), low detection of 2.53 fM, selectivity, feasibility, and stability in serum analysis.	(143) Bagheri, E., et al. (2020)(143)
DNA tetrahedron biosensor for HER2 detection using bioconjugated gold nanorods (GNR@Pd SSs—Apt—HRP).	DNA tetrahedrons enhanced detection potential compared to ss-DNA-based aptamers.	Chen, D., et al. (2019)(144)
Optical sensor for HER2-positive breast cancer detection using AuNPs with LSPR, mixed with AgNPs.	Improved sensitivity and specificity with a linear detection limit and fast action time (<1 minute).	Shahbazi, N., et al. (2022)(145)
PEG-gold nanoparticle biosensor for BRCA1 detection.	Great sensitivity with a broad linear range (50.0 fM-1.0 nM) and low detection limit (1.72 fM), showing potential for clinical investigation.	Wang, W., et al. (2015)(146)
Label-free electrochemical immunosensor for CEA detection using 3D AuNPs/PB-PEDOT nanocomposite.	Linear response to CEA concentrations (0.05-40 ng/mL), with low detection range (0.01 ng/mL), selectivity, repeatability, and stability.	Yang, T., et al. (2017) (147)

Electrochemical nanobiosensor for plasma miR-155 detection using GO sheets and thiolated gold nanorods (GNRs).	Detection limits of 0.6 fM with excellent storage ability and specificity.	Azimzadeh, M., et al. (2016)(25)
Electrochemical immunoassay for CEA detection using magnetic nanocore and silver metallic shell, with AuNP-GO as secondary antibody.	Sensitive detection of CEA down to 1.0 pg/mL with good precision in clinical serum samples.	Chen, H., et al. (2012)(148)
Nanocomposite biosensor using AuNPs, GO, and IL to detect CD44.	Improved biosensor performance by increasing surface area and facilitating charge transfer.	Ranjan, P., et al. (2022)(149)
Electrochemical biosensor for simultaneous detection of cancer antigen 15-3 and miRNA-21 using modified SPCE with GO, MoSe2, and AuNPs.	The biosensor showed excellent discrimination of biomarkers.	Pothipor, C., et al. (2022)(150)
Biosensor for MUC1 detection using AuPtBNPs and CGO to modify FTO electrode.	The electrode's conductivity was enhanced, showing excellent biomarker discrimination.	Bharti, A., et al. (2019)(151)
AuHFGNs/PnBA-MXene nanocomposite electrochemical biosensor for miRNA-122 detection.	Achieved 100% specificity and sensitivity, outperforming RT-qPCR.	Ranjbari, S., et al. (2023)(152)
AuNPs and GO-modified GCE for electrochemical detection of HER2 using DNA (ERBB2c and CD24c).	Detection limits of 0.16 nM and 0.23 nM with high sensitivity.	Saeed, A. A., et al. (2017)(153)
Electrochemical detection of HER2 using GCE modified with AuNPs, ErGO-SWCNTs.	Low detection limit of 50 fg·mL−1 and wide analytical range.	Rostamabadi, P. F. and E. Heydari-Bafrooei. (2019)(154)
Sandwich-type immunosensor for HER2 detection using AuNPs/Cu-MOF and g-C3N4.	High sensitivity with detection limit of 3.00 fg mL−1.	Yola ML. (2021)(155)
Electrochemical aptasensor for CEA and CA 15-3 detection using AuNPs/3DGH nanocomposite.	Detection limits of CEA and CA 15–3 was 11.2 pg mL–1 and 11.2 × 10–2 U mL–1, respectively.	Shekari, Z., et al. (2021)(156)
Electrochemical biosensor for HER2 detection using AuNP@HER2 aptamer.	Detection limit of 1.52 ng mL–1 with good precision and accuracy.	Hartati, Y, W., et al. (2021)(158)

Electrochemical DNA biosensor using ZnONWs on gold surfaces for BRCA1 detection.	Detection limit of 3.32 μM within a range of 10.0 to 100.0 μM.	Ranjbari, S., et al. (2023) (161)

Overall, Nanotechnology, particularly through the use of gold nanobiosensors, offers transformative potential for enhancing breast cancer diagnosis. These nanoscale sensors take advantage of the unique optical, electronic, and surface properties of gold nanoparticles, allowing for highly sensitive detection of cancer-related biomarkers at molecular levels. By integrating with biosensing technologies, nanobiosensors can detect subtle cellular changes, even at early disease stages, leading to more precise and earlier diagnoses than conventional methods. Moreover, gold nanobiosensors can be functionalized to target specific biomarkers, such as HER2, BRCA1, and CEA, significantly improving the specificity and accuracy of detection. This technology also enables non-invasive, real-time monitoring of cancer progression, providing clinicians with valuable insights into the disease's molecular profile. As nanotechnology continues to evolve, its integration into clinical diagnostics promises to revolutionize breast cancer screening, offering quicker, more accurate, and personalized diagnostic options, ultimately contributing to improved patient outcomes.

4.1. Current Clinical Applications of Gold Nanobiosensors

Gold nanobiosensors have shown excellent sensitivity and specificity regarding the detection of biomarkers related to breast cancer in preclinical and laboratory settings, although clinical translation is yet under development. Gold nanobiosensors are still at the experimental and developing phase. There is a number of promising investigations and clinical trials underway to determine the diagnostic practical efficacy of this new diagnosis, especially for early breast cancer detection and treatment monitoring.

These include liquid biopsies, where the gold nanobiosensors are now being explored for their capabilities of detecting ctDNA and miRNAs associated with breast cancer. Clinical study has reported that one biosensor based on AuNPs/GQDs/GO showed high sensitivity and specificity for detecting miRNA-21, miRNA-155, and miRNA-210—known biomarkers of breast cancer—in blood samples. The biosensor exhibited detection limits of 0.04, 0.33, and 0.28 fM, and showed excellent repeatability and selectivity. This offers a wide dynamic range from 0.001 to 1000 pM and represents a non-invasive way of observing the development or recurrence of breast cancer, potentially avoiding the need for invasive tissue samples (163).

A biosensor enhanced by gold nanoclusters entrapped in mesoporous silica nanoparticles (MSNs) was tested clinically to detect HER2-positive breast cancer cells. This biosensor showed a high sensitivity rate, leveraging MSNs as an enzyme immobilization support and gold nanoclusters as a peroxidase mimic. The inclusion of target-specific HER2 antibodies added excellent selectivity. This capability to measure HER2+ cancer cells in breast cancer tissue directly from samples provides a quick and reliable diagnostic tool, potentially speeding up treatment decisions (157).

Further, gold nanobiosensors are put into point-of-care devices intended for diagnosis of breast cancer, with the aim of extending diagnostics to the patients directly. One study evaluated the performance of a disposable voltammetric immunosensor modified with gold nanoparticles to measure CA 15-3 in human saliva and serum samples. The sensor, characterized by atomic force microscopy and electrochemical analysis, showed a linear range between 2 and 16 U/mL, a sensitivity of 0.012 μA/U mL^{-1}, a detection limit of 0.56 U/mL, and minimal interference. These findings suggest that gold nanobiosensors have the potential for real-time biomarker monitoring in decentralized health settings, such as community clinics or resource-poor regions (164).

Meanwhile, clinical trials have started to test the efficacy of gold nanoparticle-based plasmonic sensors in detecting biomarkers linked to breast cancer, such as BRCA1 and BRCA2. These trials are crucial for confirming the suitability of gold nanobiosensors for regular screening and diagnosis of breast cancer. In one study, the sensor identified BRCA mutations with a detection limit of 10 fM, showing significant potential (165).

4.2. Path to Clinical Adoption

Notwithstanding such developments, there are still some obstacles that need to be resolved before gold nanobiosensors can find their proper place in the clinical domain. First, there is a regulatory process. For safety, efficacy, and reproducibility, gold nanobiosensors should be strictly validated and clinically tested by regulatory bodies such as the U.S. Food and Drug Administration and the European Medicines Agency. Besides, clinical studies would be required to establish diagnostic validity and long-term safety and potential toxicity risks associated with the use of nanoparticles in the human body (166, 167).

Scalability in the fabrication of nanobiosensors remains an important challenge. Batch-to-batch variation during fabrication may result in non-uniform sensor performance, thereby impeding clinical translation. Strategies under study toward scalable and low-cost manufacturing include roll-to-roll processing and automated assembly techniques of nanoparticles to ensure reproducibility in manufacturing (164).

Finally, gold nanobiosensors have been incorporated into personalized medicine systems so that their applications could be made in conjunction with other sophisticated diagnostic tools, which include machine learning algorithms and artificial intelligence. AI-enabled analysis of the complex data generated in gold nanobiosensors can enhance diagnostic accuracy and allow therapy personalization based on a unique biomarker profile of individual patients. In this respect, nanotechnology blended with AI may represent the huge next step in treating breast

cancer because of the detection at an earlier stage, as well as treatments fitted to specific individuals (168).

5. Challenges and future Directions

The integration of nanotechnology into diagnostics for breast cancer-with main contributions from gold nanobiosensors-is highly promising. Yet, some basic principles and issues must be tamed for practical applications. The basis for the action of nanobiosensors is based on the specific features of nanomaterials, mainly optical and electric characteristics of gold nanoparticles, which give a chance for highly sensitive and specific detection of biomarkers of breast cancer. Performance of such nature for these sensors is realized through mechanisms such as LSPR and amplification of signals, improving the capability for the detection of low concentrations of disease markers such as HER2 and BRCA1 (169, 170). Functionalized surface chemistry that these biosensors are based on encourages specific molecular interaction with certain cancer biomarkers and hence allows for accurate and early detection. However, despite strong scientific bases that support their effectiveness, several critical challenges remain to be overcome if this technology is to see wider clinical applications (170).

The most immediate challenge in the clinical deployment of nanobiosensors involves the standardization and thorough validation of such technologies. In fact, the performances of nanobiosensors can depend on several variables such as patient population, biomarker concentration, and ambient conditions. Therefore, the introduction of standardized methodologies will be highly relevant and would easily enable confirmation of accuracy, sensitivity, and reproducibility from time to time and in different clinical settings for these biosensors. Similarly, each technique employed for biomarker detection will have to be extensively validated in such a way that the obtained results are coherent and reliable in actual practice. In addition, detailed testing methodologies will be needed regarding the clinical

efficacy of nanobiosensors in a range of conditions, for example, those pertaining to different patient demographic backgrounds and stages of disease (53, 170).

Most importantly, fabrication and scalability of nanobiosensors should be successfully developed. Because of their different fabrication techniques, currently sensor performance is varying from batch to batch and affects their reliability in clinical applications. It is only when diagnostics involving nanobiosensors enter the picture that many more patients will be covered, provided the manufacturing techniques are scalable, low-cost, and reproducible. Novel fabrication techniques need to give reliable quality to meet the requirements for large-scale manufacture, in particular in resource-poor healthcare settings. Overcoming the manufacturing challenges is what, in the main, will be important in making accessible, dependable diagnostics available everywhere around the world (171, 172).

One of the major clinical needs for the use of nanobiosensors is that of their thorough assessment for biocompatibility (173). The most sensitive gold nanobiosensors can cause toxic or some other adverse reaction if they are not thoroughly designed for application in biological tissues. Therefore, research will still aim at protective coatings and surface modifications that may positively affect the compatibility of such sensors with biological environments, providing low toxicity and long-term stability inside the human body (172). Thirdly, physical and chemical stability of such biosensors is another challenge. Changes in the environmental conditions can produce changes in pH and temperature, affecting the performance of nanobiosensors. This, therefore, calls for the formulation of stabilizing chemicals or new nanoformulation to ensure the biosensors retain functional properties across time and variable clinical environments (174).

Approval for and introduction into clinical practice are major bottlenecks. To date, diagnostics utilizing nanotechnology must go through hard scrutiny by agencies concerned with regulation

regarding questions related to their safety, effectiveness, and clinical relevance before they can be approved for general use. This needs close coordination between the researchers and physicians with the regulatory bodies so that the rules and frameworks could be clearly laid down, which ensure safety and success related to the use of nanobiosensors in healthcare. Accomplishing this effectively will link new laboratory research to clinical translation and enable these technologies to be taken into practice to improve outcomes in breast cancer (166, 167).

One of the future possibilities that remains open for nanobiosensors is the capability of multiplexed detection, meaning the capability to detect several biomarkers at once. Such a capability will allow doctors to better diagnose the disease by being able to delve more deeply into the tumor's molecular makeup. These would be critical steps toward personalized medicine, in which treatments are tailored to the distinctive biomarker profile of a patient's particular tumor. Thus, multiplexed nanobiosensors can bring a significant improvement in diagnosis and therapeutic outcomes in cancer by providing a comprehensive view regarding the condition of a patient and helping further the wide goal of precision medicine (174, 175).

Artificial intelligence integrated with technology in nanobiosensors ushers in a new frontier in the development of diagnosis related to breast cancer (176). With the use of such artificial intelligence and machine learning algorithms, one can envision that these methods would enhance the analytical capability of nanobiosensors by efficiently processing the high volume and complexity of data emanating from biomarker identification to more accurate interpretation of cancer biomarker profiles that may assist clinicians in making quicker and more appropriate decisions on diagnosis, prognosis, and treatment strategies. AI increasingly integrates with nanobiosensing technologies, offering a whole different method by which that could revolutionize the diagnostic process and ways in which doctors track disease development and therapeutic response (**Figure 3**) (177, 178).

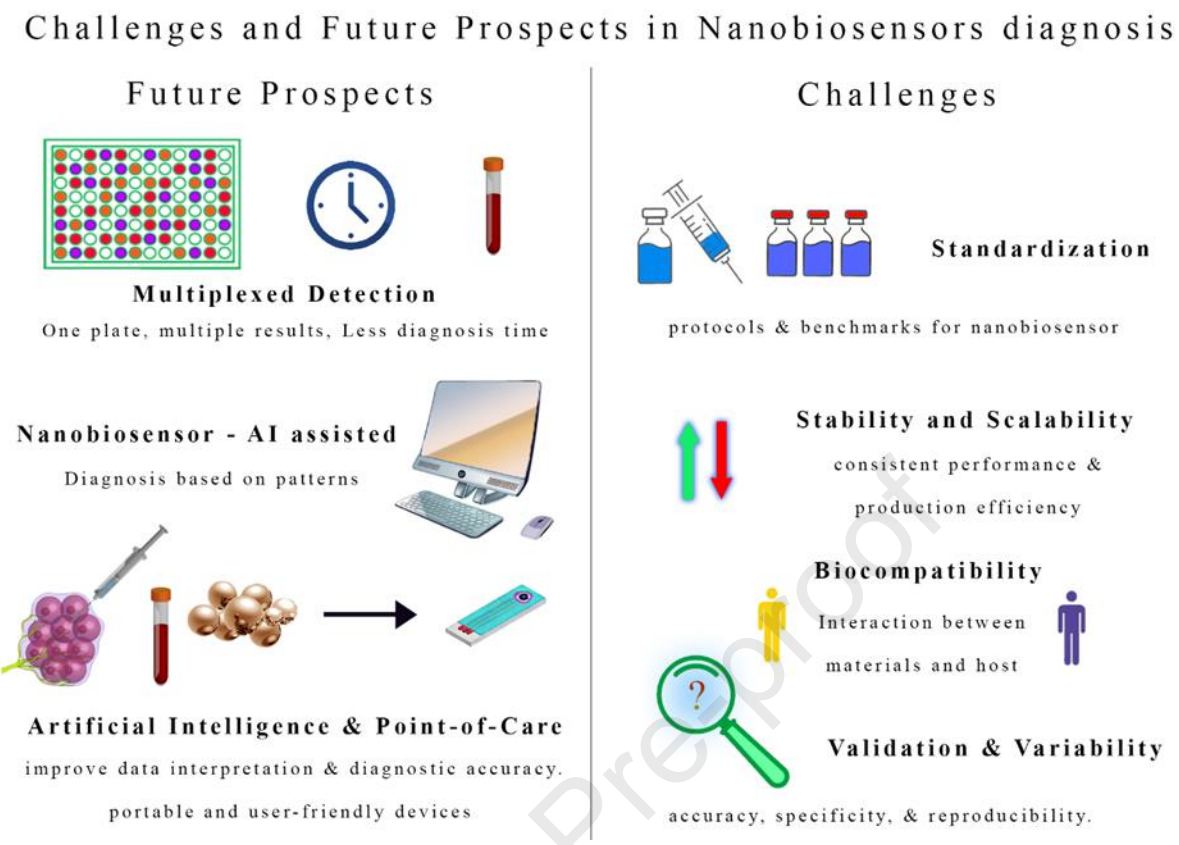


Figure 3: Challenges and prospects in nanobiosensors diagnosis

The aim of such great future innovation involves the creation of portable, point-of-care devices using nanobiosensor technology. These devices, enabled through miniaturization and portability of nanotechnology, may bring rapid, accurate, and cost-effective diagnosis of breast cancer to the bedside or far reaches of the clinic. These go in tune with the broader direction of healthcare toward decentralization, enabling diagnostic services to be rendered closer to the patient, thus enabling timely interventions and improving outcomes. It will help reduce the diagnostic disparities in resource-poor regions by increasing access to basic diagnostic tools (29, 179).

Overall, the clinical translation of the gold nanobiosensors for diagnosis of breast cancer had to overcome several challenges. Standardization, biocompatibility, scalability, and regulatory

clearances are some of the major challenges that need to be overcome. However, with sustained research along with multi-disciplinary collaboration, such challenges could be overcome. Thirdly, recent advances in multiplexed biomarker detection and their integration with AI hold immense promise for complete changes in the topography of breast cancer diagnosis and therapy and stand to substantially improve the global fight against this insidious plague. As technology evolves, nanobiosensors will be more and more likely to be at the leading edge of the future of precision medicine and decentralized health care, allowing earlier diagnosis, targeted therapies, and better patient outcomes.

6. Machine learning systems

Machine learning systems are recognized as one of the most promising approaches in analyzing complex data generated by nanobiosensors in breast cancer diagnosis (52). Since nanobiosensors can produce a huge amount of accurate data, machine learning algorithms can help identify hidden patterns in this data (180). One of the biggest advantages of this approach is that machine learning can provide information beyond traditional analysis and help identify biomarkers associated with breast cancer in the early stages (181). By accurately analyzing the data generated by nanobiosensors, these systems can create accurate predictive models that are effective in faster and more accurate cancer diagnosis (182).

The benefits of using machine learning systems are not only limited to increasing the accuracy of diagnosis but also provide the possibility of personalizing the treatment (183). Each patient with breast cancer can have specific biological and genetic characteristics that require different treatment methods. Using machine learning and data analysis of nanobiosensors, more detailed information can be obtained about the body's response to treatments (184). This information can help doctors prescribe more appropriate treatments for each patient and avoid generic and

less effective treatment methods. In this way, machine learning can help personalize treatment and make patients get better results from their treatments (185).

Additionally, machine learning systems can play an important role in predicting possible side effects and negative reactions to certain treatments (186). Using predictive machine learning models can prevent problems such as resistance to treatment or unexpected complications and help patients experience treatments with the lowest risk and the highest benefit. This possibility will help reduce treatment costs and increase patients' quality of life (187). In addition, using machine learning along with nanobiosensors can increase the speed of data analysis and reduce human errors in diagnosis and treatment, ultimately improving treatment outcomes and reducing breast cancer mortality rates (188) (**Figure 4**).

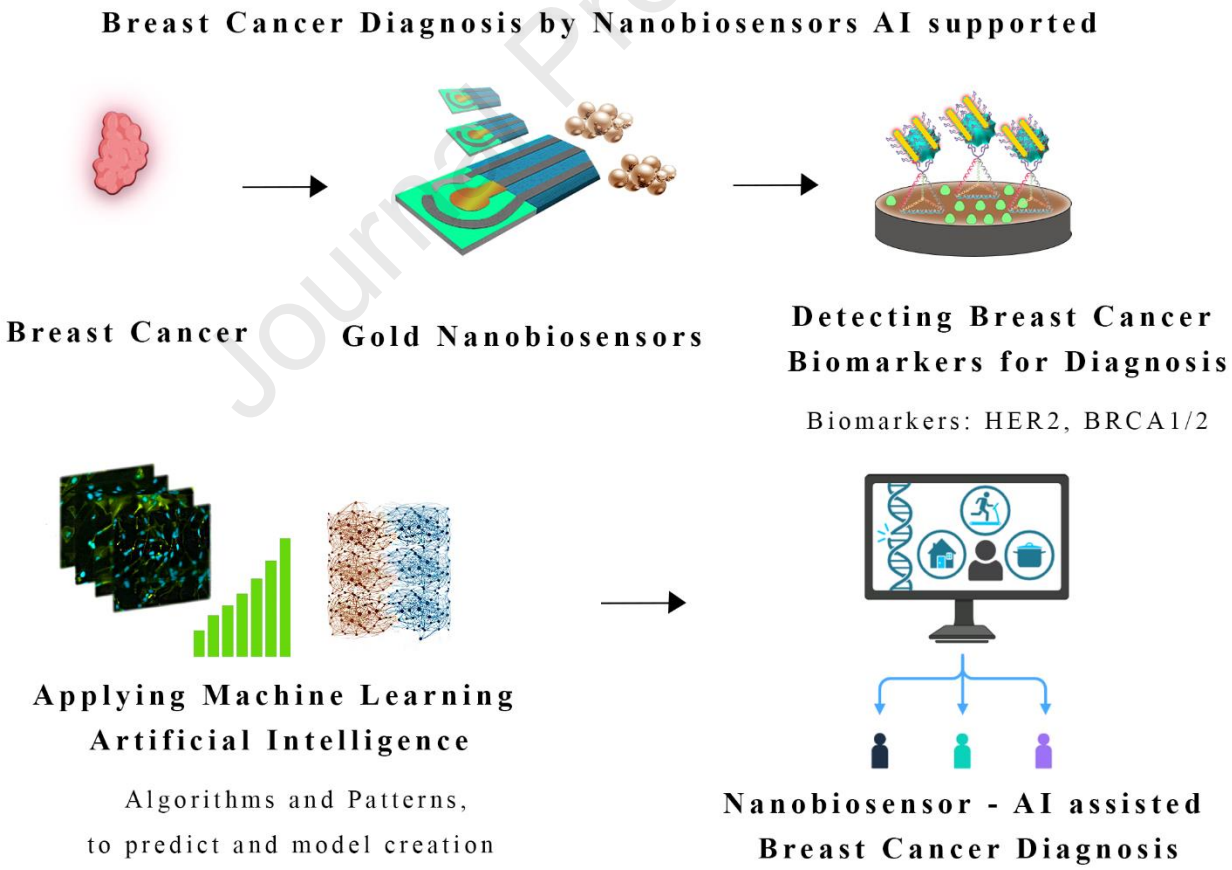


Figure 4. Machine learning systems

Machine learning systems are recognized as one of the most promising approaches in analyzing complex data generated by nanobiosensors in breast cancer diagnosis.

7. Discussion

Nanobiosensors use signal amplification as a fundamental key, including cancer biomarkers, to further improve specific biomolecule detection sensitivity (189-191). In Au nanobiosensors, researchers overcome the detection limits by using this technology, allowing for earlier diagnosis of diseases like breast cancer. Additionally, identifying biomarkers can be presented at very low concentrations (192-194). One confirming method is the integration of electrochemical signal amplification methods, specifically for detecting proteins and miRNAs (195, 196). For instance, surveys have shown combined electrochemical amplification techniques using gold nanoparticles to detect circulating tumor biomarkers like miRNA-21 (197-201). This method is connected to breast cancer diagnosis. When combined with other objects like silver ions or graphene, critical for sensitive detection, AuNPs offer a higher surface area for biomolecular interface and enhance electron transfer ratios, allowing nanobiosensors to detect biomarkers in deficient quantities (femtomolar range) (202-206). Furthermore, amplification has been used to even affect low signal outputs in complex biological fluids in breast cancer biomarkers. For instance, well-ordered nanocomposites created from gold and polymers, including poly(n-butyl acrylate), have confirmed advances in increasing signals for detecting breast cancer (207). These tactics not only improve the sensitivity of the biosensors but also impact decreasing false positives and false negatives.

Surface functionalization performs a key job in the biosensor's specificity. Gold nanoparticles are often functionalized with aptamers, antibodies, or other biomolecules to upgrade their potential to target specific breast cancer markers, such as BRCA1, HER2, or CEA (208-211).

Moreover, surface functionalization has supported multiplexed simultaneous detection of different biomarkers, which is necessary for a broad breast cancer diagnosis. Researchers have mixed surface-modified gold nanoparticles with other nanomaterials, such as conductive polymers and graphene oxide, to design stages capable of detection of one-assay multiple biomarkers (212-214). This not only improves the productivity of the biosensor but also requires a more detailed picture of the cancer's molecular profile. Integrating nanobiosensors with enhanced imaging types like surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) further enhances their diagnostic capabilities (215, 216). LSPR and SPR are label-free optical methods that develop the unique properties of gold nanoparticles to detect changes in the refractive index near the sensor surface, which happens when biomarkers bind to the functionalized nanoparticles (217, 218). Gold nanoparticles show exceptional plasmonic properties, making them a model for LSPR-based biosensors (219-221). These sensors detect very small changes in biomarker concentrations, which is especially convenient in the early detection of biomarkers related to breast cancer.

Additionally, integrating imaging modes like LSPR with gold nanobiosensors enables non-invasive and real-time monitoring of breast cancer progression and response to treatment (222). This is particularly beneficial for personalized medicine based on the patient’s exclusive molecular profile. Besides, LSPR-based systems are being explored for usage in clinical diagnostics, improving breast cancer screenings in resource-limited settings. Having their own evidence and mixing them into a single program might improve the gold nanobiosensors field (223). For example, linking surface functionalization skills with LSPR and signal amplification could make a biosensor that suggested both high specificity and sensitivity, along with real-time screening expertise. Additionally, using machine learning algorithms to study the large database created by these nanobiosensors could keep a novel understanding of breast cancer molecular mechanisms and progress diagnostic precision.

There is also a growing interest in extending low-cost and portable nanobiosensors, which could be installed in clinical laboratory settings, possibly reducing mortality rates by allowing earlier detection and treatment, making breast cancer monitoring more reachable to a broader population. Still, standardizing issues of these tools and focusing on scalability remains a big question. Surface functionalization, signal amplification, and integrating gold nanobiosensors with advanced imaging methods are key improvements in breast cancer diagnostics. Each piece of equipment with exceptional powers can offer more specific, sensitive, and available analytical kits. Future studies focus on mixing these methods into integrated programs, increasing their clinical relevance, and expanding scales.

Conclusion

In conclusion, gold nanobiosensors represent a cutting-edge technology with immense potential for revolutionizing breast cancer detection. Their high sensitivity, specificity, and ability to detect molecular biomarkers make them invaluable tools for early diagnosis and personalized treatment strategies. Integrating gold nanobiosensors with advanced imaging techniques, machine learning algorithms, and microfluidic systems enhances their usefulness, enabling rapid, accurate, and cost-effective screening methods. Although standardization, validation, and regulatory approval present challenges, ongoing research efforts propel the field forward. These obstacles can be overcome by fostering innovation and collaboration among researchers, clinicians, and industry partners, facilitating the clinical application and widespread adoption of gold nanobiosensors. Ultimately, the broad implementation of gold nanobiosensors holds the potential to significantly decrease breast cancer mortality rates by enabling early detection, personalized treatment approaches, and improved patient outcomes.

As we continue to refine and optimize these technologies, we move closer to realizing a world where breast cancer is detected early, treated effectively, and ultimately eradicated.

Declarations and statements

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The authors declare no conflict of interest.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Soheil Sadr, Ashkan Hajjafari, Parian Poorjafari Jafroodi, Narges Lotfalizadeh, Mahdi Soroushianfar, Shahla Salimpour Kavasebi, Zelal Kharaba: Investigation, Visualization, Writing – original draft, methodology, Formal analysis. **Hassan Borji:** Writing – review & editing **.Abbas Rahdar, Sadanand Pandey:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. All authors checked and approved the final version of the manuscript for publication in the present journal.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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