Applied Biochemistry and Biotechnology
https://doi.org/10.1007/s12010-026-05874-9

REVIEW

Theranostic Smart Bionanosensors for Solid Tumors: Advances, Challenges, and Future Directions

Manar T. El-Morsy[1] · Youssef Basem[2] · Amr E. Ali[3] · Abanoub Sherif[2] · Alamer Ata[2] · Fayek Sabry[2] · Nourhan M. ElMahsoub[4] · Ahmed S. Doghish[5,6] · Gharieb S. El-Sayyad[7] · Gomaa A. M. Ali[8]

Accepted: 8 August 2026

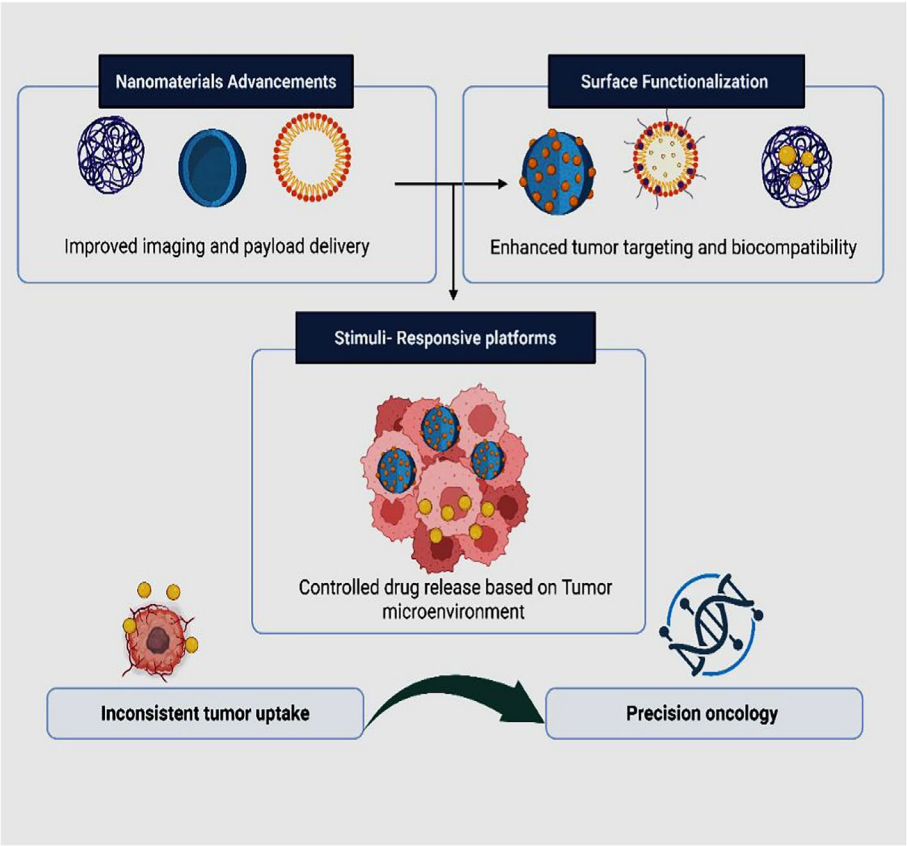
Abstract

Theranostic smart bionanosensors represent a revolutionary approach to solid tumor management, integrating accurate diagnostic functions with focused therapeutic strategies. This review thoroughly analyzes the progress of biosensors from traditional diagnostic tools to multifunctional theranostic systems, highlighting advancements in nanomaterials, surface functionalization, and tumor-targeting techniques that improve imaging contrast, payload delivery, and controlled release. Advanced bionanosensors comprising optical, electrochemical, magnetic, hydrogel-based, stimuli-responsive, and wearable platforms facilitate precise biomarker detection, real-time therapeutic monitoring, and minimally invasive diagnostics, presenting unmatched prospects for personalized cancer management. Despite these advancements, challenges persist, including inconsistent tumor uptake, prolonged biocompatibility, possible toxicity, scalability, reproducibility, and regulatory obstacles. The integration of nanomaterial studies, imaging, sensor technology, computational analytics, and clinical innovation offers a strategic framework for advancing smart theranostic bionanosensors from laboratory to clinical application, facilitating precision oncology and enhancing patient outcomes.

Extended author information available on the last page of the article

Published online: 21 August 2026

Graphical Abstract



Keywords Theranostics · Nanosensors · Solid tumors · Nanotechnology · Precision medicine

Abbreviations

QDs	Quantum Dots
NPs	Nanoparticles
HCR	Hybridization Chain Reaction
AuNPs	Gold Nanoparticles
AgNPs	Silver Nanoparticles
SPIONs	Superparamagnetic Iron Oxide Nanoparticles
PLGA	Poly(lactic-co-glycolic acid)
PEG	Polyethylene Glycol
SLNPs	Solid Lipid Nanoparticles
LNPs	Lipid Nanoparticles
MOFs	Metal Organic Frameworks
TEM	Transmission Electron Microscopy
DLS	Dynamic Light Scattering

UV-Vis	Ultraviolet-Visible Spectroscopy
XRD	X-Ray Diffraction
MRI	Magnetic Resonance Imaging
FTIR	Fourier Transform Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
DSC	Differential Scanning Calorimetry
EPR	Enhanced Permeability and Retention
siRNA	Small Interfering RNA
MMP	Matrix Metalloproteinase
PEGylation	Conjugation with Polyethylene Glycol
Ab	Antibody
HER2	Human Epidermal Growth Factor Receptor 2
EGFR	Epidermal Growth Factor Receptor
MUC1	Mucin 1
RGD	Arginine-Glycine-Aspartic Acid
GSK	Glycogen Synthase Kinase
AI	Artificial Intelligence
DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
ctDNA	Circulating Tumor DNA
miRNA	MicroRNA
MPS	Mononuclear Phagocyte System
pH	Potential of Hydrogen
NIR	Near-Infrared
NIR-II	Near-Infrared II
IV	Intravenous
177Lu	Lutetium-177
PSMA	Prostate-Specific Membrane Antigen
NETs	Neuroendocrine Tumors
SPECT	Single Photon Emission Computed Tomography
NPs-EPR	Nanoparticle–Enhanced Permeability and Retention
CRISPR/Cas	Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein
PK/PD	Pharmacokinetics/Pharmacodynamics
PDX	Patient-Derived Xenograft
PAT	Process Analytical Technology
PBPK/PD	Physiologically Based Pharmacokinetic/Pharmacodynamic Modelling
SOP	Standard Operating Procedure
SHAP	SHapley Additive exPlanations
SMART	Substitutable Medical Applications, Reusable Technologies
STFT	Short-Time Fourier Transform
TCN	Temporal Convolutional Network
TLS	Transport Layer Security
UQ	Uncertainty Quantification
U/N	Unlabeled/Unknown
XAI	Explainable Artificial Intelligence

CT	Computed Tomography
PET	Positron Emission Tomography
EMT	Epithelial-to-Mesenchymal Transition
EpCAM	Epithelial Cell Adhesion Molecule
SERS	Surface-Enhanced Raman Spectroscopy
PEC	Photoelectrochemical
MoS_2	Molybdenum Disulfide
N-doped	Nitrogen-Doped
FE-PdMnCoPt	Iron-Palladium-Manganese-Cobalt–Platinum
HPLC	High-Performance Liquid Chromatography
SSCP	Single-Strand Conformation Polymorphism
NPs	Nanoparticles
TME	Tumor Microenvironment
ROS	Reactive Oxygen Species
PA	Photoacoustic
PABI	Photoacoustic Brain Imaging
PTT	Photothermal Therapy
PPTT	Plasmonic Photothermal Therapy
Nano-CRISPR	CRISPR Integrated with Nanomedicine
PK/PD	Pharmacokinetics/Pharmacodynamics
CTC	Circulating Tumor Cells
BRCA1/2	Breast Cancer Gene 1/2
ADME	Absorption, Distribution, Metabolism, Excretion
AES-256	Advanced Encryption Standard (256-bit)
CARPA	Complement Activation-Related Pseudoallergy
CNN/1D-CNN	Convolutional Neural Network/1D Convolutional Neural Network
EHR	Electronic Health Record
FDA	Food and Drug Administration
FL	Federated Learning
FHIR	Fast Healthcare Interoperability Resources
GANs	Generative Adversarial Networks
GMP	Good Manufacturing Practice
HRV	Heart Rate Variability
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ISF	Interstitial Fluid
IoT	Internet of Things
LSTM	Long Short-Term Memory
MIRIBEL	Minimum Information Reporting in Bio–Nano Experimental Literature

Introduction

Cancer caused by solid tumors remains one of the leading causes of morbidity and mortality worldwide, with complex etiology, heterogeneous microenvironments, and persistent challenges in early detection and effective localized treatment [1]. A major limitation in current clinical practice is that most diagnostic and therapeutic strategies are still based on static

snapshots of disease rather than continuous monitoring of tumor evolution, which reduces their ability to capture real-time heterogeneity and adaptive resistance. The enormous clinical and economic burden of solid malignancies has driven multidisciplinary efforts to develop more precise diagnostic tools and targeted therapies that can adapt to tumor heterogeneity and reduce systemic toxicity [1].

Globally, cancer remains a major public health burden, with about 20 million new cancer cases and 9.7 million cancer deaths estimated in 2022. Solid tumors account for approximately 90% of adult malignancies and more than 90% of cancer-related deaths, underscoring the urgent need for more effective diagnostic and therapeutic strategies [2]. Despite this burden, survival outcomes for many solid tumors have improved only marginally over the past decades, mainly because early detection remains inefficient and therapeutic resistance develops rapidly.

Nanomedicine, the use of nanoscale materials and engineered nanocarriers, has rapidly expanded as a platform to improve drug solubility, control pharmacokinetics, and enable targeted delivery of chemotherapeutics and biologics to solid tumors [3]. Beyond drug delivery, a major paradigm shift in oncology is the integration of diagnosis and therapy into single, multifunctional systems known as "theranostics," which combine imaging, sensing, and therapeutic modalities to enable image-guided treatment and real-time monitoring of response [4]. However, despite strong preclinical performance, clinical translation of these systems remains limited due to biological complexity of tumors and insufficient real-world predictive accuracy. Nanotheranostic platforms range from multifunctional polymeric and lipid nanoparticles (LNPs) to inorganic nanocrystals and hybrid bio-inspired carriers that merge contrast agents, drug payloads, and stimulus-responsive elements in one entity [5]. The clinical promise of theranostics lies in their potential to personalize oncologic care by identifying tumor biomarkers, delivering a tailored therapy, and allowing noninvasive readouts of biodistribution, target engagement, and therapeutic efficacy [6]. However, successful translation of nanotheranostics for solid tumors requires overcoming biological barriers such as poor tumor penetration, the heterogeneous and often immunosuppressive tumor microenvironment (TME), and rapid clearance by the mononuclear phagocyte system [7]. In addition, variability of the enhanced permeability and retention (EPR) effect across tumor types further limits the reproducibility of nanomedicine-based delivery systems in clinical settings.

To address these constraints, "smart" bionanosensors have emerged as nanoscale devices and platforms that can detect molecular signatures (e.g., proteins, nucleic acids, metabolites), sense microenvironmental cues (e.g., pH, hypoxia, enzymes), and trigger or modulate therapeutic action accordingly [8]. Smart biosensing elements incorporated into theranostic systems can perform real-time monitoring via optical, magnetic, electrochemical, or acoustic readouts, enabling clinicians and researchers to track tumor progression and treatment response with high sensitivity [9]. Electrochemical and optical nanosensor platforms have shown particular promise for liquid biopsy applications, such as detecting circulating tumor DNA (ctDNA), microRNAs, exosomes, and protein biomarkers at low abundance for earlier diagnosis and therapy stratification [9]. This is particularly important because liquid biopsy overcomes key limitations of tissue biopsy, including sampling bias and inability to capture tumor spatial heterogeneity. Graphene-based nanomaterials, metallic nanoclusters, quantum dots (QDs), carbon dots (CDs) and plasmonic nanoparticles have been engineered to provide enhanced signal transduction and multiplexed detection in compact, potentially point-

of-care formats [10]. Concurrently, imaging-guided nanotheranostic systems that integrate magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) with therapeutic agents have enabled real-time, noninvasive monitoring of nanoparticle biodistribution and tumor accumulation, thereby improving image-guided interventions and optimizing radiotherapy planning [11].

Recent preclinical and early clinical studies demonstrate that theranostic nanoparticles can improve therapeutic indices and allow dose optimization, but evidence also underscores the need for standardized evaluation frameworks and more predictive preclinical models [6]. The design of successful smart theranostic platforms increasingly leverages stimulus-responsive chemistries (e.g., redox, pH, enzyme-cleavable linkers), active targeting ligands, and biomimetic coatings to improve specificity and control cargo release within TME [12]. Advances in hydrogel-based and wearable nanosensor technologies now enable sustained local sensing and therapeutic release at tumor resection sites or within interstitial spaces, offering new strategies for postoperative monitoring and preventing local recurrence [7]. Liquid biopsy coupled with nanosensor platforms is transforming minimally invasive cancer monitoring by enabling serial sampling and dynamic assessment of tumor evolution, resistance mutations, and minimal residual disease [13]. Despite these technological gains, important translational hurdles remain, including nanoparticle toxicity, long-term biocompatibility, unpredictable biodistribution, scale-up manufacturing challenges, and regulatory uncertainties surrounding multifunctional combination devices [14]. Furthermore, reproducible and clinically relevant evaluation of sensor sensitivity, specificity, and false-positive rates is critical for adoption; many proof-of-concept platforms show exceptional analytical performance in vitro but underperform in complex biological matrices and patient cohorts [15]. Another pressing challenge is the integration of multimodal data from imaging, molecular sensors, and clinical metrics into robust AI-driven decision frameworks that can guide adaptive treatment while accounting for interpatient variability [1]. Emerging regulatory and ethical considerations also demand attention, particularly when theranostic devices collect longitudinal biomarker data and when personalized dosing or automated therapeutic triggers are envisioned [14]. To accelerate clinical translation, researchers advocate for standardized reporting, collaborative consortia for interlaboratory validation, harmonized preclinical pipelines that better model human tumor physiology, and early engagement with regulatory agencies [4]. Importantly, recent innovations in polymeric nano theranostics, bio-inspired hybrid nanoparticles, and activatable near-infrared agents underscore a practical pathway where modular, clinically tractable platforms can be iteratively optimized for safety and efficacy [3]. The convergence of advanced materials, sensitive nanosensors, precision imaging, and computational analytics promises an era in which theranostic systems routinely enable earlier detection, individualized therapy selection, and dynamic adaptation of treatment plans for patients with solid tumors [16].

Current clinical biosensors face significant translational barriers that limit their widespread adoption in oncology. Traditional diagnostic methods, such as imaging and tissue biopsy, while clinically established, have major drawbacks, including limited sensitivity for early-stage cancer detection, invasiveness, and an inability to capture tumor heterogeneity [17]. Conventional platforms like ELISA and chemiluminescence immunoassays often lack sufficient sensitivity and real-time capabilities to meet the demands of detecting low-abundance biomarkers in liquid biopsies [18]. Furthermore, when biosensors are tested in clinical samples such as blood or urine, their superior performance in controlled laboratory

settings frequently degrades due to the complex nature of these fluids, which contain interfering biomolecules that cause nonspecific binding and reduce accuracy [19]. These issues are compounded by a lack of standardized protocols, high manufacturing costs, and limited reproducibility that hamper the transition from proof-of-concept to scalable, clinically reliable products [20].

Beyond technical performance, practical hurdles in scalability, regulation, and healthcare integration represent formidable obstacles. Manufacturing processes for advanced nanomaterials remain complex and expensive, with batch-to-batch variability affecting sensor reliability and consistency [21]. Navigating regulatory approval pathways is particularly challenging due to ambiguous product classification, theranostic devices often fall between drug and device categories, and the absence of globally standardized protocols for nanoparticle-specific quality testing [19].Economic constraints further impede adoption, as the high cost of specialized nanomaterials and manufacturing limits accessibility, especially in resource-limited settings, while HTA bodies demand cost-effectiveness evidence that is often lacking [20]. These interconnected challenges, spanning technical performance, manufacturing scalability, regulatory approval, and healthcare system integration, collectively represent the critical bottleneck separating promising laboratory innovations from meaningful clinical impact in cancer management.

This review summarizes the recent advances in nanotheranostic platforms and smart bionanosensors for solid tumors, highlighting how their design features, imaging and therapeutic performance, and integration with computational analytics can overcome key biological and translational barriers. The outstanding challenges, safety and regulatory considerations, and future directions required to enable their routine clinical implementation are also discussed.

Principles of Theranostic Biosensors

Theranostic biosensors are innovative devices that integrate diagnostic and therapeutic characteristics into a single system, presenting considerable promise for personalized medicine [22]. Also, theranostic biosensors facilitate real-time disease monitoring and therapy, especially in oncology [23, 24]. These biosensors use several signal transduction methods, such as fluorescence, colorimetry, and electrochemistry, to detect and analyze biomarkers [23, 25]. Additionally, the application of nanomaterials, such as CDs and QDs, significantly improves the sensitivity and specificity of biosensors. Beyond traditional metallic nanoparticles, CDs have recently garnered significant attention in the design of theranostic smart biosensors. Due to their superior biocompatibility, robust photoluminescence, and abundant surface functional groups, CDs serve a dual purpose: acting as highly sensitive optical transducers for biomarker detection while simultaneously serving as biocompatible nanocarriers for targeted therapeutic delivery. These materials also enhance drug delivery and imaging, making them suitable for theranostic applications [23, 25, 26]. Also, advancements in micro-nano fabrication and the incorporation of microneedles and biochips contribute to the evolution of wearable and non-invasive theranostic systems [27]. Moreover, low-abundance biomarkers are detected using techniques such as the hybridization chain reaction (HCR), thereby improving detection with theranostic tools [28]. Also, Microfluidic devices have been developed as efficient tools for simulating TME to assess the activ-

ity of drugs in real-time [29]. When coupled with biosensors, these platforms provide the accurate measurement of biomarkers and the administration of tailored drugs in a precise manner [30]. Overall, the theranostic biosensor indicates considerable progress in oncology and personalized medicine. These biosensors can offer accurate, real-time monitoring and treatment solutions by applying nanotechnology and innovative signal transduction methods. As shown in Fig. 1, the ongoing advancement of biocompatible and effective delivery technologies continues to enhance potential in therapeutic applications. Also, among the various biosensing platforms, electrochemical bionanosensors have emerged as one of the most promising technologies owing to their exceptional sensitivity, low detection limits, rapid response, cost-effectiveness, and compatibility with portable point-of-care devices. Their ability to operate in complex biological matrices with minimal sample preparation further provides a significant advantage over many optical and conventional analytical techniques.Their performance is strengthened by nanomaterials, which increase active surface area, accelerate electron transfer, and improve signal amplification [31, 32]. The sensing process depends on recognition of a target analyte by a bioreceptor or functional layer on the electrode surface, followed by an electrochemical change measurable by the transducer. Nanostructured materials enhance the interface by providing more binding sites and better electroactive properties, thereby lowering detection limits and improving response speed. Depending on the design, the signal may be direct, label-free, or amplified through catalytic or redox-mediated reactions [33]. Electrochemical nanosensors can be classified by transduction mode, including amperometric, potentiometric, conductometric, impedimetric, and voltammetric systems. They may also be classified by biorecognition strategy, such as enzymatic sensors, immunosensors, genosensors, aptasensors, and cytosensors [33].In addition, Fluorescence nanosensors use changes in fluorescence intensity, wavelength, lifetime, or energy transfer to detect analytes with high sensitivity. They are widely used because

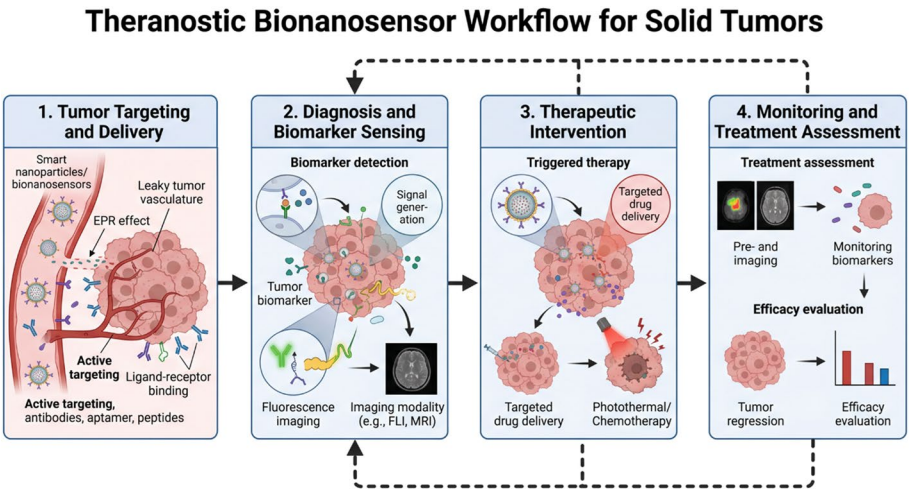


Fig. 1 Theranostic bionanosensor workflow for solid tumors: diagnosis, therapy, and real-time monitoring. This theranostic bionanosensor workflow integrates diagnosis, therapy, and real-time monitoring for solid tumors. Smart nanoparticles passively target tumors via the EPR effect and actively bind cancer cells using antibodies or peptides. They then detect biomarkers through fluorescence imaging, trigger localized drug delivery, and continuously assess treatment efficacy by tracking biomarker changes and tumor regression, enabling adaptive, personalized therapy. (Created with BioRender.com)

optical readout is simple, fast, and suitable for imaging and multiplex analysis [34]. These sensors work by coupling a fluorescent nanomaterial or fluorophore to a recognition element, where target binding changes the optical signal. Common mechanisms include fluorescence quenching, turn-on/turn-off behavior, and FRET-based responses. Nanomaterials can improve brightness, stability, and target accessibility, making the signal more robust in complex samples [35]. Fluorescence nanosensors include quantum-dot-based sensors, carbon-dot sensors, dye-loaded nanoparticles, FRET nanosystems, and metal-enhanced fluorescence platforms. They may be designed as single-channel or ratiometric sensors, depending on whether one or two emission signals are monitored. Ratiometric systems are especially useful because they reduce errors caused by environmental fluctuations [36]. The key advantage of bio-nanosensors lies in their ability to bridge the gap between analytical performance and clinical applicability, rather than serving as replacements for electrochemical or fluorescence-based sensors.

Materials and Design Strategies

Types of Nanoparticles

Nanoparticles (NPs) have become indispensable in cancer theranostics due to their versatile properties, surface tunability, and ability to integrate diagnostic and therapeutic functionalities. The main categories include polymeric, hybrid, metallic, and lipid-based NPs, each offering unique advantages and limitations [37].

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are nanoscale carriers (typically 10–300 nm) built from synthetic or natural polymers (e.g., PLGA, PEGylated polymers, chitosan, hyperbranched polymers, conjugated polymers) that can encapsulate reporters, probes, or contrast agents for tumor sensing and imaging [38].They enable signal enhancement (fluorescence, photoacoustic, MRI contrast, radionuclide labeling) and can be surface-functionalized for passive (EPR) or active (ligand-directed) tumor targeting, making them attractive for sensitive, localized biosensing in vivo [39]. They are types that include PLGA nanoparticles that are biodegradable carriers used to encapsulate fluorescent dyes, MRI agents, or enzymatic reporters for tumor detection and responsive release sensors [40]. PEGylated polymeric micelles and nanocarriers, which provide prolonged circulation and reduced opsonization, are commonly used to deliver imaging agents and sensors to tumors via EPR [41]. Chitosan and polysaccharide-based nanoparticles are naturally derived, positively charged systems used for surface adsorption of probes and for biosensing of tumor-associated markers [40]. Conjugated polymer nanoparticles, semiconducting polymer nanoparticles, are intrinsically fluorescent or photoacoustic polymer cores that act as bright reporters for fluorescence and PA tumor imaging and biosensing [38]. Stimuli-responsive polymer nanoparticles that are engineered to change optical or magnetic properties in response to pH, enzymes, redox state, or hypoxia, allowing smart detection of TME features [39]. PNPs offer several important advantages that make them highly attractive for tumor biosensing applications. Their chemical and structural tunability allows researchers to optimize particle size, surface charge,

hydrophobicity, and surface ligands to achieve an optimal balance between circulation time, cellular uptake, and signal output [41]. In addition, PNPs exhibit remarkable multifunctionality, as they can simultaneously co-deliver sensing probes and therapeutic agents, enabling both tumor detection and treatment monitoring using the same platform [39]. Another major advantage is their excellent biocompatibility and biodegradability. Many commonly used polymers, including PLGA, PEG derivatives, and chitosan, are well tolerated by biological systems and degrade into nontoxic byproducts, facilitating their potential clinical translation [40]. Furthermore, polymeric nanoparticles provide enhanced signal generation and targeting capability, particularly through conjugated polymer cores and signal-amplifying designs that increase the sensitivity for detecting low-abundance tumor biomarkers [38].

Despite their considerable advantages, polymeric nanoparticles (PNPs) face several challenges that limit their clinical translation. Biological heterogeneity and variability in the enhanced permeability and retention (EPR) effect remain major obstacles, as differences in tumor perfusion and vascular permeability across tumor types and individual patients make passive targeting inconsistent and reduce predictive sensitivity. In addition, clearance, off-target accumulation, and immune recognition continue to affect nanoparticle performance. Although PEGylation reduces protein adsorption and prolongs circulation, it also increases opsonization and uptake by the reticuloendothelial system (RES), thereby decreasing nanoparticle accumulation at tumor sites and increasing background signals [41]. Furthermore, multifunctional PNPs often require complex multistep synthesis and extensive physicochemical characterization, making large-scale production and ensuring batch-to-batch reproducibility challenging [40]. Finally, quantification and standardization remain significant hurdles, as translating PNP-based biosensor readouts into clinically meaningful and standardized quantitative measurements is difficult because the detected signal depends on delivery efficiency, the local TME, and probe stability [42]. Polymeric nanoparticles show great promise for sensitive tumor biosensing, but their clinical translation requires improved targeting, reproducible manufacturing, and standardized quantitative evaluation. Biodegradable, well-characterized polymer systems are likely to offer the greatest potential for future clinical applications.

Hybrid Nanoparticles

Hybrid nanoparticles (HNPs) pair materials such as metals, metal oxides, QDs, or upconversion/lanthanide-doped cores with organic shells (polymers, lipids, proteins, or silica) to merge strong signal generation (optical, magnetic, plasmonic) with biocompatible surface chemistry and cargo-loading capacity [43]. This combination enables multimodal imaging and activatable biosensing in the TME, supporting both sensitive detection of tumor markers and image-guided interventions [44]. Hybrid nanoparticles used in tumor biosensing comprise several representative categories that combine the advantages of both inorganic and organic materials. Metal–polymer hybrids consist of metallic (Au, Ag) or magnetic (Fe_3O_4) cores coated with polymeric shells, enabling plasmonic or photothermal sensing, magnetic resonance imaging (MRI) contrast, and surface functionalization with targeting ligands or molecular probes [45]. Silica- or polysilsesquioxane hybrids incorporate inorganic silica cores doped with luminophores or MRI contrast agents and further functionalized with polymers or peptides to create robust, multifunctional sensing platforms [43]. Furthermore, Metal–organic framework (MOF) or coordination polymer hybrids are porous inorganic–

organic structures capable of loading sensing dyes, enzymes, or therapeutic agents and generating responsive signal changes or controlled release in response to tumor-associated stimuli such as pH variations or enzymatic activity[43]. Lanthanide-doped upconversion hybrids combine lanthanide nanoparticles with pH- or enzyme-sensitive coatings to enable near-infrared (NIR)-to-visible upconversion imaging and activatable biosensing for deep-tissue tumor detection [44]. Additionally, layer-by-layer multifunctional assemblies are fabricated by sequentially depositing oppositely charged polymers, contrast agents, and targeting moieties onto an inorganic core, enabling precise control of surface chemistry and the development of multimodal imaging and biosensing platforms [46]. HNPs offer significant advantages for tumor biosensing due to their multimodal imaging capabilities, providing complementary signals from a single construct, including optical, MRI, and photoacoustic imaging, thereby enabling cross-validated detection and improved tumor localization [43]. Their tunable and activatable sensing properties arise from stimulus-responsive organic shells that are sensitive to pH, enzymes, or redox conditions, combined with stable inorganic reporters, allowing activatable readouts that minimize background signals and enhance specificity toward the TME [44]. In addition, HNPs exhibit improved functionality through the synergistic integration of inorganic cores, which provide strong intrinsic contrast via plasmonic, magnetic, or luminescent properties, with organic coatings that enhance biocompatibility, prolong circulation through stealth characteristics, and facilitate ligand conjugation for targeted delivery [47]. Furthermore, their theranostic capacity enables the simultaneous co-delivery of therapeutic agents and sensing or imaging probes, supporting image-guided therapy while allowing real-time monitoring of treatment response within the same nanoplatform [44]. Also, HNPs present manufacturing challenges because their multicomponent structure requires precise control over fabrication, reproducibility, and scale-up, increasing regulatory complexity [43]. Inorganic cores may also pose toxicity concerns due to long-term retention, limited biodegradation, and off-target effects, requiring stable coatings or biodegradable alternatives. Additionally, HNPs exhibit variable tumor accumulation due to heterogeneous EPR effects and biological barriers, thereby reducing the accuracy and reproducibility of quantitative biosensing. Their surfaces may also trigger immune recognition, leading to opsonization, RES clearance, reduced tumor targeting, and potential adverse immune responses [43]. HNPs are highly valuable for preclinical diagnostics and image-guided research because their multimodal, activatable sensing capabilities enhance biomarker detection and optimize therapy. In the long term, successful clinical translation will require simpler, biocompatible designs with improved biodegradability, reproducible manufacturing, and standardized quantitative performance. Prioritizing clinically accepted inorganic cores, biodegradable organic shells, and quantitative sensing strategies will facilitate regulatory approval and clinical adoption.

Metallic Nanoparticles

Metallic nanoparticles (MNPs), such as gold, silver, platinum, iron, and copper, have become important biosensing materials in oncology because they can amplify weak biological signals into measurable optical or electrical outputs. In tumor biosensing, they are used to detect biomarkers including ctDNA, microRNAs, exosomes, proteins, and circulating tumor cells, often at very low concentrations [48]. Their value lies in the combination of small size, tunable surface chemistry, and strong interaction with light or electrons

[48, 49]. MNPs used in biosensing include several classes with distinct sensing functions. Gold nanoparticles are the most studied for colorimetric assays, surface-enhanced Raman scattering (SERS), plasmon resonance sensing, and electrochemical biosensors [50]. Silver nanoparticles (AgNPs) have a strong plasmonic response that makes them useful in optical sensing and SERS-based tumor marker detection [47]. Furthermore, platinum nanoparticles are often used for catalytic signal amplification and electrochemical detection [51]. Iron oxide nanoparticles (Fe_3O_4) are important when magnetic behavior is needed for imaging-assisted sensing and separation of targets [51]. In addition, copper and other alloyed or hybrid metal nanoparticles are used in emerging multimodal and nanocatalytic sensing platforms [52]. MNPs offer several advantages that make them highly effective platforms for cancer biosensing. They provide very high sensitivity, enhancing signals sufficiently to detect rare cancer biomarkers in blood or other body fluids[50]. MNPs also support multiple sensing modes, including colorimetric, surface-enhanced Raman scattering (SERS), electrochemical, refractive index, and photoelectrochemical readouts [48]. In addition, they allow easy surface modification, enabling the attachment of antibodies, aptamers, peptides, and DNA probes for selective tumor targeting [49]. Their multimodal design allows a single platform to combine sensing with imaging or therapy, thereby improving diagnostic confidence [52]. Furthermore, MNPs exhibit good signal amplification, as their plasmonic or catalytic properties can boost weak biomarker signals using relatively simple assay formats [48].

Despite their advantages, nanosensors still face several limitations. Potential toxicity remains a concern, as some metals or small-particle formulations may raise biocompatibility and long-term safety concerns, especially after systemic exposure [49]. Aggregation and instability may occur because uncontrolled clustering can alter sensing performance and reduce reproducibility [37]. Matrix interference is another challenge, since blood and tissue fluids are complex, so nonspecific binding can reduce accuracy [50]. In addition, limited clinical translation persists, as many systems are still at the proof-of-concept stage, and scale-up, standardization, and regulatory approval remain major barriers [52]. Furthermore, costs and instrumentation can restrict widespread implementation, as highly specialized readout methods such as SERS or advanced photoelectrochemical setups may limit point-of-care use [48]. MNPs are among the most promising materials for tumor biosensing due to their high analytical performance and versatile surface engineering. Rather than relying on a single universal nanoparticle, current approaches focus on hybrid and multimodal platforms that combine gold or platinum cores with targeting ligands and complementary imaging or electrochemical readouts.

Lipid-Based Nanoparticles

LBNPs, including liposomes, solid lipid nanoparticles (SLNPs), nanostructured lipid carriers (NLCs), and modern ionizable lipid-based LNPs, combine a lipidic matrix with functional cargos (dyes, contrast agents, nucleic acids, or sensors) to produce sensitive, biocompatible tumor-detection tools. Their flexibility enables the incorporation of imaging reporters (fluorophores, MRI agents, and radionuclides) or molecular probes (aptamers, antibodies, and RNA sensors) to create theranostic platforms that can both detect and treat tumors [53]. They are types of LBNPs used in tumor biosensing. Liposomes are bilayer vesicles that encapsulate hydrophilic probes in the core and hydrophobic reporters in the membrane and

are commonly used for fluorescent and MRI-based tumor imaging [54]. SLNPs and nanostructured lipid carriers (NLCs) are solid or mixed-lipid matrices that stabilize hydrophobic contrast agents and can improve photothermal or photoacoustic readouts [55]. Ionizable lipid LNPs and dendrimer-based LNPs are engineered for nucleic-acid delivery with pH- or environment-responsive reporters, enabling simultaneous mRNA/siRNA delivery and tumor imaging [56]. Hybrid/functionalized LBNPs combine lipids with polymers, targeting ligands (folate, antibodies), PEGylation, or imaging lipids (Gd-lipids, NIR dyes) to enhance circulation, targeting, and signal contrast [57]. LBNPs offer several advantages for biosensing applications. Their biocompatibility and safety arise from lipid constituents that are generally well tolerated and can reduce systemic toxicity compared with inorganic nanoparticles [58]. Their payload versatility enables LBNPs to carry diverse biosensing cargos, including fluorophores, MRI agents, radionuclides, and nucleic-acid probes, within one particle for multimodal detection [37]. In addition, functionalization and targeting through surface modification with ligands, antibodies, or pH-sensitive PEG enable active targeting to tumor receptors and environment-responsive activation of imaging signals [54]. Furthermore, their theranostic capability allows the simultaneous delivery of therapeutic nucleic acids or drugs while providing diagnostics or real-time imaging readouts for treatment monitoring [57]. Furthermore, manufacturing scale-up, reproducible functionalization, regulatory safety evaluation, and definitive clinical proof of improved diagnostic outcomes remain major translational challenges [57]. Overall, LBNPs have strong potential for tumor biosensing due to their biocompatibility, modular sensor loading, and established clinical translation. Future efforts should focus on improving tumor-specific delivery, signal specificity, and overcoming storage, manufacturing, and scale-up challenges to support successful clinical translation.

Biocompatibility and Biodegradability

For successful clinical applications, NPs are required to exhibit low toxicity and predictable clearance from the body. Their biocompatibility refers to functioning effectively without eliciting adverse immune responses, while biodegradability ensures they break down into non-toxic byproducts. However, metallic NPs pose challenges regarding long-term safety. While AuNPs are considered relatively inert, their persistence in tissues may cause oxidative stress and potential organ damage over extended periods [59]. SPIONs can be broken down into iron ions within the body, supporting their metabolic compatibility. However, when these particles accumulate excessively in organs such as the liver or spleen, they may lead to long-term adverse effects and chronic toxicity [60]. Polymeric NPs like PLGA have received FDA approval since they undergo hydrolysis into lactic acid and glycolic acid, both of which are readily incorporated into the body's normal metabolic processes. PEGylation enhances the stealth characteristics of polymeric NPs by minimizing opsonization and thereby extending their circulation half-life in the bloodstream [61]. Also, Phospholipids are widely used in nanoparticle formulations; however, cationic lipids, in particular, may trigger cytotoxic effects and provoke inflammatory responses if their composition and dosage are not carefully optimized [62]. Hybrid delivery systems need to carefully balance enhanced functionality with safety considerations. Although combining different materials can improve therapeutic performance, it also adds regulatory challenges, since their breakdown products may be difficult to predict [63]. To mitigate these issues, new approaches such as biodegradable MOFs and stimuli-responsive polymers are being developed as potential solutions [64].

Surface Functionalization

Surface modification is essential for improving nanoparticle targeting, circulation time, and biosensing efficiency. Functional groups commonly employed include antibodies, aptamers, and peptides. Antibody conjugation offers strong specificity by recognizing tumor-associated antigens such as HER2 and EGFR. For instance, NPs linked with trastuzumab have shown enhanced accumulation and uptake in HER2-positive breast cancer models [65]. Furthermore, Aptamers, which are single-stranded oligonucleotides, provide advantages such as compact size, reduced immunogenicity, and customizable binding properties. NPs functionalized with aptamers against MUC1 have demonstrated effective drug delivery in lung cancer cell models [66]. Aptamer-based strategies are gaining growing attention for their dual potential in both diagnostic applications and therapeutic interventions [67]. Peptides, like RGD motifs, enable targeted delivery through integrin binding. Compared to full-length antibodies, short peptides are simpler to synthesize, promote deeper tumor penetration, and provide effective targeting capabilities [68]. Nanoparticle functionalization can be achieved through several approaches, including covalent coupling, physical adsorption, and affinity-based interactions. Among covalent coupling strategies, EDC/NHS chemistry is widely used to link carboxyl groups on nanoparticle surfaces with primary amine groups on biomolecules such as antibodies and peptides. In this reaction, EDC activates carboxyl groups to form a reactive intermediate, while NHS stabilizes it by generating an NHS ester, which subsequently reacts with amine groups to form a stable amide bond. More recently, the development of bio-orthogonal click chemistry has enabled site-specific and highly stable conjugations, which enhance reproducibility and overall therapeutic efficacy [69]. Although these strategies are effective in enhancing nanoparticle targeting, improving their stability in biological environments is crucial to prevent rapid degradation and reduce potential side effects. Additionally, integrating advanced technologies like artificial intelligence (AI) could further refine the precision and effectiveness of nanoparticle targeting in therapeutic applications.

Targeting Strategies

Efficient targeting is crucial for directing NPs to tumor tissues while reducing unintended distribution to healthy sites. Passive targeting relies on the enhanced permeability and retention (EPR) effect, in which the abnormal, leaky vasculature of tumors allows NPs in the 20–200 nm size range to accumulate within TME. Although this mechanism has been extensively investigated, its effectiveness varies greatly across different patients and tumor types, making clinical outcomes less predictable [70]. Active targeting leverages ligand–receptor interactions, where molecules such as antibodies, peptides, or aptamers are used to bind specifically to tumor-associated markers. This strategy enhances selectivity and cellular uptake. For example, NPs functionalized to target EGFR have demonstrated significantly improved internalization in lung cancer cells [71]. Nanocarriers engineered to respond to tumor-associated stimuli such as acidic pH, hypoxic conditions, or elevated glutathione levels enable localized and controlled drug release within TME. Additionally, enzyme-responsive systems, such as those incorporating matrix metalloproteinase (MMP)-cleavable linkers, provide an extra layer of specificity, further improving targeted therapeutic delivery. These smart biosensors bridge diagnostics with therapy by releasing drugs only under

tumor conditions [72]. New approaches are focusing on multi-modal targeting, which integrates passive accumulation through the EPR effect with active ligand-mediated uptake and responsiveness to TME cues. By combining these mechanisms, NPs can achieve higher therapeutic precision and potency while minimizing systemic toxicity [73].

The TME exhibits a characteristically acidic pH (6.5–6.8) arising from the Warburg effect and accumulation of acidic metabolites such as lactic acid, while regions of profound hypoxia are driven by an imbalance between oxygen supply and consumption, stabilizing hypoxia-inducible factors that promote angiogenesis, metabolic adaptation, and therapy resistance [74, 75]. Concurrently, elevated ROS levels contribute to oxidative stress, driving genetic instability and tumor progression, while overexpression of enzymes such as matrix metalloproteinases (MMPs) facilitates extracellular matrix degradation and tumor invasion [76]. Crucially, these biochemical aberrations are intimately linked to a profoundly immunosuppressive milieu wherein the recruitment of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) polarized toward an M2-like phenotype, alongside secretion of immunosuppressive cytokines including TGF-β and IL-10, collectively impair effector T cell infiltration and function, enabling immune evasion [76]. Recent literature emphasizes that these interconnected TME features form a web of obstacles that must be overcome for effective cancer immunotherapy, and the rational design of smart bionanosensors that respond to these specific endogenous stimuli, acidic pH, elevated ROS, hypoxia, and enzymatic activity, offers a promising strategy for achieving spatiotemporally controlled drug delivery, TME remodeling, and enhanced immunotherapeutic efficacy [74, 75].

As shown in Fig. 2, Passive targeting relies on the Enhanced Permeability and Retention (EPR) effect, in which drugs accumulate in tumors due to wide fenestrations (20–200 nm) in tumor vasculature, leading to simple accumulation, heterogeneous EPR. Active targeting uses antibodies (Ab) or aptamers to bind to specific receptors on tumor cells, facilitating receptor-mediated endocytosis for precise drug delivery via endosomes. TME-responsive targeting exploits tumor-specific conditions like low pH (6.5–6.8), GSH (glutathione), hypoxia, and enzymes (e.g., MMP) to trigger on-demand drug release, incorporating photothermal therapy (PTT) and small interfering RNA (siRNA) for enhanced treatment effectiveness.

Various types of NPs have distinct properties and functionalization strategies, which enable their use in targeting tumors and improving therapeutic outcomes. As shown in Table 1, metallic NPs (such as AuNPs and SPIONs) are particularly useful for imaging and photothermal therapy, while polymeric NPs offer controlled release and biodegradability. LNPs, including liposomes, are commonly used for RNA and drug delivery due to their biocompatibility. Hybrid NPs combine the stability of polymers with the biocompatibility of lipids, allowing for multifunctional design. Additionally, carbon-based NPs, like CNTs and graphene oxide, exhibit high surface areas and are effective for drug/gene loading and photothermal therapy. Recent study has included the design of multifunctional nanoplatforms that offer several features in diagnostics and treatment. Such a theranostic nanoplatform makes it possible to deliver medicines based on imaging in real time, thus helping to determine the localization of the tumor and effectiveness of the treatment. For example, magnetic nanoparticles can be used for MRI imaging and also as carriers of drugs for targeted therapy. Fluorescent and plasmonic nanoparticles can also be used for imaging and phototherapy [77].

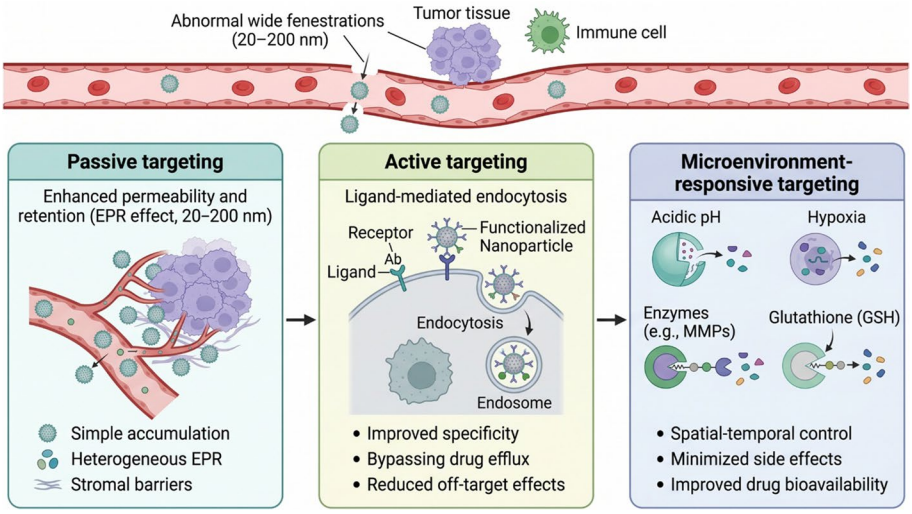


Fig. 2 The different strategies for targeted drug delivery to tumors. This figure presents three tumor-targeting strategies for nanoparticles. Passive targeting relies on the EPR effect through leaky tumor vasculature (20–200 nm pores) but faces heterogeneity and stromal barriers. Active targeting uses ligands or antibodies for receptor-mediated endocytosis, enhancing specificity, reducing off-target effects, and bypassing drug efflux. Microenvironment-responsive targeting exploits tumor traits like acidic pH, hypoxia, MMPs, and glutathione to enable spatiotemporal drug release, improving bioavailability and minimizing side effects. (Created with BioRender.com)

Advances in Smart Bionanosensors for Solid Tumors

Biomarker Detection

Human Epidermal Growth Factor Receptor 2 (HER-2)

A novel electrochemical apt sensor for detecting the HER-2 biomarker, built on a nanohybrid platform combining 3D zinc oxide tetrapod and potassium perylene tetra carboxylate, has shown remarkable potential in early breast cancer screening. This biosensor demonstrated exceptional sensitivity (2.08 μA/fg/mL/mm^2), a low detection limit (0.58 fg/mL), and a broad detection range (1 fg/mL–10 μg/mL), with a stable shelf life of over a month, making it ideal for low-cost, point-of-care use, especially in rural and resource-limited areas [82]. Traditional diagnostic techniques like mammography, ultrasound, MRI, and biopsy are often expensive and have their limitations, but electrochemical biosensors offer a promising alternative by achieving high sensitivity and low detection limits. In particular, HER2 detection has been enhanced by advanced sensor designs, which improve performance and accuracy, even in the presence of interfering agents [83]. A novel sensor using functionalized graphene, nanostructured polyaniline, and cost-effective AgNPs achieved ultrasensitive, label-free detection of breast cancer cells, with a detection limit as low as 2 cells/mL for SK-BR3 cells. This sensor is not only efficient in whole blood samples without preparation or staining but also demonstrates rapid detection within 30 min and a wide dynamic range (10^{-5}–10^6 cells/mL), showcasing its potential for both cancer diagnostics and broader applications in electrocatalysis and supercapacitors. Together, these innovations highlight

Table 1 Various applications of nanoparticles on solid tumors

Nanoparticle Type	Typical Size (nm)	Characterization Methods	Properties	Functionalization Strategies	Toxicity	Limitations	Tumor Targets/ Applications	Clinical Status	Ref
Metallic NPs (AuNPs, AgNPs, SPIONs)	10–100 (AuNPs), 10–150 (SPIONs)	TEM, DLS, UV–Vis, XRD, MRI contrast (SPIONs)	Optical, plasmonic, and magnetic properties; useful for imaging, photothermal and photodynamic therapy	Antibody conjugation (e.g., HER2, EGFR), aptamers (MUC1), peptides (RGD), PEGylation	Oxidative stress, inflammation, cytotoxicity, genotoxicity, organ accumulation (dose/size-dependent)	Safety concerns, scalability, environmental persistence, and resistance risk	Breast (HER2 +), lung (EGFR +), glioma, melanoma		[78]
Polymeric NPs (PLGA, PEG, Chitosan, Dendrimers)	20–300	DLS, SEM, FTIR, NMR, DSC	Biodegradable, versatile, controlled release, FDA-approved (PLGA)	PEGylation (stealth), antibody/ aptamer/ peptide conjugation, click chemistry	Generally low/ biocompatible; reduced via controlled release	Potential burst release, stability/ scalability optimization	Breast, prostate, colon, pancreatic cancers	Preclinical phase	[79]
Lipid-based NPs (Liposomes, SLNs, LNPs)	50–200	TEM, Cryo-EM, DLS, Encapsulation efficiency	Biocompatible, clinically validated; enable RNA/drug delivery; reduce systemic toxicity	PEGylation, antibody/ aptamer/ peptide anchoring	Reduced systemic via targeting	Targeting precision, scalability, tumor heterogeneity	Breast (Doxil®), ovarian, liver, RNA delivery in cancer & vaccines	Preclinical–early clinical	[40]

Table 1 (continued)

Nanoparticle Type	Typical Size (nm)	Characterization Methods	Properties	Functionalization Strategies	Toxicity	Limitations	Tumor Targets/ Applications	Clinical Status	Ref
Hybrid NPs (Lipid–polymer, MOFs, polymer–metal composites)	50–250	TEM, BET, FTIR, Zeta potential, Raman spectroscopy	Combine polymer stability & lipid biocompatibility; modular multifunctional design	Dual functionalization (lipid + polymer), stimuli-responsive linkers, antibody/aptamer conjugation	Lower than single systems	Synthesis complexity, potential instability, scalability	Multimodal tumor targeting (pH, hypoxia, enzyme-responsive); colon, breast, liver	Preclinical	[80]
Carbon-based NPs (CNTs, Graphene oxide)	20–200	Raman spectroscopy, TEM, AFM, BET	High surface area, photothermal capability, drug/gene loading	PEGylation, peptide/aptamer/antibody conjugation	Mitigated by functionalization (core-dependent)	Variability, functionalization scalability, long-term effects	Breast, lung, colon, melanoma	Mostly preclinical	[81]

the growing role of electrochemical biosensors as an effective, cost-efficient approach for early breast cancer diagnosis and better treatment outcomes [84].

The creation of advanced electrochemical aptamer sensors to find the HER-2 biomarker is a big step forward in early breast cancer screening. These sensors are very sensitive, cheap, and quick to use, as demonstrated in Table 2. These sensors are based on a nanohybrid platform, which gives them great sensitivity and low detection limits. This makes them ideal for point-of-care use, especially in resource-limited settings. Electrochemical biosensors are better than traditional diagnostic methods like mammography and biopsy because they are cheaper and easier to get. These new technologies can detect cancer cells directly in whole blood and provide quick results without staining. This is making breast cancer diagnostics more efficient and easier to access, which could lead to better treatment results in the end.

BRCA1/2

BRCA-1, a gene linked to hereditary breast cancer, plays a critical role in DNA repair, cell growth regulation, and tumor suppression, making its precise detection essential for early diagnosis and treatment. Traditional methods like HPLC, SSCP, PCR, and DNA sequencing, though effective, are often costly, time-consuming, and complex [91, 92]. To overcome these challenges, researchers have developed advanced biosensing technologies,

Table 2 Representative smart bionanosensors for biomarker detection

Biomarker	Cancer relevance	Sensor platform	Nanomaterial/ recognition element	Sample	Detection limit	Linear range	Ref
HER2	Breast cancer	Electrochemical aptasensor	ZnO tetrapod/ perylene tetracarboxylate nanohybrid	Serum	0.58 fg/mL	1 fg/mL–10 µg/mL	[82]
HER2	Breast cancer	Amperometric immunosensor	Nanostructured electrode + antibody sandwich assay	Serum	0.85 fg/mL	1 fg/mL–20 ng/mL	[85]
BRCA1/2	Genetic breast/ ovarian cancer risk	SERS biosensor	Ag nanoparticles + Au–Ag core–shell nanotags	Cell lysate	0.001 nM	0.001–1000 nM	[86]
Exosomes	Liquid biopsy/ metastasis monitoring	Microfluidic aptamer chip	Aptamer-functionalized nanointerface	Plasma	$<10^5$ vesicles/mL	—	[87]
Hexanal	VOC from lipid peroxidation & oxidative stress in Lung Cancer cells	Chemiresistive sensor	Au NPs/ molecularly imprinted polymer (MIP)	Exhaled breath; serum, urine, saliva, plasma	1.1 ppm	2.5–300 ppm	[88]
VEGF	Multiple solid tumors	Electrochemical immunosensor	Porous Au nanostructure (dealloyed Ag-Au)/VHH anti-VEGF nanobody	Human serum	0.05 pg/mL	0.1 pg/mL to 0.1 µg/mL	[89]
CA125	Ovarian Cancer	Electrochemical immunosensor	Ti_3C_2Tx/ NH_2-CNT	Serum	1 µU mL^{-1}	1–500 U mL^{-1}	[85]
CEA	Broad solid tumor marker	Electrochemical immunosensor	3DPt/HGO	Human serum	0.0006 ng/mL	0.001–150 ng/mL	[90]

especially electrochemical biosensors, which offer high sensitivity, speed, and adaptability. For instance, a highly sensitive photoelectrochemical (PEC) sensor, combining MoS2/CdIn2S4 heterojunctions with FePdMnCoPt high-entropy alloy/N-doped carbon spheres, provides an impressive detection range of $0.1–1.0 \times 10^5$ pg/mL and a low detection limit of just 1 pg/mL [93]. Similarly, a surface-enhanced Raman spectroscopy (SER S)-based approach, using AgNPs substrates and Au–Ag core–shell nanotags, enables selective dual detection of BRCA1 and BRCA2 over a broad range (0.001–1000 nM), with successful application in cell lysates [94]. Additionally, an electrochemical immunosensor built on pencil graphite electrodes modified with a AuNPs–MoS_2–chitosan nanocomposite achieves a wide detection range (0.05–20 ng/mL) and a low detection limit (0.04 ng/mL), with strong reproducibility and a high recovery rate in serum samples [95]. These biosensor innova-

tions, particularly those enhanced by nanomaterials, offer efficient, cost-effective, and highly sensitive solutions for BRCA1/2 detection, making them promising tools for breast cancer diagnosis and genetic screening [91, 96, 97].

CTC

Circulating tumor cells (CTCs), which are shed from primary or metastatic tumors into the bloodstream, play a central role in cancer metastasis and are valuable biomarkers for early diagnosis, treatment monitoring, and recurrence prediction [98, 99]. However, their detection is technically challenging due to their extremely low numbers, the abundance of blood cells, and cell heterogeneity. Advances in CTC isolation and detection methods, especially chip-based assays and biosensors, have significantly improved their detection, though challenges remain in clinical practice, such as assay sensitivity and sample variability [100]. Liquid biopsy, which uses biomarkers such as CTCs, cell-free DNA, and extracellular vesicles, is emerging as a powerful, minimally invasive approach for cancer detection and monitoring. Also, microfluidics, nanotechnology, and next-generation sequencing have greatly improved detection accuracy, while integrating genomic, transcriptomic, and proteomic data with AI-driven analysis supports personalized treatment strategies. However, regulatory hurdles, assay standardization, and data integration still limit clinical adoption [101]. CTCs are also closely linked to epithelial-to-mesenchymal transition (EMT), which drives cell migration, invasiveness, and chemotherapy resistance. Markers such as EpCAM, cytokeratins, CD44, CD24, HER2/neu, and vimentin are commonly used for their identification, with immune-based methods typically employed for their isolation [102]. Recent breakthroughs in nanotechnology, including NPs, advanced nanomaterials, and microfluidic platforms, have revolutionized CTC detection, offering more precise and efficient approaches [103]. These innovations represent a significant advancement in CTC research and are strengthening their potential for clinical applications in cancer diagnosis and monitoring [103].

Exosomes

Exosome-based therapies are becoming a promising way to treat cancer. These natural nanovesicles carry proteins, lipids, and nucleic acids that are like the cells they come from. They are useful for diagnostics and targeted therapies because they can help cells talk to each other [104]. Exosome-based treatments, on the other hand, pose challenges for clinical translation. These include tumor heterogeneity, difficulties in isolating and characterizing exosomes, a lack of standardized methods, and challenges in increasing production [105, 106]. Interactions between exosomes and the immune system may also lead to the development of cancer vaccines. This shows how important it is to come up with new ideas and work together to fully realize their therapeutic potential [107] Nanotechnology is making significant strides in cancer diagnostics with exosome-based chip platforms that enable early, non-invasive, and highly sensitive detection [105]. These microfluidic and nanomaterial-based systems capture and analyze exosome vesicles carrying cancer-specific molecular signatures from body fluids with greater precision than conventional methods. Engineered exosomes have significant therapeutic potential, especially for targeting metastasis. Although obstacles in standardization and clinical translation persist, continuous progress in chip-integrated nanotechnologies indicates a revolutionary transition towards exosome-based cancer detection and therapy [108].

Imaging-Guided Detection

Photoacoustic brain imaging (PABI) combines optical contrast with ultrasound penetration, enabling high-resolution, deep-tissue imaging of brain tumors. Enhanced by nanomaterials, PABI offers precise diagnosis, therapy monitoring, and clinical screening, showing strong potential to revolutionize brain disease detection and treatment [109]. Glioma, a highly aggressive brain tumor, can benefit from near-infrared II (NIR-II) fluorescence imaging, which offers deep penetration, high resolution, and non-invasiveness. NIR-II has been applied in surgery guidance, targeted drug delivery, photoacoustic therapy, and multimodal treatments, holding promise to improve outcomes, though challenges remain for future clinical use [110, 111]. Conventional imaging techniques often struggle to effectively monitor cancer therapy due to their limitations in depth, specificity, and delayed feedback. Nanophotonic photoacoustic biosensors address these gaps by enabling real-time, non-invasive, high-resolution monitoring of TME. Advances like plasmonic nanostructures, NIR-II fluorophores, SERS materials, and hybrid nanosystems enhance targeting and sensitivity, while biomimetic designs improve penetration and reduce nois [112]. Coupled with AI and IoT frameworks, these platforms support adaptive, precision-guided oncology, and with a focus on biosafety, scalability, and clinical validation, they show promise for next-generation cancer diagnostics and treatment monitoring [113]. Nanomedicine, with engineered NPs serving as contrast agents for highly sensitive imaging and nanoprobes for precise tumor detection, is emerging as a powerful approach in cancer care. Nanodrug carriers allow targeted delivery to tumors, improving treatment efficacy while reducing damage to healthy tissue and enhancing therapies like radiotherapy and photothermal therapy [114].

Photoacoustic brain imaging (PABI), especially when improved with nanomaterials, could change how brain tumors are diagnosed and treated. PABI combines optical contrast with ultrasound to make high-resolution images of deep tissues. This enables doctors to closely monitor tumors and guide treatment. Gliomas could benefit from NIR-II fluorescence imaging, which offers deep tissue penetration and non-invasive monitoring, though clinical challenges remain. Combining nanophotonic biosensors, AI, and the Internet of Things (IoT) could make real-time tumor monitoring even better, allowing for more precise and flexible treatments. Nanomedicine, which focuses on delivering drugs to specific areas and sensitive imaging, has the potential to make cancer treatments more effective while causing less harm to healthy tissues. Compared to traditional imaging techniques, each approach has significant advantages and disadvantages. CT enables rapid anatomical imaging but exposes patients to ionizing radiation and provides poor soft-tissue contrast. MRI provides great soft-tissue resolution without using ionizing radiation, yet it is associated with long acquisition times, high costs, and low molecular sensitivity [115, 116]. PET is highly sensitive for functional and metabolic imaging, but it has limited spatial resolution and requires radioactive tracers. Fluorescence imaging enables highly sensitive, real-time, image-guided surgery; however, limited tissue penetration, especially in the visible and NIR-I ranges, limits its therapeutic relevance [117–119]. In contrast, photoacoustic imaging (PAI) combines fluorescence imaging's strong optical contrast with ultrasound's superior tissue penetration and spatial resolution, enabling high-resolution detection of deep-seated malignancies without ionizing radiation [111, 119]. When combined with nanomaterial-based contrast agents, PAI enhances molecular specificity and multimodal imaging capabilities, making it a suitable platform for image-guided cancer diagnosis and therapy. As

a result, hybrid nanoplatforms that combine MRI, PET, fluorescence imaging, and PAI are being developed to leverage each modality's strengths while minimizing their limitations, thereby improving diagnostic accuracy and therapeutic guidance [118, 120].

Point-of-care & Wearable Nanosensors

Wearable point-of-care diagnostics and biosensors are changing how cancer is found and treated, and bio-inspired materials are a big part of this. These materials, which come from organic or inorganic molecules, can recognize biological signals and respond to stimuli because they can self-assemble at the molecular and supramolecular levels. When used in wearable devices, they make it possible to quickly read and detect cancer biomarkers. This new way of doing things looks very promising for cancer treatment, and recent advances in bio-inspired diagnostic platforms show that they could be used widely in the field [121]. At the same time, aptamer-based biosensing technology has become a powerful way to find and isolate extracellular vesicles (EVs), which are important in diseases like tumorigenesis. Aptamers, which are short DNA or RNA strands made through the SELEX process, are more specific, stable, and cost-effective than traditional methods like ultracentrifugation and antibody-based biosensors. Aptamers facilitate accurate EV isolation, detection, and analysis when incorporated into biosensors, thereby enhancing drug delivery and diagnostics. The increasing use of aptamers in EV-based research and diagnostics is a big step forward in making cancer-related diagnostic technologies more sensitive and effective [122].

Therapeutic Applications

Drug Delivery Nano Systems

Nanomedicine, an emerging multidisciplinary field, holds significant promise in cancer diagnosis and treatment. Engineered NPs serve as contrast agents for high-resolution tumor imaging, while nanoprobes and nanobiosensors enable innovative tumor labeling and detection. In therapy, rationally designed nanocarriers can deliver drugs or genetic material directly to tumors through targeted mechanisms, improving effectiveness while minimizing side effects. Additionally, NPs can enhance treatments like radiation sensitization and photothermal therapy, making nanotechnology an advancing frontier in oncology [114]. Smart NPs, including systems like liposomes, dendrimers, AuNPs, and QDs, are designed to respond to biological or external stimuli and target tumors with high precision. These NPs, functionalized with tumor-specific ligands, hold great promise for safer, more effective, and personalized treatments, although clinical challenges persist [8] (Fig. 3).

Combinatorial therapy, which uses multiple drugs to target different pathways, benefits from nanoparticle carriers such as liposomes and polymeric NPs, improving drug delivery, release, and stability. This approach offers promise for treating complex diseases, but challenges in clinical translation remain [123]. Nucleic acid therapeutics, which offer precise gene-targeting treatments, have faced delivery challenges, but LNPs have revolutionized the field by enabling safe and effective RNA delivery. Success stories like Patisiran, the first siRNA drug (2018), and the COVID-19 mRNA vaccines from Pfizer-BioNTech and Moderna (2020), highlight the versatility of LNPs in formulation, action, and biodistribution, positioning them as a cornerstone for future RNA-based medicines [124].

Photothermal/Photodynamic Therapy

Photothermal therapy (PTT) is an emerging cancer treatment that relies on efficient photothermal agents (PTAs) to convert light into heat, thereby killing tumor cells. A novel Fe_3O_4@PDA/ICG (FPI) nanoparticle, combining magnetic Fe_3O_4, polydopamine, and indocyanine green, was developed as a highly promising PTA for PTT. These NPs are stable, biocompatible, and uniformly shaped, generating significant heat (54.1 °C) with high conversion efficiency (35.21%) under near-infrared laser irradiation. They demonstrated low toxicity and strong tumor-killing effects on HeLa cells, positioning FPI NPs as a powerful option for future cancer PTT applications [125] (Fig. 3). Photothermal nanomaterials, including metals, semiconductors, carbon, polymers, and 2D materials, efficiently convert light into heat, and advances in their design and nanoscale heat-probing techniques are expanding their potential applications. However, challenges remain in further developing these materials for broader use [126]. A major challenge in nanomedicine is the lack of standardization, which hampers data comparison and clinical translation. To address this, guidelines for in vitro plasmonic photothermal therapy (PPTT) are proposed, covering nanomaterials, biological samples, and characterization before, during, and after irradiation. Standardized protocols and reporting can improve reproducibility and accelerate the development of PPTT as a versatile cancer therapy [127].

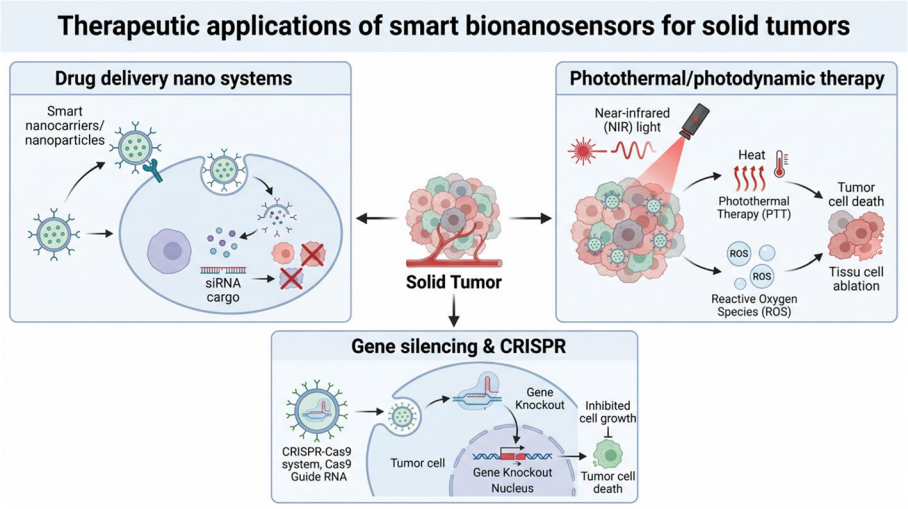


Fig. 3 Therapeutic applications of smart bionanosensors for solid tumors. Drug delivery nano-systems utilize smart nanocarriers to transport therapeutic payloads such as siRNA, enabling targeted gene silencing within tumor cells. Photothermal/photodynamic therapy employs near-infrared (NIR) light to generate either heat (photothermal therapy, PTT) or reactive oxygen species (ROS), both of which induce tissue cell ablation and tumor destruction. Finally, gene silencing and CRISPR approaches leverage the CRISPR-Cas9 system with guide RNA to achieve gene knockout, inhibiting tumor cell growth and promoting cell death. Together, these strategies offer diverse, programmable mechanisms for precision cancer treatment. (Created with BioRender.com)

Gene Silencing & CRISPR

CRISPR/Cas technology, widely known for its revolutionary gene-editing capabilities, is now expanding into the field of biosensing, offering great potential for detecting a wide range of disease biomarkers (Fig. 3). However, current CRISPR-based biosensors face limitations such as low sensitivity and selectivity. By integrating advanced materials like plasmonic nanomaterials, the signal strength and accuracy of these biosensors can be significantly enhanced. Additionally, incorporating microfluidic chips enables these biosensors to operate efficiently at physiological temperatures, reducing reagent consumption, simplifying sample processing, and increasing throughput, making them highly attractive as rapid and cost-effective alternatives to PCR, especially in applications like COVID-19 diagnostics [128]. Beyond diagnostics, CRISPR also plays a crucial role in therapeutics, but traditional delivery methods using viral vectors present safety concerns, such as immunogenicity and targeted delivery issues. Nanotechnology offers a promising solution through polymeric NPs that enable the safe, controlled, and precise delivery of CRISPR/Cas9 components to target cells [129]. This combination of CRISPR with nanomedicine, often referred to as Nano-CRISPR, holds great promises for transforming healthcare by supporting early disease detection, personalized treatments, and targeted therapies for infectious and metabolic disorders. Despite challenges in improving safety, delivery efficiency, and clinical translation, the convergence of CRISPR, nanotechnology, and advanced biosensing platforms represents a powerful step toward a new era of precision medicine [130].

Theranostic Smart Bionanosensors as Enablers of Personalized Medicine

While the principles of stratified medicine have revolutionized oncology, the practical implementation of this strategy faces significant hurdles related to the spatial and temporal heterogeneity of solid tumors [131]. The information gleaned from a single tissue biopsy provides a static snapshot that often fails to represent the complete molecular landscape of a patient's disease, including metastatic sites and the evolution of resistance under therapeutic pressure [132]. To bridge this critical gap between systemic biomarker information and lesion-specific reality, the field of nanotechnology has developed theranostic smart bionanosensors [133]. These platforms represent a fundamental shift from conventional diagnostics and therapeutics. The term "theranostic" (a portmanteau of therapy and diagnostics) refers to a single-agent platform that seamlessly integrates diagnostic capabilities with therapeutic action [133]. This allows for the simultaneous identification of a molecular target and the co-localized delivery of a therapeutic payload. The "smart" designation further signifies their ability to respond to specific triggers within TME (e.g., pH, enzymes, hypoxia) or to external stimuli (e.g., light, magnetic fields), enabling a level of spatiotemporal control unattainable with conventional drugs [134]. These platforms function as powerful enablers of personalized medicine by transforming biomarker assessment from a static, one-time event into a dynamic, real-time process [135]. They allow for the non-invasive visualization of target expression across all disease sites, guide patient selection with greater accuracy, and offer the potential to monitor therapeutic response at a molecular level long before anatomical changes are visible [136]. In essence, they provide the technological means to execute the precision promised by the stratified medicine paradigm.

As depicted in Fig. 4, the workflow outlines an integrated approach for personalized medicine, spanning from multi-omics and clinical data acquisition to computational analysis, clinical decision support, personalized therapeutic intervention, and outcome feedback. This framework emphasizes continuous data integration to enable adaptive and patient-specific treatment strategies.

As illustrated in Fig. 5, biomarkers are central to precision medicine. It demonstrates how molecular diagnostics identify genetic, proteomic, metabolic, and epigenetic biomarkers, which are then integrated into computational (in silico) models to enable patient stratification, risk–benefit analysis, dose optimization, and biomarker discovery in personalized medicine.

While much of the bionanosensor stratification literature remains preclinical, several of the platforms described above are now generating prospective, randomized, or registered clinical trial level evidence. In breast cancer, a prospective multicenter trial (NCT06672302) is now validating an AI-coupled exosome-SERS nanosensor for stratifying BI-RADS 3–5 lesions, building on earlier work showing that exosome-SERS-AI could simultaneously detect six early-stage cancers, including breast and pancreatic cancer, from a single plasma sample with an AUC exceeding 0.97 [137, 138]. In lung cancer, a multicenter SERS biosensor trial using catalytic hairpin assembly amplified gold nanorod probes (NCT06772376) is validating blood-based EGFR mutation typing as a faster alternative to tissue biopsy

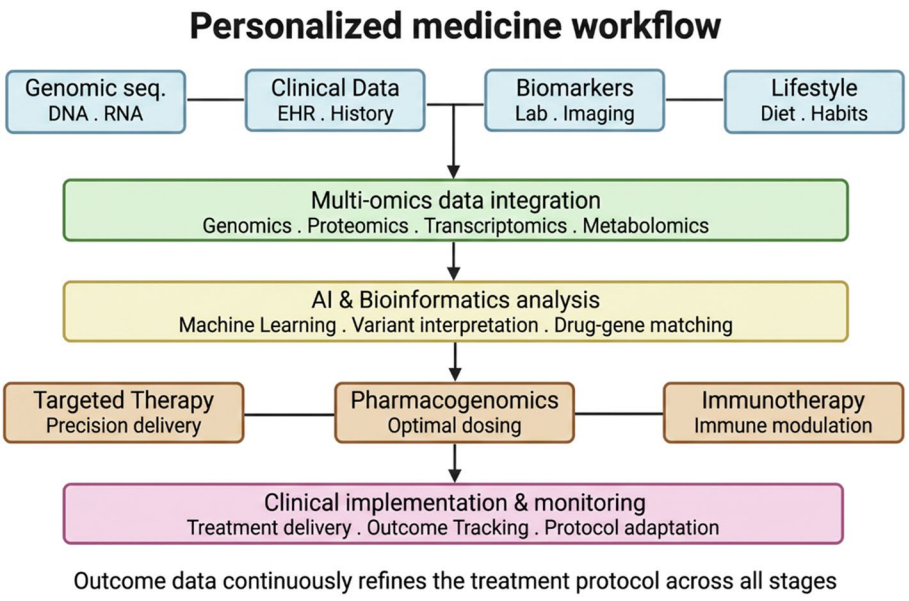


Fig. 4 The workflow regarding an integrated approach for personalized medicine. This figure outlines a comprehensive personalized medicine workflow that integrates diverse patient data, including genomic sequencing (DNA/RNA), clinical records, biomarker profiles, and lifestyle factors, to inform precision oncology care. Through multi-omics data integration (genomics, proteomics, transcriptomics, and metabolomics) and AI-driven bioinformatics analysis such as machine learning and drug-gene matching, the system identifies optimal therapeutic strategies including targeted therapy, pharmacogenomics-guided dosing, and immunotherapy. These interventions are then delivered and monitored in the clinical setting, with ongoing outcome tracking and protocol adaptation. Crucially, outcome data continuously feeds back to refine the treatment protocol across all stages, creating a dynamic, learning loop that enhances therapeutic efficacy and personalization over time. (Created with BioRender.com)

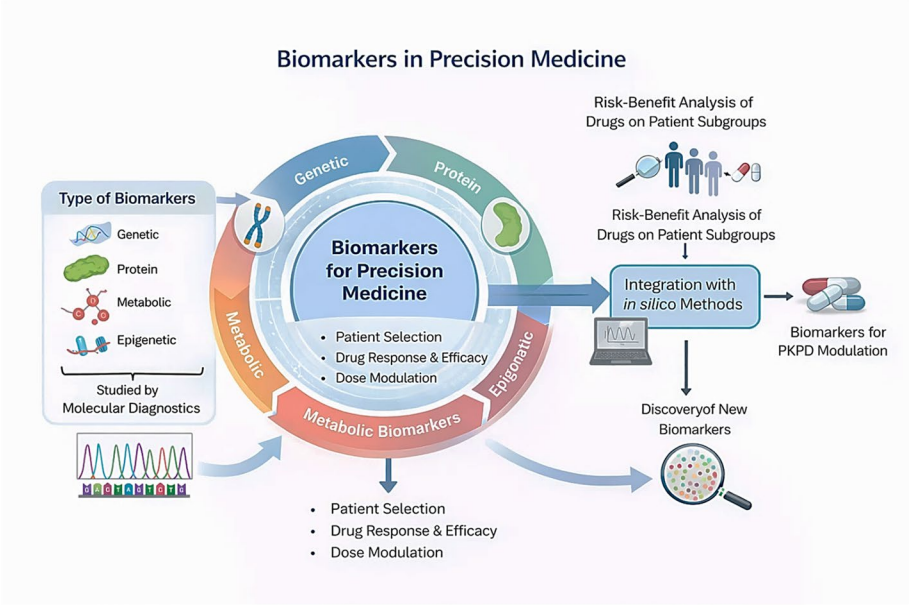


Fig. 5 Biomarkers in precision medicine. This figure illustrates the central role of biomarkers in precision medicine, categorizing them into genetic, protein, metabolic, and epigenetic types, all of which are studied through molecular diagnostics. Each biomarker class informs critical clinical decisions, including patient selection, prediction of drug response and efficacy, and dose modulation. The workflow further emphasizes risk–benefit analysis of drugs across patient subgroups, integration with in silico methods to discover novel biomarkers, and the use of biomarkers for pharmacokinetic/pharmacodynamic (PKPD) modulation. Collectively, these elements enable a data-driven, individualized approach to therapy, ensuring that treatment regimens are optimized for safety, effectiveness, and patient-specific outcomes. (Created with BioRender.com)

for TKI stratification [139]. In prostate and neuroendocrine cancers, the radiotheranostic paradigm referenced above has already achieved full clinical translation in two named pivotal trials VISION and NETTER-1 which remain the most mature real world examples of nanosensor/radiotracer-guided stratify-then-treat oncology currently in routine clinical use [140, 141]. Current evidence suggests that genuinely bionanosensor specific randomised or completed clinical trials with outcome data barely exist yet. The registered SERS trials (NCT06772376, NCT06672302) have not yet reported results, and Shin et al. (2023) remains a validation cohort study, not a randomised trial. Further large scale studies and trials with standardised protocols are still needed before these technologies can be integrated into routine oncological practice.

Stratified Treatments: The Foundation of Personalized Oncology

Stratified treatment in oncology relies on dividing patients into subgroups based on specific genetic, proteomic, or microenvironmental profiles, allowing therapy to be tailored rather than generalized [142]. As shown in Table 3, the biomarker-driven approach has fundamentally altered the standard of care, with biomarker-matched therapies significantly improving survival outcomes in multiple solid tumors, as exemplified by landmark clinical trials [143].

Table 3 Representative biomarker-driven stratified therapies in solid tumors

Biomarker Test	Solid Tumors	Prevalence (Selected Populations)	Representative Therapy	Trial Result	Ref
EGFR mutations (Exon 19 del, L858R)	NSCLC (adenocarcinoma)	10–15% (Caucasian); > 40% (East Asian)	Osimertinib (3rd-gen TKI)	*FLAURA*: Median PFS 18.9 vs 10.2 mo	[144]
HER2 amplification/ overexpression	Breast, Gastric	~15–20% (Breast)	Trastuzumab, ADCs	Trastuzumab improved DFS/OS in HER2 + disease	[145]
BRAF V600E mutation	Melanoma; CRC; Thyroid	~40–50% (Melanoma)	Vemurafenib ± MEK inhibitors	*BRIM-3*: OS & PFS improved; ORR > 50%	[146]
BRCA1/2 mutations	Breast, Ovarian, Prostate, Pancreatic	5–10%	PARP inhibitors (Olaparib)	Multiple trials: Improved PFS in BRCA-mutant cancers	[147]
PD-L1 expression (TPS ≥ 50%)	NSCLC, others	Variable (tumor-dependent)	Pembrolizumab	*KEYNOTE-024*: PFS 10.3 vs 6.0 mo; OS benefit	[148]

Extending Stratification with Real-Time Biomarker Profiling

While the biomarkers identified by conventional assays like sequencing and immunohistochemistry (IHC) are foundational to stratified medicine, these methods provide a static, often incomplete, picture of a patient's disease [135]. For instance, a primary tumor might be HER2-positive, but metastatic lesions may have lost HER2 expression. Nanosensors can overcome this limitation through several mechanisms. Smart bionanosensors extend the impact of stratification by enabling a more dynamic and comprehensive analysis through liquid biopsy-based detection, lesion-level imaging, and real-time monitoring of treatment response [149]. They can, for example, detect ctDNA carrying *EGFR* mutations in plasma, identify HER2-positive exosomes in blood, or quantify PD-L1 expression at single-cell resolution on circulating tumor cells (CTCs) [150].

Furthermore, while genomic profiling from a single biopsy identifies which patients are *likely* to benefit from a targeted therapy, smart bionanosensors provide crucial lesion-level confirmation of biomarker expression and function, addressing the critical challenge of inter- and intra-tumoral heterogeneity [151]. This is exemplified by nanosensors conjugated with anti-EGFR aptamers that can selectively bind and fluoresce in *EGFR*-mutant NSCLC lesions, thereby distinguishing heterogeneous tumors where not all metastases harbor the targetable mutation [144]. Similarly, HER2-targeted nanoparticle probes, such as Au nanorods or QDs, enhance optical and photoacoustic imaging, allowing clinicians to

visualize HER2 density on a per-lesion basis and potentially adjust HER2-directed therapy [152]. Advanced platforms like nanozyme-based sensors can even detect PD-L1 expression via catalytic signal amplification, enabling a more quantitative approach to stratification for immunotherapy that surpasses bulk tissue staining [153]. Thus, theranostic nanosensors bridge the critical gap between population-level biomarker prevalence and real-time, patient-specific lesion profiling.

Core Mechanisms of Nanosensor-Mediated Stratification

Smart bionanosensors achieve stratification in solid tumors through several core functional approaches that allow them to interrogate complex biological systems with high precision [133]. At the molecular level, this includes genomic and transcriptomic profiling, where nanoparticle-based probes are designed to detect specific mutations or mRNA expression signatures, such as *KRAS* in colorectal cancer or *EGFR* in lung cancer. It also involves proteomic biomarker monitoring, where sensors functionalized with high-affinity ligands detect overexpressed or shed proteins like HER2 in breast cancer or PSA in prostate cancer [149]. Beyond the cancer cell itself, nanosensors enable microenvironmental sensing, responding to unique features of TME like hypoxia, low pH, reactive oxygen species (ROS), or enzymatic activity from proteases like MMPs, allowing tumors with distinct microenvironments to be stratified for specific treatments [154]. Crucially, these mechanisms are often integrated into platforms designed for liquid biopsy analysis, where smart nanostructures functionalized with antibodies or aptamers can efficiently capture and analyze circulating tumor cells (CTCs) or exosomes from blood, informing treatment stratification without the need for invasive tissue biopsies [150]. Overall, nanosensor-mediated stratification integrates molecular, proteomic, and microenvironmental insights with liquid biopsy applications, offering a multidimensional view of tumor heterogeneity. It is proposed that, this convergence not only enhances diagnostic precision but also establishes nanosensors as pivotal tools for guiding personalized oncology, bridging the gap between benchside innovation and bedside decision-making.

Cancer-Specific Applications of Bionanosensors in Stratified Therapy

The application of smart bionanosensors in stratified therapy is best illustrated through cancer-specific case examples. These platforms enable precise biomarker detection, molecular subtype classification, therapy guidance, and real-time response monitoring in a manner that surpasses conventional diagnostic tools [151]. Nanosensors achieve this stratification through several functional approaches, including the detection of genomic and transcriptomic signatures, the monitoring of proteomic biomarkers from liquid biopsies, and the sensing of unique features within TME to Personalized Treatment [135] (Fig. 6).

Breast Cancer

Breast cancer is a heterogeneous disease, encompassing distinct molecular subtypes (e.g., Luminal A/B, HER2-enriched, triple-negative), where smart nanosensors play a crucial role in improving stratification and therapy monitoring [155]. For HER2 detection and therapy guidance, plasmonic nanosensors, such as Au nanorods and NPs conjugated with anti-

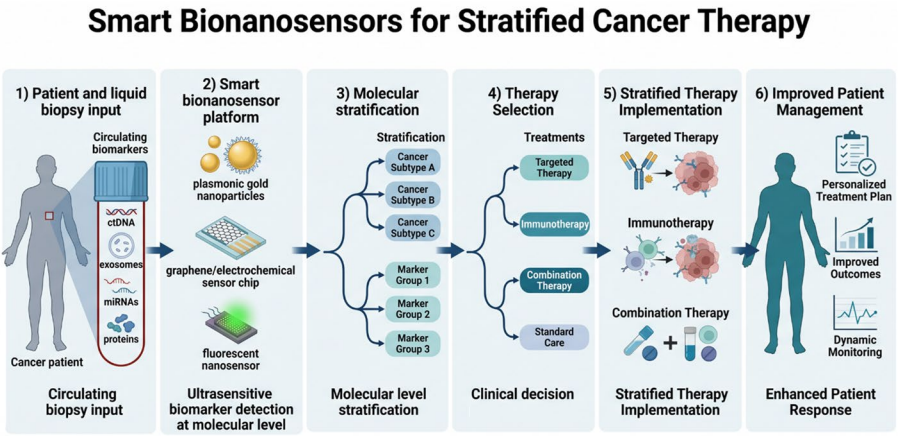


Fig. 6 Smart Bionanosensor-Driven Stratified Cancer Therapy: From Liquid Biopsy to Personalized Treatment. This figure presents a stratified cancer therapy workflow enabled by smart bionanosensors, beginning with patient liquid biopsy input to capture circulating biomarkers such as exosomes, miRNAs, and proteins. These samples are analyzed by a smart bionanosensor platform using graphene-based electrochemical or fluorescent nanosensors for ultrasensitive, molecular-level detection. The resulting data drive molecular stratification, classifying patients into distinct cancer subtypes or marker groups, which then guides clinical decision-making for therapy selection among targeted therapy, immunotherapy, combination therapy, or standard care. Following the implementation of stratified therapy, the approach supports improved patient management through personalized treatment plans, dynamic monitoring, and enhanced therapeutic responses, ultimately leading to better clinical outcomes and continuous adaptation based on real-time biomarker feedback. (Created with BioRender.com)

HER2 antibodies, enhance surface plasmon resonance signals to enable ultra-sensitive, even single-molecule, detection of HER2 expression [156]. This allows for a more quantitative stratification of patients for trastuzumab or antibody–drug conjugate (ADC) therapy [157]. Furthermore, smart QDs sensors linked to anti-HER2 and anti-ER/PR antibodies facilitate multiplexed imaging, enabling the simultaneous visualization of key receptors to provide rapid and comprehensive subtype classification from a small sample [158]. Nanosensors are also being developed for triple-negative breast cancer (TNBC), which lacks common therapeutic targets. Electrochemical nanosensors can detect TNBC-associated circulating miRNAs (e.g., miR-21, miR-155) to stratify patients for immunotherapy or PARP inhibitors [159]. Moreover, exosome-based sensors designed to isolate and analyze exosomes carrying PD-L1 mRNA can identify TNBC patients who are most likely to benefit from immune checkpoint inhibitors [160]. For therapy monitoring, smart nanosensors that detect ctDNA mutations or HER2 protein shedding in serum enable real-time tracking of treatment response and the early detection of resistance mechanisms [136] (Fig. 7).

Lung Cancer

The management of non-small cell lung cancer (NSCLC) is increasingly dependent on precise molecular stratification for mutations in genes such as *EGFR*, *ALK*, *ROS1*, and *KRAS* [151]. Smart nanosensors have revolutionized non-invasive detection and therapeutic monitoring in this context [161]. For EGFR mutations, clinically advanced silica nanoparticle probes conjugated with DNA sequences specific to mutant *EGFR* provide rapid, liquid

biopsy-based mutation detection from plasma [162]. This allows for the identification of actionable mutations as well as resistance mutations like T790M, stratifying patients for third-generation tyrosine kinase inhibitors (TKIs) such as Osimertinib [144]. At the research level, electrochemical graphene nanosensors have demonstrated the ability to detect the *EGFR* L858R mutation at femtomolar levels, potentially outperforming standard PCR-based tests in sensitivity [163]. For ALK rearrangements, exosomal RNA nanosensors integrated into microfluidic chips can capture ALK-positive exosomes from blood and analyze their RNA cargo [164]. This provides a non-invasive method for guiding crizotinib or lorlatinib therapy without requiring a tissue biopsy [164]. Similarly, for KRAS mutations, molecular beacon nanosensors are being developed to detect specific mutations like *KRAS* G12C, enabling stratification for newly approved targeted therapies like sotorasib and adagrasib [161] (Fig. 7).

Colorectal Cancer

CRC treatment is stratified by RAS/RAF mutational status, microsatellite instability (MSI), and features of TME [165]. For KRAS/NRAS mutations, which predict resistance to anti-EGFR therapy, graphene oxide-based fluorescent sensors have been designed to detect point mutations in *KRAS* (codons 12/13) [166]. These platforms can rapidly identify resistance

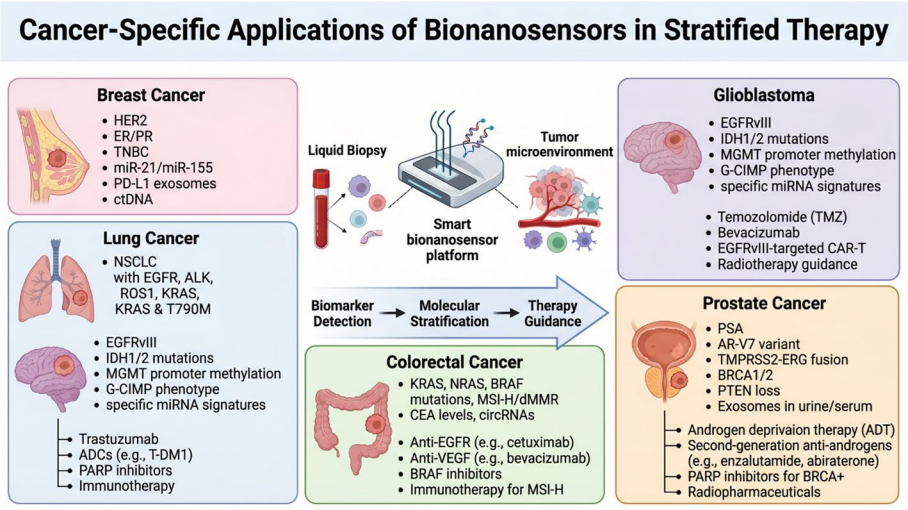


Fig. 7 Cancer-Specific Bionanosensor Platforms for Stratified Therapy and Biomarker-Guided Treatment. This figure outlines cancer-specific applications of bionanosensors in stratified therapy, highlighting key biomarkers and therapeutic strategies across major tumor types. In breast cancer, sensors detect HER2, ER/PR, TNBC markers, miR-21/miR-155, PD-L1 exosomes, and ctDNA to guide targeted and immuno-therapies. For lung cancer, biomarkers include EGFR, ALK, ROS1, KRAS, and T790M mutations in NSCLC, enabling precision drug matching. Colorectal cancer utilizes KRAS, NRAS, BRAF, MSI-H/dMMR, CEA, and circRNAs to inform anti-EGFR, anti-VEGF, BRAF inhibitor, or immunotherapy choices. Glioblastoma relies on EGFRvIII, IDH1/2, MGMT methylation, G-CIMP, and miRNA signatures, while prostate cancer uses PSA, AR-V7, TMPRSS2-ERG, BRCA1/2, PTEN loss, and urinary/serum exosomes to guide androgen deprivation, second-generation anti-androgens, PARP inhibitors, or radiopharmaceuticals. Liquid biopsy and TME analyses further enable molecular stratification and dynamic therapy guidance, emphasizing the role of bionanosensors in delivering personalized, biomarker-driven cancer care. (Created with BioRender.com)

mutations from ctDNA, helping to exclude patients from ineffective treatments. Similarly, electrochemical DNA nanosensors can facilitate personalized treatment by rapidly identifying *NRAS* mutations [159] (Fig. 7).

Prostate Cancer

Stratification in prostate cancer depends on PSA levels, androgen receptor (AR) signaling, and the emergence of resistance biomarkers like the AR-V7 splice variant [167]. PSA detection has been significantly enhanced by electrochemical nano-immunosensors, where nanostructured electrodes provide attomolar sensitivity, improving early diagnosis and monitoring of therapeutic response[168]. For advanced disease, circulating RNA nanosensors using magnetic NPs can detect AR-V7 mRNA in the blood [169]. This allows for the stratification of patients who have developed resistance to androgen deprivation therapy, helping to redirect them toward chemotherapy or other effective treatments at the point of therapeutic decision-making [170]. Additionally, smart exosome nanosensors are being developed to capture prostate cancer-derived exosomes that carry biomarkers such as PCA3, providing another avenue for non-invasive stratification [171] (Fig. 7).

Pancreatic Cancer

While pancreatic ductal adenocarcinoma (PDAC) remains challenging to stratify due to its profound heterogeneity, nanosensors represent an emerging and promising approach [172]. Smart electrochemical nanosensors are being developed to improve the specificity of the biomarker CA19-9 [159]. Furthermore, miRNA-based sensors that detect PDAC-associated miRNAs (e.g., miR-21, miR-210) can help stratify patients for gemcitabine-based chemotherapy versus immunotherapy [173]. TME-responsive nanosensors, such as those activated by hypoxia, may also help identify PDAC patients who could respond to hypoxia-targeted drugs [154]. Nanosensor technologies have the potential to transform PDAC management by enabling more precise and dynamic patient stratification. Despite the complexity of this cancer, its integration could pave the way for earlier interventions and more effective personalized therapies (Fig. 7).

Stratification Based on the Tumor Microenvironment

A significant advantage of smart nanosensors is their ability to stratify tumors based not only on intrinsic molecular features but also on the unique traits of the TME, which heavily influence therapy response [154]. pH-responsive nanosensors are designed to activate a fluorescent signal or trigger drug release specifically within acidic tumor niches, a hallmark of hypoxic and glycolytically active tumors found in pancreatic cancer and glioblastoma [174]. ROS-sensitive probes are nanoplatforms that detect elevated reactive oxygen species in aggressive breast or ovarian tumors, allowing for stratification for redox-based therapies [175]. Finally, enzyme-triggered nanosensors, which are activated by overexpressed proteases like MMPs,

can be used to detect metastatic potential, helping to stratify patients who may require more aggressive intervention [164]. In my opinion, these TME-responsive nanosensors represent a powerful step toward bridging biology and therapy, as they can translate subtle microenvironmental cues into actionable clinical insights. By aligning treatment strategies with the dynamic conditions of the tumor niche, they hold strong promises for advancing truly personalized oncology.

Integrated Theranostic Systems

Unlike conventional diagnostics that passively detect biomarkers, smart bionanosensors in integrated theranostic systems function as dual-purpose platforms, simultaneously enabling precision detection and delivering targeted therapy. This "see, decide, and treat" functionality forms the foundation of personalized nanomedicine [176]. The landscape of these systems ranges from clinically approved platforms to a rich pipeline of preclinical innovations.

The most successful clinical translation of theranostics is in radiotheranostics [177]. For neuroendocrine tumors, patients are imaged with Gallium-68 DOTATATE PET to confirm somatostatin receptor (SSTR) expression [141]. Those with positive scans are then treated with Lutetium-177 DOTATATE (Lutathera®) [141]. Similarly, for metastatic castration-resistant prostate cancer, imaging with Gallium-68 PSMA PET identifies patients for treatment with Lutetium-177 PSMA-617 (Pluvicto®) [140]. Both paradigms have demonstrated significant survival benefits in landmark trials (Table 4).

Other advanced systems are based on physical energy. NanoTherm®, CE-marked in Europe for glioblastoma, uses intratumoral magnetic NPs that generate localized heat (hyperthermia) when activated by an external magnetic field [177] (Table 3). AGuIX®, currently in clinical trials, is a gadolinium-based nanoparticle that acts as both an MRI contrast agent for tumor delineation and as a radiosensitizer to amplify the effect of radiation therapy [178]. The preclinical pipeline is rich with innovative designs that promise even greater precision. Nanozymes as theranostics are catalytic nanomaterials that mimic natural enzyme activity [197]. For example, iron oxide nanozymes with peroxidase-like activity can generate cytotoxic reactive oxygen species (ROS) from endogenous H_2O_2 within the TME, enabling a new modality called chemodynamic therapy [198]. CRISPR nanosensors are being engineered to carry CRISPR-Cas systems that can detect a specific oncogenic mutation, which triggers a diagnostic signal, and then release a therapeutic payload. Finally, immuno-theranostics are smart nanosensors designed to detect PD-L1 expression and simultaneously release immune adjuvants or checkpoint blockade agents directly within the TME, aiming to convert immunologically "cold" tumors into "hot" ones [199]. Together, these advances highlight the unique strength of integrated theranostic nanosystems, their ability to close the loop between detection and treatment within a single platform. While clinical translation is still limited beyond radiotheranostics, the convergence of molecular sensing with precision therapy represents one of the most transformative frontiers in oncology, with the potential to redefine how tumors are both diagnosed and treated in real time.

Table 4 Theranostic nanosystems in solid tumors

Name/System	Platform Class	Mechanism of Action	Target/Tumor Type	Imaging Modality	Therapeutic Modality	Clinical Status	Ref
Lutetium-177 DOTATATE (Lutathera)	Radiotheranostic (peptide)	Targets SSTR and delivers beta-emitter therapy	GEP-NETs	Ga-68 DOTATATE PET	PRRT (177Lu)	Approved (FDA/EMA)	[141]
Lutetium-177 PSMA-617 (Pluvicto)	Radiotheranostic (small molecule)	Targets PSMA and delivers beta-emitter therapy	mCRPC	Ga-68 PSMA PET	PRRT (177Lu)	Approved (FDA)	[140]
AGuIX (Gd-polysiloxane NPs)	MRI-visible radiosensitizer	Utilizes a Gd chelate for contrast enhancement and provides radiosensitization effects	Brain mets, GBM	MRI (T1)	Radiosensitizer (RT)	Phase I/II	[178]
NanoTherm® (SPIONs)	Magnetic hyperthermia	Generate local hyperthermia when exposed to an alternating magnetic field	GBM (intratumoral)	MRI/thermal mapping	Hyperthermia ± RT	CE-marked (EU)	[177]
Fe_3O_4 Nanozymes	Nanozyme (catalytic)	Generation of ROS through peroxidase-like activity	Breast, Lung, CRC (models)	MRI/optical	Chemodynamic therapy	Preclinical	[179]

Table 4 (continued)

Name/System	Platform Class	Mechanism of Action	Target/Tumor Type	Imaging Modality	Therapeutic Modality	Clinical Status	Ref
Porphyrin-MOF Nanosystems	MOF platform	Enables PDT, generates oxygen to combat hypoxia, and provides imaging capabilities	Hypoxic tumors	MRI/optical/PET	PDT ± chemo	Preclinical	[180]
HER2-targeted AuNPs	Plasmonic NP	Target HER2 receptors and utilize SERS and plasmonic heating for photothermal therapy	HER2 + Breast	Optical/PA/SERS	Photothermal therapy	Preclinical	[181]
^{89}Zr-trastuzumab	Radiolabeled antibody	Enables HER2 immuno-PET imaging	HER2 + Breast	PET	Companion diagnostic	Early clinical	[182]
PSMA-targeted NPs	Targeted NP	Utilize ligand-mediated delivery for therapeutic applications	Prostate cancer	PET/optical	Drug/siRNA/RLT	Preclinical	[183]
Hypoxia-activated MOFs	Stimuli-responsive MOF	Senses hypoxic conditions and activates prodrug release	PDAC, GBM	Optical/PET	Prodrug activation	Preclinical	[184]

Table 4 (continued)

Name/System	Platform Class	Mechanism of Action	Target/Tumor Type	Imaging Modality	Therapeutic Modality	Clinical Status	Ref
Exosome-capture Magnetic Nanosensors	Liquid biopsy	Captures exosomes and provides a readout for diagnostic purposes	Breast, Lung, Prostate	Electrochem/optical	Diagnostic	Translational	[171]
CRISPR-Cas12a Nanosensors	CRISPR-theranostic	Detects mutations and delivers gene payloads	Multiple tumors	Fluorescence/LFA	Gene/siRNA delivery	Preclinical	[185]
Lipid–Polymer Hybrid siRNA Nanosystems	Lipid/polymer NP	Deliver siRNA therapeutics and provide imaging capabilities	Lung, Liver, Pancreatic	NIR/PET	siRNA therapy	Preclinical	[186]
HER2 Au Nanorods	Plasmonic NP	Enable photoacoustic imaging and PTT	HER2 + Breast	PA imaging	Photothermal	Preclinical	[152]
MMP-responsive Probes	Enzyme-activated NP	Cleaved by matrix MMP, which triggers a signal and releases a therapeutic payload	CRC, Breast	Optical	Drug release	Preclinical	[187]
PD-L1 Nanosensors	Immuno-nanosensor	Catalytically detects PD-L1 for immune checkpoint inhibitor stratification	Multiple tumors	Electrochem/optical	ICI stratification	Preclinical	[188]

Table 4 (continued)

Name/System	Platform Class	Mechanism of Action	Target/Tumor Type	Imaging Modality	Therapeutic Modality	Clinical Status	Ref
Gd-chelated NPs Radiosensitizers	MRI-visible NP	These MRI-visible nanoparticles provide contrast enhancement and radiosensitization	GBM, Brain mets	MRI	Radiosensitization	Early clinical	[189]
Dendrimer Theranostics	Polymeric dendrimer	Utilizes multivalent targeting and payload delivery	Breast, Ovarian	MRI/optical	Drug delivery	Preclinical	[190]
Single-atom Catalyst Nanozymes	SAC nanozyme	Catalyzes the highly efficient generation of ROS	Solid tumors	MRI/optical	Chemodynamic therapy	Preclinical	[191]
Photoimmunotherapy Conjugates (IRDye700DX)	Antibody–dye conjugate	Enables tumor-targeted PIT upon NIR light activation	H&N, Breast	NIR fluorescence	Photoimmunotherapy	Early clinical	[192]
Radiolabeled Nanobodies	Nanobody radiotracers	Enable PET imaging for diagnostic and radioligand therapy applications	HER2 +, Gastric	PET	Diagnostic/RLT	Early clinical	[193]

Table 4 (continued)

Name/System	Platform Class	Mechanism of Action	Target/Tumor Type	Imaging Modality	Therapeutic Modality	Clinical Status	Ref
Polymeric Micelles (drug + dye)	Polymeric NP	Enable the co-delivery of dyes and chemotherapeutic drugs	Breast, Lung	Fluorescence/ PET	Chemotherapy	Preclinical	[194]
Bacterial OMV Theranostics	Bio-derived nanovesicles	Exhibit tumor-homing properties for immunotherapy applications	Multiple tumors	Optical/ PET	Immunotherapy	Preclinical	[195]
Multiplexed Nanosensor Chips	Microfluidic nano	Captures CTC and exosomes and measures a panel of biomarkers for diagnostic purposes	Multi-tumors	Electrochem/ optical	Diagnostic	Early clinical	[196]

Digital Integration in Theranostic Bionanosensors

Iot Integrated Smart Biobanosensors

Wearable and Remote Monitoring

Wearable platforms convert point-in-time assays into continuous, longitudinal data streams that reveal the temporal dynamics of tumor biology and treatment response [200]. Minimally invasive microneedle arrays enable repeated sampling of dermal interstitial fluid ISF, providing a practical route to monitor nucleic acids, proteins, and metabolic markers without repeated venous phlebotomy [201] (Fig. 8). Electrochemical transducers integrated on wearable patches deliver high analytical sensitivity for small molecules and many protein targets, but require on device drift compensation and periodic calibration to preserve quantitative accuracy [15]. Optical approaches fluorescence, plasmonic readouts offer high specificity for labeled assays but impose mechanical and optical alignment constraints that complicate some wearable form factors [202]. Combining multiple sensing

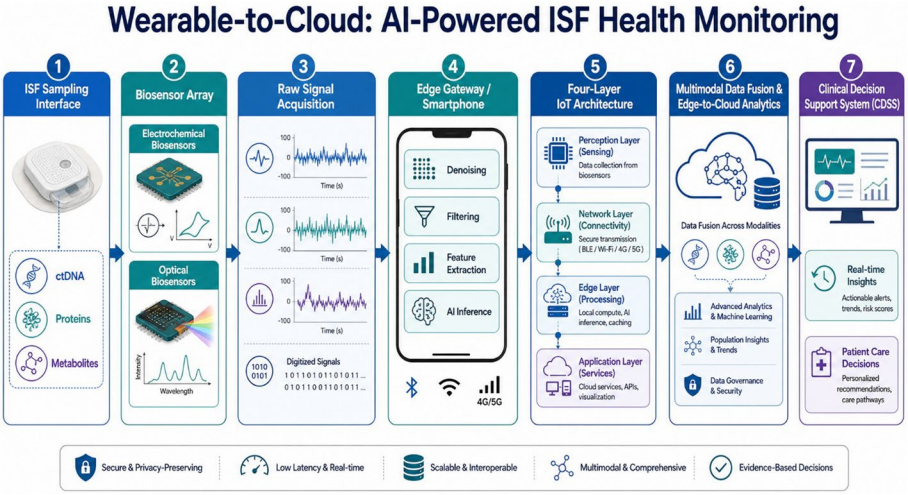


Fig. 8 Wearable-to-Cloud: AI-Powered ISF Health Monitoring. This figure illustrates a comprehensive, end-to-end framework for continuous health monitoring and clinical decision support, centered on the analysis of interstitial fluid (ISF) biomarkers. The process begins with a wearable patient patch that samples biomarkers such as ctDNA, proteins, and metabolites. These are transduced via electrochemical or optical biosensors, and the raw signals are then processed through an IoT and edge-to-cloud pipeline. At the edge (e.g., a smartphone gateway), the data undergoes AI-enhanced signal conditioning, including denoising, filtering, feature extraction, and inference using AI models, before being transmitted across a four-layer IoT architecture. This multimodal data fusion and edge-to-cloud analytics pipeline ultimately feeds into a clinical decision support system, enabling real-time, data-driven insights for patient care. (Created with BioRender.com)

modalities ISF molecular sampling, electrochemical readouts, and physiological proxies such as skin temperature or heart rate variability (HRV) increases robustness to biological variability and reduces single analyte failure risk [203]. In oncology, integration of bionanosensor outputs with tumor-specific clinical endpoints such as imaging-derived tumor burden, ctDNA levels, and histopathology permits earlier detection of minimal residual disease and treatment failure than single-modality monitoring alone [204]. Multiparametric longitudinal biosignatures that combine molecular readouts (e.g., ctDNA and proteomic markers), metabolic shifts and physiological proxies can improve discrimination between true progression, pseudo progression, and treatment-related inflammatory changes, thereby reducing false alarms and inappropriate therapeutic changes [205]. Translating continuous wearable and ISF measurements into oncology-relevant alerts requires temporally aware feature engineering and fusion with established biomarkers so that signal changes map to clinically meaningful events (e.g., biochemical relapse, immune-related adverse events) [206]. Robust clinical-grade models rely on supervised machine-learning pipelines trained on well-annotated outcome data and validated on independent cancer cohorts to ensure generalizability across tumor histologies and treatment modalities [207].

Regulatory and clinical validation for oncology applications should benchmark device outputs against gold-standard imaging and pathology endpoints, demonstrate clinical utility (for example earlier time-to-intervention or improved patient-reported outcomes), and pre-specify alert thresholds to limit overdiagnosis and unnecessary interventions [208]. To enable multicenter development while preserving patient privacy, privacy-preserving para-

digms such as federated learning and differential privacy allow collaborative model training on distributed oncology datasets without centralising sensitive genomic or sensor data [209]. Finally, successful deployment in oncology depends on EHR interoperability, clinician co-design of alert workflows to avoid alarm fatigue, and study designs that stratify feasibility cohorts by tumor type and therapy class to align sampling frequency with expected biomarker kinetics [210]. On-device and gateway edge preprocessing denoising, baseline correction, feature extraction reduce transmitted volume and enable fast local alarms while protecting raw patient signals [211]. Clinical translation requires staged validation: benchtop analytical validation detection limit, specificity, dynamic range, biocompatibility and irritation testing, small feasibility studies for adherence and signal quality, then multicenter clinical validation against gold standards [201]. Key performance indicators for readiness include time to detect clinically meaningful change, false alarm rate, device uptime, calibration drift over target intervals, and outpatient patient adherence [212]. User centred design comfort, ease of use, unobtrusive form materially improves adherence and therefore the completeness and clinical value of longitudinal biosignatures [203]. The practical translation of emerging diagnostic technologies into clinical practice typically follows a stepwise pathway. It begins with benchtop development and optimization, followed by small-scale human feasibility studies involving approximately 10–30 participants to evaluate initial performance and usability. Subsequent validation is conducted in adequately powered clinical cohorts by comparing the technology with established reference standards, such as blood biomarkers and imaging modalities, to confirm its diagnostic accuracy and reliability. Once validated, the technology can be integrated into routine clinical workflows and further assessed through prospective implementation studies to determine its feasibility, effectiveness, and potential impact in real-world healthcare settings [213].

Cloud Connected Biosensors

Cloud connectivity transforms distributed wearable streams into auditable, large-scale resources for model development, retrospective cohort analysis, and long-term patient records [214]. A reference architecture comprises four layers: device (wearable sensor), edge gateway (smartphone/home hub), cloud backend (stream ingestion, time-series DB, ML pipelines), and clinical integration (EHR/FHIR interfaces + clinician dashboards) [215] (Fig. 8). Edge processing should perform compression, denoising, and rapid anomaly detection so that only essential features or alarms are sent immediately, while bulk data are batched for cloud ingestion [216]. Time series databases and stream platforms in the cloud enable synchronized cross-patient analyses, cohort studies, and controlled model retraining while preserving provenance for regulatory audit [217]. Interoperability MUST use open clinical standards (HL7 FHIR, SMART on FHIR) to sensor observations into EHR workflows and support downstream decision support tools. End-to-end security controls are essential: TLS 1.2/1.3 for transport, AES-256 (or equivalent) for data-at-rest, certificate-based device authentication, and role-based access control for clinical users[218]. Federated learning and related privacy-preserving paradigms allow multi-institutional model development without centralizing raw patient data, though governance and technical safeguards are required to mitigate residual privacy risks [219]. Governance must include data retention policies, patient rights for access/deletion, continuous model-performance monitoring, and incident-response procedures for cybersecurity events [220]. Scalability considerations: regionally

distributed cloud deployments for latency and sovereignty, horizontal autoscaling for ingestion pipelines, and multi-tenant isolation for institutional deployments.[213]. Clinician-facing outputs should be concise, actionable, and confidence-stratified: short trend summaries, timestamped alerts with severity, and links to supporting features or model explanations to facilitate interpretation [221]. Validation of cloud-connected biosensor systems in oncology must go beyond general telemetry tests to ensure data integrity and timeliness under real clinical conditions, such as ambulatory cancer care, home-based monitoring, and infusion visits, where network variability or patient mobility may impact the detection of rapid biomarker changes [222]. Moreover, FHIR mappings and EHR integration should incorporate oncology-specific structures like mCODE profiles, tumor staging, treatment cycles, and biomarker panels, so that biosensor-derived alerts align precisely with clinical oncology workflows and decision pathways [215]. Equally important, end-to-end cybersecurity and incident-response readiness must include hospital coordination and simulation drills tailored for oncology contexts, preventing false therapeutic alarms or system downtime during critical chemotherapy sessions [215]. In addition, operational cost planning should budget for oncology-specific demands such as high-frequency sampling during tumor induction or recurrence phases, secure long-term storage for ctDNA time-series data, and compliance expenses related to cancer-device regulations [223]. These systems must also validate the temporal fidelity and quantitative accuracy of molecular biomarkers to ensure early and reliable detection of minimal residual disease or relapse, which are key indicators in cancer management [224]. Finally, combining multimodal data fusion, including sensor streams, imaging, and liquid biopsy results, with transparent clinician dashboards ensures that oncologists receive clear, actionable alerts without diagnostic ambiguity [225]. Overall, integrating these oncology-focused requirements within the validation checklist enhances clinical reliability, regulatory readiness, and the real-world impact of digital theranostic biosensor systems.

AI for Biomarker Detection

AI methods are rapidly transforming biosensor outputs into clinically useful biomarker readouts by improving signal fidelity, extracting informative features, and mapping complex sensor signatures to molecular or clinical states [226]. Successful AI-enabled biomarker detection depends on understanding three linked problems: (1) how to denoise and preprocess time series signals from physical transducers, (2) how to represent and fuse multimodal features, and (3) how to build robust, explainable models that generalize across devices and populations [227]. In solid tumors, spatial and microenvironmental heterogeneity require that biosensor-derived features be interpreted with spatial–temporal context to avoid misleading signals caused by intratumoral variation [228]. Denoising and preprocessing pipelines for tumor applications should incorporate tumor-informed models (for example, ctDNA kinetics and tumor-shedding patterns) so that transient fluctuations are not mistaken for analytic noise or vice versa.[229]. Practical multimodal fusion strategies should explicitly combine molecular sensor traces with tissue imaging (radiomics) and immune-microenvironment metrics to help distinguish true progression from pseudo progression, particularly in patients receiving immunotherapy [230]. Model training must use domain-adaptation and transfer-learning approaches across histologists and centers to ensure models generalize from one tumor type or device generation to another without los-

ing predictive performance [231]. Analytic validation for solid-tumor biomarkers should mandate paired ground-truth sampling, synchronized imaging, pathology, and circulating biomarkers across treatment cycles, so sensitivity for minimal residual disease and early relapse can be quantified [232].

Finally, clinician-facing outputs should present tumor-specific thresholds, annotated trends tied to treatment timing, and recommended follow-up actions so oncologists can interpret biosensor alerts within standard oncology workflows [233].

Signal Conditioning and Denoising

Raw biosensor outputs are commonly contaminated by thermal noise, motion artifacts, baseline drift, and biochemical fouling; therefore, preprocessing is an essential first layer before any AI model is applied [234]. Classical digital filtering (bandpass, median filters), adaptive baseline correction, and wavelet-based denoising remain effective first-line methods, particularly when paired with device-specific parameter tuning [235]. Learned denoising models, including convolutional autoencoders and denoising diffusion or generative models, can outperform fixed filters when trained on paired noisy, clean examples or on synthetic noise-augmented datasets [236]. Self-supervised and denoising-aware contrastive learning strategies have shown particular promise for noisy biomedical time series because they can learn robust representations without large labelled sets [237]. In practice, combine device physics-informed preprocessing with a learned denoiser: physics-based filters remove gross artifacts, and learned models refine residual structured noise, preserving transient biomarker events that would otherwise be suppressed [238].

Feature Extraction & Representation Learning

Feature engineering remains valuable when dataset sizes are limited: time domain statistics, spectro-temporal decompositions (STFT, wavelets), and physiologically motivated metrics (rise time, decay constant, peak width) are interpretable inputs that often improve small data model performance [227]. Where larger datasets exist, end-to-end deep architectures (1D-CNNs, temporal convolutional networks, and transformer variants) can learn hierarchical features directly from raw or minimally preprocessed signals and frequently achieve superior discrimination of subtle biomarker changes [239]. Multimodal fusion combining molecular signal features (e.g., electrochemical peak integrals) with physiological proxies (HRV, skin temperature) and contextual metadata (time post-dose, activity) consistently improves robustness and reduces single-source failure modes [240]. Representation compression (autoencoders, bottleneck layers) is useful for edge deployment because compact latent vectors reduce bandwidth and can be protected or aggregated more easily for federated training [226].Contrastive and self-supervised pretraining on large unlabeled biosensor corpora produces transferable features that markedly reduce labeled data requirements for downstream biomarker classification tasks [241]. In oncology, advanced feature extraction methods are increasingly being used to interpret biosensor data that capture molecular and physiological dynamics of solid tumors, helping to map metabolic activity and treatment response over time [222]. In breast cancer, time-domain and spectral features derived from biosensor signals can reflect variations in hormone receptor activity, HER2 expression, or metabolic reprogramming, providing early indicators of therapeutic resistance [213]. Deep

learning architectures such as CNNs and transformers enable hierarchical representation of these molecular features, allowing robust discrimination between breast tumor subtypes and prediction of response to targeted therapy [242]. Multimodal fusion of biosensor data with imaging modalities (for example, MRI radiomics or ultrasound texture) enhances precision by linking biochemical and morphological tumor features within the same analytical framework [243]. Compressed representations learned through autoencoders or contrastive pretraining can be securely shared in federated learning networks, enabling collaborative breast cancer biomarker research while preserving data privacy [244].

Supervised and Semi-Supervised Detection Models

For well-characterized biomarkers with abundant annotated examples, supervised deep learning classifiers (CNNs, TCNs, transformers) provide state-of-the-art sensitivity and specificity when trained with proper regularization and cross-validation [245]. In low-label regimes common in early translational biosensor studies, semi-supervised learners and few-shot classifiers (prototype networks, meta learning) extend performance by leveraging large pools of unlabeled sensor streams [242]. Ensemble across model families (statistical models + deep learners) can stabilize predictions and reduce overfitting to device-specific idiosyncrasies; ensembles also facilitate uncertainty estimation through variance across predictors [246]. A representative example can be seen in supervised deep-learning frameworks developed for breast cancer detection, where CNN-based classifiers trained on biosensor-derived electrochemical data successfully distinguished malignant from benign tissue samples with over 95% accuracy [213]. In another case, transformer-based models integrating time-series biosensor data with clinical metadata improved the prediction of chemotherapy response in triple-negative breast cancer patients, demonstrating the value of contextual feature learning [242]. Semi-supervised learning has also been applied to oncology biosensors where only a limited number of labeled molecular samples are available; using large pools of unlabeled interstitial-fluid data improved classifier generalization across tumor subtypes [244]. An ensemble of CNN and statistical feature models has further been used to reduce overfitting and quantify prediction uncertainty in multicenter breast cancer studies, ensuring robustness across different biosensor devices [220].

Time Series Forecasting and Early Event Detection

Predictive modeling of biomarker trajectories (nowcasting and short horizon forecasting) is crucial for theranostic because early detection of response or toxicity enables timely intervention; recurrent models (LSTM), temporal CNNs, and transformers with positional encoding are practical choices depending on dataset size and latency constraints [222]. Temporal anomaly detection frameworks combining prediction residuals with probabilistic thresholds can detect clinically relevant deviations before absolute biomarker thresholds are crossed, offering earlier warning signals [245]. Causal and counterfactual models that account for treatment timing and dosing allow AI systems to distinguish between natural biomarker variability and drug induced changes, improving decision reliability in closed-loop theranostic systems [247]. In oncology, forecasting biomarker trajectories from biosensor data can predict tumor response dynamics in real time, allowing clinicians

to intervene before clinical deterioration becomes apparent [222]. LSTM and transformer-based temporal models have been used to model changes in ctDNA, enabling early identification of minimal residual disease or resistance development in breast and lung cancer patients [248]. Time-series anomaly detection applied to longitudinal biosensor data can capture subtle metabolic or immunologic deviations that precede radiologic progression, thus supporting earlier treatment adaptation in immunotherapy cohorts [242]. Causal inference and counterfactual models further help distinguish biomarker fluctuations caused by drug toxicity from those reflecting tumor regression, improving the reliability of AI-assisted decision-making during oncologic therapy [220]. Integrating predictive modeling and anomaly detection within oncology workflows thus transforming biosensor data into proactive monitoring tools, enhancing personalized treatment and preventing delayed clinical responses.

Calibration, Uncertainty Quantification, and Robustness

Quantitative biomarker readouts require careful calibration: model outputs should be mapped to concentration units via calibration curves that are periodically updated to account for sensor drift and batch effects [224]. Uncertainty quantification (UQ) techniques, such as Bayesian neural networks, Monte Carlo dropout, and ensemble spread, are essential to present clinicians with confidence intervals rather than point estimates, which supports safer decision making [224]. Robustness to distributional shift should be tested explicitly: simulate device aging, different demographic cohorts, and varied use environments (motion, temperature) to measure model degradation and trigger retraining policies when performance drops [249]. Adversarial and worst-case testing (including synthetic perturbations and spoofing attacks) is recommended for systems that will influence clinical actions, to verify that alarms are not easily triggered by benign environmental changes or malicious inputs [250]. In the context of digital theranostic bionanosensors, calibration protocols ensure that AI-driven biosensor outputs remain quantitatively aligned with molecular concentrations, allowing closed-loop systems to adjust therapeutic dosing based on real-time biomarker dynamics [224]. Uncertainty quantification within these integrated platforms provides clinicians with confidence intervals for each biosensor-derived biomarker, supporting safer autonomous feedback control in theranostic applications [226]. In oncology-focused theranostic systems, continuous recalibration compensates for sensor drift and biological variability across tumor types, ensuring accurate prediction of treatment response and minimizing false alerts [251]. Testing model robustness against environmental and demographic variability, such as motion, temperature, and patient physiology, strengthens reliability for remote cancer monitoring and cloud-connected biosensor networks [249]. Finally, adversarial and stress testing integrated into theranostic pipelines ensures that biosensor-driven alarms and treatment adjustments remain trustworthy under both clinical and cyber-physical uncertainty conditions [250]. Overall, linking calibration, uncertainty modeling, and robustness evaluation directly to digital theranostic bionanosensor design reinforces the review's central theme, ensuring reliability, safety, and adaptive intelligence in next generation biosensing healthcare systems.

Explainability and Clinician Trust

Explainable AI (XAI) methods, such as SHAP, LIME, integrated gradients, and attention visualization, help map model predictions back to sensor features and time windows, enabling clinicians to audit and interpret alerts [252].For time series biosensor models, temporal feature attribution (which intervals contributed to a prediction) is more informative than static feature importance and should be included in clinician dashboards [253]. Explainability must be tested with real clinicians because an explanation that looks correct from a technical perspective might still be useless or even misleading in real medical practice. For this reason, user studies that measure how much clinicians trust the system, how easy the explanations are to use, and how these explanations influence their clinical decisions are required before the system can be safely deployed in hospitals [253].

Small Data Strategies

Data scarcity is endemic in early biosensor development; practical remedies include physics-based data augmentation (noise injection, temporal warping), generative models for synthetic time series, and transfer learning from related physiological datasets [254]. Generative models (GANs, diffusion models) can produce realistic sensor traces for rare biomarker events, but synthetic data must be validated to avoid reinforcing artefactual patterns [255]. Pretraining on large unlabeled biosensor corpora followed by task-specific fine-tuning provides the most reliable path to high performance when labeled clinical samples are limited [236]. In oncology-focused nano biosensor projects, small-data strategies are essential because early translational studies often contain very few labelled tumor samples; targeted augmentation and synthetic-data methods therefore expand training sets while preserving clinically relevant signal features [256]. Physics-aware time-series augmentation (for example, noise injection, temporal warping and device-specific perturbations) improves model robustness on biosensor traces and is particularly useful for nano biosensor signals that reflect fast tumor metabolic dynamics [257]. Generative time-series models (Time GAN/TS-GAN and diffusion variants) can synthesize realistic biosensor episodes for rare but clinically important events, e.g., ctDNA spikes or transient metabolic shifts, enabling models to learn low-frequency tumor behaviors [258]. Crucially, synthetic traces for nano biosensors must be validated against paired clinical ground truth (imaging, pathology and liquid-biopsy measurements) to avoid introducing artefactual patterns that could mislead oncology classifiers [259]. Transfer learning and domain-adaptation.

Pretraining on larger related physiological or molecular datasets and fine-tuning on small tumor-specific nano biosensor cohorts helps models generalize across histologists and different sensor generations [260]. Finally, combining these small-data remedies with federated learning and privacy-preserving aggregation accelerates multi-center nano biosensor development for cancer while keeping patient data local and compliant with clinical governance [260]. Overall, embedding augmentation, careful synthetic-data validation, transfer of learning and federated workflows into nano biosensor pipelines make small clinical datasets far more useful for oncology applications and speed safe translation into cancer monitoring and theranostic use.

Multisite Learning & Privacy-Preserving Training

Multi-institutional datasets are critical to ensure generalizability, but patient privacy and regulatory barriers commonly block centralization; federated learning (FL) and split learning are practical alternatives that enable collaborative model training without sharing raw data [261]. Several recent reviews highlight both the promise and pitfalls of FL in healthcare: communication overhead, non-IID data across sites, and governance/consent complexity remain active research challenges that must be addressed for wide deployment [220]. Practical FL deployments for biosensor models should combine heterogeneity-aware aggregation, personalization layers, and mechanisms for differential privacy or secure aggregation to balance performance and privacy [244]. Multisite learning is essential for oncology biosensor models because federated approaches can harness heterogeneous data from many cancer centers to improve vulnerability without centralizing sensitive patient records [262]. Federated learning and split-learning frameworks have been successfully proposed and reviewed for healthcare and cancer applications, showing promise to combine distributed biosensor, imaging, and clinical data while preserving privacy [261].

A concrete example is the multi-site initiative led by Indiana University and partners that applies privacy-preserving federated learning to improve breast cancer risk prediction across diverse health systems [263]. In practical implementations, federated frameworks for breast cancer have been demonstrated and simulated to train classifiers on local mammography/biomarker data and aggregate models centrally, improving performance while keeping raw data onsite [264]. For nano biosensor deployments, federated learning must be paired with heterogeneity-aware aggregation and personalization layers so that models adapt to device differences (sensor batch effects, manufacturing variability) and to non-IID patient cohorts [265]. Finally, successful multisite FL campaigns in oncology combine technical safeguards (secure aggregation, differential privacy), clinical governance (consent, data dictionaries), and operational support (synchronised evaluation protocols) to produce reproducible, regulatory-ready models [250]. Federated learning represents a crucial step toward scalable, privacy-preserving AI in oncology. By allowing collaboration between cancer centers without data sharing, it accelerates biomarker discovery and ensures equitable model performance across populations, though it still requires harmonized data standards and robust evaluation pipelines.

AI-driven Precision Oncology and Clinical Decision Support

AI is becoming a key component of precision oncology by transforming theranostic bionanosensor data into clinically actionable information that supports personalized cancer management. Instead of functioning solely as analytical tools, AI and machine learning algorithms can integrate biosensor outputs with imaging, genomic, transcriptomic, proteomic, and clinical data to generate comprehensive patient-specific profiles that improve therapeutic decision-making [266]. Advanced predictive models enable patient stratification according to molecular characteristics, predict treatment response before therapy initiation, identify patients at high risk of recurrence, and detect the emergence of drug resistance during longitudinal monitoring. These predictive capabilities allow clinicians to optimize treatment selection, minimize unnecessary toxicity, and dynamically adjust therapeutic strategies based on continuously updated biomarker information generated by theranostic

bionanosensors [267]. Furthermore, explainable artificial intelligence (XAI) increases clinician confidence by providing transparent explanations for model predictions, allowing physicians to understand which biomarkers or biosensor features contribute most significantly to therapeutic recommendations. Such transparency is essential for regulatory acceptance and for the successful integration of AI-assisted biosensors into routine clinical practice [268]. Looking forward, the combination of intelligent theranostic bionanosensors with multimodal AI models is expected to further advance precision oncology through real-time disease monitoring, adaptive treatment optimization, and highly personalized therapeutic strategies. As these technologies continue to evolve, AI-driven clinical decision support systems will play an increasingly important role in translating biosensor data into actionable insights that improve patient outcomes [269]. Overall, AI is expected to accelerate the clinical translation of theranostic bionanosensors by integrating biosensor outputs with multimodal clinical and omics data to support personalized treatment decisions. Future progress will depend on standardized datasets, robust clinical validation, and explainable AI models that ensure reliable and transparent decision-making. Together, these advances have the potential to enable adaptive, data-driven precision oncology and improve patient outcomes.

Challenges in Clinical Translation

The translation of promising theranostic bionanosensors from bench to bedside remains slowed by a web of scientific, technical and regulatory obstacles that interact and amplify one another rather than acting in isolation [270]. At the heart of the problem is an inconsistent and incomplete characterization of nanomaterials and preclinical workflows, which undermines reproducibility and makes it hard to predict clinical performance [271].

Preclinical Clinical Pipeline

Preclinical cancer models, including many commonly used xenograft systems, often fail to reproduce human tumor heterogeneity, stromal architecture and immune contexture, so efficacy and targeting measured preclinically may not reflect patient outcomes [272]. Routine in vitro assays and 2D cell cultures systematically misrepresent nanoparticle transport, retention, and activation of smart sensing components, producing favourable sensitivity specificity estimates that collapse in vivo [273]. There is still no community consensus on a minimum battery of orthogonal preclinical models, orthotopic, syngeneic, PDX and humanized systems that together best predict human biodistribution and tumor penetration for different nanosensor designs [274]. Because many studies omit clinically relevant dosing regimens, longitudinal biodistribution sampling and quantitative clearance measurements, it is difficult to select a safe and potentially efficacious first-in-human dose [275]. The gap between preclinical biomarker readouts and clinically measurable companion diagnostics is especially damaging: when a nanosensor signals a therapeutic opportunity preclinically, an equivalent, validated clinical assay is often missing [276]. Taken together, these issues create a funnel where only a few leads with forgiving PK/PD and transparent mechanisms survive to the clinic while many rational, innovative theranostic concepts never get an honest translational test [277].

Safety, Toxicity, and PK/PD Considerations for Theranostic Nanoparticles

Nanoparticle ADME is multidimensional: size, shape, surface chemistry and the dynamic protein corona jointly determine circulation time, tissue tropism and clearance, producing dose response relationships that do not follow classical small molecule rules [278]. The composition and evolution of the protein corona can mask targeting ligands or produce unexpected opsonization, thereby altering both efficacy and off-target toxicity in patient-specific ways [279]. Immune activation phenomena, notably complement activation and complement activation-related pseudoallergy (CARPA), can cause acute infusion reactions in humans that are poorly predicted by short-term rodent screens [280]. Long-term persistence, slow biodegradation, and organ accumulation (particularly in liver and spleen) raise the possibility of delayed toxicities that require extended, mechanistically informed toxicology programs [281]. Because theranostic nanosensors combine diagnostic moieties and therapeutic cargos, safety evaluation must consider interactions between imaging labels, sensors, and drug payloads a combination that complicates toxicology study design and interpretation [282]. Mechanistic PK/PD and physiologically based (PBPK) models tailored to nanoparticle properties are necessary to integrate multi-scale data (in vitro corona, animal biodistribution, human physiology) and to support rational dose selection [283]. Theranostic NPs exhibit complex safety and PK/PD behaviors due to their size, shape, surface properties, and dynamic protein corona, which together govern biodistribution, clearance, and unexpected toxicity profiles. Immune-related reactions like CARPA, long-term organ accumulation, and interactions between diagnostic and therapeutic components complicate toxicology assessments. Therefore, rigorous mechanistic studies and nanoparticle-tailored PK/PD and PBPK models are essential for accurate safety evaluation and rational dose design.

Scalability, Manufacturing and Characterization

Moving from bench scale recipes to GMP manufacture while holding tight tolerances on size distribution, surface ligand density, and payload loading is nontrivial and often reveals hidden failure modes (aggregation, loss of activity, contamination) [284]. Many bench synthesis methods (batch precipitation, manual conjugation) do not map easily to closed system, reproducible, GMP-compatible processes, forcing expensive reformulation late in development [283]. Analytical characterization methods (DLS, TEM, single particle ICP-MS, ligand quantification) exist, but are variably applied and often lack standard operating procedures that regulators will accept without extensive justification [283]. Sterility assurance, endotoxin control and stability (shelf life, aggregation on storage, preservation of sensor responsiveness) introduce logistical constraints such as cold chain needs that increase cost and complexity for clinical translation [285]. To avoid last-mile redesigns, early integration of design for manufacture principles, continuous flow manufacture, microfluidic mixing, and in-line PAT (process analytical technology) must inform materials selection and conjugation chemistries [286].

Regulation, Classification, and Approval Pathways

Regulators have produced evolving guidance for nanomaterials, but a product can still land ambiguously between drug, device or combination pathways, which triggers different evidence expectations and complicates global submission strategies [287]. Because many nano-specific critical quality attributes (CQAs), for example, corona composition or ligand functional density, are not yet codified as accepted release tests, developers must negotiate case by case with agencies, prolonging timelines [287]. Proving clinical utility for a theranostic requires trials that demonstrate not only patient benefit from treatment but also that the diagnostic readout changes clinical decision making in a way that improves outcomes or cost effectiveness [286]. Finally, rare adverse events or long-term accumulation effects may only appear in post-marketing use, so robust post-approval surveillance and registries are essential to capture real-world safety and performance [273]. Regulatory approval of theranostic nanomaterials is challenging due to ambiguous product classification, inconsistent global requirements, and the absence of standardized nanoparticle-specific quality tests. Demonstrating clinical utility requires proving both therapeutic benefit and diagnostic impact on decision-making, while rare or long-term risks often emerge only after market entry, making post-approval surveillance essential.

Cost-effectiveness and reimbursement considerations

Despite their promising clinical potential, theranostic bionanosensors must also demonstrate economic value to facilitate widespread adoption in healthcare systems. Beyond regulatory approval, reimbursement agencies and Health Technology Assessment (HTA) bodies evaluate whether a new technology provides sufficient clinical benefit relative to its overall cost compared with the current standard of care [288]. The manufacturing complexity of multifunctional nanosystems, together with extensive quality control requirements and costly clinical trials, can substantially increase development expenses and final product prices. Consequently, even clinically effective nanomedicines may encounter barriers to adoption if they fail to demonstrate favorable cost-effectiveness or meaningful improvements in patient outcomes [286].. Early incorporation of health-economic analyses during product development can guide target selection, clinical trial design, and pricing strategies while improving reimbursement prospects. Integrating economic endpoints with clinical evidence generation allows developers to better align innovative nanomedicines with the expectations of regulators, payers, clinicians, and healthcare systems [289].

Commercialization Challenges

Successful clinical translation of theranostic bionanosensors ultimately depends on effective commercialization strategies that extend beyond scientific innovation. Many promising nanosystems fail to reach patients because of insufficient technology transfer, limited industrial partnerships, inadequate investment, and difficulties bridging the gap between academic research and commercial development [290]. Commercial success also requires robust intellectual property protection, scalable manufacturing processes, reliable supply chains, and early engagement with industrial stakeholders. Venture capital investment and pharmaceutical partnerships frequently depend not only on proof-of-concept efficacy but

also on manufacturing feasibility, regulatory readiness, market demand, and reimbursement potential [291]. Recent perspectives advocate a "commercialization-by-design" approach, in which market needs, clinician requirements, reimbursement pathways, and regulatory expectations are considered during the earliest stages of nanomedicine development rather than after proof-of-concept has been achieved. This strategy shifts development from a technology-push model toward a market-pull approach, thereby improving the likelihood of successful clinical implementation and long-term commercial sustainability [292]. Ultimately, successful commercialization is essential to ensure that promising theranostic bionanosensors can progress beyond laboratory research and become accessible tools that improve patient care in real-world clinical practice [293].

Cross-cutting solutions and practical roadmap

Community adoption of minimum reporting standards (MIRIBEL and related checklists) and open data deposition will make cross-study comparison and meta-analysis feasible, accelerating identification of robust leads [273]. Early, iterative engagement with regulators (pre-IND/Scientific Advice), together with submission of standardized analytical packages, lowers regulatory uncertainty and helps align preclinical assays with clinical evidence expectations [294]. Coupling mechanistic PBPK/PD modelling with richer preclinical biodistribution datasets enables more informed dose prediction and trial design, reducing attrition caused by unexpected human PK [270]. Designing nanosensors with biodegradability, rapid clearance or known metabolic fate in mind and validating these properties in long-term toxicology studies will reduce regulatory risk and improve patient safety profiles [271]. Finally, adopting design for manufacture early, including scalable mixing, in-line analytics, and stability-focused formulation chemistry, shortens the path from a publishable prototype to a clinical-grade product [295].

Conclusion, Limitations and Future Perspectives

Smart bionanosensors and nanotheranostic platforms represent a significant evolution in the management of solid tumors by integrating real-time molecular detection with targeted therapeutic intervention. This review highlights the transition from conventional diagnostic and therapeutic strategies, which are limited by static, invasive, and often delayed assessments, toward more dynamic and responsive systems capable of capturing tumor heterogeneity and temporal evolution. Despite advances in imaging, biopsy-based diagnostics, and systemic therapies, major challenges persist, including poor tumor penetration, biological variability of drug delivery systems, and the inability to continuously monitor treatment response at the molecular level.

The emergence of smart nanosensors addresses several of these limitations by enabling sensitive, multiplexed, and minimally invasive detection of cancer-associated biomarkers through liquid biopsy, imaging enhancement, and TME sensing. When integrated with nanotheranostic platforms, these systems offer a unique opportunity to close the gap between diagnosis and therapy through feedback-driven, adaptive treatment strategies. However, their clinical translation remains constrained by issues related to biosafety, reproducibility, large-scale manufacturing, and lack of standardized validation

frameworks. In addition, integration with computational analytics and AI-based decision systems is still in early stages, limiting their full clinical potential. The creation of smart bionanosensors for application in complicated biological matrices such as blood, serum, and tissue samples is a major area in biomedical engineering. However, these devices have considerable technological and material restrictions, which do not allow them to reach the clinic outside the laboratory. One of the main challenges is the signal-to-noise ratio in complex biological fluids where background interference, non-specific protein adsorption (biofouling), and the presence of competing molecules can greatly diminish or mask the detection of target analytes.

Future progress in this field will depend on improving biocompatibility, enhancing vivo stability, and developing robust clinical validation pipelines that accurately reflect real tumor biology. Standardization of nanosensor performance metrics and early regulatory alignment will also be essential for successful translation. Overall, while significant challenges remain, the convergence of nanotechnology, molecular sensing, and precision oncology provides a strong foundation for next-generation cancer management systems capable of enabling earlier detection, personalized therapy, and real-time treatment monitoring in patients with solid tumors. The future of healthcare is fast becoming a model of continuous, anticipatory and highly tailored monitoring. In this regard, CRISPR included nanosensors, a new breakthrough in molecular diagnostics, have a key role to play. These sensors may allow for fast point-of-care diagnostics of viral infections and genetic modifications, using the programmability of CRISPR-Cas systems selectivity to detect ultra-low quantities of nucleic acid biomarkers in real time.

Acknowledgements The authors acknowledge BioRender.com for providing the platform used to create Figures.

Author Contributions Conception and design: M.T.E, Y.B., A.E.A., A.S., A.A., F.S., and N.M.E. Collection and/or assembly of data: M.T.E, Y.B., A.E.A., A.S., A.A., F.S., and N.M.E. Manuscript writing: M.T.E, Y.B., A.E.A., A.S., A.A., F.S., N.M.E., A.S.D, G.S.E, and G.A.M.A. All authors have read and approved the published version of the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Data Availability The current work does not comprise new or analyzed data.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Clinical Trial Number Not applicable.

Conflict of interest The authors declare they have no conflict of interest.

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Authors and Affiliations

Manar T. El-Morsy[1] · Youssef Basem[2] · Amr E. Ali[3] · Abanoub Sherif[2] · Alamer Ata[2] · Fayek Sabry[2] · Nourhan M. ElMahsoub[4] · Ahmed S. Doghish[5,6] · Gharieb S. El-Sayyad[7] · Gomaa A. M. Ali[8]

✉ Gharieb S. El-Sayyad
gelsayyd@imamu.edu.sa

✉ Gomaa A. M. Ali
gomaa.ali@ukf.ac.ae; gomaasanad@gmail.com

1 Faculty of Nanotechnology for Postgraduate Studies, Cairo University, Giza 12613, Egypt

2 Medical and Pharmaceutical Industrial Biotechnology Department, College of Biotechnology, Misr University for Science and Technology (MUST), 6th of October City, Giza 12566, Egypt

3 Faculty of Pharmacy, October University for Modern Sciences & Arts, 6th of October City, Giza 12451, Egypt

4 Biotechnology Department, Faculty of Science, Mansoura University, Mansoura, Egypt

5 Department of Biochemistry, Faculty of Pharmacy, Badr University in Cairo (BUC), Badr CityCairo 11829, Egypt

6 Biochemistry and Molecular Biology Department, Faculty of Pharmacy (Boys), Al-Azhar University, Nasr City, Cairo 11231, Egypt

7 Department of Biology, College of Science, Imam Mohammad Ibn Saud Islamic University (IMSIU), 11623 Riyadh, Saudi Arabia

8 Sharjah Marine Science Research Centre, College of Marine Sciences and Aquatic Biology, University of Khorfakkan, Sharjah18119, United Arab Emirates