

Nanobiosensors in neurodegenerative disease diagnosis: A promising pathway for early detection

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Abstract

Neurodegenerative diseases, including Alzheimer's and Parkinson's, are characterized by progressive neuronal loss, leading to cognitive and motor impairments. Early diagnosis remains a challenge due to the slow progression of symptoms and the limitations of current diagnostic methods. Nanobiosensors, leveraging the high sensitivity and specificity of nanotechnology, offer a promising, noninvasive, and cost-effective approach for detecting disease biomarkers at ultra-low concentrations. This review highlights recent advancements in nanobiosensor technology, including the integration of gold nanoparticles, quantum dots, and carbon nanotubes, which have significantly enhanced biomarker detection precision. Furthermore, it examines the advantages of nanobiosensors over traditional diagnostic techniques, such as improved sensitivity, rapid detection, and minimal invasiveness. The potential of these innovative sensors to revolutionize early disease detection and improve patient outcomes is discussed, along with existing challenges in clinical translation, including stability, reproducibility, and regulatory considerations. Addressing these limitations will be crucial for integrating nanobiosensors into routine clinical practice and advancing personalized medicine for neurodegenerative disorders.

Keywords

Neurodegenerative diseases, nanobiosensors, Alzheimer's disease, Parkinson's disease, biomarkers, nanotechnology, biosensing, electrochemical sensors

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Introduction

Neurodegenerative diseases, which progressively damage the central nervous system (CNS) and lead to a gradual decline in nerve cell function, are challenging to diagnose early due to their slow progression.^{1,2} Subtle first symptoms may resemble other illnesses. The absence of precise diagnostic tools exacerbates the problem. Early warning indicators may be misinterpreted by both patients and clinicians. Undiagnosed or misdiagnosed patients waste critical therapy time. Earlier treatment slows disease development. Research seeks biomarkers.³ This trend necessitates early detection. Furthermore, healthcare systems face significant stress.⁴ An integrated approach could improve results. Ongoing research aims to develop nanobiosensors for early diagnosis of neurodegenerative diseases, including Alzheimer's and Parkinson's (PD).⁵

Nanobiosensors employ nanotechnology for the detection of biological indicators.⁶ Their sensitivity is remarkable. Furthermore, specificity is achieved. Their potential is under

investigation.⁷ Nanotechnology-based nanobiosensors hold promise for revolutionizing healthcare by enabling early and precise diagnosis, which is essential for improving therapeutic outcomes and potentially halting disease progression.⁸ This innovative research focuses on enhancing patient outcomes by diagnosing CNS disorders through the detection of specific biomarkers.⁹ Neurological disorders

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correlate with specific biomarkers. Diagnosing CNS disorders poses notable challenges due to the limitations of traditional methods, which are often invasive, costly, and imprecise.^{10,11} Nanobiosensors provide a promising, non-invasive, and cost-effective method for early detection, potentially enhancing patient outcomes.¹² While still under development, research suggests that these sensors could offer improved biocompatibility and lower risks compared to traditional options.¹³ Ongoing studies aim to clarify their capabilities, limitations, and ethical implications. Specifically, nanobiosensors are being explored for better detection of neurodegenerative diseases such as Alzheimer's and PD, focusing on identifying genetic mutations and environmental risk factors, including toxin exposure.^{14–18} Nanobiosensors, known for their high sensitivity and specificity, have become valuable in early biomarker detection, although early diagnosis remains challenging.¹⁹ It is common for biomarkers to be found in small amounts in body fluids because they are complicated, have a wide range of protein changes, and are biologically variable in human samples.²⁰ Conventional detection methods face challenges in accurately identifying specific proteins. Techniques like affinity capture and advanced liquid chromatography-mass spectrometry (LC-MS) enhance protein enrichment and separation, addressing these limitations.²¹ Using a panel of biomarkers improves test sensitivity and specificity by providing complementary disease insights.²² Advanced detection technologies, including biosensors, further enhance biomarker assays in physiological fluids by minimizing matrix interference.²³ Nanobiosensors, leveraging nanomaterials' unique properties such as increased surface area and reactivity, offer significant advantages in biomarker detection.²⁴ Increase biomarker-sensor surface interactions. This improves detection limits. Thus, facilitating earlier diagnosis. Nanobiosensors use biorecognition elements as their underlying concept.²⁵ Nanobiosensors utilize elements like antibodies, aptamers, or enzymes to selectively bind specific biomarkers, with transducers converting these interactions into detectable signals—whether electrical, optical, or mechanical.²⁶ Researchers are developing electrochemical, optical, and piezoelectric nanobiosensors, each with unique advantages: electrochemical sensors offer high sensitivity and compact design,²⁷ optical sensors provide real-time monitoring, and piezoelectric sensors ensure precise measurements.²⁸ The integration of nanotechnology has improved traditional biosensors, enabling simultaneous detection of multiple biomarkers and enhancing diagnostic accuracy.^{29,30} Nanobiosensors offer promising advances for diagnosing neurodegenerative diseases, despite challenges in achieving stability, reproducibility, and handling complex biological samples that may affect detection performance.^{31,32} With enhanced sensitivity and specificity, nanobiosensors show promise in facilitating early diagnosis and improving patient outcomes, while ongoing research seeks to resolve current limitations and advance clinical adoption.³³ This review highlights the role of nanobiosensor technology in diagnosing neurodegenerative diseases,

particularly Alzheimer's and PD—two age-related disorders of critical neurological importance. Alzheimer's disease primarily impairs memory and cognitive function due to amyloid plaque buildup, causing neuron degeneration and symptoms such as language confusion, mood changes, and behavioral issues.^{34,35} In contrast, PD involves dopamine depletion, leading to motor-related symptoms like tremors, rigidity, and bradykinesia.^{36,37} Early diagnosis in both diseases can greatly improve patient quality of life. Nanobiosensors, with their high sensitivity and specificity, show promise for early detection.³⁸ Traditional diagnostic methods often lack the sensitivity needed, resulting in potential false positives or negatives. For instance, enzyme-linked immunosorbent assays (ELISA) detect cancer biomarkers, such as prostate-specific antigen, at levels of 10–100 ng/mL, whereas nanobiosensors using materials like quantum dots, carbon nanotubes, and gold nanoparticles achieve detection limits down to 10 pg/mL, significantly improving sensitivity.^{39,40} Constructing nanobiosensors requires careful selection of nanomaterials and biological components to ensure high sensitivity and specificity, along with functionalization to maintain sensor bioactivity.⁴¹ Table 1 illustrates a nanobiosensor application for neurodegenerative disease detection, with added technologies like photonic crystals, microfluidics, and wearable devices enhancing sensitivity, specificity, and user convenience.^{42–44} These devices are essential for diagnostics, environmental monitoring, and drug discovery applications.⁴⁵ Optical microscopy, integrated with nanoparticle tracking and surface-sensitive imaging, allows for biomolecule size analysis on lipid bilayers, while wide-field extinction microscopy provides data on nanoparticle size, shape, and orientation.⁴³

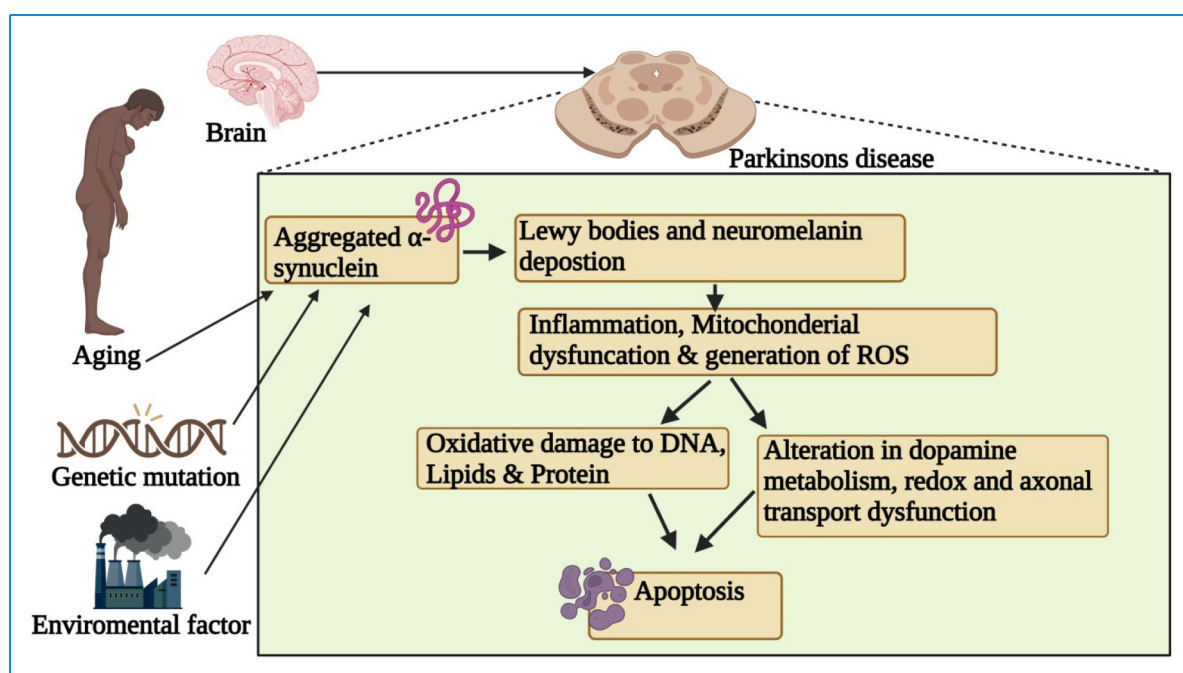
Incorporating carbon nanotubes and silver nanoparticles into electrodes enhances electrochemical catalysis, improving selectivity and sensitivity with micromolar detection limits.⁵⁷ Emerging technologies such as photonic crystals, microfluidics, and wearable systems can significantly improve the sensitivity, specificity, and ease of use of nanobiosensor-based diagnostic tools for neurodegenerative conditions, including Alzheimer's and PD.

Parkinson's disease

PD is characterized by a progressive decline in motor functions due to the loss of dopamine-releasing neurones, as depicted in Figure 1. This neurodegenerative disorder (NDD) impacts neurones, leading to memory loss and cognitive deficits, as well as issues in coordination, balance, tremors, ambulation difficulties, and rigidity. The onset of PD symptoms is gradual, intensifying over time, typically affecting individuals aged 50 and above, regardless of gender. PD is primarily linked to the degeneration or destruction of neurones in the brain responsible for regulating bodily movements. The resulting decrease in dopamine release causes movement disorders. Additionally, patients with PD experience a loss of nerve endings that produce norepinephrine, contributing to

Table 1. Nanobiosensor for neurodegenerative disease detection.

Sensor type	Detection technique	Detection limit	References
Polysaccharide	Optical-based detection	70 nM	46
Chemical	Microcantilever sensing	6 ng	47
Aptamer	Electrochemical detection	10 pM	48
Peptide	Surface plasmon resonance technique	—	49
Antibody	Conjugation-based method	13057.0 pg/mL	50
Antibody	Graphical analysis	Derived from gut	51
Indirect	Ultrasonication-based detection	Cerebrospinal fluid	52
Antibody	Enzyme-linked immunosorbent assay	Plasma	53
Aptamer	Colorimetric assay	1 nM	54
Aptamer	Surface plasmon resonance detection	0.64 fM	55
Antibody	Voltammetric analysis	10 aM	56

**Figure 1.** Parkinson's disease pathophysiology.

further neurological impairments. Currently, no specific treatments exist for PD, and available therapies, procedures, and drugs aim only to mitigate its symptoms.^{58–61}

Therapeutic options for PD encompass proteins such as human glial cell line-derived neurotrophic factor (hGDNF), which has demonstrated potential efficacy.

Ansorena et al.⁶² devised a rapid and efficient method for producing high concentrations of pure hGDNF using mammalian cell-derived technology. Moreover, nanoparticle (NP)-mediated biomarker identification has shown potential for diagnosing PD (Table 1). PD is characterized by the degeneration of dopaminergic neurones in the substantia nigra and a

decrease in dopamine levels in the striatum, leading to motor symptoms including tremors, rigidity, and cognitive decline. A significant feature of PD is α -synuclein amyloid accumulation, a disease hallmark. Adam et al.⁶³ designed a biosensor for detecting α -synuclein aggregation, a critical biomarker, facilitating early diagnosis and management of PD. Additionally, ZnO nanocomposites on aluminum microelectrodes serve as effective substrates for antibody binding to the α -synuclein antigen. Aghili et al.⁶⁴ developed an electrochemical nanobiosensor targeting circulating biomarkers like miR-195 for early PD detection.

Gold nanowires (GNWs) and exfoliated graphene oxide (EGO) were utilized to modify a screen-printed carbon electrode. A thiolated single-stranded probe selectively hybridized to miRNA-195, while doxorubicin acted as an electrochemical indicator for differential pulse voltammetry. This miR-195-based nanobiosensor shows promise as a diagnostic instrument for PD.

Aging, genetic mutations, and environmental factors contribute to α -synuclein aggregation, forming Lewy bodies that trigger inflammation, mitochondrial dysfunction, and ROS generation, ultimately leading to oxidative stress, DNA damage, altered dopamine metabolism, axonal dysfunction, and dopaminergic neuron apoptosis.

Alzheimer's disease

The degenerative neurological condition Alzheimer's causes cognitive decline and memory loss.

It affects critical functions such as communication, cognitive reasoning, and the ability to perform daily tasks. Early symptoms include trouble recalling recent conversations, problem-solving difficulties, and disorientation related to time and place.⁶⁵ As Alzheimer's disease advances, patients experience worsening memory impairment and a decline in language abilities, which makes it challenging to express thoughts clearly.⁶⁶ Behavioral symptoms, such as mood fluctuations, agitation, and aggression, may also emerge.⁶⁷ Alzheimer's disease is caused by genetic, environmental, and lifestyle factors that lead to amyloid plaque buildup and tau tangles, resulting in neuronal damage and cell death.⁶⁸ The hippocampus, essential for memory, is notably impacted. Aging is the primary risk factor, with most patients over age 65, although early-onset cases can affect younger individuals. A family history of Alzheimer's and certain health conditions, such as cardiovascular disease and diabetes, further elevate risk.⁶⁹

Diagnosis involves a thorough assessment, including physical, neurological, and mental exams, as well as brain imaging to exclude other conditions. Emerging cerebrospinal fluid (CSF) biomarkers improve diagnostic accuracy.⁷⁰ While Alzheimer's lacks a cure, cholinesterase inhibitors and memantine provide temporary cognitive improvements, aiding symptom management and quality of life. Nonpharmacological approaches, like cognitive therapy and social engagement, are also crucial. The exact cause of the cause of Alzheimer's

is unknown, however genetic, environmental, and lifestyle factors may contribute. Familial predisposition is a crucial genetic factor that raises the risk.³⁴ Researchers are also examining environmental influences, though the interaction between these factors is complex. Understanding these interactions may enable earlier detection and intervention. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, contributes significantly to Alzheimer's disease progression.⁷¹ The brain's high oxygen demand and lipid content make it particularly susceptible to ROS damage, impairing proteins, lipids, and DNA, leading to neuronal dysfunction and cell death.^{72,73} This oxidative stress accelerates synaptic dysfunction—a precursor to neuronal death and cognitive decline—by interfering with essential synaptic processes, thereby creating a cycle that worsens disease progression.^{74–76} Understanding this relationship may uncover new therapeutic targets, with antioxidants being explored as potential treatments. Although antioxidants have shown promise in reducing oxidative damage, clinical trial results have been inconsistent, suggesting that addressing multiple disease pathways may be more effective.⁷⁷ The global Alzheimer's population is over 50 million and estimated to reach 152 million by 2050. The societal and economic impact of Alzheimer's is immense, with global costs reaching an estimated \$1 trillion annually. Despite extensive research, a cure remains elusive. Figure 2 compares the brain and neuronal structures of healthy individuals with those affected by Alzheimer's.⁷⁸

While amyloid-beta is a well-known biomarker, other potential biomarkers, such as the tau protein, may also be detected using advanced technologies like nanobiosensors. Acetylcholine-generating subcortical nuclei have a structure with similar properties. The buildup of hyperphosphorylated tau protein forms neurofibrillary tangles, a key feature of Alzheimer's disease.^{79,80} Tau levels in CSF and neuroimaging techniques offer insights into disease mechanisms and support early diagnosis, with neuroinflammatory markers also emerging as useful diagnostic indicators.⁸¹ Neuroinflammation, marked by increased inflammatory cytokines and activated microglia, is essential to Alzheimer's disease progression and may serve as a valuable biomarker for enhancing diagnostic accuracy and understanding of the disease.⁸²

Role of nanobiosensors in Alzheimer's biomarker detection

Nanobiosensors integrate nanotechnology with biosensing mechanisms to detect biological markers with high sensitivity and specificity. Their application in Alzheimer's diagnosis enhances the detection of amyloid-beta and tau proteins in biological fluids like blood, saliva, and CSF, allowing for noninvasive, rapid, and cost-effective screening.^{3,83}

1. *Electrochemical nanobiosensors*: These sensors utilize nanomaterials such as gold nanoparticles, carbon

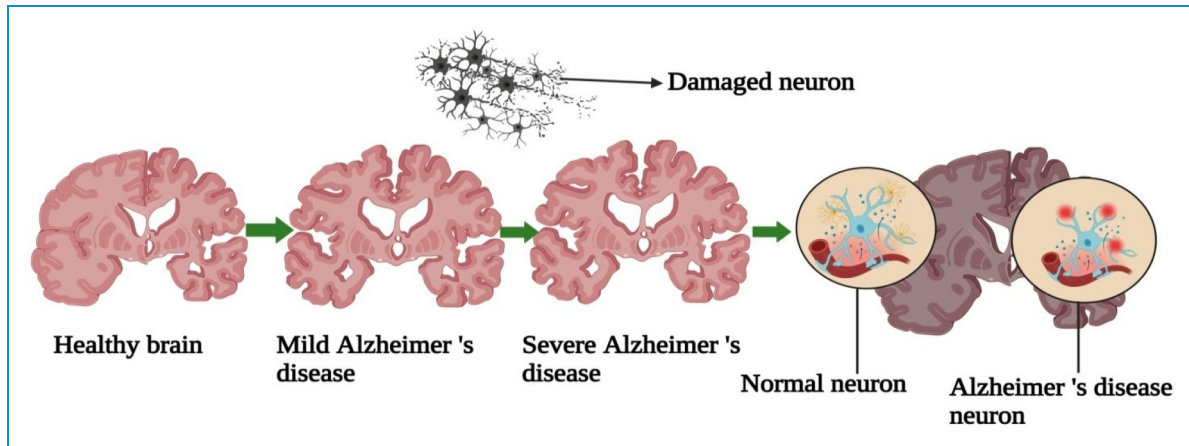


Figure 2. Structures and neurons of healthy and Alzheimer's brains.

nanotubes, and graphene to improve electron transfer and enhance detection sensitivity. They can detect amyloid-beta peptides and phosphorylated tau proteins at ultra-low concentrations, significantly outperforming conventional immunoassays.⁸⁴

2. **Optical nanobiosensors:** Leveraging techniques like surface plasmon resonance (SPR), fluorescence resonance energy transfer (FRET), and quantum dot-based detection, optical nanobiosensors enable real-time monitoring of biomarker interactions. These sensors have shown promise in detecting amyloid-beta aggregates with high specificity.⁸⁵
3. **Piezoelectric nanobiosensors:** Utilizing nanoscale materials such as zinc oxide nanowires and quartz crystal microbalances, piezoelectric biosensors detect biomarker interactions by measuring frequency shifts upon binding of amyloid-beta or tau proteins, providing label-free and highly sensitive analysis.⁸⁶
4. **Magnetic nanobiosensors:** These sensors use magnetic nanoparticles (MNPs) conjugated with antibodies or aptamers to selectively capture and detect biomarkers in complex biological samples. They enhance sensitivity and enable efficient biomarker separation, reducing background noise in detection assays.⁸⁷
5. **Surface-enhanced Raman spectroscopy (SERS)-based nanobiosensors:** These sensors exploit the unique optical properties of nanomaterials, such as gold and silver nanoparticles, to amplify Raman signals from biomarker molecules. This technique allows for ultra-sensitive detection of amyloid-beta and tau proteins at very low concentrations.⁸⁵

Multiple sclerosis

Multiple sclerosis (MS) involves inflammatory lesions in the brain and spinal cord's white matter, leading to axonal loss, neuronal damage, and demyelination (Figure 3).⁸⁷ Peripheral

macrophages cross a compromised blood-brain barrier (BBB), contributing to axonal injury and demyelination, while leukocyte infiltration occurs due to increased adhesion molecule synthesis.⁸⁵ Advances in nanoscience provide novel strategies for diagnosing neurological diseases and developing therapies. Neuroimaging techniques like CT, MRI, and magnetic resonance spectroscopy have proven effective in monitoring neurodegenerative illnesses.^{88–91} Nanotechnology improves imaging techniques and supports the creation of novel diagnostic methods for CNS diseases.^{92–94} The heterogeneity of MS complicates the identification of a universal diagnostic marker. However, a synthetic glycoprotein antigen probe, CSF114(Glc), has shown promise in detecting autoantibodies associated with MS.⁹⁵ Additionally, a gold SPR biosensor was developed to differentiate MS patients from healthy individuals, although it exhibited low sensitivity but high specificity.⁹⁶ Nanoparticle-based biomarker detection is also being explored for MS diagnosis.

Nanobiosensors in MS diagnosis

Recent advancements in nanobiosensor technology have significantly improved the detection of MS biomarkers. These sensors offer enhanced sensitivity, specificity, and real-time monitoring capabilities. Notable developments include:

1. **Electrochemical biosensors:** These devices have been engineered to detect specific MS-related biomarkers such as neurofilament light chain (NfL), myelin basic protein (MBP), and chitinase-3-like protein 1 (CHI3L1). Research has demonstrated that graphene-based electrochemical sensors can detect NfL at picomolar concentrations, improving diagnostic accuracy.⁹⁷
2. **SPR sensors:** SPR-based nanobiosensors have shown potential in differentiating MS patients from

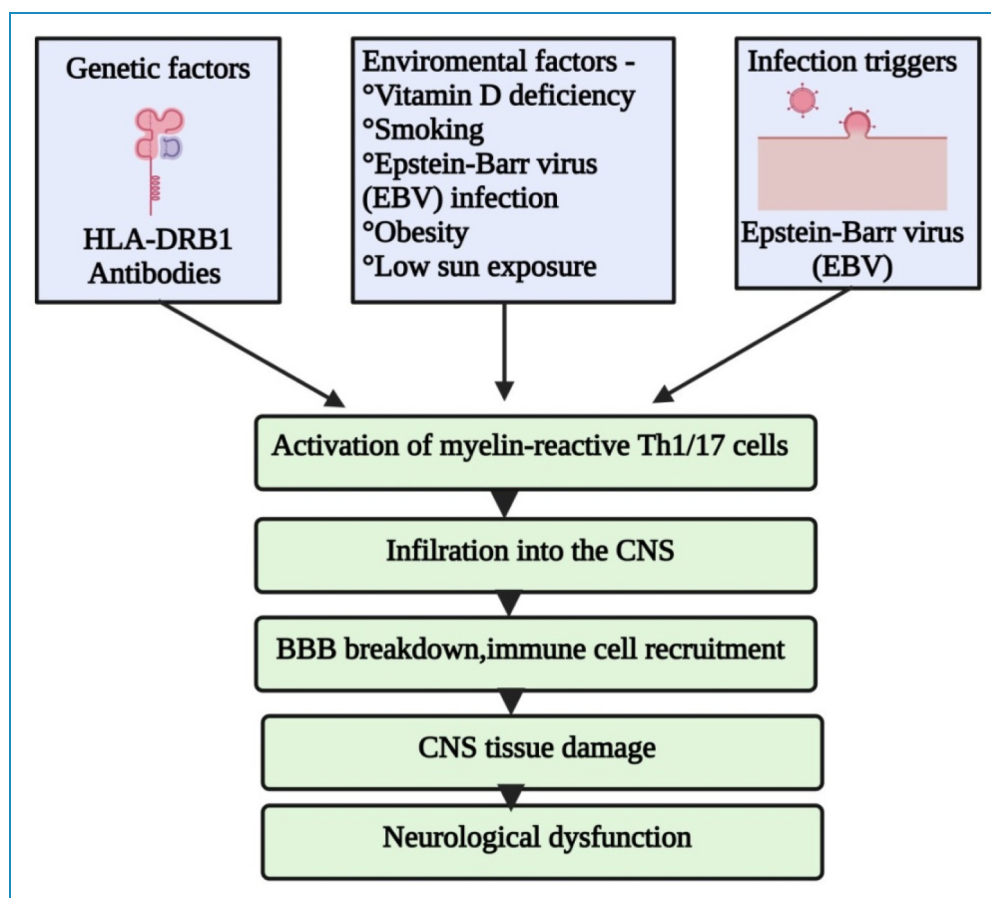


Figure 3. Pathophysiology of multiple sclerosis: potential factors that cause MS.

healthy individuals. Gold nanoparticle-enhanced SPR sensors exhibit high specificity in detecting autoantibodies linked to MS, facilitating early-stage diagnosis with minimal invasiveness.⁹⁸

3. *Quantum dot-based biosensors:* These nanobiosensors leverage fluorescent quantum dots for highly sensitive biomarker detection. Recent studies indicate that quantum dots conjugated with antibodies against MBP can identify early demyelination events, providing a novel approach for MS diagnosis.⁹⁹
4. *Point-of-care (POC) nanobiosensors:* Wearable and portable biosensors are emerging as viable tools for real-time MS monitoring. These devices, integrated with microfluidic chips, enable rapid biomarker detection in CSF and blood, allowing continuous disease tracking.⁹⁹
5. *Magnetic nanoparticle-based biosensors:* Functionalized MNPs are used for the highly selective capture and detection of MS-related biomarkers. MNP-based biosensors enhance signal amplification, improving the detection of MS-specific autoantibodies.⁹⁷
6. *Graphene-based field-effect transistor (FET) Biosensors:* These highly sensitive biosensors

utilize graphene's unique electrical properties to detect MS biomarkers at ultra-low concentrations, making them valuable for early-stage diagnosis.¹⁰⁰

7. *Nanopore biosensors:* Nanopore-based biosensors offer real-time, label-free detection of MS-associated protein biomarkers. These sensors provide high specificity by analyzing single-molecule interactions within a confined nanopore environment.¹⁰¹
8. *Optical fiber biosensors:* Using fiber optic technology, these biosensors detect MS biomarkers with high precision by measuring changes in refractive index, enabling noninvasive and real-time diagnostics.¹⁰²
9. *Aptamer-based biosensors:* Aptamer-functionalized nanobiosensors provide a highly selective approach for MS biomarker detection. These biosensors utilize synthetic DNA or RNA aptamers that bind to specific proteins associated with MS, improving diagnostic accuracy.¹⁰³
10. *Nanocantilever biosensors:* These biosensors detect molecular interactions by measuring mechanical deflections in nanocantilever structures, offering high sensitivity for detecting MS-associated proteins in biofluids.¹⁰⁴

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fast-progressing NDD that primarily affects motor neurons, leading to muscle weakness, paralysis, and eventual respiratory failure. ALS affects about 1–3 people per 100,000 worldwide, with a typical survival of 2 to 4 years after diagnosis, and currently has no effective treatments.¹⁰¹ Recent studies in biomarker research indicate that the Bcl-2-SODox complex, particularly in sporadic and familial ALS cases, might act as a biomarker due to mutant SOD1 protein's interaction with mitochondrial Bcl-2.¹⁰² While elevated cystatin C levels in CSF have been associated with ALS progression, they do not predict disease onset.¹⁰³ A three-protein CSF biomarker panel, including VGF and cystatin C, showed 91% sensitivity and 97% specificity in predicting ALS, outperforming individual proteins.¹⁰⁴ A panel of 14 biomarkers associated with iron homeostasis, growth factors, and cytokines distinguished ALS patients from healthy controls with 89.2% accuracy, 87.5% sensitivity, and 91.2% specificity.¹⁰³

Nanobiosensor applications in ALS diagnosis

Nanobiosensors integrate biological recognition elements with nanomaterial-based transducers, offering high sensitivity, specificity, and real-time monitoring capabilities. The following nanobiosensor platforms have shown significant potential for ALS biomarker detection:

Electrochemical nanobiosensors. Electrochemical biosensors utilize conductive nanomaterials such as carbon nanotubes (CNTs), graphene, and gold nanoparticles (AuNPs) to enhance signal transduction. These sensors detect biomarkers through redox reactions, generating measurable electrical signals. Some notable applications in ALS diagnosis include:⁸⁴

- *Graphene-based electrochemical sensors* for detecting neurofilament proteins in blood samples with high sensitivity.¹⁰⁵
- *Gold nanoparticle-functionalized electrodes* for the rapid quantification of TDP-43 aggregates in CSF.¹⁰⁶
- *Screen-printed carbon electrodes (SPCEs) modified with nanomaterials* to enhance signal amplification and facilitate portable ALS diagnostics.¹⁰⁷
- *Enzyme-based electrochemical biosensors* for detecting oxidative stress markers in ALS patients.¹⁰⁸
- *Nanozymes in electrochemical sensors* to mimic enzymatic activity and enhance biomarker detection.¹⁰⁹

Optical nanobiosensors. Optical biosensors rely on fluorescence, SPR, and colorimetric assays to detect ALS-related

biomarkers with high specificity. Key innovations include:⁸⁵

- *Quantum dot (QD)-based biosensors* for the multiplexed detection of ALS biomarkers such as TDP-43 and SOD1.¹¹⁰
- *SERS biosensors* for real-time monitoring of neurofilament levels in biofluids.¹¹¹
- *Localized LSPR sensors* functionalized with aptamers to detect ALS-related protein aggregates at ultra-low concentrations.¹¹²
- *FRET sensors* for detecting misfolded protein aggregates in ALS.¹¹³
- *Biosensors integrated with microfluidic platforms* for high-throughput ALS biomarker screening.¹¹⁴

Nanoplasmonic and piezoelectric biosensors

- *Nanoplasmonic biosensors* utilize metal nanoparticles to enhance light-matter interactions, improving the sensitivity of ALS biomarker detection.¹¹²
- *Piezoelectric biosensors* employ nanomaterials such as zinc oxide (ZnO) nanowires to measure the mechanical changes induced by biomarker binding, allowing label-free detection of ALS-associated proteins.¹¹⁵
- *Magnetoplasmonic biosensors* that combine magnetic and plasmonic properties for improved biomarker specificity.¹¹⁶
- *Molecularly imprinted polymer (MIP) nanobiosensors* designed to selectively capture ALS biomarkers.¹¹⁷

Advantages of nanobiosensors in ALS detection.¹¹⁸ The application of nanobiosensors for ALS diagnostics provides several key advantages:

1. **Early detection:** The ultra-high sensitivity of nanobiosensors enables the detection of ALS biomarkers at pre-symptomatic stages, allowing for timely intervention.
2. **Noninvasive sampling:** Many nanobiosensors are designed for use with blood, saliva, or urine, reducing the need for invasive lumbar punctures.
3. **POC testing:** Portable and cost-effective biosensor platforms facilitate ALS screening outside of traditional laboratory settings.
4. **Rapid and real-time analysis:** Unlike conventional assays, nanobiosensors provide immediate readouts, improving diagnostic turnaround time.
5. **Multiplexing capabilities:** Advanced biosensors can simultaneously detect multiple ALS biomarkers, enhancing diagnostic accuracy and specificity.

Importance of early diagnosis

Neurodegenerative disorders are typically detected late, after significant neuron loss and reduced neuroplasticity, when symptoms manifest.^{115–117} This delay contributes to the inefficacy of conventional symptomatic treatments.^{118–120} Preventative treatments and early (preclinical) diagnosis could extend quality of life during the preclinical phase, yet no effective early diagnostic methods exist.^{121,122} Neurological disorders, resulting from brain or nervous system dysfunction, rank as the second leading cause of global disability, with approximately 80% of cases occurring in low- and middle-income countries. No single test can conclusively diagnose most neurological diseases. Multiple diagnostic methods, including EEG, EMG, MRI, enzymatic assays, and genetic testing like PCR, are employed.¹²³ However, traditional diagnostic techniques face challenges such as automation, cost, and accuracy. Advanced biosensors and nanobiosensors are emerging as promising tools for early disease detection and improving diagnosis.^{124,125}

Role of nanobiosensors in early diagnosis

Nanobiosensors offer a highly sensitive and specific approach to detecting neurodegenerative disease biomarkers in their early stages. These sensors integrate nanotechnology with biosensing elements, allowing for real-time, noninvasive, and cost-effective diagnostics. Compared to conventional methods, nanobiosensors can detect lower concentrations of biomarkers in biological fluids such as CSF, plasma, and serum, significantly improving early disease identification.

Examples of nanobiosensor technologies

1. *Electrochemical nanobiosensors*—provide high sensitivity for detecting neurotransmitters like dopamine and biomarkers like α -synuclein, aiding in early PD diagnosis.³
2. *Optical nanobiosensors*—utilize quantum dots and plasmonic nanoparticles to enhance fluorescence-based detection, enabling precise identification of amyloid-beta plaques associated with Alzheimer's disease.⁸⁵
3. *Piezoelectric nanobiosensors*—detect molecular interactions at ultra-low concentrations, facilitating the early detection of multiple NDDs.⁸⁶
4. *Magnetoplasmonic nanobiosensors*—combine magnetic and plasmonic properties to improve the specificity of biomarker detection for neurodegenerative diseases.¹¹⁶
5. *Microfluidic nanobiosensors*—integrate lab-on-a-chip technology to enable high-throughput

screening of biomarkers, enhancing early detection efficiency.¹¹⁸

6. *SERS nanobiosensors*—Utilize nanostructured substrates to amplify Raman signals, allowing ultra-sensitive detection of neurodegenerative disease biomarkers.⁹⁵
7. *FET-based nanobiosensors*—use semiconductor nanomaterials for real-time, label-free detection of biomolecules with high specificity.¹²⁶

Importance of nano-transducers

Regardless of the condition's contagiousness, healing and therapy hinge on a prompt and precise diagnosis. Immunofluorescence, ELISA, and microscopic techniques are therapeutically relevant; nonetheless, they possess some drawbacks, such as elevated costs, imprecise results, low specificity, awkward application, and restricted sensitivity.¹²⁷ To address the previously mentioned disadvantages, the clinical demand for high-throughput, biocompatible, efficient, and rapid diagnostic techniques remains unmet. Over recent decades, various sensing methods have been used to detect biomarkers linked to both communicable and noncommunicable diseases.¹²⁸ These technologies employ high-conductivity electrodes that may track or identify electroactive proteins relevant to a medical condition, hence providing a robust signal.¹¹⁸ All the aforementioned properties are incorporated in a sensing apparatus known as a biosensor. Consequently, employing biosensors for the detection of biological markers may represent a feasible approach.

Recent advancements in biosensor technology have initiated transformative shifts across various sectors, including food processing, agriculture, healthcare, and biological research.⁹⁵ Biosensors are now categorized based on their biological component, which can be a nucleic acid, enzyme, or antibody, and their transducing element, which may be calorimetric, optical, acoustic, or electrochemical.^{126,129} The large surface area of nanoparticles enhances their role as transducers, indicating that incorporating nanomaterials into electrical systems may advance transduction mechanisms in nanoelectromechanical systems (NEMS).¹³⁰ Modern biosensors offer distinct advantages, including increased observability, faster response times, higher sensitivity and accuracy, and improved outcomes compared to earlier glucose- and chemical-based biosensors.¹³¹ Biosensors employ tissue-specific macromolecules, organic organelles, microbes, enzymes, and immunosensors (antibodies) as detection methods. The transduction methods rely on the physiochemical differences produced by detection and sensing mechanisms. Consequently, many biosensor transducer mechanisms encompass calorimetric, optical, piezoelectric, and electrochemical methods.¹³² Acoustic and ultrasonic represent two prominent biosensor methodologies utilizing piezoelectric transducers; electrochemical, amperometric, and

conductometric constitute three principal mechanisms of electrochemical transducer biosensors; and optical transducer biosensor mechanisms encompass fluorescence, absorbance, and chemiluminescence (CL).^{124,133,134}

Biosensors operate based on cell signaling, and as previously mentioned, the essential components of an effective biosensor are electronic parameters, a biotransducer, and a biorecognition element, which may encompass a monitor/display, amplifier, and microprocessor.¹³⁵ The biorecognition element, or bioreceptor, is tailored to detect a specific analyte, allowing for evaluation of its properties.¹³⁶ The transducer then converts this interaction into a measurable signal, which is processed and amplified by electrical components, with the output signal's strength reflecting the analyte concentration.¹³⁷ In an amperometric sensor, the bioreceptor includes a specialized biomaterial placed near the transducer or an inactivated enzyme. The analyte undergoes a chemical interaction with the biomaterial. This leads to the creation of a novel analyte that yields a measurable electrical response. Occasionally, an analyte is conveyed to the system, which is subsequently discharged, cooled, or heated using hydrogen ions or electrons. The transducer may subsequently regulate the corresponding mechanism and transform it into electrical signals that could be computed and modified.^{133,137,138}

A biosensor's functionality depends on its core components, including the specific bioreceptor (e.g. antibody, enzyme, DNA) and the transduction mechanism used to detect targets. The transducer generates a small electrical signal, typically against a high baseline, which is then refined by extracting a baseline signal from an uncoated transducer for accuracy. Due to the biosensor's relatively slow reaction rate, issues like electrical noise are minimized, resulting in an analog signal output that can be digitized and processed by a microprocessor. This processed data is then either stored or analyzed as needed. Biosensors can operate *in vivo* or *ex vivo*, sourcing data directly from environmental or biological parameters.¹³⁹ Consequently, Figure 4 illustrates various types of biosensors, including mass-based, calorimetric, photoelectrochemical, microbiological, optical, and electrochemical biosensors, along with their subcategories. Electrochemical biosensors utilize electrochemical transducers and are categorized into impedimetric, conductometric, potentiometric, and amperometric types. Conversely, optical biosensors use an optical transducer paired with a biorecognition element and are classified into types like optical fiber, SPR, interferometric, colorimetric, luminescent, and fluorescent sensors. Microbial biosensors incorporate microbial components as transducers to produce measurable signals corresponding to analyte concentration.

Photoelectrochemical biosensors capitalize on the photon-to-electricity conversion process that transpires simultaneously with photon absorption and charge separation. Calorimetric biosensors measure heat changes

during chemical reactions, while mass-based biosensors detect binding events through changes in surface acoustic wave oscillation due to mass increases on the sensor surface.¹³⁹

Biomarkers

Biomarkers facilitate more accurate and rapid disease diagnosis, stratify patient populations to identify individuals likely to respond to pharmacological therapies, confirm that medication is effectively targeting the CNS or peripheral nervous system (PNS), and offer prognostic insights regarding disease progression. They also determine optimal drug responses. Biomarkers will enable preclinical drug development and the identification of potential therapeutic targets. Moreover, biomarkers may function as an essential connection between the human patient population and preclinical disease models, with shared biomarkers providing crucial mechanistic links and identifying potential therapy targets within the model system. Due to the intrinsic heterogeneity of the patient population with neurodegenerative diseases, which is characterized by numerous and sporadic genetic variants, patient stratification through biomarkers is essential. This approach significantly reduces the number of patients required for clinical studies and enhances clinical trial design.¹³³

Biomarkers exist in various forms, including imaging, biochemical, and genetic markers, and are measured by many methods. Currently, genetic mutations linked to a specific NDD are the most clinically relevant biomarkers, but emerging technologies are uncovering additional biomarkers for epigenetic modifications, microRNAs, and messenger RNA. Recent findings indicate that long noncoding RNAs function as biomarkers for certain neurological disorders and play a role in neurodegenerative mechanisms. A substantial amount of research is exploring the potential of extracellular RNAs as biomarkers for human diseases, such as brain injuries and NDDs. Genetic markers for neurodegenerative diseases span noncoding RNA, RNA, and DNA, with RNA-based biomarkers conserved across neurodegenerative diseases. This suggests common molecular pathways and interconnected functions among RNAs and genes across CNS cell types.¹³³ The recent failure of Alzheimer's disease-modifying drugs may indicate that patients in clinical trials were already in compromised states. Validated biomarkers are essential for the diagnosis and detection of preclinical stages of Alzheimer's, facilitating the development of therapeutic interventions. The integration of biomarkers from biological fluids, including CSF, with neuropsychological evaluations and molecular imaging may enhance diagnostic specificity and sensitivity, facilitating the identification of patients in early stages when pharmacological interventions are most viable. Biomarkers such as brain hypoperfusion or hypometabolism assessed via 18F-fluorodeoxyglucose (FDG)-PET, brain atrophy through MRI, increased CSF tau and/or

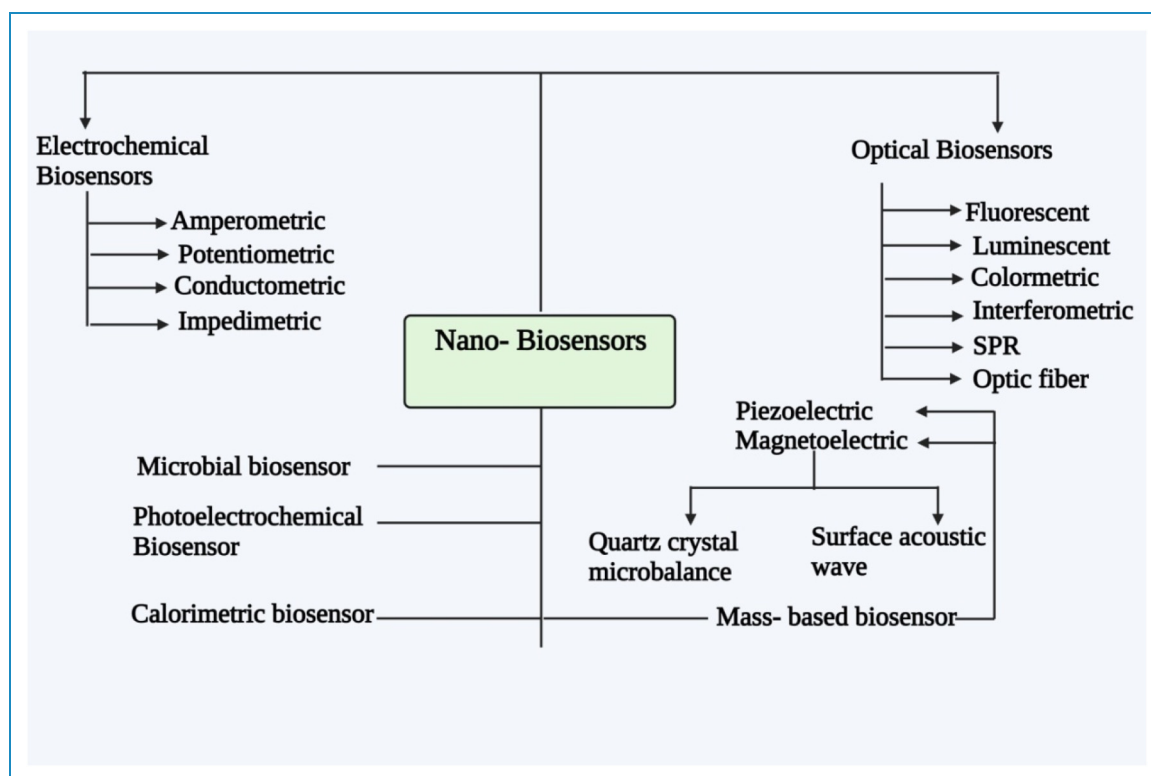


Figure 4. Several of the most prevalent biosensor types and subtypes.

phosphotau concentrations, decreased CSF amyloid-1–42 peptide (A42) levels, and affirmative amyloid or tau PET imaging have all been identified as indicators of progression to Alzheimer’s disease, with clinical potential.

Although biochemical biomarkers are still developing, they have potential as pharmacodynamic tools in clinical trials, facilitating pharmaceutical development and serving as diagnostic tools. Thus, there is an urgent need to expand biomarkers for PD and to accelerate the identification of biomarkers that can detect the transition from pre-motor to motor symptoms. Nonmotor symptoms, such as mood disturbances, olfactory deficits, gastrointestinal dysfunction, and sleep disturbances, often precede motor symptoms in PD but are not exclusive to the disease. Therefore, biomarkers predicting the course from nonmotor to motor symptoms would be highly valuable in research assessing pharmacological interventions aimed at halting disease progression. Additional biomarkers are required for monitoring pharmaceutical efficacy in disease progression and in clinical trials, possibly combining biochemical, imaging, and genetic markers.¹³⁴

Many studies on nanoparticles for PD diagnostics have emphasized dopamine nanobiosensors.¹⁴⁰ Shin et al.¹⁴¹ engineered silver–molybdenum disulfide (Ag/MoS₂) nanoparticles to improve electrochemical signaling for dopamine detection, showing promise for diagnostic applications in

PD. Additionally, Vazquez-Guardado et al.¹³⁸ developed an enzyme-free dopamine biosensor that combines a nanostructured plasmonic substrate with a plasma-separating microfluidic chip and oxygen-deficient cerium oxide (CeO₂) nanoparticles, enabling label-free detection of antigens and biomarkers in unprocessed bodily fluids.

Optical biosensors

Specificity and sensitivity are key metrics in evaluating biosensors, which typically consist of a biological recognition element to capture the target analyte and a sensing component that converts biological interactions into measurable signals. The specificity is determined by the combination of biological sensing elements and recognition mechanisms, whereas sensitivity largely depends on the receptor, which can include a microbe, enzyme, nucleic acid (such as an aptamer), or antibody.

Recent advances have focused on improving the immobilization process, substrate, and procedural methodologies to enhance sensitivity. Nanomaterials with unique optical properties, including quantum dots, carbon nanotubes, graphene, and metallic nanoparticles (e.g. silver and gold) Have been increasingly employed to amplify the detection of targets. Quantum dots are favored for fluorescence detection due to their broad absorption spectrum and resistance to

photobleaching. Metallic nanoparticles play a crucial role in amplifying signals for SERS-based detection, making optical biosensors with nanomaterials central to modern analytical diagnostics, particularly in cancer diagnosis. They offer short detection times, ease of use, and high sensitivity. Optical detection techniques for exosomal cancer biomarkers include fluorescence, electrochemiluminescence (ECL), CL, immunochromatographic assay (ICA), colorimetric analysis, SPR, and SERS.¹³⁸ Shawky et al.¹⁴⁰ developed a simplified optical biosensor utilizing gold nanoparticles for detecting nucleic acid transcripts, specifically tyrosyl DNA phosphodiesterase 2 (TDP2) and topoisomerase 1 (TOP1), which are linked to neurological and malignant conditions. This gold aggregating gold (GAG) assay offers rapid RNA quantification, serving as an alternative to traditional methods like real-time PCR. Haes et al.¹⁴² A nanoscale optical biosensor utilizing localized SPR was developed to detect antibodies against amyloid-derived diffusible ligands (ADDLs), presenting an innovative diagnostic approach for Alzheimer's disease by analyzing human brain extracts and CSF from Alzheimer's patients and healthy controls.

Electrochemical biosensors

The fundamental principle of the electrochemical sensor, illustrated in Figure 5, involves the application of a variable or constant voltage to the electrode, leading to alterations in the detection material on the electrode surface, which generates an electrical signal.¹⁴² Electrochemical sensors are utilized to ascertain the electrochemical and electrical properties of target substances or molecules for quantitative or qualitative detection and analysis. Chemically modified electrodes are currently a prominent subject of investigation in the field of electrochemistry. Most current research centers on electrochemical biosensors, classified into affinity and catalytic types. Catalytic biosensors leverage enzymes' transfer and catalytic properties; however, maintaining enzyme activity in neutral conditions imposes strict operational and material requirements and adds significant cost.¹⁴¹

Consequently, developing more efficient methods for building electrochemical enzyme-free sensors, stabilizing immobilized media, and identifying effective electron transfer media are among the critical challenges that require advancement in this field. Electrochemical sensors offer high sensitivity compared to other sensing methods, including calorimetric, magnetic, optical, piezoelectric, and acoustic techniques, while also being cost-effective, portable, and compatible with microfabrication, making them popular in therapeutic settings. Neurobiological signs exist in minimal amounts in biological fluids, requiring the implementation of highly sensitive detection technologies.¹⁴³

Since 1962, when Lyons and Clark introduced the glucose enzyme electrode, Numerous techniques have been established to alter electrode surfaces in biosensors,

enhancing accuracy, sensitivity, and selectivity.^{143,144} Enzyme-based electrochemical sensors, building on this innovation, offer high selectivity due to enzyme specificity, allowing precise detection of individual enzymes in complex samples.¹⁴⁵ Nonetheless, alterations in environmental conditions, like the pH and temperature, substantially impact the activity of enzymes and other physiologically active compounds, significantly limiting the applicability of enzyme biosensors. The production process for the enzyme sensor is intricate, and inconsistent thickness may lead to reduced repeatability and oxygen interference.¹⁴⁶ Furthermore, enzyme-based biosensors may incur high costs attributed to the significant expense of enzymes.¹⁴⁷

The utilization and advancement of nonenzyme biosensors represent a novel research domain. Various enzyme-free methods are available for detecting biomarkers linked to neurodegenerative diseases, including colorimetric sensors, surface-enhanced Raman scattering biosensors, fluorescence imaging sensors, and electrochemical techniques.¹⁴⁸ Khalilzadeh et al.¹⁴⁹ developed an electrochemical method utilizing microRNA (miR) to identify miR-146a, a recognised biomarker for neurological disorders. The gold substrate was functionalized with capture microRNA (C-miR) to detect target microRNA (T-miR) miR-146a in a bioassay, using an optimized C-miR concentration for capturing T-miR on the electrode surface. Results from unprocessed human blood samples show that this biosensor effectively detects miR-146a, a potential biomarker for neurodegenerative diseases. Liu et al. describe a similar ratiometric electrochemical biosensor for detecting trinucleotide repeat sequences d(CAG)_n, employing Exo III-assisted amplification on a graphene-modified electrode. This biosensor, with dual signals from ferrocene- and methylene blue-labeled DNAs, offers a reliable method for d(CAG)_n repeat analysis and potential clinical application in neurodegenerative disease diagnostics (Figure 5).

Nanobiosensor

A sensor is a device that detects and measures an analyte within a sample.¹⁵⁰ In a biosensor, a biological reaction is sensed and converted into an electrical signal, involving a transducer and a detection system (receptor). Biosensors convert biological reactions from enzymes, tissues, or cells into electrical signals via a transducer, with their efficacy relying on stable biological elements and sensor interactions. Nanobiosensors leverage nanotechnology to enhance detection accuracy and sensitivity, making them essential tools in medical diagnostics, environmental monitoring, and food safety. Their compact size supports minimally invasive applications, enabling regular health monitoring.^{151–153} In environmental settings, nanobiosensors detect low-concentration pollutants and toxins, allowing for timely interventions, while in food safety, they expedite the identification of contaminants like pathogens and pesticides.^{154,155}

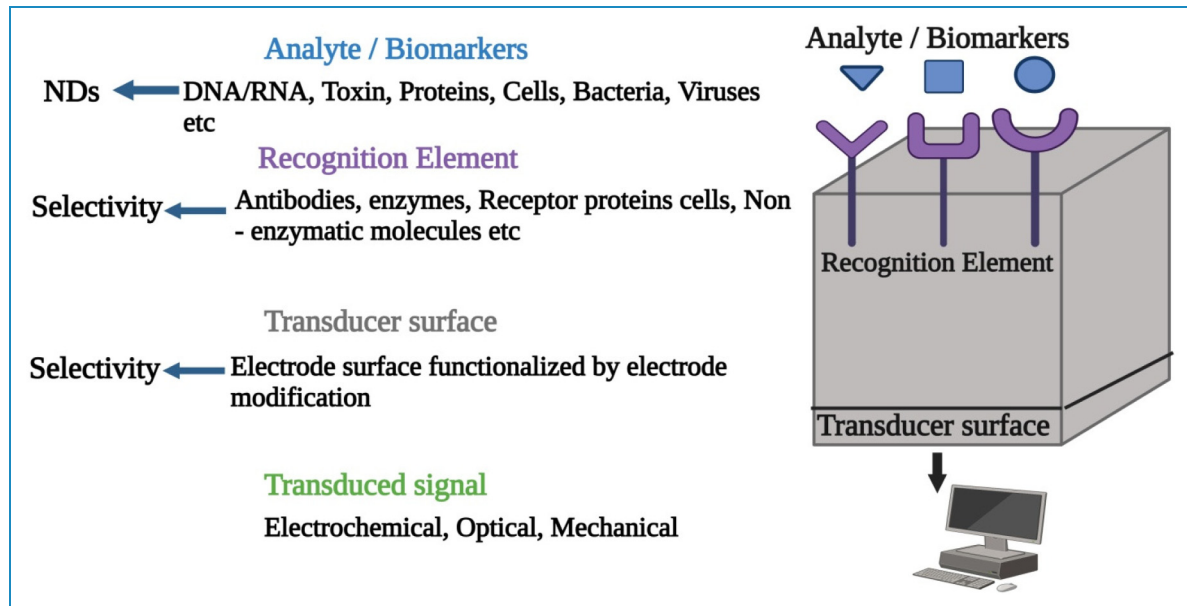


Figure 5. Basic concept of a biosensor system and the major components used to detect NDs.

Nanobiosensors comprise three core elements—a bioreceptor, transducer, and electronic system—that detect target molecules and transform these interactions into quantifiable signals. Known for their compactness, portability, and ability to provide real-time data, these sensors have advanced with new nanomaterials, enhancing their utility in personal healthcare and disease monitoring.^{155,156} Nanobiosensors also show promise as an alternative to traditional diagnostics like neuroimaging, offering enhanced sensitivity and specificity.¹⁵⁷ Nanoscale components, including nanoparticles and nanostructures, enhance nanobiosensor sensitivity through enzyme immobilization, improving both testing efficiency and cost-effectiveness.^{158,159} The integration of nanotechnology with electrochemical methods has also increased the speed and reliability of these sensors.¹⁶⁰ This advancement holds significant potential for transformative applications in disease management, notably for early cancer detection.¹⁶¹ Nanobiosensors have demonstrated their utility in diagnosing chronic conditions like kidney disease and tuberculosis.¹⁶² Some nanobiosensors operate without labels, allowing the detection of difficult-to-tag molecules, expanding their application in healthcare.¹⁶³ They significantly improve molecular diagnostics, offering more sensitive and rapid biomarker detection.¹⁶⁴ Nanomaterials, including nanoparticles and carbon nanotubes, are increasingly utilized in biosensor platforms to improve performance and expand application scope.¹⁶⁵ A notable advancement is multiplexed nanobiosensors, enabling simultaneous detection of multiple analytes for a thorough patient assessment.¹⁶⁶ Additionally, microfluidics and lab-on-a-chip technologies have further enhanced these capabilities¹⁶⁷ (Table 2).

Nanobiosensors for neurodegenerative disease diagnosis

Nanobiosensors significantly enhance clinical diagnostics by integrating biological detectors with sensor-transducer systems, offering high sensitivity and specificity in disease detection, including PD.²⁵ Recent advancements in nanofabrication, as demonstrated by Kalinke et al.,¹⁷³ have improved diagnostic accuracy for biomarkers like dopamine and ascorbic acid. Carbon paste electrodes modified with carbon nanotubes and silver nanoparticles¹⁷⁴ and zinc oxide nanowire arrays¹⁷³ have effectively lowered detection limits for biomarkers, such as dopamine and uric acid, critical in Parkinson's diagnosis. Additionally, electrochemical and immunosensors facilitate the precise detection of alpha-synuclein, a key protein linked to the disease.^{175,176} Innovations in molecular fingerprint polymers and graphene-based biosensors have demonstrated superior analytical performance, enabling real-time, *in vivo* detection with exceptional sensitivity.^{162,177,178} These advancements indicate that nanobiosensors may transform the early diagnosis and management of neurodegenerative diseases through accurate, real-time monitoring of disease progression.¹⁷⁸

Future prospective

Nanobiosensor technology shows significant potential for advancing neurodegenerative disease diagnostics. With ongoing research, sensor miniaturization and performance improvements are making these devices increasingly suitable for POC and routine screening applications. Wearable nanobiosensors, for instance, enable real-time biomarker

Table 2. PD: a selection of NP-based assays for the identification of particular indicators.

Marker of disorder	NP	Diagnosis modality	Experiment type	BBB crossing	Ref.
α -Synuclein	Immuno/magnetic particle	Immunoassay	<i>In vitro</i>	Not applicable	168
	Gold nanorod	Surface plasmon	<i>In vitro</i>	Not applicable	169
DA Receptor	Immuno-targeted far-red QDs	Fluorescence	<i>In vivo</i> (acute rat brain slide)	Intraventricular injection	170
DA	PEGylated PFPBA NPs (100 nm)	Near-infrared fluorescence	<i>In vivo</i> (mouse)	Yes	171
	PEGylated PFPBA NPs (120 nm)	Fluorescence quenching	<i>In vivo</i> (zebrafish)	Yes	172

monitoring, potentially allowing early detection of diseases like Alzheimer's and PD, even before symptoms appear. Furthermore, integrating nanobiosensors with artificial intelligence and machine learning can enhance diagnostic accuracy through complex data analysis and predictive capabilities. Multiplexed biosensors, which detect multiple biomarkers simultaneously, will facilitate differential diagnosis based on distinct biomarker profiles. Furthermore, innovations in nanomaterial synthesis will enhance the sensor stability, biocompatibility, and sensitivity, supporting their reliability in clinical applications. These advancements could drive widespread adoption of nanobiosensors for early intervention and better management of neurodegenerative diseases. Future research should also focus on addressing current challenges, such as regulatory approval, cost reduction, and large-scale manufacturing, to ensure that these technologies can be effectively integrated into healthcare systems worldwide.

Conclusion

The early diagnosis of neurodegenerative diseases is crucial for improving patient outcomes and slowing disease progression. Traditional diagnostic methods often fail to provide early detection due to their invasive nature and limited sensitivity. Nanobiosensors represent a groundbreaking advancement, integrating the specificity of biological recognition elements with the unparalleled sensitivity of nanomaterials. By enabling ultra-sensitive and real-time biomarker detection, these innovative tools offer a noninvasive and highly accurate diagnostic approach.

Nanotechnology-driven biosensing systems have revolutionized early disease detection by significantly enhancing biomarker specificity, stability, and signal amplification. The integration of quantum dots, carbon nanotubes, and gold nanorods has led to superior diagnostic accuracy, reducing the risks of false positives and negatives. Furthermore, the real-time monitoring capabilities of electrochemical, optical, and piezoelectric

biosensors make them indispensable in the field of neurodegenerative diagnostics.

Despite their immense potential, challenges such as reproducibility, biocompatibility, and large-scale clinical translation remain. Future advancements in sensor miniaturization, multiplexed detection, and artificial intelligence-driven analysis will further refine nanobiosensor applications, making them an essential component of personalized medicine. As these sensors continue to evolve, they have the potential to revolutionize neurodegenerative disease management by facilitating early intervention, enhancing patient monitoring, and ultimately transforming the landscape of neurological healthcare.

Abbreviations

CNS	central nervous system
LC-MS	liquid chromatography-mass spectrometry
ELISA	enzyme-linked immunosorbent assays
PD	Parkinson's disease
hGDNF	human glial cell line-derived neurotrophic factor
GNWs	Gold nanowires
EGO	exfoliated graphene oxide
MS	Multiple sclerosis
BBB	blood-brain barrier
ALS	Amyotrophic lateral sclerosis
NEMS	nanoelectromechanical systems
CL	chemiluminescence
PNS	peripheral nervous system
NDD	neurodegenerative disorder
FDG	fluorodeoxyglucose
Ag/MoS ₂	silver-molybdenum disulfide
SERS	surface-enhanced Raman scattering
ECL	electrochemiluminescence
ICA	immunochromatographic assay
SPR	surface plasmon resonance
TDP2	tyrosyl DNA phosphodiesterase 2
TOPI	topoisomerase I
GAG	gold aggregating gold
ADDLs	amyloid-derived diffusible ligands
miR	microRNA

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Consent to publication

All authors read and agreed to the final copy of the findings as contained in the manuscript.

Author contributions

Shikha Yadav and Ananda Kumar Chettupalli conceived and designed the study. Ajaypal Singh, Shatrudhan Prajapati, Shikha Yadav, Ananda Kumar Chettupalli, Buyinza Nicholas and Sarad Pawar Naik Bukke, carried out the study, analyzed and interpreted the data. Buyinza Nicholas, Ananda Kumar Chettupalli, Sarad Pawar Naik Bukke, drafted the manuscript and revised the manuscript. All authors read and make the final corrections.

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Data availability statement

The datasets/information used for this study are available on within the manuscript.

Declarations

I hereby declare that this submission is entirely my own work, in my own words, and that all sources used in researching it are fully acknowledged and all quotations properly identified.

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