DNA

Review

Applications and Challenges of DNA-Based Electrochemical Biosensors for Monitoring Health: A Systematic Review

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Abstract: DNA-based biosensors have emerged as cutting-edge tools with significant potential to revolutionize medical diagnostics and environmental monitoring. These biosensors leverage the specificity and sensitivity of DNA interactions to detect a wide range of biomolecular targets, making them ideal for early disease detection, genetic analysis, and real-time environmental assessment. Despite their promising applications, several challenges impede their widespread adoption. Key issues include the stability of DNA molecules, which are prone to degradation under environmental conditions, and the need for enhanced specificity and sensitivity to accurately detect target molecules in complex samples. Technological hurdles in miniaturizing and integrating these sensors into portable, user-friendly devices, along with ethical concerns regarding data privacy and the misuse of genetic information, also pose significant barriers. This systematic review examines the current state of DNA-based biosensor technology, highlights the main challenges, and discusses potential strategies to overcome these obstacles. By addressing these multifaceted issues through ongoing research and innovation, DNA-based biosensors can be developed into robust tools for various applications, contributing to improved public health outcomes and environmental sustainability.

Keywords: DNA-based biosensors; biomolecular target detection; early disease diagnosis; sensor miniaturization

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Citation: Mondal, H.S.; Feng, Y.; Biswas, G.; Hossain, M.Z. Applications and Challenges of DNA-Based Electrochemical Biosensors for Monitoring Health: A Systematic Review. *DNA* **2024**, *4*, 300–317. https://doi.org/10.3390/dna4030020

Academic Editor: Darren Griffin

Received: 20 June 2024
Revised: 9 August 2024
Accepted: 19 August 2024
Published: 11 September 2024

1. Introduction

DNA biosensors are beneficial in various fields, such as cancer and mutation detection. These biosensors offer precise and rapid detection capabilities, making them invaluable tools in early diagnosis and personalized medicine. They can identify specific DNA sequences associated with genetic mutations or cancer biomarkers, enabling timely and accurate interventions. Figure 1 represents the overview of biosensor. The stated figure outlines the key operational stages of a biosensor system, emphasizing the integration of recognition, transduction, and signal processing elements. It begins with the 'Recognition' stage, where targets such as antibodies/antigens, nucleic acids, rare cells, proteins, chemicals, and mechanical forces are identified. The recognition mechanisms are depicted as they interact with their specific targets, highlighting the versatility of biosensors in detecting a broad range of biological entities. Transitioning to the 'Transducer' stage, the infographic categorizes the transduction mechanisms into optical, electrochemical, and other forms (including mechanical). It details various detection methods like fluorescence, colorimetric, and amperometric readouts, showcasing how these transducers convert biological interactions into measurable signals. Specific attention is given to optical phenomena such as LSPR (Localized Surface Plasmon Resonance), SERS (Surface Enhanced Raman Spectroscopy), and FRET (Förster Resonance Energy Transfer), underscoring the sophistication of current biosensor technologies. Finally, the 'Signal Processing' stage is illustrated, where the signals from the transducers are recorded, displayed, and analyzed, typically using computers and mobile devices. The process of interpreting these signals to derive meaningful, actionable biological information is emphasized, signifying the critical role of data analysis in the effectiveness of biosensors. This infographic serves as a concise visual summary of the complex processes involved in biosensor operations, suitable for educational purposes or as a quick reference for professionals in the field of biotechnology and medical diagnostics.

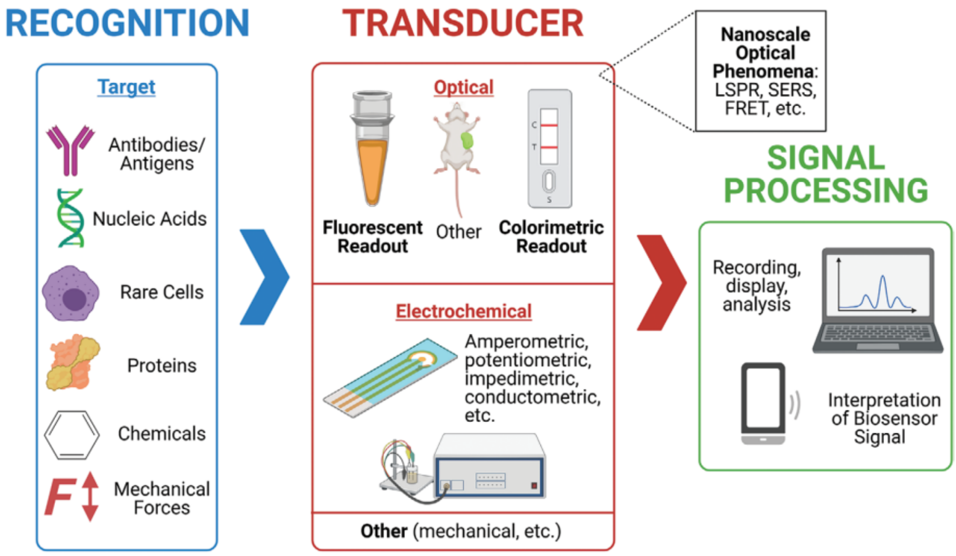

Figure 1. Key components of biosensors. Biosensors function by identifying biologically significant entities like rare cells, nucleic acids, and mechanical forces, among others. They detect these targets using methods such as affinity interactions and use a transducer to convert these interactions into a detectable signal. These transducers typically operate on optical, electrochemical, or mechanical modalities. The transducer emits a signal that needs to be analyzed and presented through a signal processing and readout system. Ultimately, biosensors are utilized to gather and analyze critical biological data, such as the detection of infectious diseases, cancer biomarkers, or glucose levels [1].

In addition to applications in cancer and mutation detection, DNA biosensors have also proven to be important in the fight against infectious diseases, including COVID-19. The COVID-19 pandemic has highlighted the need for rapid and reliable diagnostic methods to control the spread of the virus. DNA biosensors, particularly those utilizing various materials such as gold or graphene, have shown great promise in detecting COVID-19 biomarkers. These advanced biosensors leverage the unique properties of graphene or gold, such as high surface area, excellent electrical conductivity, and biocompatibility, to achieve high sensitivity and specificity in detecting viral RNA or DNA [2]. This research will discuss and highlight the developments, discoveries, and areas of DNA biosensors.

Electrochemical DNA biosensors have emerged as powerful tools for sensitive and specific detection of various analytes, offering advantages such as rapid response times, high sensitivity, and cost-effectiveness [3]. These biosensors utilize electrochemical techniques such as cyclic voltammetry, differential pulse voltammetry, and electrochemical impedance spectroscopy to detect DNA sequences with high specificity and sensitivity. These techniques allow for precise measurement of the electrical properties of the biosensors, enabling the detection of specific DNA sequences related to HER2 (ERBB2), which is crucial for accurate breast cancer diagnosis [4]. The design of electrochemical DNA biosensors involves the integration of innovative materials like graphene oxide-silk fibroin composites and gold nanoparticles to enhance the immobilization of probe oligonucleotides and improve the overall performance of the biosensor. Furthermore, recent advancements have focused on developing label-free and immobilization-free electrochemical biosensors for the detection of specific DNA sequences, showcasing the continuous innovation in this field [5].

Figure 2 presents a comprehensive overview of advancements in biosensor technology, particularly focusing on DNA-based sensors. Here's a breakdown of each panel: Panel A Illustrates the integration of nanomaterials with DNA-based biosensors. It highlights their application in environmental monitoring and biosecurity, suggesting the use of advanced materials to enhance sensor sensitivity and specificity. Panel B shows various aspects of biosensor development, from fabrication methods to final applications. It shows different types of biosensors, like portable, implantable, and wearable, and their uses in various fields including health monitoring and diagnostics. Panel C explores the molecular process of a DNA-based electrochemical biosensor. It shows the sequence of detection from target DNA to signal output, illustrating the chemical reactions involved and displaying a graph of current response, specifically for detecting the TP53 gene, which is crucial in cancer studies. Panel D focuses on the applications of nanoengineered surfaces in biosensors. It emphasizes enhancements like antifouling layers and hydrogels which improve the performance and durability of sensors, particularly in challenging environments.

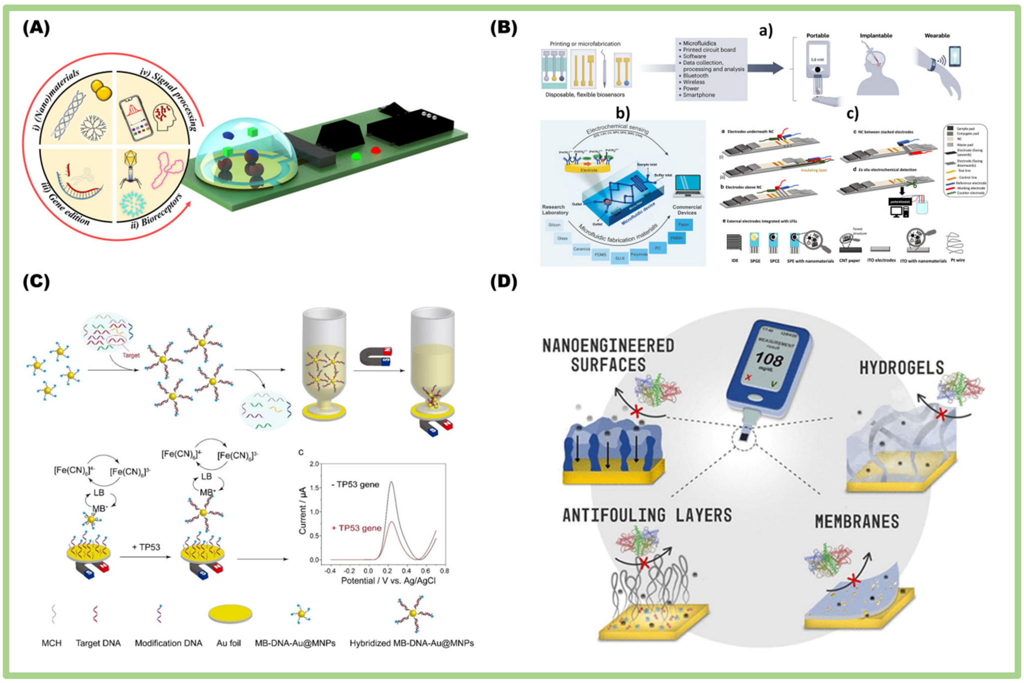

Figure 2. Advanced DNA-based Biosensor Technologies: From Nanoengineering to Practical Applications—This diagram provides an in-depth look at the latest innovations in DNA biosensor technology, illustrating the synthesis of nanomaterials, diverse sensor types, molecular detection mechanisms, and the application of nanoengineered surfaces to enhance sensor functionality and reliability. (**A**) DNA Biosensor Platform: Overview of a DNA biosensor system integrating biomaterials with sensor components for biomolecular detection. The system consists of bio-recognition elements that capture specific targets and a device to convert this interaction into a measurable, digital output. (**B**) Biosensor Types and Fabrication: Depiction of various biosensor forms including portable, implantable, and wearable devices, highlighting the use of microfluidics and printed circuit boards for compact design. It also shows an electrochemical setup in a laboratory environment for the development and testing of biosensors, with emphasis on data collection and processing (refer to Supplementary Materials S1). (**C**) DNA Detection Mechanism: Schematic representation of the DNA detection process using a DNA biosensor. This includes the targeting and binding of specific DNA sequences by complementary DNA probes, followed by signal amplification using metallic nanoparticles and electrochemical methods to quantify the presence of target DNA. (**D**) Surface Enhancements for Biosensors: Innovations in biosensor technology showcasing nanoengineered surfaces to increase interaction efficiency, antifouling layers to prevent biomolecular contamination, and the use of hydrogels and membranes to stabilize and protect the sensor elements in a bio-mimicking environment [6].

Figure 3 illustrates the diverse types of Metal-Organic Frameworks (MOFs) and their critical attributes that enhance sensing performance. At the core, the diagram emphasizes 'Sensing Performance', highlighting essential factors such as sensitivity, selectivity, stability, and accuracy. Various forms of MOFs are depicted, including Nano-MOFs, which utilize nanoscale structures; Meso-MOFs with medium-sized pores; flat, two-dimensional MOFs that provide extensive surface areas; and Hybrid MOFs that combine MOFs with other materials to boost functionality. Also featured are MOF Films and derivatives tailored for specific applications. The image further explores composites such as MOFs combined with biomolecules for improved selectivity, core-shell structured MOFs for enhanced protection, and composites with electro-active molecules to augment electrochemical properties. This comprehensive representation underscores the versatility and adaptability of MOFs in sensor technology applications.

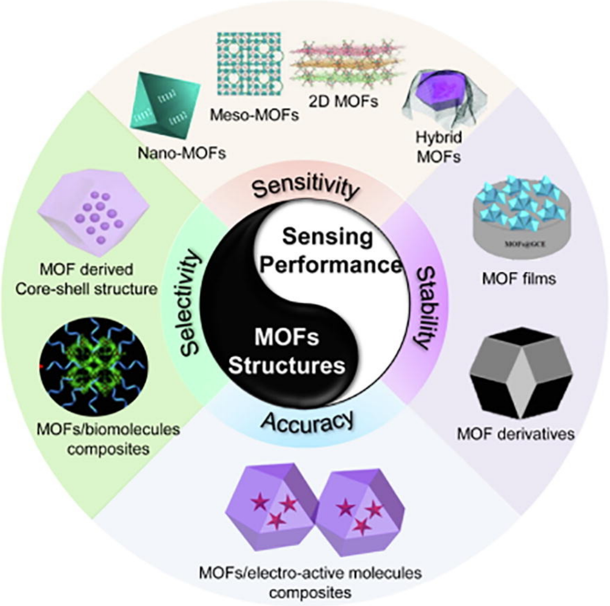

Figure 3. The Diversity and Performance of Metal-Organic Frameworks (MOFs): This diagram categorizes various MOF structures and composites, emphasizing their roles in enhancing the sensitivity, selectivity, stability, and accuracy of sensor applications. Highlighted are Nano-MOFs, Meso-MOFs, 2D MOFs, Hybrid MOFs, MOF Films, and several composites, each contributing uniquely to the field of advanced sensing technology [7].

One critical application area for electrochemical DNA biosensors is in disease diagnostics, with studies demonstrating their potential for early-stage cancer detection, such as cervical cancer and breast cancer [8,9]. These biosensors offer high sensitivity and selectivity, making them valuable tools for detecting specific biomarkers associated with various diseases. Another notable biosensor technology includes optical biosensors, which utilize light-based detection methods to identify biomolecules, providing rapid and non-invasive diagnostic options [10]. Additionally, electrochemical DNA biosensors have been explored for the detection of viral infections, including human papillomavirus (HPV) and hepatitis B virus (HBV), highlighting their versatility in pathogen detection [11]. The development of electrochemical biosensors for neglected tropical diseases (NTDs) underscores their potential as efficient and affordable diagnostic tools for a wide range of health conditions [12].

In the context of material innovation, the use of carbon-based frameworks and multi-walled carbon nanotubes has been instrumental in enhancing the sensitivity and signal-to-noise ratios of electrochemical DNA biosensors [13]. These materials provide a robust sensing interface for DNA detection, enabling the accurate quantification of target DNA sequences. Moreover, the integration of topological insulators like Bi_2Se_3 in biosensor design has shown promise in improving the sensitivity and detection limits of electrochemical

DNA biosensors [14]. The ordered assembly of DNA on Bi_2Se_3 surfaces, combined with octadecylamine layers, has led to the development of highly sensitive biosensors with wide linear detection ranges and low limits of detection.

2. Literature Review

As technology advanced, DNA biosensors were found to be highly effective for both DNA mutation detection and the detection of cancer biomarkers, thereby increasing their significance in medical diagnostics and research. DNA biosensors have been categorized into various types, including hybridization biosensors, SPR-DNA biosensors, label-based detection, and label-free detection [15]. Additionally, DNA biosensors can be categorized by their physical types, which include electrochemical, optical, acoustic, and piezoelectric biosensors. Based on the effectiveness and usability this research will focus on electrochemical DNA biosensors.

2.1. Electrochemical DNA Biosensor

Techniques for electrochemical DNA biosensors are substantially more affordable, straightforward, and stable when used with Point-of-Care (POC) analysis [16]. Furthermore, these biosensors have shown great potential in various applications due to their high sensitivity and rapid response times. Recent advancements in this field have also highlighted the potential for integration with other technologies to enhance their performance and usability. A more straightforward outcome may be seen in the study conducted by [6], which demonstrates the several advantages of employing electrochemical biosensors and nanomaterial with nucleic acids, including their sensitivity, affordability, speed of reaction, and low sample consumption. The detection strategy employed for DNA-based electrochemical biosensors involved the use of nucleic acids as receptors combined with nanomaterials, particularly carbon nanomaterials. These biosensors were used to detect a range of analytes, including ions, low and high molecular weight compounds, nucleic acids, proteins, and even whole cells. The integration of nanomaterials enhanced the sensitivity, selectivity, and detection limits of the biosensors, making them suitable for applications in medical diagnostics and environmental monitoring. When coupled with nanomaterials and electrochemistry, as well as labeling techniques, these combinations have the potential to create DNA biosensors with a highly promising future. Such advancements are expected to revolutionize diagnostics by enabling the development of highly sensitive and efficient biosensors for detecting a wide range of diseases and pathogens. However, several challenges remain, including the need for advanced automation and sophisticated data analysis capabilities, especially for implementation in mobile devices. Ensuring seamless integration of these features is crucial for the practical deployment of DNA biosensors in real-world settings. Electrochemical sensors have become valuable tools for detecting various analytes, with DNA being a significant target in biological and medical applications. Notably, electrochemical DNA sensors based on nanocomposites like Multi-walled Carbon Nanotubes/Manganese Dioxide/Polyaniline have shown high sensitivity and selectivity in detecting DNA targets [17,18]. These sensors have low limits of detection and wide linear ranges for DNA detection, making them promising for applications in detecting pathogenic agents. Silicon-based electrodes have been used for highly sensitive and label-free DNA detection, highlighting the advantages of different materials in enhancing sensor performance [19]. Advancements in sensor design include the use of zirconia and graphene nanocomposites for constructing electrochemical DNA biosensors, showcasing ongoing innovation in sensor materials and structures [20].

2.2. Hybridization DNA Biosensors

In order to improve the responses, DNA hybridization-based biosensors rely on the nucleic acid amplification strategy. Earlier, there have been studies relating optic fiber and DNA hybridization biosensors. Researchers found that hybridization events could be detected using quartz optical fibers. These studies not only highlight the advantages of being long-lasting, regenerable, and reproducible but also highlight potential areas for future development, such as reducing response times and being highly protegeable [21]. This study has provided a foundation for further research into enhancing the performance and capabilities of DNA hybridization-based biosensors. Researchers have been exploring various approaches to address the limitations of current technologies, including improving the sensitivity detection and response time. The challenge of Fibre optic SPR biosensing of DNA hybridization is not commercially available due to its high cost and complexity of operation, as identified in 2009 [22]. Despite these challenges, ongoing research continues to focus on innovative solutions to make this technology more accessible and user-friendly. The recent finding may be traced back to [23], who proposed a fibre optical structure DNA hybridization sensor that achieves high sensitivity, real-time low cost, temperature adjustment, and low detection limit. These advancements indicate a promising future for the practical application of DNA hybridization biosensors in various fields.

To develop advanced biosensors for the sensitive detection of biomarkers like DNA, key materials such as graphene and carbon-based nanomaterials play a crucial role due to their unique properties [24]. These materials have been utilized in various biosensors, including those designed for the detection of DNA hybridization. For instance, a study by introduced a reduced graphene oxide (R-GO)-based field-effect transistor (FET) biosensor for ultrasensitive label-free detection of DNA through peptide nucleic acid (PNA)-DNA hybridization [25]. This research highlights the significance of graphene-based materials in achieving high sensitivity in detecting DNA analytes. The combination of DNA with π-conjugated polyelectrolytes (CPEs) like cationic polythiophene has shown promise in developing DNA hybridization biosensors for detecting DNA lesions and single-nucleotide polymorphisms [26]. This approach demonstrates the potential of utilizing specific materials to enhance the specificity and accuracy of DNA detection in biosensing applications. Additionally, materials like GaN have been explored for fabricating FET-based biosensors due to their non-toxicity, high sensitivity, and stability, as reported in a study by [27]. In the realm of biosensors for DNA detection, the use of conductance-based biosensors that leverage DNA-mediated long-range electron transport has been proposed for label-free and direct electrical detection of DNA hybridization [28]. This approach showcases the innovation in sensor design to enable efficient and direct detection of DNA analytes. Furthermore, the integration of hybrid 2D nanomaterials like MoS_2 in biosensors for detecting Bacillus subtilis DNA signifies advancements in sensor technologies with applications in biomedical and environmental monitoring [29]. Efforts have also been made to enhance the detection sensitivity of DNA hybridization using innovative approaches. For example, the utilization of porous silicon (PS) photonic crystal biosensors based on fluorescence resonance energy transfer (FRET) between quantum dots (QDs) and gold nanoparticles (AuNPs) has shown efficient detection capabilities [30]. This method capitalizes on the unique properties of nanomaterials to achieve highly sensitive DNA detection through FRET mechanisms. The development of biosensor architectures based on dynamic DNA assembly programmed surface hybridization has enabled single-step, reusable, and amplified electrochemical nucleic acid analysis [31]. This approach demonstrates the potential for creating versatile biosensors that offer enhanced performance and usability in DNA detection applications. Additionally, the use of graphene-based materials in biosensors for detecting DNA hybridization kinetics through electricity-fluorescence double-checking mechanisms showcases the multifaceted nature of sensor technologies [32]. In the context of specific DNA detection applications, biosensors have been tailored for detecting target DNA sequences related to various diseases and conditions. For instance, electrochemical DNA biosensors have been designed for the detection of specific DNA sequences associated with diseases like prostate cancer and hepatitis B virus [33,34]. These biosensors demonstrate the versatility of sensor platforms in addressing diverse healthcare challenges through precise DNA detection.

3. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a comprehensive, transparent, and methodologically sound approach to the selection, evaluation, and synthesis of the literature. Adherence to the PRISMA guidelines was rigorously maintained throughout the review process, enhancing the clarity, reproducibility, and overall reliability of the findings. This framework facilitated a thorough and unbiased assessment of the current state of DNA-based biosensor technology, highlighting critical challenges and potential solutions in the field. The review was prepared by conducting an extensive search in three major electronic databases: Web of Science, Scopus, and IEEE Xplore. These databases were selected for their comprehensive collections of scientific and engineering literature, representing a broad spectrum of studies. The search identified a total of 539 papers (refer to Supplementary Materials S2), with 435 papers from the Web of Science, 62 from Scopus, and 42 from IEEE Xplore. These research articles were compiled to present recent developments and applications of DNA-based biosensors, particularly targeting disease detection and health monitoring (refer to Supplementary Materials S3).

The search strategy was meticulously developed, employing specific searchable terms and Boolean operators. The query used was: ((dna biosensor OR nucleic acid sensor) AND (optical OR fluorescence) AND (disease diagnosis OR health monitoring)). This strategy aimed to locate research articles focusing on the utilization of optical or fluorescence detection-based DNA biosensors for diagnosing diseases and monitoring health. The chosen keywords helped to refine the search, excluding irrelevant works and focusing on relevant publications in clinical and health monitoring applications. The search covered research articles published from 2014 to June 2024, ensuring a comprehensive overview of the field’s current state.

First, duplicates across the databases were identified and removed, which reduced the number of articles from 539 to 528. This step was crucial to ensure the uniqueness of each study included in the analysis. Following this, a screening for content type was conducted where review articles, book chapters, and short letters were excluded. These document types were removed because they often do not present original research data, which is essential for a systematic review aiming to synthesize empirical findings. This screening process further reduced the pool to 509 articles.

The second stage of filtering focused on the content specificity with respect to DNA biotechnologies. Studies were excluded if the articles did not mention “DNA” explicitly, which was justified as studies that may focus on DNA-based biosensor technologies central to this review. Only 210 articles ultimately met this criterion, which highlights the fact that many of the initially captured studies were not directly relevant to DNA sensing technologies. Subsequently, articles that did not include “electrochemical” approaches were also excluded. Given the importance of electrochemical methods in enhancing the sensitivity and specificity of DNA biosensors, this criterion was vital for focusing on articles that contribute directly to the field of electrochemical DNA biosensors. This step further narrowed the selection to 99 articles.

The final filtering stage involved a careful examination of the titles of the remaining studies. Any article whose title did not explicitly include terms related to “biosensor” or analogous research was deemed outside the scope of this review, as the title often reflects the core content of the study. This final criterion reduced the number of articles to 52, which are considered highly relevant and form the basis for in-depth analysis in the review. Figure 4 represents the review process.

This rigorous and methodical approach to article selection ensures that the studies included in the review are directly relevant to the advancement of DNA-based biosensor technologies in disease diagnosis and health monitoring, providing a focused and comprehensive synthesis of the current state of the field.

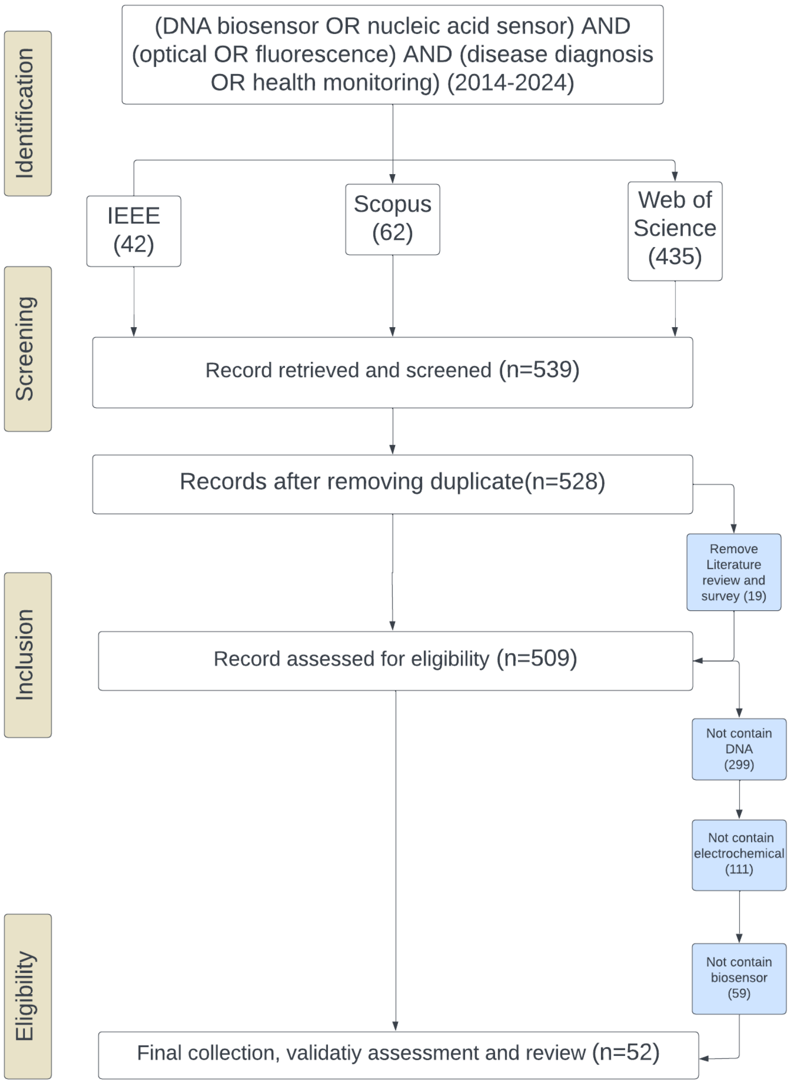

Figure 4. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the study selection process.

4. Results

4.1. Application Area of DNA Detection

This section of the systematic review, the focus was primarily on the application of DNA-based biosensors across two critical sectors: medical and environmental. Within the medical sector, the studies showcased diverse applications of these biosensors in diagnosing a wide array of diseases, from infectious pathogens to genetic disorders. The sensitivity and specificity of DNA-based biosensors have been highlighted as particularly advantageous in early disease detection, which is crucial for effective treatment outcomes. Moreover, the incorporation of advanced materials and novel detection strategies has been noted to enhance the performance of these biosensors, making them integral tools in clinical diagnostics. Figure 5 shows the application area of DNA detection throughout the systematic literature review process.

Conversely, in the environmental sector, DNA-based biosensors have been employed to monitor pollutants and detect pathogens in various environments. These studies reveal how biosensors are being adapted to handle complex samples from water, soil, and air, providing rapid and accurate environmental monitoring. The ability of these biosensors to detect low concentrations of environmental toxins and pathogens marks a significant step forward in ecological management and safety. The integration of these biosensors with portable and user-friendly devices also highlights the growing trend towards on-site environmental assessment, which is vital for real-time monitoring and decision-making.

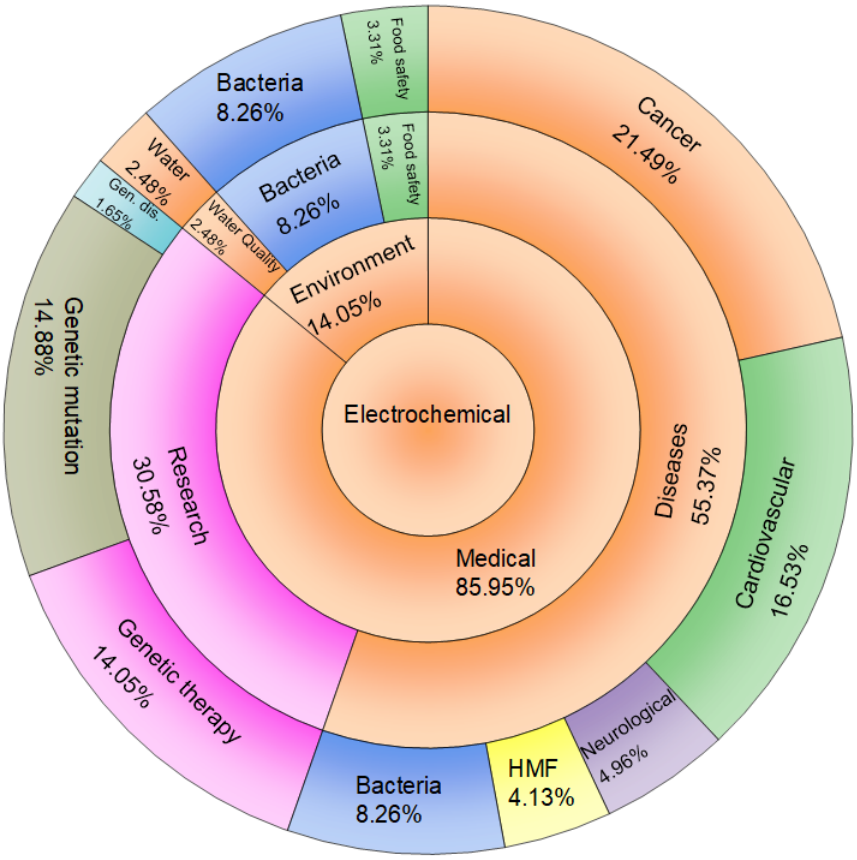

Figure 5. This figure provides an overview of the application areas for DNA-based detection technologies, segmented by their primary usage in various fields. The review focused on, "Electrochemical, detection" indicates the primary detection method, surrounded by three main application layers. The innermost layer, "Medical," accounts for the majority at 85.95%, showcasing the broad utilization of DNA-based detection in medical diagnostics. This includes a substantial focus on "Diseases" (55.37%), with significant portions dedicated to "Cancer" (21.49%) and smaller segments for "Cardiovascular" and "Neurological" conditions. The middle layer highlights "Environment" and "Research," with environmental applications capturing 14.05% and research-related uses, particularly in "Genetic Mutation" and "Genetic Therapy," at substantial rates. The outermost layer reflects applications in detecting specific agents like "Bacteria" and "HMF" (Hazardous Material Forms), emphasizing the versatility and broad scope of DNA-based electrochemical detection technologies.

In the medical sector, DNA-based biosensors have shown remarkable potential in addressing a wide array of diseases, with a significant emphasis on cancer detection. Among the studies reviewed, 26 articles were dedicated to exploring biosensors in cancer research, underscoring the critical role these devices play in identifying specific biomarkers associated with various types of cancer. This includes sensors designed for the detection of oncogenes, tumor suppressors, and other molecular markers that are pivotal in the early diagnosis and monitoring of cancer. The specificity and sensitivity of these biosensors are particularly advantageous for tracking the effectiveness of treatments and for recurring monitoring, which is essential for improving patient outcomes in oncology.

Cardiovascular diseases also featured prominently in the research articles, with 20 studies focusing on the development of biosensors for detecting conditions such as heart attacks and chronic heart diseases. These biosensors are engineered to identify biomarkers like cardiac troponin or natriuretic peptides, which are crucial for the early diagnosis and management of cardiovascular events. The capability of DNA-based biosensors to provide rapid and accurate results is vital in emergency medical scenarios, where time is critical.

Neurological disorders, although less represented with only 6 studies, highlight an emerging area of interest where DNA-based biosensors are being utilized to detect biomarkers associated with diseases like Alzheimer's and Parkinson's. These biosensors offer a non-invasive means of monitoring disease progression and response to therapies, which is a significant advancement in the field of neurology. Additionally, infectious diseases such as Hand, Foot, and Mouth disease were the focus of 5 studies, where biosensors were developed to rapidly detect viral pathogens, thereby facilitating quicker and more effective public health responses.

The research into bacterial infections revealed the application of DNA-based biosensors in diagnosing bacterial diseases, with 10 articles detailing their use. These biosensors are critical for identifying specific bacterial strains, helping to tailor antibiotic treatments more effectively and combat antibiotic resistance by ensuring appropriate medication use.

Beyond disease diagnosis, the review also highlighted extensive research into genetic aspects of health conditions. Seventeen articles focused on genetic therapy, investigating how DNA-based biosensors can be integrated into therapeutic protocols to monitor gene editing tools like CRISPR and ensure precision in treatment delivery. Eighteen studies examined genetic mutations, where biosensors were used to detect mutations that predispose individuals to diseases, supporting the advancement of personalized medicine. Finally, genetic disorders, though the focus of only 2 studies, represented a niche but vital application of DNA-based biosensors, offering hope for the detection and management of rare genetic conditions that are often challenging to diagnose with traditional methods. The diverse applications of DNA-based biosensors across the medical field highlight their transformative potential, not only in diagnosing a wide range of diseases but also in facilitating the development of genetic-based therapies and personalized medicine approaches. This technology stands at the forefront of a healthcare revolution, where rapid, precise diagnosis and tailored treatments could significantly enhance patient care and outcomes.

Water quality monitoring, covered in three studies, focuses on the use of DNA-based biosensors to detect pollutants and toxins in freshwater and marine environments. These biosensors are designed to identify specific chemical contaminants and harmful biological agents, providing rapid and precise assessments of water safety. This capability is crucial for the prevention of waterborne diseases and for ensuring the ecological balance of aquatic ecosystems. The studies illustrate the integration of biosensors with current water monitoring systems to enhance response times and accuracy in detecting potential threats, which is vital for maintaining public health and environmental integrity.

Bacterial detection in environmental samples was the subject of 10 studies, emphasizing the importance of rapid identification methods in preventing bacterial outbreaks. DNA-based biosensors used in these studies are tailored to detect pathogenic bacteria in various environments, from natural environment to urban environment. These devices are critical in managing risks associated with bacterial contamination, offering a tool for early detection that can lead to timely interventions and minimize public health risks. The specificity and adaptability of these biosensors make them invaluable in environmental surveillance and management programs.

Food safety, addressed in four studies, highlights the role of DNA-based biosensors in detecting pathogens and contaminants in the food supply chain. These sensors are utilized to ensure the safety of food products by rapidly identifying potential threats such as bacterial contamination, toxins, or chemical residues. This rapid testing capability is essential for compliance with health regulations and for preventing foodborne illnesses. The application of DNA-based biosensors in food safety not only enhances the efficiency of quality control processes but also supports the implementation of more stringent safety standards, thereby protecting consumers and maintaining trust in food markets.

Collectively, these applications in the environmental sector reveal how DNA-based biosensors are becoming essential tools in managing environmental health. Their ability to provide quick, accurate, and sensitive detection of various biological and chemical agents plays a pivotal role in safeguarding public health and preserving environmental quality. As these technologies continue to evolve, their integration into broader environmental management and public health strategies will likely expand, offering more robust and proactive responses to environmental challenges.

4.2. Detection of Biomolecules Based on Their Interactions with DNA

DNA-based biosensors are emerging as revolutionary tools in the scientific community, with their applications spanning various fields. A significant portion of the research, as indicated by 27 studies, has been dedicated to the detection of general nucleic acids such as DNA, mRNA, microRNAs, specific sequences, and mutations. This wide array of target molecules reflects the comprehensive capabilities of DNA-based biosensors in capturing a broad spectrum of genetic and molecular biomarkers, crucial for both diagnostic and therapeutic purposes. In clinical diagnostics, these biosensors offer the advantage of detecting genetic variations that may predispose individuals to certain diseases or influence their response to drugs, thereby facilitating personalized medicine approaches. Moreover, their ability to detect mRNA and microRNAs provides insights into gene expression patterns, which can be critical for understanding disease mechanisms and developing targeted treatments. Figure 6 shows DNA based Bio-molecules detection.

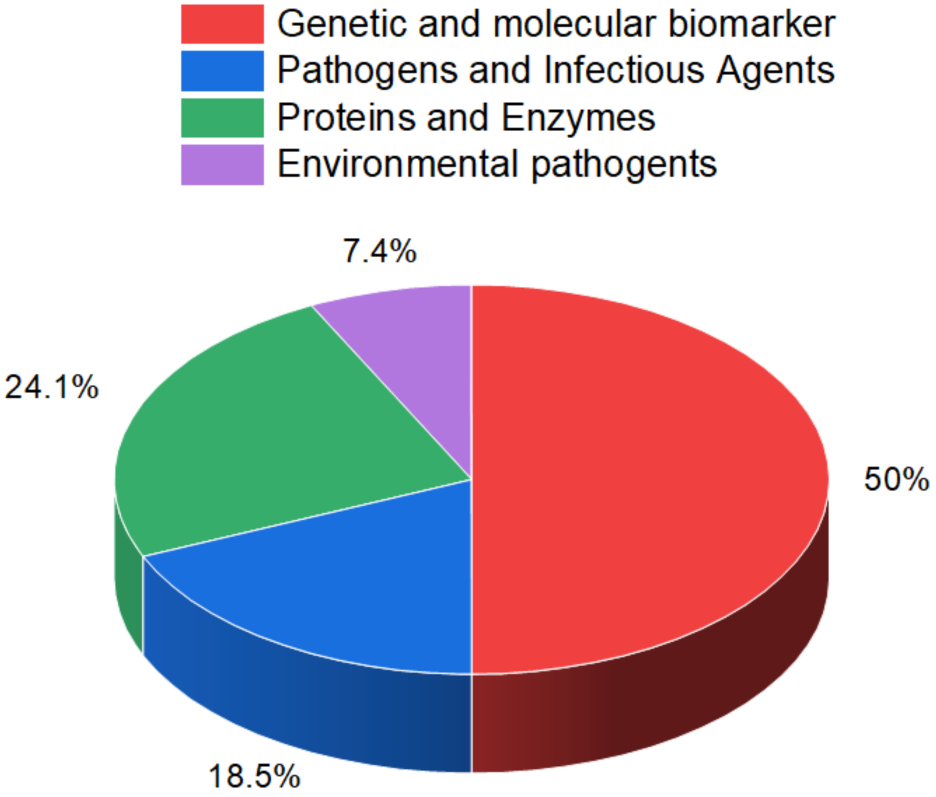

Figure 6. This figure displays the distribution of DNA-based biomolecules detection across various categories, depicted in a pie chart format. The largest segment, "Genetic and molecular biomarker" detection, constitutes 50% of the applications, indicating its predominant role in DNA-based detection technologies. The "Pathogens and Infectious Agents" category accounts for 24.1% of the detection focus, reflecting significant usage in identifying disease-causing organisms. "Proteins and Enzymes" represent 18.5% of the applications, highlighting their importance in diverse biochemical and diagnostic processes. Lastly, "Environmental pathogens" make up 7.4% of the distribution, underscoring the application of DNA-based detection in environmental monitoring and safety. This chart effectively illustrates the broad scope and varied applications of DNA-based technologies in biomolecules detection.

In the field of infectious disease management, 10 studies have focused on the utilization of DNA-based biosensors for the identification of pathogens and disease-specific genes. These biosensors are specifically designed to quickly detect and quantify pathogenic organisms, thereby enabling timely and effective medical interventions. This rapid diagnostic capability is essential in outbreak scenarios where swift action can significantly alter the course of disease spread and patient outcomes. By providing specific genetic information about the pathogens, these biosensors help in tailoring treatment strategies that are more effective and less prone to resistance development.

Another critical application of DNA-based biosensors is in the detection of proteins, enzymes, and related biomarkers, with 13 articles exploring this area. These studies highlight the adaptability of DNA-based biosensors to detect not only nucleic acids but also protein-based markers, which play pivotal roles in numerous biological processes and disease states. For instance, the detection of tumor markers through these biosensors can aid in early cancer diagnosis, monitor disease progression, and evaluate the effectiveness of ongoing treatments. Similarly, in the context of enzyme-related disorders, biosensors provide essential data that can guide enzyme replacement therapies and other management strategies.

Lastly, the environmental applications of DNA-based biosensors, although less frequently studied with only 4 articles, demonstrate their potential beyond human health. These biosensors are employed to monitor environmental contaminants, detect pollutants at low concentrations, and assess ecological health. This capability is particularly valuable for environmental protection agencies and industries committed to maintaining ecological balance and ensuring compliance with environmental regulations.

Overall, the diverse applications of DNA-based biosensors underscore their transformative impact across various domains. By enabling precise and rapid detection of a wide range of biomarkers, these tools are at the forefront of advances in medical diagnostics, infectious disease management, and environmental monitoring. Their continued development and integration into research and clinical practices promise to enhance our ability to diagnose, treat, and manage complex diseases and environmental challenges more effectively.

4.3. Materials Used for DNA Detection

The materials used in constructing DNA-based biosensors are critical to their functionality and efficiency, often serving dual roles as both electrode materials and modifiers. Gold is the most commonly mentioned material, appearing in 45 instances, frequently in combination with others. Its widespread use in biosensor technology is due to its excellent electrical conductivity and biocompatibility, making it ideal for sensitive and accurate detection systems. Gold is often paired with carbon, platinum, graphene, and DNA itself, enhancing the biosensors' performance by improving electron transfer properties and providing a larger surface area for biomolecule immobilization. Figure 7 illustrates the most common materials used in DNA detection.

Carbon-based materials play a significant role in DNA-based biosensors, appearing in 23 instances, often in combination with gold, platinum, and graphene. These materials, including carbon nanotubes and graphene, are valued for their high surface area, chemical stability, and excellent conductivity, making them excellent supports or modifiers for biomolecules. This ensures that biosensors can operate effectively in detecting various biomarkers.

Platinum, mentioned in 13 instances, is typically used for its robust catalytic properties, crucial for enzymatic biosensors. It is often combined with elements like gold, carbon, and graphene to enhance the biosensor's responsiveness and durability under different analytical conditions. Graphene, noted in 10 instances, is lauded for its outstanding electrical, mechanical, and thermal properties, which make it an ideal candidate for increasing biosensor sensitivity and stability.

Other materials cited in the studies include titanium, polydopamine (PDA), gold-platinum alloys (AuPt), molybdenum disulfide, and various metals like nickel, cobalt, platinum, and copper. Each of these materials brings unique properties to the biosensors, such as enhanced catalytic activity, increased durability, or specific binding capabilities. For example, quantum dots and glucose oxidase are used for their specific properties—quantum dots for their photoluminescence and glucose oxidase for its enzymatic activity in glucose sensors.

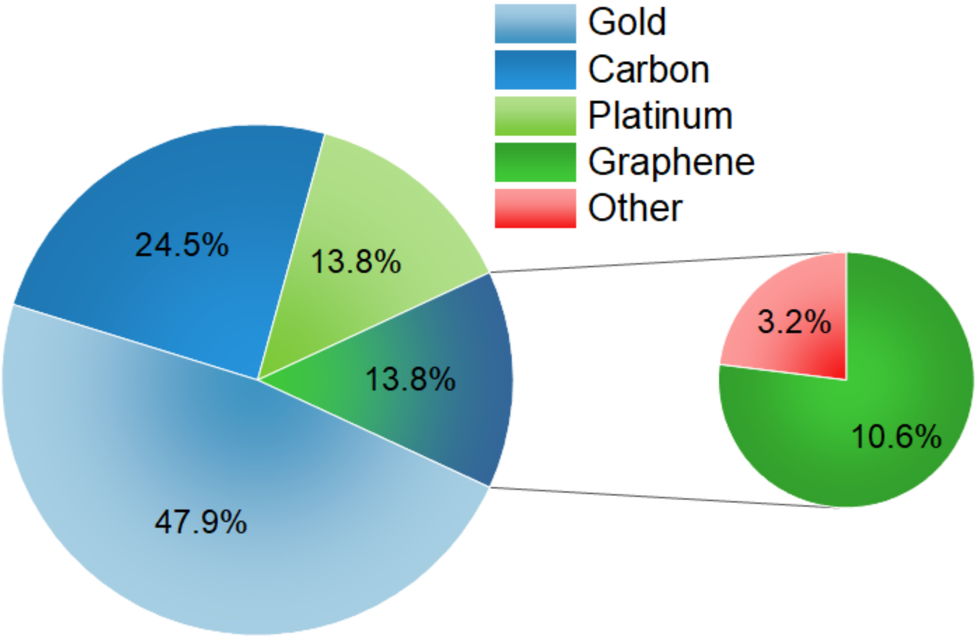

Figure 7. This figure presents a pie chart depicting the distribution of materials used in DNA detection technologies. Gold leads as the most prevalent material, constituting 47.9% of usage due to its effective properties in sensor applications. Carbon and Platinum each makeup 13.8%, reflecting their significance in creating sensitive and stable detection environments. Graphene, known for its high conductivity and surface area, accounts for 24.5%. The "Other" category, which includes less common materials, represents 10.6% of the total, with a detailed segment showing that 3.2% of this category involves unspecified materials, highlighting the diversity of materials employed in the field of DNA detection.

Table 1 summarizes various DNA-based sensor technologies, detailing their areas of use, detection methods, targets, and key analytical characteristics. Electrochemical DNA sensors, used primarily in medical diagnostics, are recognized for their high sensitivity and selectivity, particularly useful in detecting cancer biomarkers through electrochemical methods. Fluorescent DNA sensors, employed in environmental monitoring, utilize fluorescence spectroscopy to rapidly identify pathogens. In the food safety sector, nanoparticle-based sensors offer a simple, visual colorimetric detection method for identifying bacterial contaminants. Microarray DNA sensors, useful in genetic testing, employ hybridization techniques to detect genetic mutations and are noted for their high throughput and ability to handle multiple samples simultaneously. Lastly, aptamer-based sensors, used in therapeutic monitoring, leverage binding assays to detect drugs and proteins with high specificity and are designed to be reusable. Each sensor type is engineered to meet specific requirements in sensitivity, selectivity, and operational efficiency, catering to diverse applications in scientific and healthcare settings.

Overall, the choice of materials in DNA-based biosensor development, whether as electrode materials or modifiers, is pivotal, significantly affecting performance characteristics such as sensitivity, selectivity, response time, and stability. This diversity in material usage underscores the interdisciplinary approach in biosensor technology, integrating insights from materials science, chemistry, and molecular biology to tailor biosensors to specific applications.

Table 1. Examples of DNA-Based Sensors.

DNA Sensor Type	Area of Use	Method	Target	Analytical Characteristics
Electrochemical DNA Sensor	Medical diagnostics	Electrochemical detection	Cancer biomarkers	High sensitivity and selectivity, quantitative analysis
Fluorescent DNA Sensor	Environmental monitoring	Fluorescence spectroscopy	Pathogens	Rapid response, real-time monitoring
Nanoparticle-based Sensor	Food safety	Colorimetric detection	Bacterial contaminants	Easy to use, visual detection
Microarray DNA Sensor	Genetic testing	Hybridization	Genetic mutations	High throughput, multiplexing capabilities
Aptamer-based Sensor	Therapeutic monitoring	Binding assay	Drugs and proteins	High specificity, reusable

5. Challenges and Concerns

DNA-based biosensors offer immense potential for revolutionizing fields such as medical diagnostics and environmental monitoring, yet their practical application is hampered by a range of challenges and concerns. One of the foremost issues is the inherent instability of DNA molecules. DNA is prone to degradation by environmental factors such as temperature fluctuations, humidity, and the presence of nucleases—enzymes that break down nucleic acids [35]. This instability can significantly reduce the operational lifespan and reliability of DNA-based biosensors, making them less effective for long-term monitoring or repeated use. Researchers are actively exploring methods to enhance the stability of these sensors, including encapsulating DNA in protective coatings, using nanomaterials such as graphene and gold nanoparticles, and developing synthetic analogs of DNA that are more resistant to environmental degradation.

DNA-based biosensors offer a versatile platform for sensitive and specific detection of target molecules, with applications ranging from disease diagnostics to genetic analysis. These biosensors leverage the specificity of DNA interactions to detect target molecules with high sensitivity and selectivity [25]. The use of optical and spectroscopic measurements in DNA biosensors has shown great potential, offering a non-invasive and highly sensitive approach to detecting DNA hybridization events [36]. The field of DNA-based biosensors encompasses a wide range of applications, each posing unique challenges that require innovative solutions [37].

Achieving high specificity and sensitivity is another challenge in the development of DNA-based biosensors [38]. Non-specific binding, where molecules other than the target bind to the sensor, can result in false positives, while weak binding of the target molecules can lead to false negatives. These issues undermine the reliability of the biosensors, especially in clinical diagnostics where accurate detection is important. Advanced molecular recognition elements, such as aptamers and engineered proteins, are being developed to improve specificity. Additionally, techniques such as signal amplification and advanced surface chemistry modifications are being employed to enhance sensitivity and reduce the impact of non-specific interactions [39]. These improvements are essential for ensuring that DNA-based biosensors can deliver reliable and accurate results in real-world applications.

One significant challenge in DNA biosensors is enhancing the sensitivity of detection without the need for complex catalytic processes or extensive sample preparation. For instance, the development of conducting polyaniline nanotube array-based DNA biosensors has shown comparable sensitivity to other nanoparticle-based biosensors, highlighting the potential for achieving high sensitivity through novel material design [40]. Additionally, the integration of gold nanoparticles in biosensors has been explored to enhance signal detection, although limitations in sensitivity at low analyte concentrations remain a concern [41].

Electrochemical DNA biosensors have gained attention due to their rapid response times, specificity, and potential for miniaturization, making them valuable tools for various applications, including tumor biomarker screening [42]. However, improving the sensitivity and detection limits of electrochemical DNA biosensors remains a critical challenge that researchers are actively addressing [43]. Strategies such as incorporating palladium nanoparticles and carbon nanotubes have been investigated to enhance the performance of electrochemical DNA sensors [44].

Moreover, the design of DNA biosensors based on unique structures, such as G-quadruplexes, offers a novel approach to detecting specific DNA sequences, including those related to viral infections like SARS-CoV-2 [45]. These innovative biosensor designs highlight the versatility of DNA-based platforms in addressing diverse diagnostic needs. Additionally, the development of biosensors utilizing carbon-based frameworks demonstrates the ongoing efforts to enhance sensitivity and signal-to-noise ratios in DNA detection [46].

Furthermore, the reusability of DNA biosensors is a critical factor in their practical application and cost-effectiveness. Strategies involving the covalent attachment of multiwalled carbon nanotubes and gold nanoparticles have been explored to improve the reusability and stability of DNA biosensors [47]. Additionally, advancements in piezoelectric DNA-based biosensors have enabled the detection of specific genomic sequences, such as those associated with Mycobacterium tuberculosis, showcasing the potential for DNA biosensors in infectious disease diagnostics [48].

Beyond technical challenges, the practical deployment of DNA-based biosensors involves significant technological and ethical considerations. From a technological perspective, there is a need to miniaturize these sensors and integrate them into portable, user-friendly devices [49]. This involves overcoming challenges related to the fabrication of small-scale, reliable components that can function consistently in diverse environments. Moreover, these devices must be affordable and accessible to ensure widespread use, particularly in resource-limited settings. On the ethical front, the use of DNA-based biosensors raises important concerns about data privacy and the potential misuse of genetic information. DNA biosensors, particularly those used in genetic testing, could inadvertently reveal sensitive information about an individual's genetic predispositions, leading to potential privacy breaches or discrimination. Establishing robust regulatory frameworks and ethical guidelines is imperative to address these concerns. Such regulations must ensure that data collected by DNA-based biosensors is handled with the highest standards of confidentiality and used solely for intended and consensual purposes.

Overall, DNA-based biosensors offer a promising avenue for various applications, with researchers continuously working on improving sensitivity, enhancing reusability, and exploring novel biosensor designs to expand the capabilities of DNA biosensing technologies. By leveraging innovative materials, structures, and detection strategies, the field of DNA biosensors is poised to make significant contributions to healthcare, biotechnology, and environmental monitoring.

6. Conclusions

DNA-based biosensors represent a transformative advancement in the fields of medical diagnostics and environmental monitoring. Their high specificity and sensitivity, combined with the ability to detect a wide range of biomolecular targets, position them as powerful tools for early disease detection, genetic analysis, and real-time environmental assessment. Despite their promising potential, the deployment and widespread adoption of DNA-based biosensors face significant challenges. Stability issues, arising from the inherent susceptibility of DNA to environmental degradation, need to be addressed through innovative stabilization techniques and protective materials. Enhancing the specificity and sensitivity of these biosensors in complex sample matrices is crucial to ensure reliable and accurate results. This requires continuous advancements in molecular recognition elements and signal processing methods. Technological challenges related to the miniaturization and integration of these sensors into portable, user-friendly devices also need to be overcome to facilitate their practical use in diverse settings. Ethical considerations, particularly concerning data privacy and the potential misuse of genetic information, are paramount. Establishing stringent regulatory frameworks and ethical guidelines is essential to protect individuals' privacy and foster public trust in these technologies. Transparent practices and education initiatives can help mitigate public concerns and promote the acceptance of DNA-based biosensors. In conclusion, while the path to the widespread implementation of DNA-based biosensors is fraught with challenges, ongoing research and innovation continue to push the boundaries of what is possible. By addressing the technical, technological, and ethical issues, DNA-based biosensors can fulfill their potential as revolutionary tools in diagnostics and environmental monitoring, ultimately contributing to improved public health and environmental sustainability.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/dna4030020/s1, S1: Figure 2B: Biosensor Types and Fabrication. S2: List of articles used in this systematic review. S3: PRISMA Checklist [50].

Author Contributions: H.S.M. and Y.F. were primarily responsible for drafting the original manuscript and conducting the data analysis that supports the findings of this study. G.B. contributed to the review and analysis of the data, ensuring the accuracy and relevance of the results presented. M.Z.H. reviewed the manuscript, provided critical revisions that significantly shaped the final content. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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